EFFECTIVENESS OF SGLT2I RELATIVE TO OTHER SECOND-LINE DRUGS ON CHRONIC KIDNEY DISEASE IN TYPE 2 DIABETES PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF REAL-WORLD DATA

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ABSTRACT

The sodium-glucose cotransporter-2 inhibitors (SGLT2i) can reduce risk of heart failure and composite cardiovascular outcomes. However, the effects of SGLT2i on chronic kidney disease (CKD) remain unclear. This systematic review and meta-analysis were conducted to evaluate the effectiveness of SGLT2i relative to other second-line glucose lowering drugs (i.e., thiazolidinediones, glucagon-like peptide 1, dipeptidyl peptidase-4 inhibitors and sulfonylurea) on CKD in type 2 diabetes mellitus (T2DM) patients. Relevant studies were identified from Medline and SCOPUS databases through July, 2023. Any cohort studies of T2DM that apply the propensity score method to compare the effect of SGLT2i with other second line drugs on CKD were included. Data were independently extracted by 2 reviewers. Direct meta-analysis was applied for pooling adjusted hazard ratio (HR) from propensity score. Meta-regression analysis was applied to explore sources of heterogeneity. Eight cohorts with 13 sub-cohorts with 400,211 patients were included. The results showed that HRs (95% CI) of SGLT2i was 0.53 (0.43, 0.66), with high degree of heterogeneity (I2 = 91.75%; Q test p-value = <0.001). It means that the risk of CKD was 47% statistically significant lower in SGLT2i treated subjects than other second line drugs.

Keywords: Type 2 Diabetes, Sodium-Glucose Transporter 2 Inhibitors, Thiazolidinediones, Glucagon-Like Peptide 1, Dipeptidyl-Peptidase IV Inhibitors, Sulfonylurea, Chronic Kidney Disease, Propensity Score

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INTRODUCTION

Diabetes mellitus (DM) with suboptimal glycemic control is one of the major health problems among people around the world, including Thailand (World Health Organization, 2021b). The World Health Organization (WHO) estimated that 422 million people worldwide have DM, the majority living in low-and middle-income countries, and 1.5 million deaths are directly attributed to DM each year (World Health Organization, 2021a). Previous Thai National Health Examination Surveys (NHES) reported that the prevalence of DM among the Thai population aged 20 years and over increased from 7.1% in 2004 to 7.5% in 2009 (Aekplakorn et al., 2007; Aekplakorn et al., 2011). Type 2 diabetes mellitus (T2DM), accounting for around 90% of DM cases (Zheng et al., 2018), is characterized by high insulin resistance and inadequate insulin production, resulting in high glycemic levels (Fonseca, 2009). Inadequate glycemic control can lead to various complications for the individual (Bailey, 2016).

T2DM represents the main cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD), approximately 30% to 40% of patients with T2DM have been estimated to have CKD (Feng et al., 2022) or accounting for almost 50% of all patients starting renal replacement therapy (RRT) worldwide (Koye et al., 2017). At least half of patients with T2DM develop diabetic kidney disease (DKD), characterized clinically by a persistent reduction in estimated glomerular filtration rate (eGFR) and/or increased urinary excretion of albumin (micro or macro-albuminuria). DKD is the predictor of morbidity and premature mortality in patients with DM (De Cosmo et al., 2016). Therefore, kidney protection is a critical target in T2DM.

The first recommendation for the initial treatment for DM patients by the American Diabetes Association (ADA) standards of medical care are dietary and physical exercise (American Diabetes Association, 2020). However, this method cannot change glycemic control, metformin monotherapy is the recommended first-line glucose-lowering agent in patients with T2DM (American Diabetes Association, 2020; Zaccardi, Khunti, Marx, & Davies, 2020). For patients who continue to have uncontrolled glycemic levels within 3 months or who have any complications such as cardiovascular disease (CVD) or CKD, a second-line antihyperglycemic drugs are added to metformin. Currently, second-line antihyperglycemic treatment options include sodium-glucose cotransporter-2 inhibitors (SGLT2i), thiazolidinedione (TZD), glucagon-like peptide-1 (GLP-1) analogues, dipeptidyl peptidase-4 inhibitors (DPP4i), insulin and sulfonylureas (SU). The selection of a second-line drug is depends on many factors including physician, accessibility to health care, health insurance, reimbursement system, drug efficacy, side effects and cost for drugs (Gottlieb, Yanover, Cahan, & Goldschmidt, 2017; Siriyotha et al., 2022). The SGLT2i is recommended for patients with T2DM who failed from first-line metformin (Yang et al., 2022).

LITERATURE REVIEWS

There is one network meta-analysis (NMA) (Giugliano et al., 2022) of RCTS which had assessed the efficacy of oral antidiabetic drugs (i.e., GLP-1, SGLT2i and DPP4i) on renal composite outcomes (i.e., sustained decline in the estimated glomerular filtration rate (eGFR) of at least 50%, ESRD, doubling of serum creatinine and renal death). They combined evidences of 23 RCTs and found that SGLT2i are superior to GLP-1, DPP4i and placebo in reducing the risk of renal events with risk ratio (RR) and 95% confidence interval CI) of 0.78 (0.67, 0.91), 0.60 (0.49, 0.75) and 0.64 (0.58, 0.72) lower risk, respectively. However, there was no head-to-head comparison among these antidiabetic drug classes.

There are many observational studies that compared renal outcomes between SGLT2i and other second-line drugs in T2DM patients found that SGLT2i reduce risk of renal outcome when compare with other second-line drug (Au et al., 2022; Birkeland et al., 2021; Idris et al., 2021, 2022; Karasik et al., 2023; Komuro et al., 2021; Lim et al., & Cho, 2022; Lui et al., 2022; Nyström et al., 2023; Peng et al., 2022; Seino et al., 2021; Siriyotha et al., 2022; Xie et al.,

2020; Yang et al., 2022). Additionally, there was one systematic review of real-world studies compared the renal outcomes between SGLT2i and DPP4i (Yang et al., 2022). They included 11 real-world studies in Asian population with last search in May 13, 2021. All included studies were retrospective cohort and applied propensity score (PS) methods to adjust for imbalanced baseline patient characteristics. There were 3 studies (Birkeland et al., 2021; Komuro et al., 2021; Seino et al., 2021) focused on renal outcome, 2 studies on CKD and 1 study on ESRD. However, this systematic review did not perform meta-analysis for renal outcome because of small number studies.

However, when comparing the effect of treatments in real-world studies, we need to take into account confounding effects in the model. The conventional multivariate regression model is not enough to adjust confounding factors and there could be bias due to ignore factors related with selective prescribing treatments. The PS methods were suggested to balance patient characteristics and enable to direct comparison of the outcomes among different treatments and thereby closely to emulate RCT (Allan et al., 2020).

In recent years, several observational studies compared the effectiveness of SGLT2i with other second-line drugs on CKD, ESRD and composite renal outcome by using PS methods in Western and Asian populations were published (Au et al., 2022; Birkeland et al., 2021; Idris et al., 2021, 2022; Karasik et al., 2023; Komuro et al., 2021; Lim et al., 2022; Lui et al., 2022; Nyström et al., 2023; Peng et al., 2022; Seino et al., 2021; Siriyotha et al., 2022; Xie et al., 2020; Yang et al., 2022). Therefore, this systematic review with meta-analysis was conducted to compare treatment effectiveness of SGLT2i relative to other second-line drugs in prevention of CKD, ESRD and composite renal outcome in T2DM patients and apply the PS methods for estimating the treatment effects.

RESEARCH METHODOLOGY

This systematic review and meta-analysis (SRMA) was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Liberati et al., 2009).

Databases and search strategies

A systematic literature searches was performed to all available published studies from online database MEDLINE via the PubMed search engine and Scopus from inception to July 2023. The search terms and strategies were constructed based on PICO.

Selection of studies

Any type of cohort studies with apply propensity score (PS) method for estimating treatment effect were included if they met all the following criteria: studied in adult patients diagnosed with T2DM, compare SGLT2i with any of other second-line drugs of diabetes (i.e., TZD, GLP-1, DPP4i and SU) with or without metformin, and had outcomes CKD. Studies were excluded if they had insufficient data for pooling after three contact attempts with authors every two weeks and published in languages that untranslatable by google translate.

Data extraction

Data was extracted independently by 2 reviewers. (O.M. and C.A.) using a data extraction form which consist of general information (i.e., the author, year of publication), study characteristics (i.e., country, study design, periods of study, duration of follow up, types of treatment and outcome models, PS methods), general characteristics of participants (i.e., duration of T2DM, mean age, percentage of female, mean BMI, mean systolic and diastolic blood pressure, mean eGFR, mean FBS, mean HbA1c, mean albumin, mean creatinine and percentage of comorbidities), Interventions and comparator information (i.e., number of interventions, specific name of intervention, dosage and duration of drug), definition of outcome, and data for pooling. For time to event outcome, the adjusted HR with 95% confidence intervals (95% CI) that estimated from PS approach were extracted. For dichotomous outcome, the adjusted

RR with 95% CI, average treatment effect (ATE) with 95% CI, and potential outcome mean (POM) with 95% CI from propensity score were extracted.

Risk of bias assessment

The quality of studies was independently assessed by 2 reviewers (O.M. and C.A.). Disagreement was solved by discussion with supervisors (S.R., T.A. and A.T.). Risk of bias in non-randomized studies-of interventions (ROBINS-I) (Sterne et al., 2016) was used for assessment. This tool consisted of 7 domains of risk of bias; bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. Individual question in each domain was answered as “Yes”, “Probably yes”, “Probably no”, “No”, "Not applicable”, and “No information”. Risk of bias judgement was assessed according to that domain algorithm to classify to “Low risk”, “Moderate risk”, “Serious risk” and “Critical risk”. The overall risk of bias judgment used criteria of the ROBINS-I tool. The study was judged to be overall low, moderate, serious and critical risk of bias if all seven domains were low risk of bias, all domains to be low and moderate risks of bias, at least one of all domains to be serious risk of bias and at least one of all domains to be critical risk of bias, respectively.

Statistical analysis

Pairwise meta-analysis was performed according to types of outcome as follows:

The adjusted HR and 95% CI which estimated from PS model were pooled across studies for time-to-event outcome, while the adjusted RR along with 95% CI which estimated by PS analysis were pooled across studies for dichotomous outcome. A random-effect model of DerSimonian and Laird method were applied if heterogeneity was present, otherwise a fixed-effect model by inverse-variance method was used.

Heterogeneity was expressed by the I^2 statistic and the Cochran’s Q test. The I^2 is classified as low, moderate, or high if it is < 25%, 25%-74% and ≥ 75% respectively, and moderate degree or higher ($I^2 \geq 25\%$) was considered to account for between-study variations. The Cochran’s Q test, p-value less than 0.1 was considered as having heterogeneity.

If heterogeneity was present, source of heterogeneity (i.e., age, sex, eGFR, FBS, HbA1c, ACEi, albumin, metformin used, insulin used, type of propensity score, and setting) was explored by fitting each covariate in a meta-regression model. Then, each of these covariates was considered as source of heterogeneity if the result of meta-regression of that variable showed significance and an I^2 statistic or Tau^2 was decreased more than 50% after fitting the covariable in the regression model, subgroup analysis was subsequently performed for that covariable.

For publication bias was assessed using Egger’s test and funnel plot. If a P value of Egger’s test less than 0.05 or funnel plot showed asymmetry, a contour-enhanced funnel plot according to significant and non-significant areas (e.g., < 0.01, < 0.05, and ≥ 0.05) was then applied to distinguish the cause of asymmetry. If the plot still showed missing studies in non-significant areas, asymmetry would be assumed due to publication bias. However, if the contour-enhanced funnel plot showed missing studies in both significant and non-significant areas, this asymmetry might be more likely due to heterogeneity.

All analyses were performed using STATA version 18.0 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC.). A P-value < 0.05 was considered statistically significant, except for heterogeneity test which a p-value of Cochran’s Q test less than 0.1 was considered statistically significant.

RESEARCH RESULTS

A total of 259 articles were identified from PubMed and Scopus; 159 remained after deleting duplicates. 9 articles met the inclusion criteria and 1 article insufficient data for pooling resulting in 8 studies for the quantitative analysis.

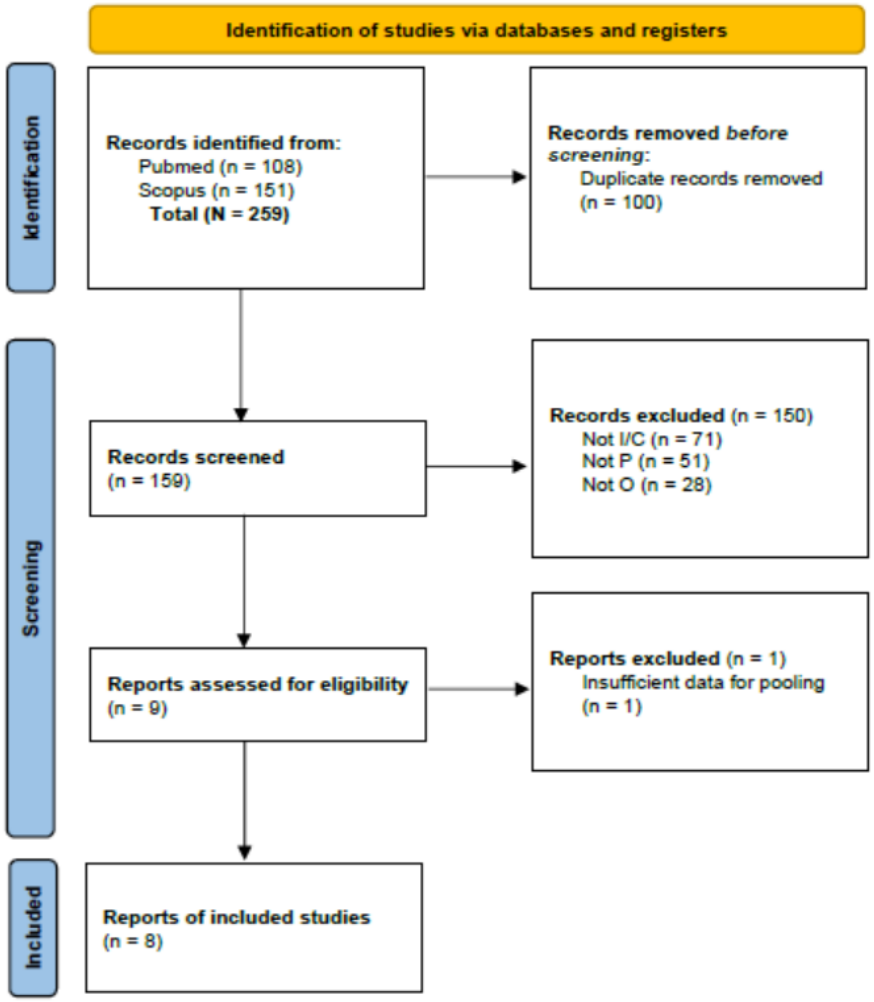

Figure 1 PRISMA Flow diagram

Characteristics of included studies

This review included 8 cohort studies (13 sub-cohorts) published between 2021 and 2023 in patient with T2DM. The details of patients' characteristics, and treatments of included studies are described in Table 1. Treatment and comparator consist of SGLT2i VS DPP4i include 7 cohort studies (12 sub-cohorts) and SGLT2i VS GLP-1 include 1 cohort studies (1 sub-cohort). The mean age ranged from 54.55 to 67.5 years. The percentage female ranged from 35.2% to 58.05%. The mean eGFR ranged from 76.41 to 84.46 (mL/min/1.73 m^2). The mean HbA1c ranged from 8.14 to 8.9 %. The mean FBS ranged from 171 to 176.25 mg/dL.

Table 1 Characteristics of patients, and treatments of included studies

Author, year	Country	Treatment comparison	Mean age (yr.)	Female (%)	Mean eGFR (mL/min/1.73 m^2)	Mean HbA1c (%)	Mean FBS (mg/dL)
Birkeland KI, 2021	England	SGLT2i VS DPP4i	59.8	46.6	N.A.	N.A.	N.A.
Birkeland KI, 2021	Germany		66.2	44.8	N.A.	N.A.	N.A.
Birkeland KI, 2021	Japan		67.5	41.4	N.A.	N.A.	N.A.
Birkeland KI, 2021	Korea		N.A.	N.A.	N.A.	N.A.	N.A.
Birkeland KI, 2021	Norway		61.2	49.2	N.A.	N.A.	N.A.
Birkeland KI, 2021	Sweden		63.9	46.8	N.A.	N.A.	N.A.
Idis I, 2021	UK	SGLT2i VS DPP4i	54.55	44.66	N.A.	N.A.	N.A.
Au PCM, 2022	Hong Kong	SGLT2i VS DPP4i	61.71	44.33	86.46	8.5	N.A.
Lui DTW, 2022	Hong Kong	SGLT2i vs GLP1	56.2	44	78	8.9	171
Peng ZY, 2022	Taiwan	SGLT2i VS DPP4i	58	43.5	N.A.	N.A.	N.A.
Siriyotha S, 2022	Thailand	SGLT2i VS DPP4i	61.46	58.05	76.41	8.14	176.25
Yang CT, 2022	Asia	SGLT2i VS DPP4i	58.23	43.15	N.A.	N.A.	N.A.
Nyström T, 2023	Sweden	SGLT2i VS DPP4i	63.43	35.2	N.A.	N.A.	N.A.

N.A., not available

Treatment effectiveness of SGLT2i for CKD compare with other second line drug

Pairwise meta-analysis was performed on CKD outcome in each pair at least 3 studies. For time-to-event outcome, HRs along with 95% CI from 8 cohort studies (13 sub-cohorts) were pooled using a random effect model, yielding a statistically significant pooled HR (95% CI) of 0.53 (0.43, 0.66), with high degree of heterogeneity (I^2 = 91.75%; Q test: χ^2 = 145.49, degrees of freedom = 12, p-value = <0.001) (Figure 2). The pooled HR suggested that the risk of CKD was 47% significant lower in SGLT2i treated subjects than other second line drugs. The forest plot was shown in Figure 2. For exploring source of heterogeneity, subject's characteristics (age, sex, eGFR, FBS, HbA1c, ACEi, albumin, metformin used, insulin used, type of propensity score, and setting) were inspected in Table 2.

The results of meta-regression analysis showed non- significance and the I^2 statistic or Tau^2 were not decreased more than 50% after fitting the covariable in the regression model, therefore, subgroup analysis was not subsequently performed. According to the available data, sensitivity analysis was performed by excluding one study (Lui et al., 2022) that compared SGLT2i and GLP-1. The results of comparison between SGLT2i and DPP4i indicated that the pooled HR (95% CI) was 0.52 (0.42, 0.64) with the I^2 = 92.14%. It means that the pooled HR suggested that the risk of CKD was 48% significant lower in SGLT2i treated subjects than other second line drugs.

Publication bias was explored by funnel plot and Egger's test (Figure 3). A funnel plot for overall pooling suggested asymmetry funnel plot that one study was outside the range of the symmetrical funnel and Egger test showed no significant evidence of asymmetry (coefficient = -0.67, SE = 1.21, p = 0.5807). The contour enhanced-funnel plot was further performed to

explore caused of asymmetry. The plot showed signal of missing study in non-significant region (white region), see (Figure 4). As a result, asymmetry of the funnel might be caused by publication bias.

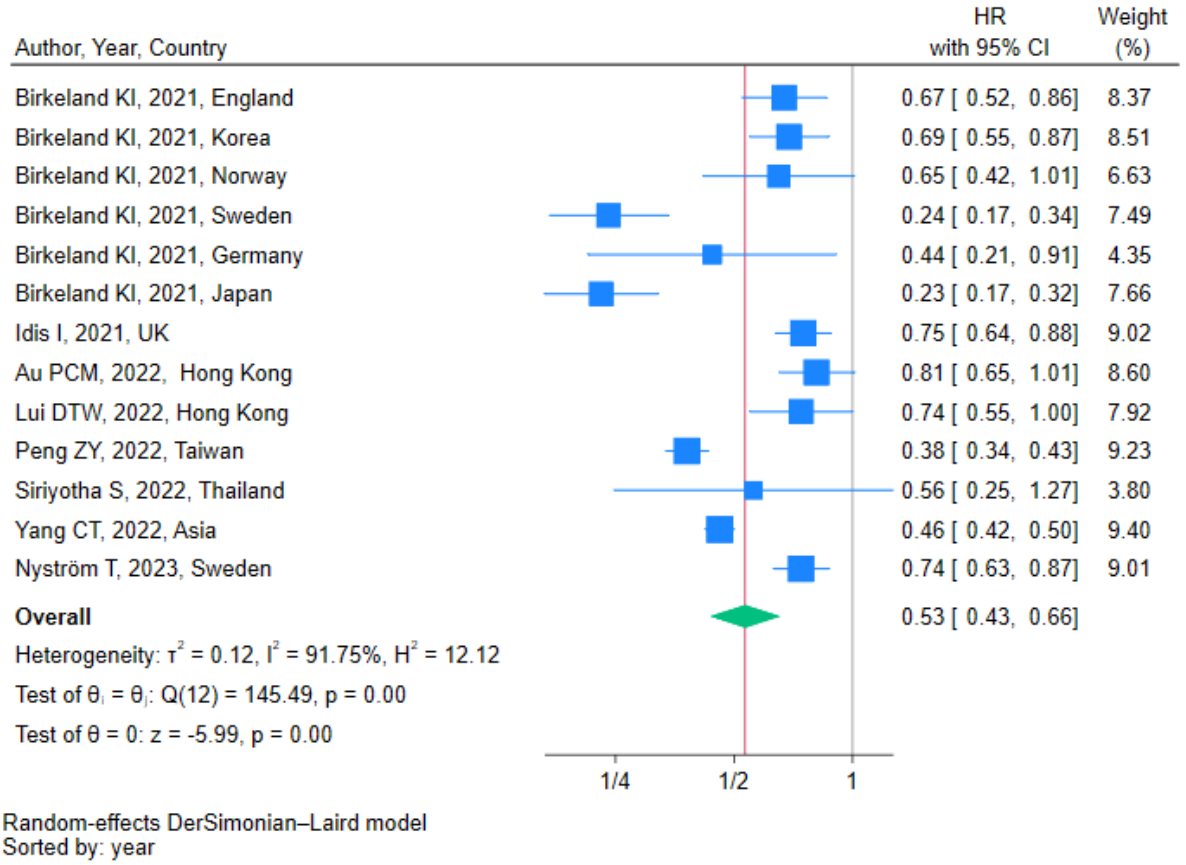

Figure 2 Forest plot of effect of SGLT2i vs other second line drug for CKD

Table 2 Exploring source of heterogeneity by meta-regression analysis

Factor	Number studies	I^2 without covariate	I^2 with covariate
Mean age (yr.)	12	92.11	92.67
Percentage of female	12	92.11	92.55
Percentage use of ACEi	10	88.85	81.27
Percentage use of metformin	11	92.82	83.94
Percentage use of insulin	11	92.82	93.5
Type of propensity score (Match/Unmatch)	13	91.75	92.44
Setting (Asia/Europe)	13	91.75	90.04

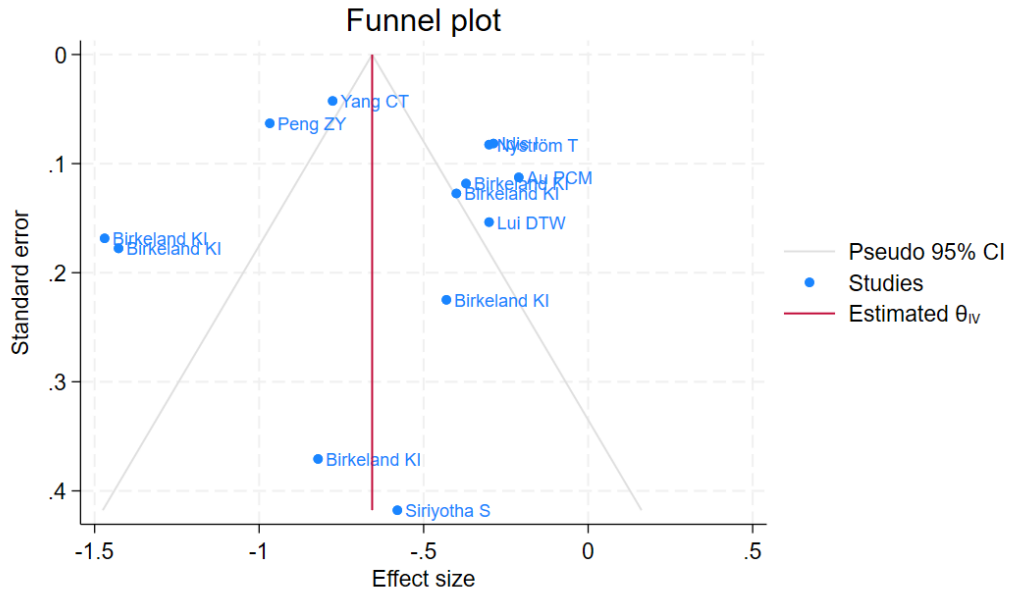

Figure 3 Funnel plot of SGLT2i vs other second line drug for CKD

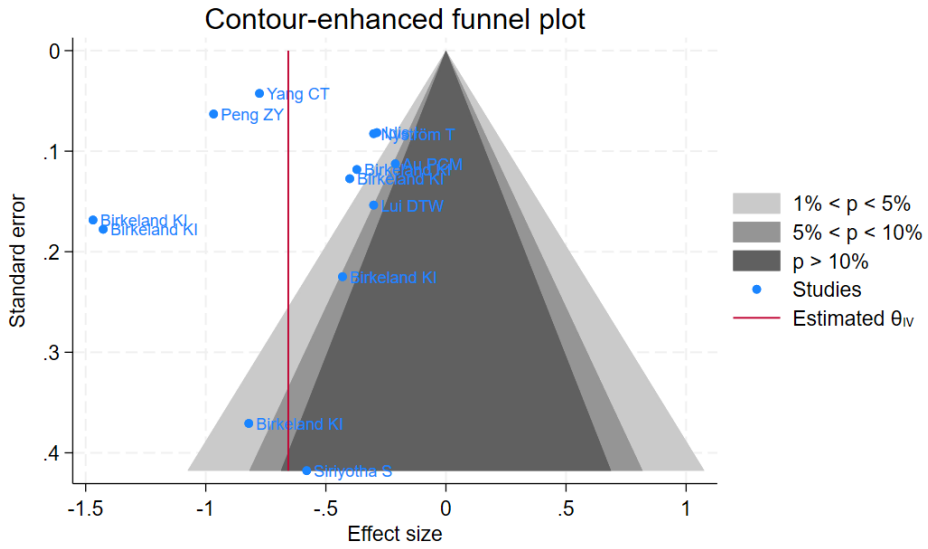

Figure 4 Contour funnel plot of SGLT2i vs other second line drug for CKD

DISCUSSION & CONCLUSION

The main finding results from our SRMA of real-world studies that apply propensity score (PS) to pool the effect of SGLT2i indicated that risk of CKD was 47% significantly lower than other second-line drugs with high heterogeneity. However, the results of meta-regression cannot detect the sources of heterogeneity. Sensitivity analysis was performed by excluding one study that compared SGLT2i and GLP-1 (Lui et al., 2022). Therefore, the results of comparison between SGLT2i and DPP4i indicated that the pooled HR (95% CI) was 0.52 (0.42, 0.64) with the I^2 =92.14%. It means that the risk of CKD was 48% significant lower in patients who treated with SGLT2i than DPP4i. Our results showed consistency with previous NMA studies of RCT (Giugliano et al., 2022). Their finding results suggested that SGLT2i was significant associated with lower risk of renal outcome as compared with DPP4i about 40% with moderate degree of heterogeneity (42.3%). However, previous NMA pooled RR, but in this research pool HR. Pooling HR can offer enhanced statistical efficiency, particularly when analyzing time-to-event

data and incorporating censored observations. This makes HRs advantageous in systematic reviews for their ability to provide insights into temporal outcome dynamics and accommodate variations in follow-up durations across studies. Consequently, HR serve as a valuable tool for synthesizing evidence, especially in studies where event timing holds significant importance.
To the best of our knowledge, there is the first meta-analysis compared treatment effectiveness of SGLT2i relative to other second-line drugs in prevention of CKD in adult patients with T2DM in real-world data. However, the results of all included studies are still controversial and had high heterogeneity and the sources of heterogeneity cannot be detected. The large number of real-world studies with apply PS are required to confirm the effectiveness of SGLT2i and other second line drugs.

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