

Association of SGLT2 Inhibitors With Risk of Atrial Fibrillation and Stroke in Patients With and Without Type 2 Diabetes: A Systemic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract: Sodium-glucose cotransporter 2 (SGLT2) inhibitors have well-documented effects on reducing hospitalization for heart failure and cardiovascular mortality, although the effect on atrial fibrillation (AF) has not been comprehensively investigated. Therefore, we performed a meta-analysis to assess the association between SGLT2 inhibitors and AF risk by systematically searching PubMed, Embase, and ClinicalTrials.gov. Two investigators independently identified randomized controlled trials, which compared SGLT2 inhibitors with control in patients with type 2 diabetes, heart failure, or chronic kidney disease. Primary outcomes were incident AF and stroke. We included 20 randomized trials involving 63,604 patients. The SGLT2 inhibitors used were dapagliflozin (7 studies, 28,834 patients), canagliflozin (7 studies, 17,440 patients), empagliflozin (5 studies, 9082 patients), and ertugliflozin (1 study, 8246 patients). Follow-up ranged from 24 weeks to 202 weeks. SGLT2 inhibitors treatment was associated with a significant attenuation in the risk of incident AF (odds ratio = 0.82; 95% confidence interval, 0.72–0.93; $P = 0.002$) compared with control. No significant difference in stroke between SGLT2 inhibitors and control groups was found (odds ratio = 0.99; 95% confidence interval, 0.85–1.15; $P = 0.908$). This present meta-analysis indicates that SGLT2 inhibitors are associated with a lower risk of incident AF and do not significantly affect stroke risk for patients with and without type 2 diabetes.

Key Words: atrial fibrillation, sodium-glucose cotransporter 2 inhibitors, diabetes mellitus, meta-analysis

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INTRODUCTION

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is a leading cause of mortality worldwide. As is reported, the estimated prevalence of AF is 1%–4% in western countries and China,¹ and its prevalence is expected to surge in the next 3 decades owing to factors such as an aging population, economic growth, and increased prevalence of risk factors for AF.² AF increases the risk of heart failure and stroke that causes a huge burden on human health and social economy. Diabetes mellitus has been well established as a critical risk factor for AF.³ Accumulating evidence demonstrates that diabetes is closely associated with increased risk of AF promotion.^{4–6} As far back as the Framingham Heart Study, it was suggested that the risk of developing AF was significantly increased in patients with diabetes during a long-term follow-up.⁵ A meta-analysis of 29 studies, which included 8,037,756 individuals, also found similar results that patients with diabetes had a 49% increased risk in the development of AF.⁷ In addition, higher glycemic levels were shown to be correlated with increased risk of AF.⁸ Generally, the link between diabetes mellitus and AF is clear and close.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, a novel class of oral antihyperglycemic agents for treating type 2 diabetes by selectively inhibiting renal reabsorption of glucose and increasing urinary glucose excretion,^{9,10} have been fully demonstrated to attenuate the risk of hospitalization for worsening heart failure and the risk of cardiovascular death or serious renal outcomes, in recent, large, multicenter, randomized controlled trials (RCTs).^{11–14} Recently, an animal study suggested that canagliflozin had an effect on preventing developing AF and suppressing the promotion of atrial remodeling.¹⁵ In addition, Zelniker et al¹⁶ reported that dapagliflozin was associated with a decreased risk of AF in patients with type 2 diabetes regardless of the history of AF or other cardiovascular diseases in a post hoc analysis of the DECLARE-TIMI58. SGLT2 inhibitors seem to possess therapeutic potential for AF. However, the association has not been comprehensively established, and evidence is inconclusive. Thus, we carried out this present meta-analysis, pooling data from all available RCTs, which compared SGLT2 inhibitors with placebo and reported AF as an adverse event, to further evaluate the effect of SGLT2 inhibitors on AF risk, including sensitivity and subgroup analyses.

TABLE 1. Baseline Characteristics of Included Trials and Quality Assessment

Study (Trial Name)	Study Design (NCT Number)	Mean Age (SD)		Study Population	No. of patients	
		Treatment	Control		Treatment (Female/Male)	Control (Female/Male)
Wilding 2012	RCT (NCT00673231)	59.5 ± 8.1	58.8 ± 8.6	Type 2 diabetes	607 (320/287)	193 (98/95)
Bailey 2013	RCT (NCT00528879)	53.7 (NA)	54.0 (NA)	Type 2 diabetes	409 (194/215)	137 (62/75)
Leiter 2014	RCT (NCT01042977)	63.9 ± 7.6	63.6 ± 7.0	Type 2 diabetes, cardiovascular disease	480 (159/321)	482 (159/323)
Mathieu 2015	RCT (NCT01606320)	55.2 ± 8.6	55.0 ± 9.6	Type 2 diabetes	160 (90/70)	160 (84/76)
DARELARE-TIMI58	RCT (NCT01730534)	63.9 ± 6.8	64.0 ± 6.8	Type 2 diabetes, cardiovascular disease	8582 (3171/5411)	8578 (3251/5327)
DAPA-HF 2019	RCT (NCT03036124)	66.2 ± 11.0	66.5 ± 10.8	Type 2 diabetes, heart failure with reduced ejection fraction	2373(564/1809)	2371(545/1826)
DAPA-CKD 2020	RCT (NCT03036150)	61.8 ± 12.1	61.9 ± 12.1	Type 2 diabetes, chronic kidney disease	2152 (709/1443)	2152(716/1436)
CANTATA-MSU 2013	RCT (NCT01106625)	56.8 ± 9.7	56.7 ± 8.3	Type 2 diabetes	313 (150/163)	156 (80/76)
Yale 2014	RCT (NCT01064414)	68.7 ± 8.2	68.2 ± 8.4	Type 2 diabetes, chronic kidney disease	179 (73/106)	90 (33/57)
Bode 2014	RCT (NCT01106651)	63.9 ± 6.2	63.2 ± 6.2	Type 2 diabetes	477 (224/253)	237 (94/143)
CANVAS-R 2017	RCT (NCT01989754)	63.9 ± 8.42	64 ± 8.28	Type 2 diabetes, chronic kidney disease	2904 (1111/1794)	2903 (1053/1854)
CANVAS 2017	RCT (NCT01032629)	62.5 ± 8.1	62.3 ± 7.9	Type 2 diabetes, cardiovascular disease	2888(983/1905)	1442(486/956)
CREDESCENCE 2019	RCT (NCT02065791)	62.9 ± 9.2	63.2 ± 9.2	Type 2 diabetes, chronic kidney disease	2202(762/1440)	2199(732/1467)
CANTATA-SU 2013	RCT (NCT00968812)	56.2 ± 9.2	56.3 ± 9.0	Type 2 diabetes	968/(475/493)	482/(219/263)
Kovacs 2014	RCT (NCT01210001)	54.5 ± 9.4	54.6 ± 10.5	Type 2 diabetes	333 (165/168)	165(92/73)
Barnett 2014	RCT (NCT01164501)	63.7 ± 8.9	64.1 ± 8.7	Type 2 diabetes, chronic kidney disease	419 (170/249)	319 (138/181)
Rosenstock 2016	RCT (NCT01011868)	59.2 (NA)	58.1(NA)	Type 2 diabetes	324 (138/186)	170 (80/90)
Softeland 2017	RCT (NCT01734785)	54.9 ± 9.7	55.9 ± 9.6	Type 2 diabetes	222 (85/137)	110 (49/61)
EMPA-REG OUTCOME 2015	RCT (NCT01131676)	63.1 ± 8.6	63.2 ± 8.8	Type 2 diabetes	4687 (1351/3336)	2333 (653/1680)
VERTIS CV	RCT (NCT01986881)	64.4 ± 8.1	64.4 ± 8.1	Type 2 diabetes	5499 (1633/3866)	2747 (844/1903)

Study (Trial Name)	Female (%)	Interventions	Background Hypoglycaemic Therapy	Mean Follow-up (wk)	Quality Assessment
Wilding 2012	52.2	Dapagliflozin (2.5/5/10 mg once daily) matching placebo	Insulin	48	A
Bailey 2013	46.9	Dapagliflozin (2.5/5/10 mg once daily) matching placebo	Metformin	102	A
Leiter 2014	33.1	Dapagliflozin (10 mg once daily) matching placebo	Insulin	24	B
Mathieu 2015	54.4	Dapagliflozin (10 mg once daily) matching placebo	Metformin saxagliptin	24	A
DARELARE-TIMI58	37.4	Dapagliflozin (10 mg once daily) matching placebo	Metformin insulin sulfonylurea	102	A
DAPA-HF 2019	23.4	Dapagliflozin (10 mg once daily) matching placebo	DPP-4i GLP-1 receptor agonist Metformin insulin sulfonylurea	72	A

TABLE 1. (Continued) Baseline Characteristics of Included Trials and Quality Assessment

Study (Trial Name)	Female (%)	Interventions	Background Hypoglycaemic Therapy	Mean Follow-up (wk)	Quality Assessment
DAPA-CKD 2020	33.1	Dapagliflozin (10 mg once daily) matching placebo	Metformin insulin sulfonylurea	125	A
CANTATA-MSU 2013	49.0	Canagliflozin (100/300 mg once daily) matching placebo	Metformin suiphonylurea	52	A
Yale 2014	36.1	Canagliflozin (100/300 mg once daily) matching placebo	Insulin sulphonylurea	52	A
Bode 2014	44.5	Canagliflozin (100/300 mg once daily) matching placebo	Insulin sulphonylurea	104	A
CANVAS-R 2017	37.3	Canagliflozin (100/300 mg once daily) matching placebo	Metformin insulin sulfonylurea DPP-4i GLP-1 receptor agonist	187	A
CANVAS 2017	33.9	Canagliflozin (100/300 mg once daily) matching placebo	Metformin insulin sulfonylurea DPP-4i GLP-1 receptor agonist	202	A
CREDENCE 2019	33.9	Canagliflozin (100 mg once daily) matching placebo	Metformin insulin sulfonylurea DPP-4i GLP-1 receptor agonist	125	A
CANTATA-SU 2013	47.9	Canagliflozin (100/300 mg once daily) matching glimepiride	Metformin	52	A
Kovacs 2014	51.6	Empagliflozin (10/25 mg once daily) matching placebo	Metformin pioglitazone	24	A
Barnett 2014	41.7	Empagliflozin (10/25 mg once daily) matching placebo	Metformin pioglitazone insulin	52	A
Rosenstock 2016	42.4	Empagliflozin (10/25 mg once daily) matching placebo	Insulin	78	A
Softeland 2017	40.4	Empagliflozin (10/25 mg once daily) matching placebo	Metformin	24	A
EMPA-REG OUTCOME 2015	28.5	Empagliflozin (10/25 mg once daily) matching placebo	Metformin insulin sulfonylurea DPP-4i	161	A
VERTIS CV	30.0	Ertugliflozin (5/15 mg once daily) matching placebo	Metformin insulin sulfonylurea DPP-4i GLP-1 receptor agonist	182	A

METHODS

This present meta-analysis was performed in accord with the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.¹⁷

Search Strategy

A comprehensive literature search of PubMed, Embase, and ClinicalTrials.gov was carried out for all relevant publications on SGLT2 inhibitors and the risk of AF from inception to May 2021 without language restriction. Keywords or mesh terms used in the searches included “AF” combined with “SGLT2 inhibitor”, “empagliflozin”, “canagliflozin”, “dapagliflozin”, “ertugliflozin”, “sotagliflozin”, “ipragliflozin”, “remogliflozin”, “sergliflozin”, or “tofoliflozin”. The detailed search strategies are shown in **Supplemental Digital Content 1** (see **Supplementary file**, <http://links.lww.com/JCVP/A733>). In addition, a manual search of retrieving the references listed in identified studies and previous reviews to identify any additional studies was conducted.

Selection Criteria

Studies considered eligible for inclusion were RCTs that met the following criteria: (1) included patients with SGLT2 inhibitors exposure or nonexposure and (2) reported the risks of AF using hazard ratio, odds ratio (OR), or risk ratio (RR) estimates with 95% confidence intervals (CI) or

sufficient data to calculate them. Letters to the editor, review articles, and case reports were excluded. Two reviewers independently identified all records by title and abstract and subsequently retrieved and evaluated the full text of any potential articles. When there were multiple RCTs from the same patient cohorts, only the trial with a larger sample size and more informative data was included. Disagreements were resolved by consensus.

Data Extraction and Outcome Assessment

Data were extracted onto a standardized form manually by 2 independent authors. Data extracted from the eligible studies were as follows: information regarding the quality of study, first author, year of publication, study design, participants characteristics, study period, interventions (dose and agent type of SGLT2 inhibitors), and effect estimates with 95% CIs for each outcome. We attempted to contact the corresponding authors to obtain additional data when complete information was unavailable. Any discrepancies were resolved by referring back to the original report.

The primary analyses were focused on evaluating the risk of overall AF among SGLT2 inhibitors users and nonusers. Besides, we also checked stroke as the primary outcome. Further subgroup analyses were performed to investigate the performance of SGLT2 inhibitor treatment between different agent types and length of follow-up.

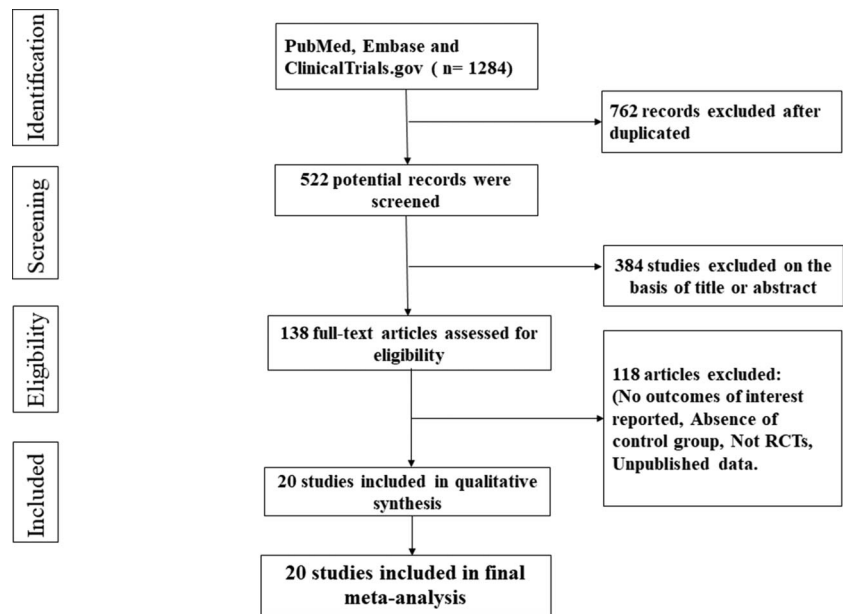


FIGURE 1. Flow diagram of study selection.

Quality Assessment

Two authors independently assessed the methodological quality of the RCTs using the Cochrane risk-of-bias tool.¹⁸ Any disagreement on the risk-of-bias assessments was resolved by discussion of the 2 authors.

Statistical Analysis

All meta-analyses were performed with the random-effect model using STATA SE software (version 16.0, StataCorp, TX). The Mantel–Haenszel test with fixed-effects model, which predicted a low heterogeneity for the outcomes of interest, with pooled OR and corresponding 95% CIs was applied to summarized dichotomous data. Statistical heterogeneity was assessed using the Cochrane Q test and quantified by the I^2 statistics. A P value less than 0.1 was considered statistically significant for the Q test, and I^2 of $\geq 50\%$ indicated a substantial level of heterogeneity. When significant heterogeneity was identified, random-effects model was performed. Several subgroup analyses were conducted to evaluate the robustness of results. Publication bias was investigated graphically with a funnel plot and quantitatively with Egger's test if numbers of included studies were more than 10 in accordance with Cochrane Handbook.

RESULTS

Study Selection and Characteristics

The search strategy is outlined in Figure 1. A total of 1284 records were initially identified. No records were identified through other sources. After the removal of duplicates, 384 records were further excluded with respect to titles and abstracts, leaving 138 records for full-text review. After careful assessment, 20 studies, comprising a total of 63,604 participants, matched our prespecified criteria and were included

for the final meta-analysis. All of the included studies were RCTs. Table 1 summarized the characteristics of the included studies. These studies were published between 2012 and 2020 and had sample sizes ranging from 269 to 17,160 patients. The proportion of female subjects ranged from 28.5% to 51.6%. The study population was type 2 diabetes for all studies except for 2 trials, DAPA-HF,¹² and DAPA-CKD.¹⁹ DAPA-HF included patients with symptomatic heart failure and an ejection fraction of 40% or less, and it had 42% of participants with type 2 diabetes. DAPA-CKD included patients with chronic kidney disease and an estimated glomerular filtration rate of 25–75 mL per minute per 1.73 m², and it had 67.5% of patients with type 2 diabetes. Of all the included studies, 7 RCTs^{12,19–24} assessed the effect of dapagliflozin, 7 RCTs^{11,25–29} assessed the effect of canagliflozin, 5 RCTs^{30–34} assessed the effect of empagliflozin, and 1 RCT³⁵ assessed the effect of ertugliflozin. Across all 20 studies, 14 studies evaluated the effects of different pharmacologic dosages.

Quality Assessment

Randomized sequence generation and allocation concealment were conducted adequately in most studies. The risk of bias for most studies was assessed as low, and all data were derived from randomized trials (Table 1).

Effects of Sodium-Glucose Cotransporter 2 Inhibitors on AF

AF was reported in all 20 studies. SGLT2 inhibitors therapy was associated with a significant 18% reduction in the odds of incident AF compared with control (OR = 0.82; 95% CI, 0.72–0.93; $P = 0.002$; Fig. 2). In subgroup analysis based on the types of SGLT2 inhibitors used (see **Figure 1, Supplemental Digital Content 1**, <http://links.lww.com/JCVP/A733>), only dapagliflozin was associated with

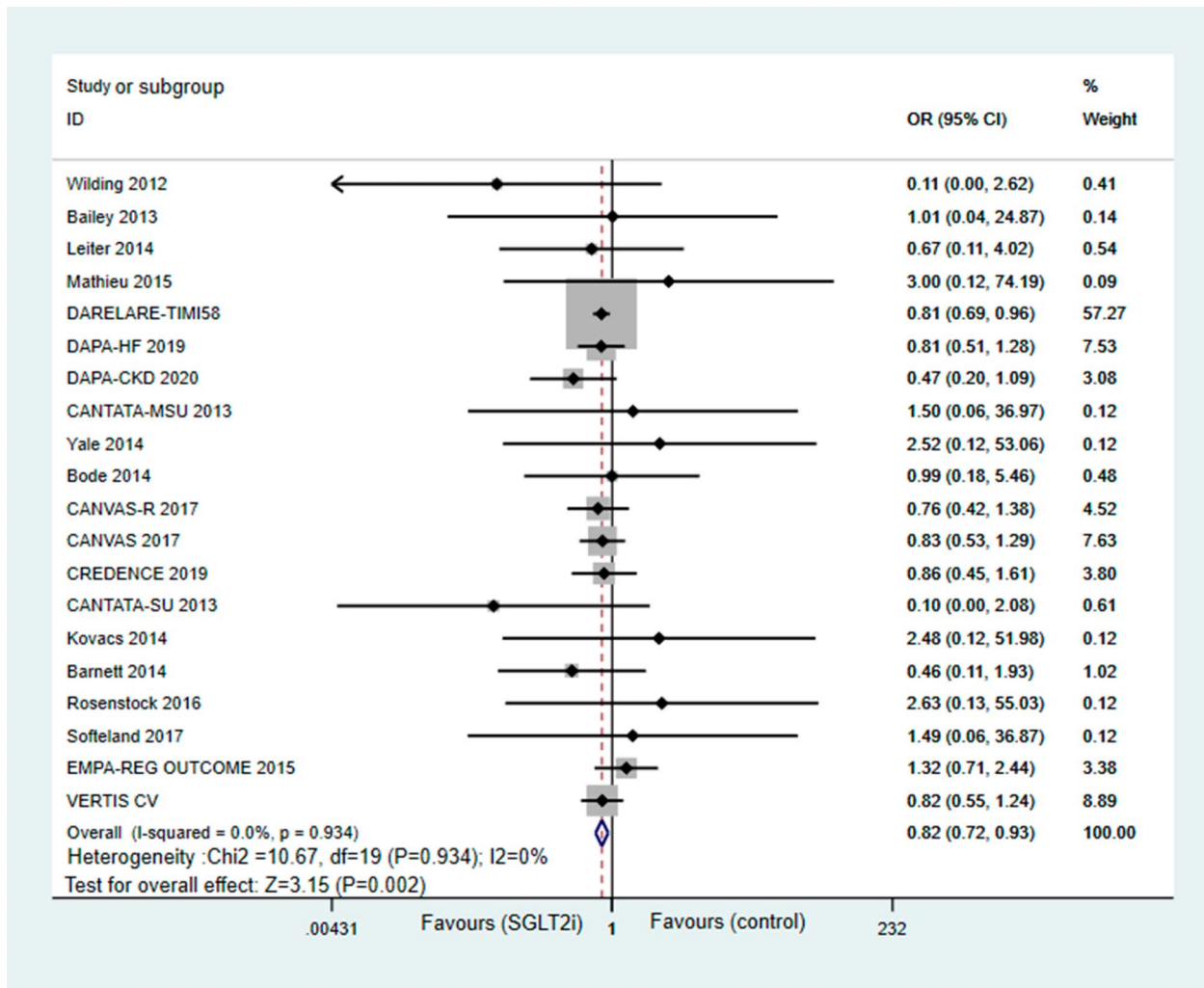


FIGURE 2. Forest plot for meta-analyses comparing the effects of SGLT2 inhibitors with control in AF risk.

significant attenuation on the risk of AF (OR = 0.80; 95%CI, 0.68–0.93; $P = 0.003$). Canagliflozin showed a similar trend but not a statistically significant risk reduction of AF (OR = 0.82; 95% CI, 0.60–1.10; $P = 0.187$). As for empagliflozin, there was no difference in the risk of AF (OR = 1.19; 95% CI, 0.69–2.04; $P = 0.537$). In the subgroup analysis regarding the length of follow-up (see **Figure 2, Supplemental Digital Content 1**, <http://links.lww.com/JCVP/A733>), SGLT2 inhibitors significantly attenuated the risk of incident AF in trials with less than 2 years of follow-up (OR = 0.81; 95% CI, 0.70–0.94; $P = 0.008$). A trend for lower risk of incident AF in the SGLT2 inhibitors group was detected in studies with more than 2 years of follow-up when compared with controls (OR = 0.82; 95%CI, 0.55–1.24; $P = 0.117$). Notably, the subgroup analyses were more susceptible to type II errors because of less power than the overall pooled analysis, which includes all studies regardless of the length of follow-up.

Effects of SGLT2 Inhibitor on Stroke

Apart from 5 studies,^{26,29,31,33,35} 15 studies reported stroke. Compared with controls, SGLT2 inhibitors treatment

did not increase the risk of stroke (OR = 0.99; 95%CI, 0.85–1.15; $P = 0.908$; Fig. 3). In subgroup analysis, there were 7 studies in the dapagliflozin group, 4 studies in the canagliflozin group, and 3 studies in the ertugliflozin group, and all suggested no significant differences between SGLT2 inhibitors treatment and control groups (see **Figure 3, Supplemental Digital Content 1**, <http://links.lww.com/JCVP/A733>).

Publication Bias

No obvious asymmetry was revealed on the funnel plot (see **Figure 4, Supplemental Digital Content 1**, <http://links.lww.com/JCVP/A733>). Additionally, no evidence of publication bias was indicated by Egger’s test ($P = 0.858$).

DISCUSSION

This large meta-analysis of 20 RCTs involving 63,604 patients suggests that SGLT2 inhibitors treatment significantly attenuated the risk of incident AF for patients with type 2 diabetes, heart failure, or chronic kidney disease. In

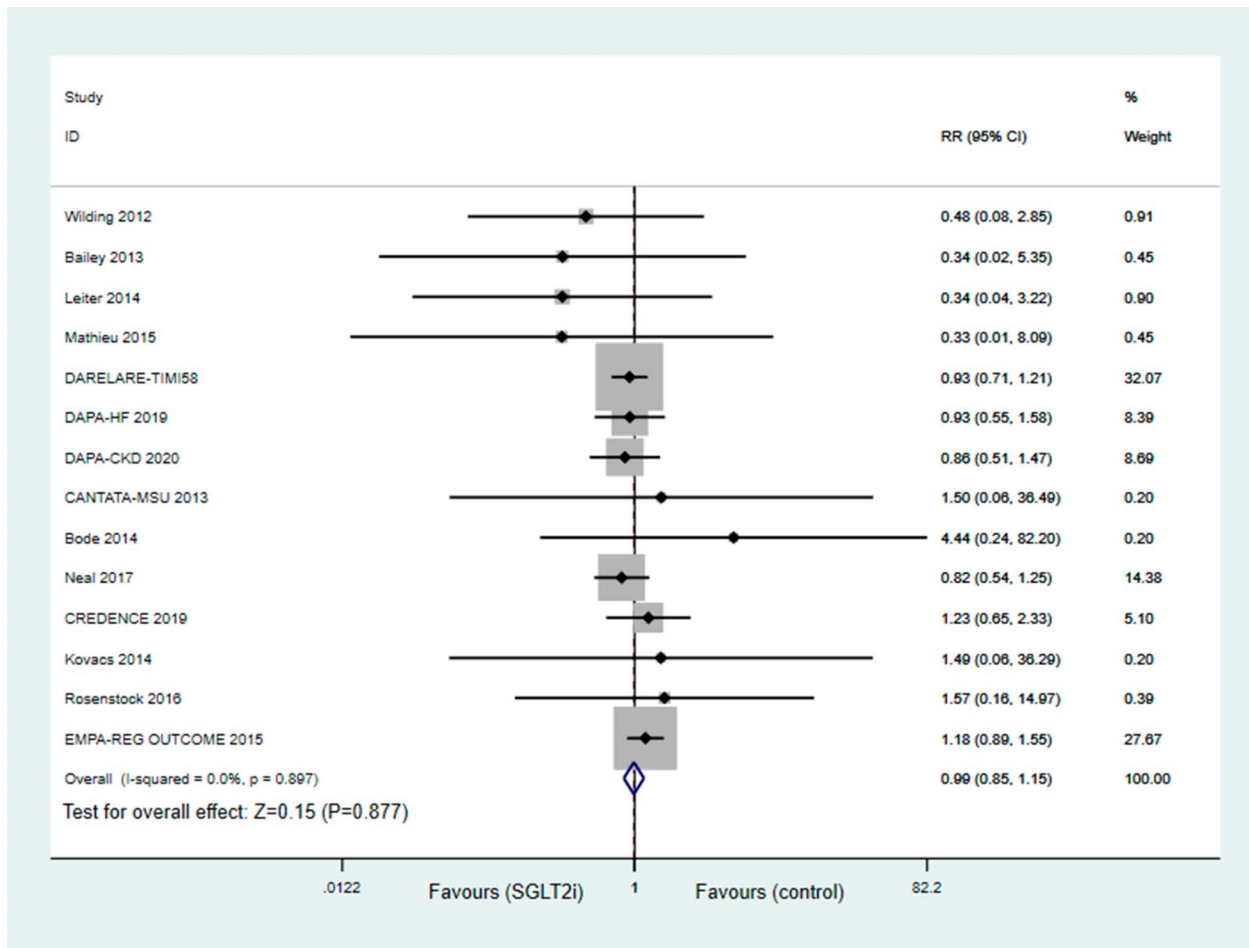


FIGURE 3. Forest plot for meta-analyses comparing the effects of SGLT2 inhibitors with control in stroke.

addition, we also found that the use of SGLT2 inhibitors did not affect the risk of stroke in individuals with and without type 2 diabetes. According to previous animal experiments and clinical studies, SGLT2 inhibitors have been hypothesized a sympathetic inhibitory effect, which may be involved in the antiarrhythmic effect.³⁶ However, up to now, the molecular mechanisms underlying the antiarrhythmic effect of SGLT2 inhibitors remain unclear. Thus, more studies should be conducted to further explain how SGLT2 inhibitors exert antiarrhythmic effects.

Except for the well-established effect on rehospitalization for heart failure and cardiovascular mortality, SGLT2 inhibitors appear to attenuate the incidence of AF. Experimental and clinical data have provided several possible explanations for the protective heart benefits of SGLT2 inhibitors. SGLT2 inhibitors are thought to play a key role in reducing glucose, body weight, and blood pressure. By suppressing SGLT2 in the proximal renal tube, SGLT2 inhibitors induce glucosuria and natriuresis.^{37,38} Increased glucose and sodium excretion, causing osmotic diuresis and contraction of plasma volume, thereby reducing atrial blood pressure and atrial dilation.³⁹ Owing to the natriuretic and diuretic effects, a 7% reduction in the plasma volume in

patients with type 2 diabetes using dapagliflozin was found at week 12.⁴⁰ In diabetic patients, the sodium–hydrogen exchanger 1 upregulates, leading to a significant increase in the intracellular sodium content, which results in a higher activity of the Na⁺/Ca²⁺ exchanger and subsequently an increase in the calcium levels in the sarcoplasmic reticulum. However, this mechanism is burdened by a high risk of arrhythmia because of the mitochondrial activation of the Na⁺/Ca²⁺ exchanger.^{41,42} SGLT2 inhibitors suppress sodium–hydrogen exchange, promote natriuresis, and lower cardiac intracellular Na⁺ and Ca²⁺, which have been connected to the reduction of myocardial hypertrophy,^{43,44} adverse remodeling and fibrosis, and hence decrease the risk of arrhythmia. Epicardial fat could lead to localized inflammation and is thought to increase the incidence of AF. Besides, some studies have shown that SGLT2 inhibitors are associated with a reduction in epicardial fat, contributing to the antiarrhythmic effect.⁴⁵ Recently, a population-based propensity score-matched cohort study involving 79,150 diabetic patients on SGLT2 inhibitors compared with 79,150 matched diabetic patients on DPP-4 inhibitors⁴⁶ showed that there was a 17% reduction of new-onset AF. This is the first real-world study focusing on the risk of AF among type 2 diabetes patients

treated with SGLT2 inhibitors. More studies should be conducted to further understand the relationship between SGLT2 inhibitors and arrhythmia.

AF as a known risk factor for incident stroke has been well demonstrated in previous studies. However, it is still unclear whether a reduced risk of incident AF associated with SGLT2 inhibitors affects the incidence of stroke. In EMPA-REG OUTCOME, there was a higher incidence of AF in the empagliflozin-treated group, as well as fatal or nonfatal stroke. Similarly, CANVAS-R and CANVAS trials suggested that a lower risk of incident AF in the canagliflozin group was associated with a decreased risk of stroke compared with control. In contrast, similar incidence of ischemic stroke was found in the dapagliflozin and placebo groups, whereas the DECLARE-TIMI 58 trial reported the lowest incidence of AF with dapagliflozin. In this present meta-analysis, we found that SGLT2 inhibitors do not significantly affect the risk of stroke (95% CI, 0.85–1.15; $P = 0.908$). Taken all together, the association between SGLT2 inhibitors and the risk of stroke ought to be interpreted cautiously due to currently insufficient data.

There are several limitations to this meta-analysis. AF in the included studies was reported as a serious adverse event, not as an outcome. Thus, no clear predefinitions and no standard method for assessing AF events were described, which may cause reporting bias. Because AF was not the outcome of interest in the included studies, risk factors for AF may not balance in SGLT2 inhibitors and control groups. Although a significantly decreased incidence of AF with SGLT2 inhibitors was detected in this present meta-analysis, more studies are needed to conduct and identify whether it is clinically important.

CONCLUSIONS

Overall, SGLT2 inhibitors are associated with a lower risk of incident AF and do not significantly affect stroke risk in patients with and without type 2 diabetes. Based on the above limitations, these findings should be interpreted with caution until more specifically designed trials are available.

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