Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Sodium-Glucose Co-Transporter Inhibitors and Atrial Fibrillation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: Sodium-glucose co-transporter (SGLT) inhibitors reduce cardiovascular outcomes including mortality in several populations; however, their effect on atrial fibrillation/flutter (AF) remains unclear. Our objective was to determine whether SGLT inhibitors reduce AF and whether a history of AF modifies the effect of SGLT inhibitors on the composite of heart failure hospitalization or cardiovascular death.

METHODS AND RESULTS: We searched MEDLINE, Embase, and CENTRAL to March 2021. Pairs of reviewers identified randomized controlled trials that compared an SGLT inhibitor with placebo or no therapy. We pooled data using RevMan 5.4.1, assessed risk of bias using the Cochrane tool, and determined the overall quality of evidence using Grades of Recommendation, Assessment, Development and Evaluation. Thirty-one eligible trials reported on AF events (75 279 participants, mean age 62 years, 35.0% women). Moderate quality evidence supported a lower risk of serious AF events with SGLT inhibitors (1.1% versus 1.5%; risk ratio 0.75 [95% CI, 0.66–0.86]; I^2=0%). A similar reduction in total AF events was also noted with SGLT inhibitors. Three trials reported on heart failure hospitalization/cardiovascular death stratified by a baseline history of AF (18 832 participants, mean age 66 years, 38.1% women); in patients with a history of AF, SGLT inhibitors resulted in a lower risk in the composite of heart failure hospitalization or cardiovascular death (hazard ratio, 0.70 [95% CI, 0.57–0.85]; I^2=0%)—similar to the effect estimate for patients without AF, *P* value for interaction: 1.00.

CONCLUSIONS: SGLT inhibitors may reduce AF events and likely reduce heart failure hospitalization/cardiovascular death to a similar extent in patients with and without AF.

Key Words: atrial fibrillation ■ atrial flutter ■ gliflozins ■ SGLT inhibitors

Atrial fibrillation (AF) affects an estimated 33.5 million adults worldwide and is associated with a significantly increased risk of stroke, heart failure (HF), and overall mortality.[1] Currently, there are limited therapies for primary prevention of AF in at-risk patients.[2–5] HF is the most common cause of death in patients with AF.[6–8] AF and HF share many risk factors and have a complex and interdependent pathophysiology; when they occur together, the risk of adverse outcomes significantly increases.[5–9] For patients with AF, medical therapies to reduce HF-related outcomes such as hospitalization and mortality are lacking.[9] Established therapies including beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022222

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In a pooled analysis of 31 randomized controlled trials (75 279 patients), sodium-glucose co-transporter (SGLT) inhibitors were associated with a lower risk of serious and total atrial fibrillation (AF)/flutter events compared with placebo/control.
- In a pooled analysis of 3 randomized controlled trials (18 832 patients), SGLT inhibitors reduced the risk of heart failure hospitalization or cardiovascular death to a similar extent in patients with and without AF/flutter at baseline.

What Are the Clinical Implications?

- Treatment with SGLT inhibitors may be associated with a lower incidence/recurrence of AF/flutter.
- SGLT inhibitors appear to reduce cardiovascular outcomes in patients with and without AF/flutter.
- More research is needed to characterize the effect of SGLT inhibitors on AF burden and symptoms.

Nonstandard Abbreviation and Acronym

SGLT	sodium-glucose co-transporter

may be less effective at reducing HF hospitalizations and mortality in patients with HF with concomitant AF as compared with those in sinus rhythm.[10–12]

Sodium-glucose co-transporter (SGLT) inhibitors, originally developed as glucose-lowering agents, reduce HF hospitalization and cardiovascular death in several populations, including patients with type 2 diabetes mellitus, renal impairment, HF, and cardiovascular disease.[13–17] However, whether patients with AF treated with an SGLT inhibitor receive the same risk reductions for HF hospitalization and cardiovascular death as patients without AF has yet to be systematically assessed.

The primary objective of this systematic review and meta-analysis was to explore the association between treatment with an SGLT inhibitor and the occurrence of AF. The secondary objective was to evaluate whether a history of AF modifies the effect of SGLT inhibitors on the composite of HF hospitalization or cardiovascular death.

METHODS

The protocol for this systematic review and meta-analysis is registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021228865). The data underlying this article are available in the article and in its online supplementary material.

Eligibility Criteria

We included randomized controlled trials (RCTs), irrespective of publication status, date of publication, risk of bias, or language. We included trials assessing SGLT2 inhibitors or dual SGLT1/2 inhibitors. We included trials that enrolled adults regardless of prior AF history or other comorbidities, such as diabetes mellitus, HF, chronic kidney disease (CKD), cardiovascular disease, or multiple cardiovascular risk factors. Outcomes of interest were AF and atrial flutter events and the composite of HF hospitalization or cardiovascular death as defined by study authors. We excluded studies with <100 participants and those with <24 weeks of follow-up.

Search Methods

We searched MEDLINE, Embase, and Cochrane CENTRAL for keywords related to SGLT inhibitors from inception to March 2021. An academic librarian reviewed the search strategy, which included a validated filter to exclude reports that were not RCTs.[18] We screened the references of eligible papers and consulted experts to identify additional trials.

Selection of Studies

Pairs of reviewers independently screened titles and abstracts for eligibility. Full texts of the potentially eligible studies were retrieved. Pairs of reviewers then independently screened full texts in duplicate and recorded the main reason for exclusion. Disagreements were resolved through discussion.

Data Extraction and Management

Two reviewers independently abstracted data on intervention and outcome, and recorded study and participant characteristics including age, sex, and relevant comorbidities (eg, diabetes mellitus, CKD, HF, and cardiovascular risk). Review authors searched appendices and supplements of published articles and the adverse events reporting section of ClinicalTrials.gov for relevant information. Reviewers compared results and resolved disagreements by discussion with a third party.

Assessment of Risk of Bias

In duplicate, 2 review authors assessed risk of bias.[19] In each trial, reviewers evaluated the following domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome

assessors, incomplete outcome data, and selective reporting. The results were compared, and disagreements were resolved by discussion. Reviewers assessed performance and detection bias separately. For analysis and presentation purposes, risk of bias was dichotomized as high (or likely high) or low (or likely low). For subgroup analyses, the study-level risk of bias was assessed for each outcome. If a trial was at risk of selection, performance, detection, or reporting bias for that outcome, it was categorized as high risk of bias.

Effect Estimates

We used risk ratios (RR) to report effect estimates for AF events and hazard ratios (HR) for HF hospitalization/cardiovascular death. We obtained the absolute risk difference for clinical outcomes by applying the RR with 95% CI to the baseline risk in the control group.

We assessed clinical and methodological heterogeneity based on study characteristics. We assessed heterogeneity qualitatively by evaluating overlapping of CIs and quantitatively by using the I^2 statistic.[19] Random-effects models with Mantel-Haenszel weighting were used because we expected comparisons to show heterogeneity. HR for the composite of HF hospitalization or cardiovascular death were pooled using the generic inverse-variance method.[19] All analyses followed the intention-to-treat principle and were conducted using RevMan 5.4.1 (The Cochrane Collaboration, Denmark) and R software (version 3.6.1; The R Foundation). We considered $P<0.05$ (2-sided) to be statistically significant.

Post-Hoc Sensitivity Analyses

Considering the rareness of AF events in the underlying data, we performed 2 sensitivity analyses to assess the robustness of the primary results using (1) a 1-stage individual-participant-data logistic regression analysis with Firth's correction for rare events, treating study as a fixed effect in the model, and (2) a fixed-effects meta-analysis without homogeneity assumption using multiple estimation methods (Maximum Likelihood Estimator, Woolf's inverse-variance estimator, and the logarithm of Cochran-Mantel-Haenszel statistic).[20] Both sensitivity analyses yield odds ratio (OR), but when events are rare, estimates of OR and RR are nearly identical.[21]

Subgroup Analyses

We performed prespecified subgroup analyses to compare the effect of SGLT inhibitors on AF events among different patient populations (diabetes mellitus, HF, CKD, and high cardiovascular risk), SGLT inhibitor medications (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, and sotagliflozin), and SGLT inhibitor types (dual SGLT1/2 and SGLT2 inhibitors). We performed a simple significance test to investigate differences between subgroups using the methods described in Borenstein et al., involving a standard test for heterogeneity across subgroup results.[19,22]

Assessment of the Quality of the Evidence

Reviewers used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach to assess the quality of evidence.[23] GRADE appraises the confidence in estimates of effect by considering within-study risk of bias, directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias. We inspected funnel plots of SEs versus effect estimates for publication bias and small-study effects.

RESULTS

Screening

The electronic search identified 5224 citations (Figure S1). After reference and full-text screening, 33 studies met eligibility criteria.[24–56] Table 1 presents details on included studies.

Included Studies

Thirty-one RCTs reported data on AF events.[24–54] These RCTs included a total of 75 279 participants, with a mean age of 62.3±5.0 years and including 35.0% women. In 28 studies, participants were required to have diabetes mellitus (with diabetes mellitus being the key inclusion criterion in 16 studies), 2 trials enrolled patients with HF, 6 enrolled patients with CKD, and 7 enrolled patients at high cardiovascular risk. Twenty-nine RCTs studied an SGLT2 inhibitor (6 canagliflozin, 11 dapagliflozin, 8 empagliflozin, and 4 ertugliflozin).[24–32,34,35,37–54] Two studied the dual SGLT1/2 inhibitor sotagliflozin.[33,36] In all trials, data concerning AF events were obtained from adverse-event reporting. One trial, Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), published a dedicated report on AF events.[24] All other trials reported on AF in supplementary appendices and/or on clinical trial databases such as ClinicalTrials.gov (Table S1). None of the studies provided details on the method of ascertainment, including descriptions for rhythm monitoring or other methods for detection of AF. All studies used the *Medical Dictionary of Regulatory Affairs* (MedDRA) classification system for adverse AF events.[24–54] In this system, serious adverse events are defined as those that resulted in death, were life-threatening, required inpatient hospitalization or extended a current hospital stay, resulted in an ongoing or significant incapacity, interfered substantially with normal life functions, or

Table 1. Study Characteristics of Included Randomized Controlled Trials

Study ID	Study acronym	Trial registration	Sample size	Follow-up duration	Trial population	Control/placebo and dose	Intervention and dose
Bailey, 2010[28]		NCT00528879	915	102 wk	T2DM	Placebo	Dapagliflozin 2.5 mg, Dapagliflozin 5 mg, Dapagliflozin 10 mg
Barnett, 2014[29]	EMPA-REG RENAL	NCT01164501	741	52 wk	T2DM+renal impairment	Placebo	Empagliflozin 10 mg, Empagliflozin 25 mg
Bhatt, 2021[55]	SOLOIST-WHF	NCT03521934	1222	Median: 170 wk	T2DM+worsening HF	Placebo	Sotagliflozin 200/400 mg
Bhatt, 2021[56]	SCORED	NCT03315143	10 584	Median: 304 wk	T2DM+cardiovascular risk factors+CKD	Placebo	Sotagliflozin 200/400 mg
Bode, 2013[30]		NCT01106651	716	104 wk	T2DM	Placebo	Canagliflozin 100 mg, Canagliflozin 300 mg
Cannon, 2020[31]	VERTIS-CV	NCT01986881	8246	Mean: 183 wk	T2DM+CVD	Placebo	Ertugliflozin 5 mg, Ertugliflozin 15 mg
Cefalu, 2015[32]		NCT01031680	922	24 wk	T2DM+CVD+hypertension	Placebo	Dapagliflozin 10 mg
Danne, 2019[33]	inTandem1	NCT02384941	793	52 wk	T1DM	Placebo	Sotagliflozin 200 mg, Sotagliflozin 400 mg
Ferrannini, 2010[34]		NCT00528372	1067	102 wk	T2DM	Placebo	Dapagliflozin 2.5 mg, Dapagliflozin 5 mg, Dapagliflozin 10 mg
Frías, 2016[35]	DURATION-8	NCT02229396	695	104 wk	T2DM	Placebo+exenatide 2 mg	Dapagliflozin 10 mg+exenatide 2 mg
Garg, 2017[36]	inTandem3	NCT02531035	1405	24 wk	T1DM	Placebo	Sotagliflozin 400 mg
Grunberger, 2017[37]	VERTIS RENAL	NCT01986855	468	52 wk	T2DM+CKD	Placebo	Ertugliflozin 5 mg, Ertugliflozin 15 mg
Haering, 2015[38]	EMPA-REG EXTEND MONO	NCT01289990	2705	76 wk	T2DM	Placebo	Empagliflozin 10 mg, Empagliflozin 25 mg
Heerspink, 2020[39]	DAPA-CKD	NCT03036150	4304	Median: 125 wk	CKD	Placebo	Dapagliflozin 10 mg
Kovacs, 2015[40]	EMPA-REG PIOTM	NCT01210001	499	76 wk	T2DM	Placebo	Empagliflozin 10 mg, Empagliflozin 25 mg
Mathieu, 2015[42]		NCT01646320	320	52 wk	T2DM	Placebo	Dapagliflozin 10 mg
McMurray, 2019[25]	DAPA-HF	NCT03036124	4744	Median: 79 wk	HFrEF	Placebo	Dapagliflozin 10 mg
Neal, 2015[26,43]	CANVAS	NCT01032629	4330	Mean: 86.5 wk	T2DM+cardiovascular risk factors/ history of CVD	Placebo	Canagliflozin 100 mg, Canagliflozin 300 mg
Neal, 2017[26]	CANVAS-R	NCT01989754	5813	Mean: 188.2 wk	T2DM+cardiovascular risk factors/ history of CVD	Placebo	Canagliflozin 100 mg, Canagliflozin 300 mg
Leiter, 2014		NCT01042977	964	104 wk	T2DM+CVD	Placebo	Dapagliflozin 10 mg
Perkovic, 2019[44]	CREDENCE	NCT02065791	4401	Median: 137 wk	T2DM+albuminuric CKD	Placebo	Canagliflozin 100 mg

(*Continued*)

Table 1. Continued

Study ID	Study acronym	Trial registration	Sample size	Follow-up duration	Trial population	Control/placebo and dose	Intervention and dose
Wilding, 2013[45]	CANTATA-MSU	NCT01106625	469	52 wk	T2DM	Placebo	Canagliflozin 100 mg, Canagliflozin 300 mg
Packer et al[54]	EMPEROR-Reduced	NCT03057977	3730	Median: 69 wk	HFrEF	Placebo	Empagliflozin 10 mg
Pollock, 2019[46]	DELIGHT	NCT02547935	459	24 wk	T2DM+albuminuric CKD	Placebo	Dapagliflozin 10 mg
Pratley, 2018[47]	VERTIS-FACTORIAL	NCT02099110	1233	52 wk	T2DM	Sitagliptin 100 mg	Ertugliflozin 5 mg+Sitagliptin 100 mg, Ertugliflozin 15 mg+Sitagliptin 100 mg
Roden, 2013[48]		NCT01177813	986	24 wk	T2DM	Placebo	Empagliflozin 10 mg, Empagliflozin 25 mg
Rosenstock, 2015[49]	EMPA-REG BASAL	NCT01011868	494	78 wk	T2DM	Placebo	Empagliflozin 10 mg, Empagliflozin 25 mg
Rosenstock, 2018[50]	VERTIS-MET	NCT02033889	621	104 wk	T2DM	Placebo (Glimepiride if glycemic rescue criteria met)	Ertugliflozin 5 mg, Ertugliflozin 15 mg
Søfteland, 2017[51]		NCT01734785	607	24 wk	T2DM	Placebo	Empagliflozin 10 mg, Empagliflozin 25 mg
Wilding, 2012[52]		NCT00673231	1240	104 wk	T2DM	Placebo	Dapagliflozin 2.5 mg, Dapagliflozin 5 mg, Dapagliflozin 10 mg
Wiviot, 2019[24]	DECLARE-TIMI 58	NCT01730534	17 190	Median: 220 wk	T2DM+cardiovascular risk factors/ history of CVD	Placebo	Dapagliflozin 10 mg
Yale, 2014[53]	DIA3004	NCT01064414	272	52 wk	T2DM+renal impairment	Placebo	Canagliflozin 100 mg, Canagliflozin 300 mg
Zinman, 2015[27]	EMPA-REG OUTCOME	NCT01131676	7064	Median: 160 wk	T2DM+high risk of CV events	Placebo	Empagliflozin 10 mg, Empagliflozin 25 mg

CKD indicates chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; T1DM, type 1 diabetes mellitus; and T2DM, type 2 diabetes mellitus.

put patients in danger or need of medical or surgical intervention to prevent one of the results listed above. Nonserious adverse events are defined by MedDRA as other adverse events that did not meet any of the above criteria. Data were rarely provided regarding the characteristics of AF events (ie, the number of patients with events, whether the events were incident or recurrent, as well as the duration/burden of AF/flutter) or the characteristics of patients with events (including demographics, comorbidities, or medications).

We identified 1 relevant ongoing trial.[57] Empagliflozin and Atrial Fibrillation Treatment (EMPA-AF; NCT04583813) aims to enroll 400 patients with diabetes mellitus who are overweight and who have HF and AF. Participants will be allocated to empagliflozin or placebo and followed for 24 months with a primary outcome of AF burden. The last publicly posted update on April 2, 2021 listed the trial as not yet recruiting.

Three RCTs reported on HF hospitalization/cardiovascular death in the subgroup of patients with AF; all 3 trials required participants to have diabetes mellitus.[27,55,56] These RCTs included a total of 18 832 participants, with a mean age of 66.8±2.9 years and 38.1% were women. Among the 3 studies, 1 trial enrolled patients with HF, 1 enrolled patients with CKD, and 1 enrolled patients at high cardiovascular risk. Two of these trials studied the SGLT1/2 inhibitor sotagliflozin and 1 studied the SGLT2 inhibitor empagliflozin. In the 2 sotagliflozin trials, urgent visits for HF were included in the composite outcome in addition to HF hospitalization and cardiovascular death.[55,56]

Risk of Bias

All 33 included RCTs used a double-blind design.[24–56] We had no concerns regarding randomization, allocation concealment, performance bias, or incomplete data (Table S2). Because AF was not systematically assessed, we expected that patients with more healthcare encounters, including hospitalizations, would be more likely to have AF captured. SGLT inhibitors have shown a reduction in cardiovascular hospitalizations; therefore, we judged that the included studies were at high risk of detection bias for AF events.

Outcomes

AF/Flutter Events

Pooled data from 31 studies (75 279 participants, 951 total events; 2 studies with 0 events in either group; mean follow-up: 2.6 years) (Figure 1) suggested a significant reduction in the risk of serious AF events in patients who received an SGLT inhibitor (1.1% versus 1.5%; RR 0.75 [95% CI, 0.66–0.86]; I^2=0%).[24–56] Based on the GRADE framework, we judged that this was moderate quality evidence because of a serious risk of bias (Table S3). A post-hoc sensitivity analysis of all other trials excluding the largest study (DECLARE-TIMI 58,[21] 41.4% of weight, RR 0.74 [95% CI, 0.60–0.90]) yielded consistent results (RR 0.76 [95% CI, 0.64–0.90], I^2=0%, *P*-for-interaction=0.80).

In all studies except for DECLARE-TIMI 58, Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction (DAPA-HF), and Canagliflozin and cardiovascular and renal events in type 2 diabetes (CANVAS),[24–26] AF was only detected by scanning through reports of serious adverse events. These 3 studies also reported other adverse AF events that did not qualify as serious adverse events according to the MedDRA criteria. A post-hoc meta-analysis of these 3 studies showed a significant reduction in total (serious and nonserious) AF events (26 223 participants, 1159 events; 4.0% versus 4.9%; RR, 0.83 [95% CI, 0.73–0.94], I^2=0%).

Prespecified sensitivity analyses restricting results to either serious (1) AF events only or (2) atrial flutter events only yielded similar effect estimates (Table 2). Subgroup analyses that separated trials according to the type of SGLT inhibitor used (including comparisons of individual agents as well as of dual SGLT1/2 inhibitors versus SGTL2 inhibitors), trial population (history of HF, diabetes mellitus, CKD, or high cardiovascular risk), as well as duration of follow-up (greater than/equal to versus <2 years of follow-up) did not result in statistically significant subgroup effects (Table 2, Figure S2). Post-hoc sensitivity analyses including logistic regression with Firth's correction, treating study as fixed effect as well as fixed effects meta-analysis without homogeneity assumption using several estimation methods (Maximum Likelihood Estimator, Woolf's inverse-variance estimator, and the logarithm of Cochran-Mantel-Haenszel statistic) demonstrated very similar effect estimates and CIs to random effects meta-analysis (Table S4).

HF Hospitalization or Cardiovascular Death

Three trials reported on HF hospitalization/cardiovascular death stratified by a history of AF at the time of enrollment (18 832 participants, 2060 events, mean follow-up: 4.6 years) (Figure 2).[27,55,56] Among patients with diabetes mellitus and a history of AF, SGLT inhibitors compared with placebo resulted in a lower risk of HF hospitalization or cardiovascular death (HR, 0.70 [95% CI, 0.57–0.85]; I^2=0%). This was similar to what was observed in patients without AF (HR, 0.70 [95% CI, 0.61–0.79]; I^2=0%; *P*-for-interaction: 1.00). Based on the GRADE framework, we judged that this was high-quality evidence.

Publication Bias

The funnel plot for AF events was symmetrical, suggesting against the presence of publication bias

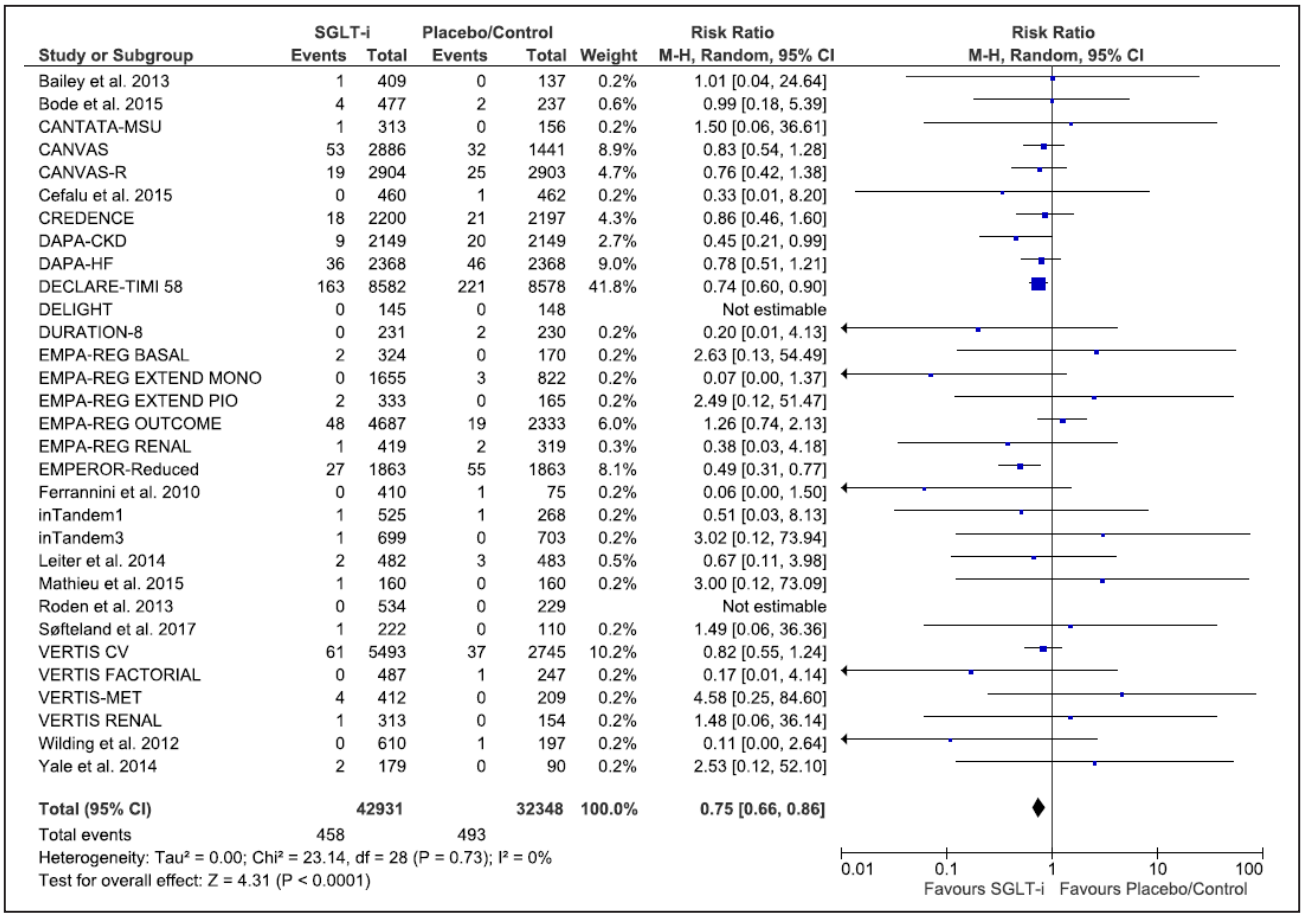

Figure 1. Forest plot comparing serious atrial fibrillation or atrial flutter events between patients on SGLT inhibitors vs placebo/control in randomized controlled trials.

Square markers represent point estimates of RR for individual studies, with square size representing proportional weight given to each study in the meta-analysis. Horizontal lines indicate 95% CIs. The solid diamond represents the estimated 95% CI for effect size of all meta-analyzed data. M-H, Mantel-Haenszel; RR, relative risk; and SGLT, sodium-glucose co-transporter.

(Figure S3). Publication bias was not assessed for the composite outcome of HF hospitalization or cardiovascular death given the small number of available studies.

DISCUSSION

To our knowledge, this is the largest and most comprehensive systematic review to address the role of SGLT inhibitors in reducing the incidence and recurrence of AF with twice as many total AF events as any prior meta-analysis.[58,59] This is also the first pooled report on the impact of SGLT inhibitors on HF hospitalization and cardiovascular death in patients who are known to have AF.

In this systematic review and meta-analysis of RCTs, SGLT inhibitors resulted in a 25% (95% CI, 14%–34%) relative risk reduction in serious AF events across 31 RCTs and a similar relative reduction in total AF events, suggesting that SGLT inhibitors may reduce the incidence and recurrence of AF. Consistent effects were observed across subgroups of trials in patients with high cardiovascular risk, HF, or CKD and across comparisons of individual agents. These trials were limited in how they captured and defined AF events. Appropriately designed RCTs with standardized monitoring and adjudication of incident AF and rigorous capture of AF-related healthcare utilization are needed to confirm whether SGLT inhibitors reduce new-onset AF and other patient-important AF events. Nonetheless, the consistent reduction in AF events highlights the promise of SGLT inhibitors both in primary prevention for high-risk patients and as therapy to reduce progression in those with AF. Retrospective analyses of large, population-wide pharmacovigilance databases have also suggested that patients prescribed SGLT inhibitors have a lower rate of AF compared with patients treated with other glucose-lowering therapies.[60,61] There are multiple possible mechanisms through which SGLT inhibitors may reduce AF such as through reduction in body weight, blood pressure, and

volume.[62,63] Mechanistic studies and animal models indicate that SGLT inhibitors may reduce atrial fibrosis and adverse remodeling, in addition to improving cellular metabolism and bioenergetics such as ion handling and mitochondrial function.[64–66] Reductions in HF could also reduce AF, and vice versa.[62,63]

This meta-analysis also suggests that patients with diabetes mellitus with and without AF benefit from the same risk reduction in HF hospitalization and cardiovascular death from SGLT inhibitors. The pooled estimate from 3 trials showed a 30% reduction in the hazard of HF hospitalization or cardiovascular death, without statistical heterogeneity. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) was the only trial to report a dedicated post-hoc analysis assessing the treatment effect of SGLT inhibitors on the subgroup of patients with AF.[27] HF hospitalization or cardiovascular death were 1.85 to 3.43 times more frequent in patients with than in those without AF, suggesting a much higher baseline risk in these patients.[27] Because patients with and without AF benefited from a similar relative reduction in these outcomes, these findings suggest that patients with AF could benefit from a greater absolute risk reduction from SGLT inhibitors when compared with patients without AF. Whether SGLT inhibitors improve outcomes of patients with AF who would not have been eligible for these trials, in particular those without diabetes mellitus, is uncertain. Additionally, 2 of these trials studied sotagliflozin, which is unique, being a dual SGLT1/2 inhibitor. The RCTs that studied sotagliflozin were stopped early because of a loss of sponsor funding; this agent may never become available for patient use.[55,56] Future RCTs should assess the impact of SGLT inhibitors on HF hospitalization and cardiovascular death in patients with AF, particularly in those who were excluded from previous trials.

Limitations

The main limitation of this systematic review and meta-analysis relates to the ascertainment of both prevalent and incident AF in the included studies. We urge caution when interpreting these findings because the studies captured in this review were not specifically designed to assess AF and therefore did not provide the level of details that are available in most contemporary HF and AF studies including burden and symptoms of AF. Compared with contemporary population-wide analyses of the incidence and recurrence of AF in patients with and those without diabetes mellitus, the relatively low rate of AF events suggests that AF was likely underestimated.[67] Most trials only reported AF events that met the criteria for serious adverse event as described above. Although our pooled analysis of total AF events also showed a consistent reduction in AF with SGLT inhibitors, further research prospectively assessing for total AF incidence, prevalence, arrhythmia burden, and symptomatology is needed to definitively characterize the role and impact of SGLT inhibitors on AF. Similar to the previously published report from the DECLARE-TIMI 58 trial, AF events in our systematic review and meta-analysis came from adverse event reporting and MedDRA classification

Table 2. Pooled Risk Ratio of Atrial Fibrillation and Atrial Flutter Events

			Event rate (SGLT inhibitor)	Event rate (placebo)	Pooled risk ratio (random effects model)	Test for interaction
Atrial fibrillation events only	29 RCTs	n=72 955	0.92%	1.31%	RR, 0.75 (95% CI, 0.65–0.87), I^2, 0%	
Atrial flutter events only	13 RCTs	n=57 264	0.23%	0.32%	RR, 0.74 (95% CI, 0.53– 1.03), I^2, 1%	
Trial population						
DM	16 RCTs	n=11 916	0.23%	0.27%	RR, 0.74 (95% CI, 0.35– 1.55), I^2: 0%	*P*=0.75
Renal disease	6 RCTs	n=10 462	0.57%	0.85%	RR, 0.69 (95% CI, 0.43– 1.09), I^2, 0%	
CVD/risk factors	7 RCTs	n=44 439	1.36%	1.78%	RR, 0.79 (95% CI, 0.68– 0.92), I^2, 0%	
HFrEF	2 RCTs	n=8462	1.52%	1.94%	RR, 0.62 (95% CI, 0.51– 1.21), I^2: 53%	
Duration of follow-up						
≥2 y	13 RCTs	n=51 519	1.13%	1.56%	RR: 0.77 (95% CI: 0.66, 0.90), I^2: 0%	*P*=0.52
<2 y	18 RCTs	n=23 760	0.93%	1.43%	RR: 0.70 (95% CI– 0.55, 0.90), I^2: 0%	
Medication	Canagliflozin (n=15 983) vs dapagliflozin (n=30 993) vs empagliflozin (n=16 048) vs ertugliflozin (n=10 060) vs sotagliflozin (n=2195)					*P*=0.88
SGLT2 inhibitor vs dual SGLT1/2 inhibitor	Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (n=73 084) vs sotagliflozin (n=2195)					*P*=0.73

CVD indicates cardiovascular disease; DM, diabetes mellitus; HFrEF, heart failure with reduced ejection fraction; RCTs, randomized controlled trials; RR, relative risk; and SGLT, sodium-glucose co-transporter.

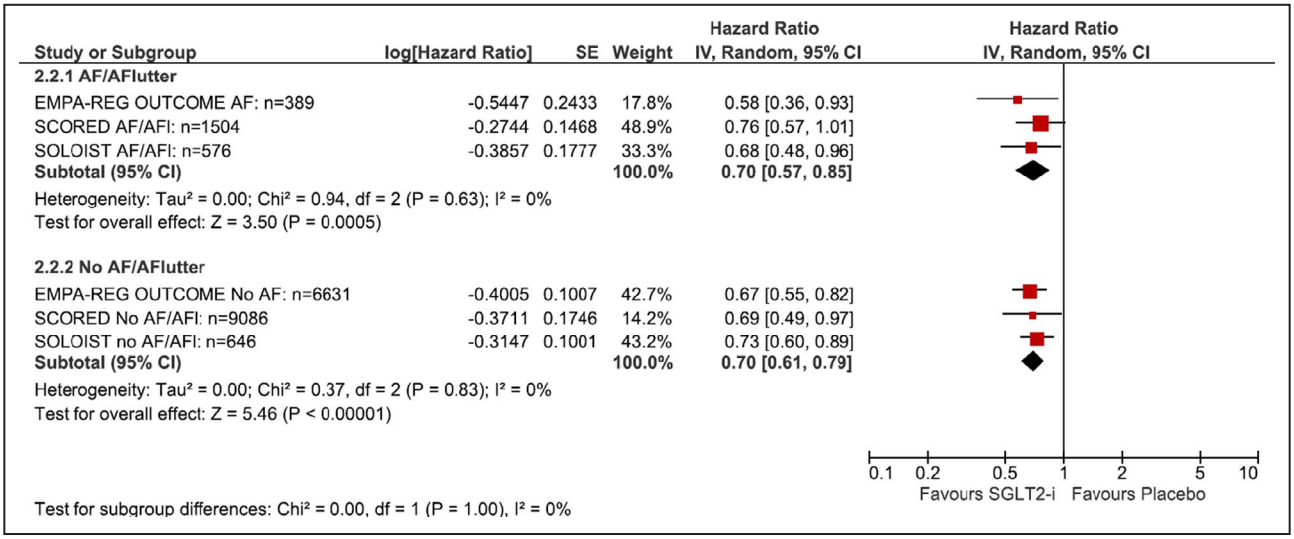

Figure 2. Forest plot demonstrating composite of heart failure hospitalization/urgent visit or cardiovascular death between patients on SGLT inhibitors vs placebo/control in randomized controlled trials stratified by presence or absence of atrial fibrillation/flutter at baseline.

Square markers represent point estimate of HR for individual studies, with square size representing proportional weight given to each study in the meta-analysis. Horizontal lines indicate 95% CIs. The solid diamonds represent the estimated 95% CI for effect size of all meta-analyzed data. AF indicates atrial fibrillation; AFl, atrial flutter; EMPA-REG OUTCOME, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; HR, hazard ratio; SGLT, sodium-glucose co-transporter; SOLOIST, Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure; and SCORED, Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease.

in all studies.[24] Higher rates of AF events may have been driven in part by arrhythmias detected during HF hospitalizations, which were more common in patients allocated to placebo. For studies of patients with a past history of AF, the proportion of patients with different patterns of AF (paroxysmal, persistent, and permanent) is not known. AF pattern impacts baseline risk of HF events, and treatment effect may vary for different AF patterns.[68]

CONCLUSIONS

SGLT inhibitors may reduce the incidence or recurrence of AF. In patients with type 2 diabetes mellitus, SGLT inhibitors may reduce a composite of HF hospitalization or cardiovascular death, both in patients with and without AF. Appropriately designed RCTs are needed to clarify their role in preventing AF and reducing HF hospitalization and cardiovascular death in patients with AF.

ARTICLE INFORMATION

Received April 26, 2021; accepted June 25, 2021.

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Sources of Funding

Pandey is supported by the McMaster Medical Student Research Excellence Award (MAC RES) from the Michael G. DeGroote School of Medicine, McMaster University.

Disclosures

Dr Belley-Cote reports grants from Bayer and grants from Roche, outside the submitted work. Dr Conen reports consulting fees from Roche Diagnostics outside of the current work. Dr Verma reports grants from Amarin, grants and personal fees from Amgen, grants and personal fees from AstraZeneca, grants and personal fees from Bayer, grants and personal fees from Boehringer-Ingelheim, personal fees from Bristol-Myers Squibb, grants and personal fees from Eli Lilly, personal fees from EOCI Pharmacomm Ltd, grants and personal fees from HLS Therapeutics, grants and personal fees from Janssen, grants and personal fees from Merck, personal fees from Novartis, grants and personal fees from Novo Nordisk, grants from Pfizer, grants from PhaseBio, grants and personal fees from Sanofi, personal fees from Sun Pharmaceuticals, personal fees from Toronto Knowledge Translation Working Group, outside the submitted work. Dr Gerstein reports grants and personal fees from Sanofi, grants and personal fees from Eli Lilly, grants and personal fees from Novo Nordisk, grants from AstraZeneca, grants from Merck, personal fees from Abbott, personal fees from Pfizer, personal fees from Boehringer Ingelheim, personal fees from DKSH, personal fees from Zuellig, sitting on a Data Safety Monitoring Board for Covance and sitting on a Data Safety Monitoring Board for Kowa, outside the submitted work. The remaining authors have no disclosures to report.

Supplementary Materials

Tables S1–S4
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Data Collection Sources and Atrial Fibrillation Definitions.

Study ID	Study Acronym	Trial Registration	Source	Definition	Source of definition	Type of AF event
Bailey, 2010[28]		NCT00528879	ClinicalTrials.gov	Serious adverse event	MedDRA 13.0	Not recorded
Barnett, 2014[29]	EMPA-REG RENAL	NCT01164501	ClinicalTrials.gov	Serious adverse event	MedDRA 15.0	Not recorded
Bode, 2013[30]		NCT01106651	ClinicalTrials.gov	Serious adverse event	MedDRA 14.0/16.0	Not recorded
Cannon, 2020[31]	VERTIS-CV	NCT01986881	ClinicalTrials.gov	Serious adverse event	MedDRA 22.1	Not recorded
Cefalu, 2015[32]		NCT01031680	ClinicalTrials.gov	Serious adverse event	MedDRA 14.0	Not recorded
Danne, 2019[33]	inTandem1	NCT02384941	ClinicalTrials.gov	Serious adverse event	MedDRA 20.0	Not recorded
Ferinnini, 2010[34]		NCT00528372	ClinicalTrials.gov	Serious adverse event	MedDRA 13.0	Not recorded
Frias, 2017[35]	DURATION-8	NCT02229396	ClinicalTrials.gov	Serious adverse event	MedDRA 20.1	Not recorded
Garg, 2017[36]	inTandem3	NCT02531035	ClinicalTrials.gov	Serious adverse event	MedDRA 20.0	Not recorded
Grunberger, 2017[37]	VERTIS RENAL	NCT01986855	Supplementary Appendix	Serious adverse event:	MedDRA 19.0	Not recorded
Haering, 2015[38]	EMPA-REG EXTEND MONO	NCT01289990	ClinicalTrials.gov	Serious adverse events	MedDRA 16.0	Not recorded
Heerspink, 2020[39]	DAPA-CKD	NCT03036150	ClinicalTrials.gov	Serious adverse events	MedDRA	Not recorded

Kovacs, 2015[40]	EMPA-REG PIOTM	NCT01210001	ClinicalTrials.gov	Serious + Non-serious adverse events	MedDRA 15.0	Not recorded
Mathieu, 2015[42]		NCT01646320	ClinicalTrials.gov	Serious + Non-serious adverse events	MedDRA 17.1	Not recorded
McMurray, 2019[25]	DAPA-HF	NCT03036124	ClinicalTrials.gov	Serious adverse events	MedDRA 22.0	Not recorded
Neal, 2015[26,43]	CANVAS	NCT01032629	ClinicalTrials.gov	Serious adverse events	MedDRA 19.1	Not recorded
Neal, 2017[26]	CANVAS-R	NCT01989754	ClinicalTrials.gov	Serious adverse events	MedDRA 19.1	Not recorded
Leiter, 2014		NCT01042977	ClinicalTrials.gov	Serious adverse events	MedDRA 14.0	Not recorded
Perkovic, 2019[44]	CREDENCE	NCT02065791	ClinicalTrials.gov	Serious adverse events	MedDRA 23.0	Not recorded
Wilding, 2013[45]	CANTATA-MSU	NCT01106625	ClinicalTrials.gov	Serious adverse events	MedDRA 21.0	Not recorded
Packer et al.[54]	EMPEROR-Reduced	NCT03057977	ClinicalTrials.gov	Serious adverse events	MedDRA 14.0/15.0	Not recorded
Pollock, 2019[46]	DELIGHT	NCT02547935	ClinicalTrials.gov	Serious adverse events	MedDRA 21.0	Not recorded
Pratley, 2018[47]	VERTIS-FACTORIAL	NCT02099110	ClinicalTrials.gov	Serious adverse events	MedDRA 19.0	Not recorded
Roden, 2013[48]		NCT01177813	ClinicalTrials.gov	Serious adverse events	MedDRA 14.1	Not recorded
Rosenstock, 2015[49]	EMPA-REG BASAL	NCT01011868	ClinicalTrials.gov	Serious adverse events	MedDRA 15.0	Not recorded

Rosenstock, 2018[50]	VERTIS-MET	NCT02033889	ClinicalTrials.gov	Serious adverse events	MedDRA 20.0	Not recorded
Softeland, 2017[51]		NCT01734785	Published paper	Serious + Non-serious adverse events	MedDRA 17.1	Not recorded
Wilding, 2012[52]		NCT00673231	ClinicalTrials.gov	Serious adverse events	MedDRA 12.0	Not recorded
Wiviot, 2019[24]	DECLARE-TIMI 58	NCT01730534	ClinicalTrials.gov	Serious adverse events	MedDRA 21.0	First event, Recurrent event, Hospitalization-associated events, Myocardial infarction-associated events and Heart Failure Hospitalization-associated events recorded
Yale, 2014[53]	DIA3004	NCT01064414	ClinicalTrials.gov	Serious adverse events	MedDRA 14.1/15.0	Not recorded
Zinman, 2015[55]	EMPA-REG OUTCOME	NCT01131676	ClinicalTrials.gov	Serious adverse events	MedDRA 18.0	Not recorded

MedDRA, Medical Dictionary for Regulatory Activities.

Table S2. Risk of Bias Assessment of Included Randomized Controlled Trials.

Study ID	Study Acronym	Trial Registration	Random Sequence Generation (Allocation Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Researchers (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Other Bias
Bailey, 2010[28]		NCT00528879	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Barnett, 2014[29]	EMPA-REG RENAL	NCT01164501	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Bode, 2013[30]		NCT01106651	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Cannon, 2020[31]	VERTIS-CV	NCT01986881	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Cefalu, 2015[32]		NCT01031680	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Danne, 2019[33]	inTandem1	NCT02384941	Low	Likely Low	Low	AF/AFL Outcome: Likely high	Low	Low
Ferinnini, 2010[34]		NCT00528372	Likely Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low

Frias, 2017[35]	DURATION-8	NCT02229396	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Garg, 2017[36]	inTandem3	NCT02531035	Likely Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Grunberger, 2017[37]	VERTIS RENAL	NCT01986855	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Haering, 2015[38]	EMPA-REG EXTEND MONO	NCT01289990	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Heerspink, 2020[39]	DAPA-CKD	NCT03036150	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Kovacs, 2015[40]	EMPA-REG PIOTM	NCT01210001	Low	Likely Low	Low	AF/AFL Outcome: Likely high	Low	Low
Mathieu, 2015[42]		NCT01646320	Low	Likely Low	Low	AF/AFL Outcome: Likely high	Low	Low
McMurray, 2019[25]	DAPA-HF	NCT03036124	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Neal, 2015[26,43]	CANVAS	NCT01032629	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low

Neal, 2017[26]	CANVAS-R	NCT01989754	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Leiter, 2014		NCT01042977	Likely Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Perkovic, 2019[44]	CREDENCE	NCT02065791	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Wilding, 2013[45]	CANTATA-MSU	NCT01106625	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Packer et al.[54]	EMPEROR-Reduced	NCT03057977	Low	Likely Low	Low	AF/AFL Outcome: Likely high	Low	Low
Pollock, 2019[46]	DELIGHT	NCT02547935	Likely Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Pratley, 2018[47]	VERTIS-FACTORIAL	NCT02099110	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Roden, 2013[48]		NCT01177813	Low	Likely Low	Low	AF/AFL Outcome: Likely high	Low	Low
Rosenstock, 2015[49]	EMPA-REG BASAL	NCT01011868	Low	Likely Low	Low	AF/AFL Outcome: Likely high	Low	Low

Rosenstock, 2018[50]	VERTIS-MET	NCT02033889	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Softeland, 2017[51]		NCT01734785	Low	Likely Low	Low	AF/AFL Outcome: Likely high	Low	Low
Wilding, 2012[52]		NCT00673231	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Wiviot, 2019[24]	DECLARE-TIMI 58	NCT01730534	Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Yale, 2014[53]	DIA3004	NCT01064414	Likely Low	Low	Low	AF/AFL Outcome: Likely high	Low	Low
Zinman, 2015[55]	EMPA-REG OUTCOME	NCT01131676	Low	Low	Low	AF/AFL Outcome: Likely high HFH/CV Death: Low	Low	Low
Bhatt, 2020[56]	SOLOIST-WHF	NCT03521934	Low	Low	Low	HFH/CV Death: Low	Low	Low
Bhatt, 2020[57]	SCORED	NCT03315143	Low	Low	Low	HFH/CV Death: Low	Low	Low

AF, Atrial Fibrillation; AFl, Atrial Flutter; HFH, Heart Failure Hospitalization; CV Death, Cardiovascular Death.

Table S3. GRADE table, summarizing the evaluation of the quality of evidence.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[intervention]**	**[comparison]**	**Relative (95% CI)**	**Absolute (95% CI)**	
Serious AF/AFlutter Outcome											
31	randomised trials	serious	not serious	not serious	not serious	none	458/42931 (1.1%)	493/32348 (1.5%)	**RR 0.75** (0.66 to 0.86)	**4 fewer per 1,000** (from 5 fewer to 2 fewer)	⨁⨁⨁◯ MODERATE

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

Table S4. Pooled Odds ratio calculated using logistic regression with Firth's method treating study as fixed effect and fixed-effects meta-analysis without homogeneity assumption.

Methods	Odds ratio (95% CI)	P value
Logistic regression with Firth's method	0.75 (0.66-0.86)	<0.001
Fixed-effects meta-analysis without assuming homogeneity		
CMH estimator	0.75 (0.64-0.87)	<0.001
Woolf's estimator	0.75 (0.66-0.85)	<0.001
MLE	0.75 (0.66-0.86)	<0.001

CI: Confidence Interval; MLE: Maximum Likelihood Estimator; CMH: Cochran-Mantel-Haenszel

Figure S1. PRISMA Systematic Review Flow Diagram.

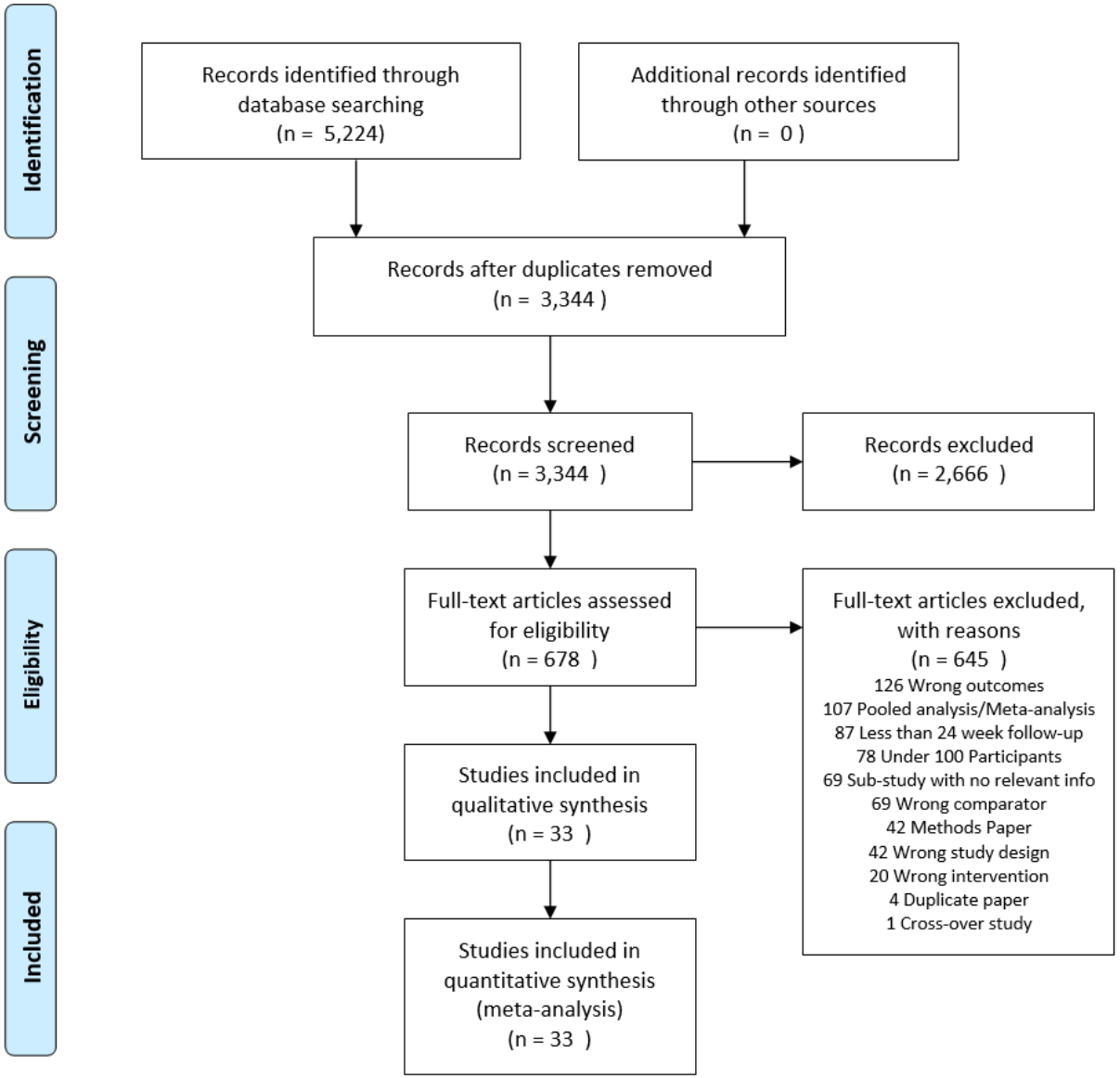
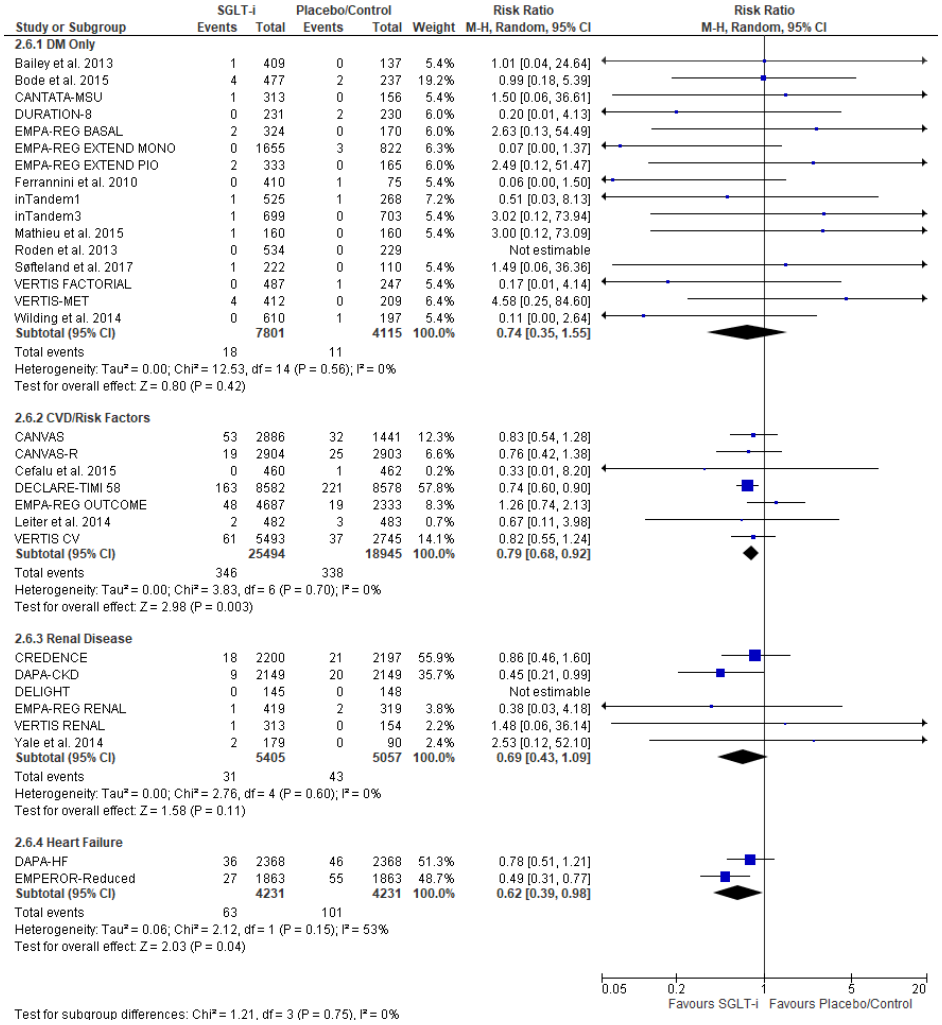


Figure S2. Forest plot demonstrating serious atrial fibrillation or atrial flutter events between patients on SGLT inhibitors versus placebo/control in Randomized Controlled Trials stratified by trial population.



Square markers represent point estimate of RR for individual studies, with square size proportional weight given to each study in the meta-analysis. Horizontal lines indicate 95% CIs. The solid diamond represents the estimated 95% CI for effect size of all meta-analysed data. CI, confidence interval; CVD, Cardiovascular Disease; DM, Diabetes Mellitus; RR, relative risk.

Figure S3. Funnel plot showing symmetrical distribution of studies indicating absence of publication bias.