BMC Cardiovascular Disorders

RESEARCH

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Sodium glucose co-transporter 2 (SGLT2) inhibitors versus dipeptidyl peptidase-4 (DPP-4) inhibitors and the risk of Atrial Fibrillation in patients with type 2 diabetes mellitus: a meta-analysis

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Abstract

Background Several studies showed higher risks of cardiovascular complications to have been observed in patients with type 2 diabetes mellitus (T2DM). Atrial fibrillation (AF) and atrial flutter have been more pronounced in patients with hyperglycemia. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are now considered as second-line treatment for patients with T2DM following inadequate glycemic control with first line agents. In this analysis, we aimed to compare the risk of AF in patients with T2DM who were treated with SGLT-2 inhibitors versus DPP-4 inhibitors.

Methods Relevant publications comparing AF in patients with T2DM treated by SGLT-2 inhibitors versus DPP-4 inhibitors were searched through electronic databases. AF was the clinical endpoint in this analysis. Revman 5.4 software was used to carry out this analysis. Risk ratios (RR) with 95% confidence intervals (CIs) were used to assess the outcome.

Results Eleven studies with a total number of 1,019,476 participants with T2DM were included in this analysis whereby 480,549 patients were assigned to SGLT-2 inhibitors and 538,927 patients were assigned to DPP-4 inhibitors. Result of this analysis showed SGLT-2 inhibitors to be associated with a significantly lower risk of AF compared to DPP-4 inhibitors in these patients with T2DM (RR: 0.57, 95% CI: 0.39 – 0.85; $P=0.006$).

Conclusions Based on the result of this analysis, the risk of AF was significantly reduced with SGLT-2 inhibitors when compared to DPP-4 inhibitors in these patients with T2DM. This hypothesis should be confirmed in future larger studies.

Keywords Atrial fibrillation, Type 2 diabetes mellitus, SGLT-2 inhibitors, DPP-4 inhibitors

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Introduction

Type 2 diabetes mellitus (T2DM) is on the rise and this chronic disease often co-exists with cardiovascular diseases [1]. Recently, several newer oral hypoglycemic agents (OHAs), including sodium glucose co-transporter 2 inhibitors (SGLT-2 inhibitors) [2], and dipeptidyl peptidase inhibitors (DPP-4 inhibitors) [3] have been approved for use. These newer OHAs have several cardio-protective effects and therefore, they have shown to be beneficial to the cardiovascular system [4].

Patients with T2DM are at higher risk of cardiovascular complications [5]. Arrhythmias such as atrial fibrillation (AF) and atrial flutter are more pronounced in patients with hyperglycemia [6]. In addition, patients with cardiovascular diseases and heart failure are at increased risk of developing AF as an outcome of their disease manifestation [7].

SGLT2 inhibitors are now considered as second-line or third line treatments for patients with T2DM following inadequate glycemic control with first line agents such as metformin. This is because SGLT2 inhibitors have shown to reduce blood glucose level as well as the risk of cardiovascular outcomes. The DECLARE-TIMI 58 trial has confirmed that SGLT-2 inhibitors could significantly reduce the risk of AF in patients with T2DM when compared to placebo [8]. However, a comparison of SGLT2 inhibitors versus DPP-4 inhibitors to systematically assess the risk of AF has seldom been carried out. Therefore, through this meta-analysis, we aimed to compare the risk of AF in patients with T2DM who were treated with SGLT-2 versus DPP-4 inhibitors.

Methods

Search databases

Online databases comprising of the Web of Science, MEDLINE, EMBASE, Mendeley, Google Scholar, http://www.ClinicalTrials.gov and the Cochrane database were searched for publications comparing AF in patients with T2DM treated with SGLT-2 inhibitors versus DPP-4 inhibitors. The authors also went through the reference lists of suitable publications in order to look for relevant articles.

Search strategy

During this searched process, the following search terms were used:

- Cardiovascular outcomes, sodium glucose co-transporter 2 and dipeptidyl peptidase inhibitors;
- Atrial fibrillation, sodium glucose co-transporter 2 and dipeptidyl peptidase inhibitors;
- Atrial fibrillation and SGLT-2 inhibitors and DPP-4 inhibitors;
- Cardiovascular outcomes and SGLT-2 inhibitors and DPP-4 inhibitors.

Criteria of inclusion and exclusion

Criteria for inclusion:

(a) Studies that compared AF in patients with T2DM treated with SGLT-2 inhibitors versus DPP-4 inhibitors;
(b) Randomized or non-randomized control trials;
(c) Studies that were published in English language.

Criteria for exclusion:

(a) Literature reviews, systematic reviews and network meta-analyses;
(b) Editorials;
(c) Case studies;
(d) Studies that did not report AF;
(e) Repeated studies from the same trial or cohort;
(f) Relevant studies that were repeated from different search databases.

Data extraction and quality assessment

The authors independently extracted data from the relevant studies. The total number of patients with T2DM who were assigned to SGLT-2 inhibitors and DPP-4 inhibitors respectively, the total number of events (AF) reported in the experimental and control groups, the baseline characteristics of the participants, the time period of patients' enrollment (years), the study type, the medications which were used by the participants, features of the methodological quality of the studies were carefully extracted. Any disagreement which occurred was discussed among the authors and a final decision was reached.

The Newcastle Ottawa scale (NOS) [9] was used to assess the methodological quality of the studies. The bias risk was assessed and a grade was allotted: grade A indicated a low risk of bias, grade B indicated a moderate risk of bias and grade C denoted a high risk of bias appropriately.

Statistical analysis

Revman 5.4 software was used to carry out this analysis. Risk ratios (RR) with 95% confidence intervals (CIs) were used to assess the outcome.

Heterogeneity was assessed in this analysis. A *P* value less or equal to 0.05 was considered statistically significant whereas a *P* value greater than 0.05 was considered insignificant. The I^2 statistical method was another method to assess heterogeneity whereby the higher the I^2 value, the greater the heterogeneity. If I^2 was > 50%, a random effect statistical model was used during analysis and if I^2 was less than 50%, a fixed effect model was used.

Sensitivity analysis was carried out by a method of exclusion and publication bias was visually assessed through the auto generated funnel plot.

Compliance with ethical guidelines

This study did not involve experiment using animals or humans carried out by any of the author. Data were obtained from previously published original studies. Therefore, no ethical approval was required for this meta-analysis.

Results

Search outcomes

The Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) guideline was followed [10]. Our search resulted in a total number of 412 publications.

At first, publications were directly eliminated following a thorough study/assessment of the titles and abstracts. One hundred and twelve (112) full text articles were assessed for eligibility.

Full text articles were eliminated because of the following reasons:

(a) They were editorials ($n = 8$);
(b) They were literature reviews, systematic reviews and network meta-analyses ($n = 15$);
(c) They did not report AF as outcome ($n = 10$);
(d) They were case studies ($n = 22$);
(e) They were repeated studies from the same trial or cohort ($n = 10$);
(f) They were repeated studies through several databases ($n = 36$).

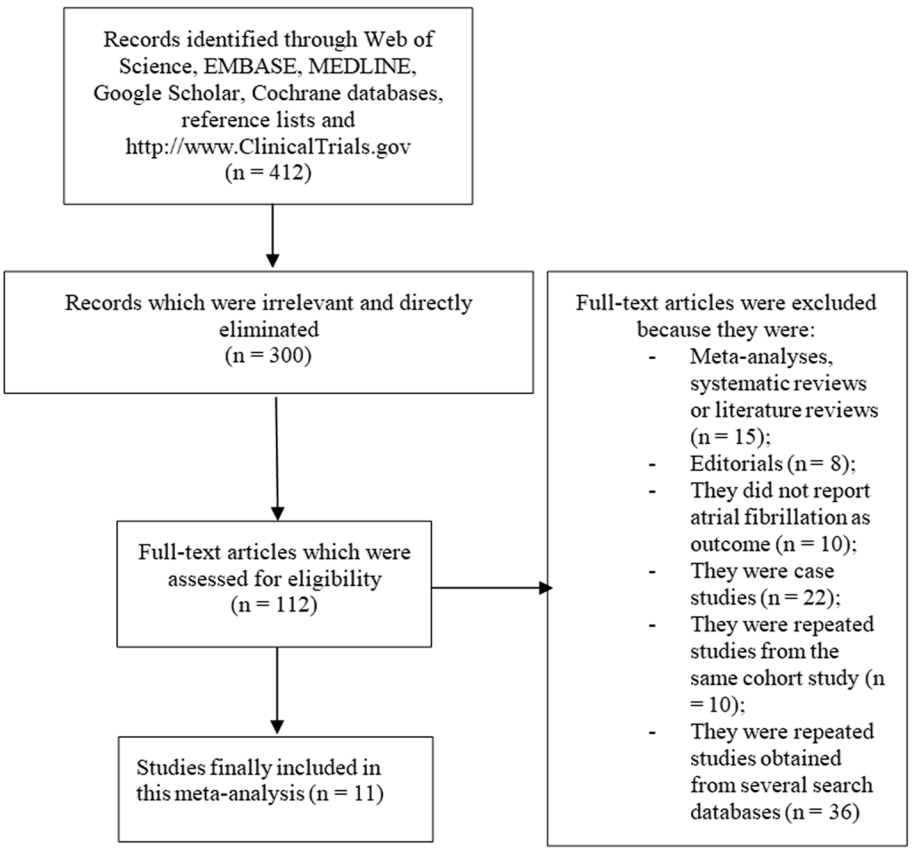

Fig. 1 Flow diagram showing the selection of studies for this analysis

Table 1 General features of the studies

Studies	Type of study	No of participants assigned to SGLT-2 inhibitors (n)	No of participants assigned to DPP-4 inhibitors (n)	Time period of participants' enrollment (years)	Type of participants	Type of SGLT-2 inhibitor	Bias risk assessment
Birkeland2017 [11]	MOS	22830	12566	2012 – 2013	T2DM	Not specified	B
Chan2022 [12]	NCS	245442	245442	2010 – 2019	T2DM	Empaglifozin,Dapaglifozin,Canaglifozin,Ertuglifozin	B
Chang2017 [13]	NCS	74863	16017	2014	T2DM	Not specified	B
Kim2024 [14]	NCS	42786	42786	2016—2018	T2DM	Dapagliflozin,Empagliflozin, and Ipragliflozin	B
Lee2021 [15]	RCS	12526	36582	2015 – 2019	T2DM	Not specified	B
Lee2023 [16]	RCS	21713	21713	2015—2020	T2DM	Not specified	B
Li2024 [17]	RCS	16487	80949	2017 – 2018	T2DM	Canagliflozin, Dapagliflozin, or Empagliflozin	B
Ling2020 [18]	ROS	15606	12383	2016 – 2018	T2DM	Empaglifozin, Dapaglifozin, and Canaglifozin	B
Persson2017 [19]	MOS	10227	30681	2012—2015	T2DM	Dapagliflozin	B
Real2021 [20]	RCS	12917	12917	2013 – 2016	T2DM	Canagliflozin, Dapagliflozin, or Empagliflozin	B
Wood2022 [21]	RCS	5152	26891	2014 – 2018	T2DM	Empaglifozin,Dapaglifozin,Canaglifozin,Ertuglifozin	B
Total no of participants (n)		480549	538927				

Abbreviations: MOS Multinational observational study, Type 2 diabetes mellitus, *NCS* Nationwide cohort study, *RCS* Retrospective cohort study, *ROS* Retrospective observational study

Table 2 Baseline features of the participants

Studies	Mean age (years)	Males (%)	CVD (%)	MI (%)	HF (%)	CKD (%)
	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4
Birkeland 2017 [11]	61.2/61.2	59.4/60.5	24.9/24.8	7.60/7.70	5.00/5.00	1.20/1.10
Chan 2022 [12]	59.0/60.3	56.5/56.4	4.00/4.17	-	0.66/0.68	14.9/14.8
Chang 2017 [13]	54.9/54.4	58.0/58.0	2.11/2.10	-	0.16/0.15	7.17/7.11
Kim 2024 [14]	54.7/54.7	57.5/57.6	3.90/3.80	3.30/3.20	4.70/4.70	1.30/1.20
Lee 2021 [15]	60.0/61.0	62.5/62.4	12.7/12.2	-	1.12/1.11	7.72/7.56
Lee 2023 [16]	57.6/59.1	59.9/59.8	12.6/10.7	3.29/3.17	1.86/1.80	0.54/0.54
Li 2024 [17]	67.1/72.2	52.4/43.8	51.1/58.7	3.82/5.46	21.3/31.3	69.5/72.3
Ling 2020 [18]	58.5/62.5	58.3/55.8	9.50/6.70	-	3.80/3.90	16.9/19.5
Persson 2017 [19]	61.0/60.8	59.0/59.6	23.0/22.7	7.10/7.10	4.70/4.70	2.10/2.00
Real 2021 [20]	62.9/62.8	56.3/44.0	27.5/26.8	6.40/6.20	5.60/5.40	5.20/7.90
Wood 2022 [21]	-	60.2/57.7	-	2.60/2.60	3.00/7.30	8.50/17.9

Abbreviations: CVD Cardiovascular diseases, *MI* Myocardial infarction, *HF* Heart failure, *AF* Atrial fibrillation, *CKD* Chronic kidney disease, *SGLT-2 inhibitors* Sodium glucose co-transporter 2, *DPP-4 inhibitors* Dipeptidyl peptidase 4 inhibitors

Finally, a total number of 11 studies [11–21] were confirmed for this analysis. The flow diagram for the study selection has been represented in Fig. 1.

General features of the studies

A total number of 1,019,476 participants with T2DM (enrolled between year 2010 and year 2020) were included in this analysis whereby 480,549 patients were assigned to SGLT-2 inhibitors and 538,927 patients

Table 3 Medications taken by the participants

medications	Birkeland 2017 [11]	Chan 2022 [12]	Persson 2017 [13]	Chang 2017 [14]	Kim 2024 [15]	Lee 2021 [16]	Lee 2023 [17]	Li 2024 [18]	Ling 2020 [19]	Real 2021 [20]	Wood 2022 [21]
	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4	SGLT2/DPP4
Metformin	74.2/77.4	64.0/64.7	83.3/83.8	-	70.2/70.4	64.3/65.4	-	62.0/42.0	89.8/66.4	-	-
Sulfonylurea	26.5/27.2	53.4/53.1	26.1/25.8	-	26.9/27.4	9.50/9.22	-	35.0/38.1	66.3/40.6	-	-
GLP-1 receptor agonist	17.0/14.8	-	7.80/7.50	-	0.00/0.00	1.47/1.36	-	22.0/3.05	-	-	-
Thiazolidinediones	1.50/1.40	11.4/11.4	1.40/1.40	-	4.30/4.50	4.50/4.26	-	8.57/7.66	24.5/5.60	-	-
Insulin	29.9/30.1	14.3/14.3	30.4/29.1	-	7.40/7.30	29.7/28.5	-	32.3/21.8	16.4/17.4	-	-
Aspirin	36.1/36.3	-	34.2/34.0	-	31.7/31.9	24.8/0.62	-	1.84/2.23	33.9/28.3	-	14.9/23.2
Statin	67.4/68.3	62.2/62.2	63.1/63.2	27.2/27.2	66.7/66.9	57.2/0.22	-	-	60.6/41.7	65.3/64.9	80.1/79.0
Loop diuretic	-	4.99/4.86	13.3/13.2	-	3.80/3.80	5.04/0.00	-	-	6.80/10.9	11.7/11.6	9.30/17.5
ACEI/ARB	-	53.9/53.8	-	31.6/31.7	1.80/1.70	-	-	-	60.5/48.7	38.3/38.3	75.8/75.9
MRA	-	2.69/2.64	-	-	-	-	-	-	3.00/3.00	-	4.20/5.20
Beta-blocker	-	27.1/27.2	-	13.8/13.7	12.2/12.2	-	-	-	33.6/27.7	27.0/26.6	26.2/30.3
Nitrate	-	3.90/3.93	-	-	3.80/3.80	-	-	-	6.30/5.80	-	-

Abbreviations: GLP-1 Glucagon-like peptide-1, *SGLT-2* Sodium-glucose co-transport 2, *DPP-4* Dipeptidyl peptidase-4, *ACEI* Angiotensin converting enzyme inhibitor, *ARB* Aldosterone-renin blocker, *MRA* Mineralocorticoid receptor antagonist

were assigned to DPP-4 inhibitors mostly derived from retrospective cohort studies as shown in Table 1. Study Chan2022 consisted of the highest number of participants whereas study Real2021 consisted of the lowest number of participants when compared to the other studies which were included in this analysis.

The baseline features of the participants have been listed in Table 2. These patients with T2DM had a mean age ranging from 54.4 years to 72.2 years with a predominance of male participants in majority of the original studies (43.8% to 62.5%) as shown in Table 2. The mean percentages of participants with cardiovascular diseases (2.10% to 27.5%), myocardial infarction (2.60% to 7.70%), heart failure (0.15% to 31.3%), and chronic kidney disease (0.54% to 19.5%) have also been listed.

Table 3 lists the medications which were used by the participants. A mean percentage of participants ranging from 64.0% to 89.8% were on metformin, 9.22% to 66.3% participants were on sulfonylurea, 0.00% to 22.0% participants were on GLP-1 receptor agonist, 1.40% to 24.50% participants were on thiazolidinediones, 7.30% to 32.3% participants were on insulin therapy. The mean percentage of participants on aspirin, statin, diuretics, angiotensin converting enzyme inhibitor, mineralocorticoid receptor antagonist, beta-blocker and nitrates have also been listed.

Result of this analysis showed SGLT-2 inhibitors to be associated with a significantly lower risk of AF compared to DPP-4 inhibitors in these patients with T2DM (RR: 0.57, 95% CI: 0.39 – 0.85; $P=0.006$) as shown in Fig. 2.

Sensitivity analysis was carried out and consistent results were reported throughout. When study Birkeland2017 was excluded and a new analysis was carried out, a similar result was obtained with RR: 0.66, 95% CI: 0.51 – 0.86; $P=0.002$. Study Chan2022 was excluded and the result was still in favor of this current analysis with RR: 0.55, 95% CI: 0.34 – 0.87; $P=0.01$. When study Chang2017 was excluded, the result obtained was not significantly different from this current result with RR: 0.51, 95% CI: 0.34 – 0.77; $P=0.001$. Similarly, when study Kim2024 was excluded, result of the new analysis was not significantly different with RR: 0.56, 95% CI: 0.37 – 0.85; $P=0.006$. No significantly different result was obtained compared to this current analysis throughout.

Publication bias was visually assessed. There was a low evidence of publication bias across the studies that were involved in assessing the risk of AF in T2DM patients who were treated with SGLT-2 inhibitors versus DPP-4 inhibitors. The funnel plot representing publication bias has been illustrated in Fig. 3.

Discussion

In this analysis, we aimed to compare the risk of AF in patients with T2DM who were treated with SGLT-2 inhibitors versus DPP-4 inhibitors. Our result showed the risk of AF to be significantly lower with SGLT-2 inhibitors showing a beneficial effect of this drug on the cardiovascular system.

A systematic review and meta-analysis of randomized controlled trials based on the protective effects of SGLT-2 inhibitors on AF and atrial flutter showed SGLT-2 inhibitors to be associated with a 19.33% lower risk of AF and atrial flutter when compared to placebo [22]. The analysis consisted of 33 trials and specifically, dapagliflozin was associated with this significantly reduced risk of AF. However, even though the discussed analysis compared SGLT-2 inhibitors with placebo, and supported the result of this analysis which is in favor of SGLT-2 inhibitors, this

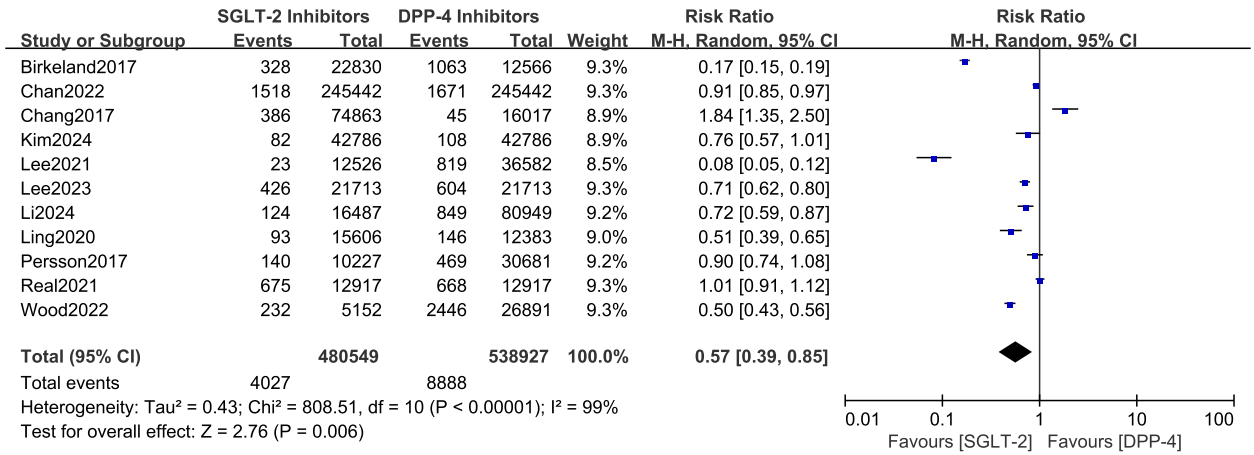

Fig. 2 Comparing Atrial fibrillation observed in patients with T2DM who were assigned to SGLT2 inhibitors versus DPP-4 inhibitors

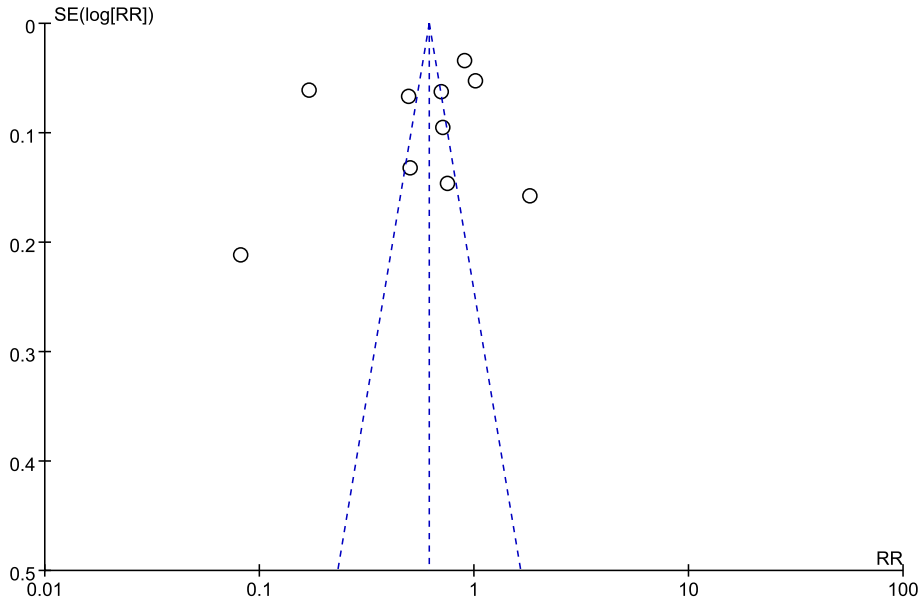

Fig. 3 Funnel plot showing publication bias

current analysis was based on a comparison of SGLT-2 inhibitors versus DPP-4 inhibitors. Similarly, another meta-analysis which was published in the Journal of the American Heart Association was significantly in favor of SGLT-2 inhibitors in preventing AF [23]. Another systematic review and meta-analysis of 16 randomized controlled trials published in Cardiovascular Diabetology showed SGLT-2 inhibitors to reduce AF in patients with T2DM, without specific regard to age, body weight, systolic blood pressure and glycosylated hemoglobin at baseline [24].

Insights from a global federated electronic medical database including a total number of 131,189 and 2, 692,985 patients who were treated with and without SGLT-2 inhibitors showed the latter to be associated with a significantly reduced risk of AF [25]. The study was a retrospective observational study which was conducted using the TriNetX research network which consisted of data from more than 85 million patients derived from more than 60 health care centers across 7 countries with a pre-dominance in the United States of America.

In a real world systematic review and meta-analysis, cardiovascular outcomes associated with SGLT-2 inhibitors versus other glucose lowering drugs in patients with T2DM involving 3, 157, 259 participants, showed a beneficial effect of SGLT-2 inhibitors on the cardiaovascular outcomes including AF further supporting the result of this analysis [26].

Different types of SGLT2 inhibitors have shown beneficial effects in patients with cardiac impairment. In the EMPEROR-Reduced trial which included of more than 3500 participants with different category of heart failure [27], 1863 participants were treated with empagliflozin, one of the most effective SGLT2 inhibitors. The result of this trial showed empagliflozin to be associated with a lower risk of cardiac death and admission for heart failure favoring its use. Similarly, in the DECLARE TIMI 58 trial, dapagliflozin was associated with a lower risk of cardiovascular mortality and hospitalization for heart failure supporting its use in patients with T2DM [28]. This cardiovascular benefit has also been observed with canagliflozin, another SGLT2 inhibitor [29].

Our analysis was based on the comparison of patients with T2DM who were treated with SGLT-2 inhibitors versus DPP-4 inhibitors. However, a recent meta-analysis of reconstructed Kaplan–Meier Curves with Trial Sequential Analysis based on the impact of SGLT-2 inhibitors on AF recurrence after catheter ablation in patients with T2DM further proved that SGLT-2 inhibitors were associated with a significantly lower risk of AF recurrence after catheter ablation [30].

Limitation

The limitations were: This paper only included non-randomized studies (Nationwide cohort study, retrospective cohort study, Multinational observational study) which contributed to the greater extent of heterogeneity during analysis. Moreover, one study compared SGLT-2 inhibitors with other glucose lowering drugs which also included DPP-4 inhibitors together with other glucose lowering drugs. Moreover, study Chang2017 compared DPP-4 inhibitors versus non-DPP-4 inhibitors which

included SGLT-2 inhibitors as well as other glucose lowering drugs together. Another limitation is the fact that the events associated with all SGLT-2 inhibitors including canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin were mixed and analyzed. This could also have an impact on the result. In addition, the other medications used by the participants were not taken into consideration during analysis.

Conclusions

Based on the result of this analysis, the risk of AF was significantly reduced with SGLT-2 inhibitors when compared to DPP-4 inhibitors in these patients with T2DM. Further randomized control trials should be able to confirm this hypothesis.

Abbreviations

AF	Atrial fibrillation
T2DM	Type 2 diabetes mellitus
SGLT2	Sodium glucose co-transporter 2
DPP-4	Dipeptidyl peptidase
RR	Risk ratio
CI	Confidence intervals

Acknowledgements

Not applicable.

Authors' contributions

Authors contributing statement: Dr XL, Dr JD, and Dr FW were responsible for the conception and design, drafting the initial manuscript and revising it critically for important intellectual content. Dr XL wrote the final draft. All the authors approved the final manuscript as it has been written.

Authors' information

Dr Xiaoyan Liang is the first author and Dr Feifei Wang is the corresponding author of this manuscript.

Clinical trial number

Not applicable.

Funding

There research was funded by Xinjiang Uygur Autonomous Region People's Hospital In Hospital Project Fund, Project No.20210215.

Data availability

All data and materials used in this research are freely available in electronic databases (MEDLINE, EMBASE, http://www.ClinicalTrials.gov, Web of Science, Cochrane database, Google scholar). References have been provided.

Declarations

Ethics approval and consent to participate

Ethical approval was not applicable for this systematic review and meta-analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 2 November 2024 Accepted: 19 December 2024
Published online: 28 January 2025

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