Xuehong Hu[1], Chen Tan[1], Xingpeng Liu[2], Na Zhang[1], Fengnan Wang[1], Zhijuan Wang[1]
[1] Hebei Yanda Hospital, Department of Cardiology, Langfang, China
[2] Department of Cardiology, Beijing Chaoyang Hospital of Capital Medical University, Beijing, China

Dapagliflozin Mediates the Protective Effect against atrial fibrillation/atrial flutter and the Reduction in All-Cause Mortality Risk

Objective	This study aimed to investigate the association between dapagliflozin and the incidence of atrial fibrillation (AF) and atrial flutter (AFL), along with its impact on all-cause mortality in patients with diabetes mellitus (DM).
Material and methods	Adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this meta-analysis conducted a comprehensive search across PubMed, Embase, and ClinicalTrials.gov databases up to June 2021. We focused on randomized controlled trials (RCTs) that compared dapagliflozin with a placebo. Trial sequential analysis (TSA) was utilized to assess the reliability of the findings. All statistical analyses were performed using Review Manager software.
Results	The final analysis included nine studies, encompassing a total of 30,235 patients. The findings indicated a statistically significant reduction in the incidence of AF/AFL in the dapagliflozin group compared to the placebo group (relative risk (RR) = 0.73, 95% confidence interval (CI) = 0.59 to 0.89, p=0.002), although this result was not corroborated by TSA. The occurrences of AF and all-cause mortality were also lower in the dapagliflozin group than in the placebo group (RR = 0.71, 95% CI = 0.57 to 0.89, p=0.003 and RR = 0.90, 95% CI = 0.82 to 0.98, p=0.02, respectively). However, TSA did not confirm these outcomes.
Conclusion	Dapagliflozin appears to offer a significant protective effect against AF/AFL and may reduce the risk of all-cause mortality in patients with DM. However, further research is needed to confirm these findings due to the lack of confirmation by TSA.

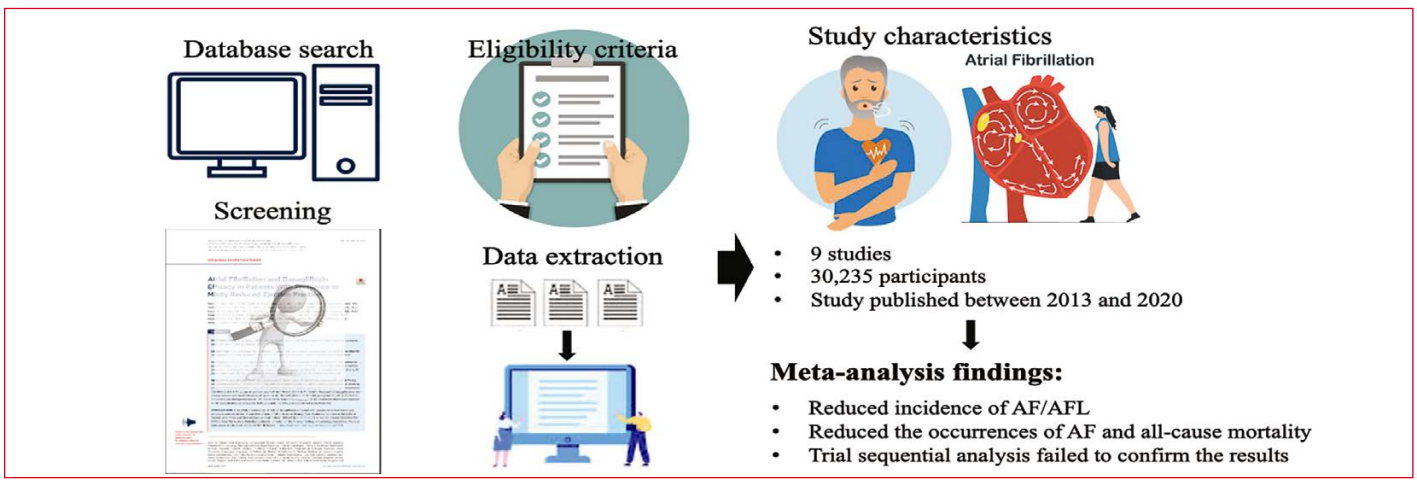
Keywords	Atrial fibrillation; atrial flutter; diabetes mellitus; meta-analysis; dapagliflozin
For citations	Xuehong Hu, Chen Tan, Xingpeng Liu, Na Zhang, Fengnan Wang, Zhijuan Wang. Dapagliflozin Mediates the Protective Effect Against Atrial Fibrillation/Atrial Flutter and the Reduction in All-Cause Mortality Risk. Kardiologiia. 2025;64(12):68–76. [Russian: Сюэхун Ху, Чэнь Тан, Синпэн Лю, На Чжан, Фэннань Ван, Чжицзюань Ван. Дапаглифлозин опосредует защитный эффект в отношении фибрилляции/трепетания предсердий и снижает риск смертности от всех причин. Кардиология. 2025;64(12):68–76].

Corresponding author Xuehong Hu. E-mail: xhonghu@yeah.net

Introduction

Approximately 537 million individuals, constituting 10.5% of the world's populace, were affected with diabetes mellitus (DM) [1]. The prevalence of DM in China has increased from 10.9% in 2013 to 12.4% in 2018 [2]. Comorbidities associated with diabetes, such as obesity, heart failure, chronic kidney disease, and hypertension, are linked to a higher incidence of atrial fibrillation (AF) and atrial flutter (AFL) [3–5]. AF

Central illustration. Dapagliflozin Mediates the Protective Effect against atrial fibrillation/atrial flutter and the Reduction in All-Cause Mortality Risk



ISSN 0022-9040. Кардиология. 2024;64(12). DOI: 10.18087/cardio.2024.12.n2701

is a common arrhythmia that becomes more prevalent with aging, physical health status, and various clinical indicators, and AF is significantly associated with an increased risk of stroke [6]. Similarly, AFL poses a distinct stroke risk, with different clinical outcomes [7].

DM has been recognized as a critical and independent risk factor for AF/AFL, aside from other cardiovascular diseases [8]. The pathogenesis of AF in DM involves complex interactions among increased oxidative stress, mitochondrial dysfunction, and atrial remodeling [9]. Routine screening for AF/AFL in DM patients is beneficial, offering opportunities for therapeutic and other preventive measures to avoid strokes and other risks, especially in younger patients [10]. These preventive measures include traditional and new anticoagulants including Non-vitamin K oral anticoagulants.

Traditional treatments for DN, including those that focus on insulin sensitization and secretion, often face challenges due to side effects and patient noncompliance. This situation can lead to negative outcomes or even cessation of treatment, which exacerbates the condition [11]. In the case of type 2 DM, the pharmacological landscape has significantly evolved with the introduction of various agonists like GLP-1, and inhibitors, such as, DPP-4 and SGLT2. These advancements have demonstrated improvements in cardiovascular outcomes and metabolic regulation [12]. Among these, dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, has gained prominence for its role in managing type 2 DM [13]. Dapagliflozin is one of the most frequently utilized SGLT2 inhibitors. There is increasing evidence supporting the benefits of dapagliflozin in reducing the incidence and mortality rates associated with type 2 DM, especially in patients with concurrent heart failure. This suggests a projected rise in the use of dapagliflozin for treating comorbidities associated with heart failure [14].

However, the link between DM and AF/AFL remains unclear [15]. Studies exploring the mechanisms underlying the association between DM and AF/AFL are still lacking, as are investigations of effective treatments for AF/AFL in DM patients. This meta-analysis aimed to address these gaps by assessing the incidence of AF/AFL in selected randomized controlled trials (RCTs) that compared dapagliflozin to a placebo in the treatment of DM.

Material and methods

This meta-analysis conformed to the guidelines of PRISMA statement [16].

Data origin and search method

A comprehensive and systematic search was conducted across relevant databases, Embase, PubMed, and ClinicalTrials.gov, from their inception until June 2021. The search terms employed were "dapagliflozin", "randomized controlled trial", and "atrial fibrillation". The focus was solely on studies involving human subjects, without any restrictions on language or publication status. Additionally, the references of the cited literature were meticulously examined independently to uncover any further relevant studies.

Study selection

The following are the inclusion criteria: 1) study method: RCTs; 2) age of patients: older than 18 yrs; 3) treatment: dapagliflozin compared with placebo; 4) consequence: assessed at least one of the following: the occurrence of atrial fibrillation (AF), atrial flutter (AFL), or all-cause mortality. The exclusion criteria were: 1) animal experiment; 2) studies that didn,t solely assessed Dapagliflozin 3) Short articles with insufficient data and outcomes.

Data extraction and quality assessment

Data were extracted by two independent reviewers using a pre-defined, standardized format that included the first author, publication date, sample size, participant characteristics, treatment details, and all clinical outcomes, specifically the incidence of AF/AFL and all-cause mortality. Quality assessment was conducted independently by different reviewers using the Cochrane Risk of Bias tool. In cases of disagreement, a third reviewer was consulted to reach a consensus. The criteria for quality assessment encompassed several key areas: the randomization process, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, absence of selective reporting, and other potential biases. Each criterion was evaluated for the risk of bias and categorized as low, unclear, or high.

Trial sequential analysis

In this meta-analysis, trial sequential analysis (TSA) was utilized to evaluate the robustness of the results [17]. It was determined that conclusive evidence had been reached, and no further studies were needed if the cumulative Z-curve crossed the trial sequential monitoring boundary or entered the futility zone. Conversely, evidence was considered inconclusive, indicating the need for additional research, if the Z-curve remained within all bounds or the required information size (RIS) was not met [18]. The TSA was performed with a 5% risk of Type I error and calculated the RIS based on a 20% relative risk reduction (RRR) at 80% power. Control event rates were derived from the data of the comparison groups [19]. If applying the random-effects model, both Biggerstaff-Tweedie (BT) and DerSimonian-Laird (DL) methods produced divergent outcomes, further analysis with these results was conducted, and their

Figure 1. Flow chart of the trial selection

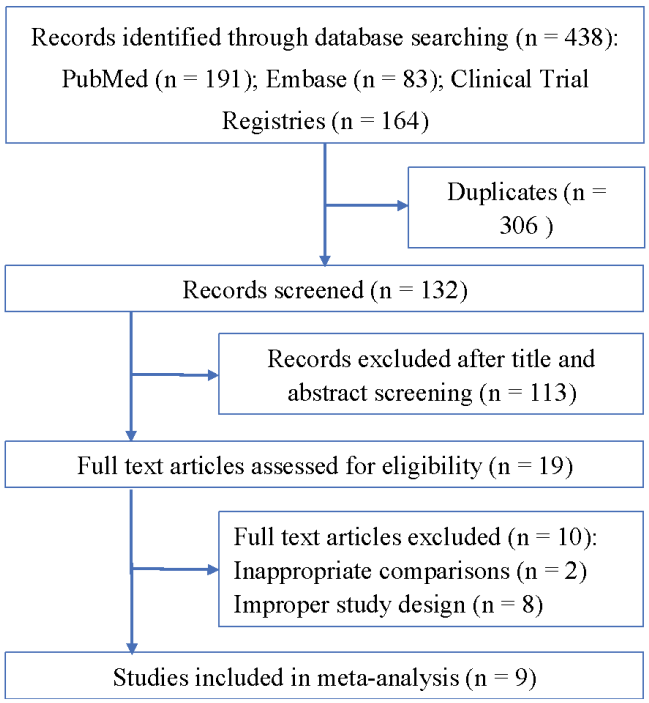
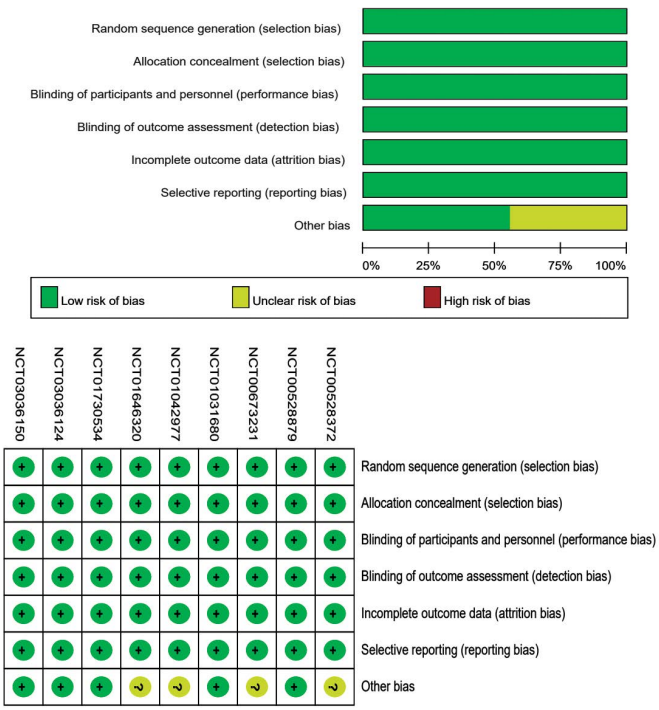


Figure 2. Quality assessment of risk of bias of included trials



implications were thoroughly examined. For these analyses, TSA software version 0.9 beta (http://www.ctu.dk/tsa) was used [18].

Statistical analysis

Risk ratios (RRs) for dichotomous variables were calculated with 95% confidence intervals (CIs), and mean differences (MDs) for continuous variables were also determined with 95% CIs. Study heterogeneity was assessed using the I2 statistic, with I2 values greater than 50% indicating high heterogeneity [20]. A fixed-effect model was applied for I2 values below 25%; otherwise, a random-effects model was utilized. Sensitivity analyses were conducted to explore the sources of heterogeneity among the studies. The presence of publication bias was evaluated using funnel plots. All comparisons were made using two-sided tests, and a p-value of less than 0.05 was considered statistically significant. In cases where statistical data such as means or standard deviations could not be directly obtained, they were estimated from the available data [21, 22]. Review Manager software (version 5.3, The Cochrane Collaboration, Oxford, United Kingdom) was used for all statistical analyses.

Results

Search results

The process of selecting trials for this meta-analysis is depicted in Figure 1, which illustrates the flowchart of the study selection process. Initially, a total of 438 potential trials were identified based on the search strategy. Following the removal of duplicates and studies that did not meet the inclusion criteria, nine studies involving 30,235 participants were finally included [23–31]. Details regarding the characteristics of the included studies are presented in Table 1. These trials were published between 2013 and 2020, with sample sizes ranging from 320 to 17,160.

Bias assessment risk based on the included trials

The quality of the included studies was assessed using Review Manager 5.3, and the outcomes of this assessment are summarized in Figure 2. All the trials screened were found to have a low risk of bias, encompassing biases related to selection, performance, attrition, detection, and reporting. However, four trials exhibited unclear risks of bias due to certain, unspecified aspects.

The incidence of AF or AFL

AF or AFL were considered adverse events in the included trials, both of which are types of arrhythmias. Each of the studies included in this meta-analysis reported on the incidence of AF or AFL [23–31]. The aggregated data from these trials indicated that the incidence of AF/AFL was significantly lower in participants treated with dapagliflozin compared to those receiving placebo, with a risk ratio (RR) of 0.73, a 95% CI ranging from 0.59 to 0.89, and a p-value of 0.002. Heterogeneity among the studies was negligible (I2<0.001) (Figure 3A).

Given the substantial variance in sample sizes across the trials, random-effects models, the DerSimonian-Laird (DL) and Biggerstaff-Tweedie (BT) models, were utilized for the Trial Sequential Analysis. According to this analysis, the outcomes from both DL and BT models indicated

ISSN 0022-9040. Кардиология. 2024;64(12). DOI: 10.18087/cardio.2024.12.n2701

that the cumulative Z-curve crossed the conventional significance boundary but did not surpass the trial sequential monitoring boundary (Figures 3B and 3C).

The incidence of AF

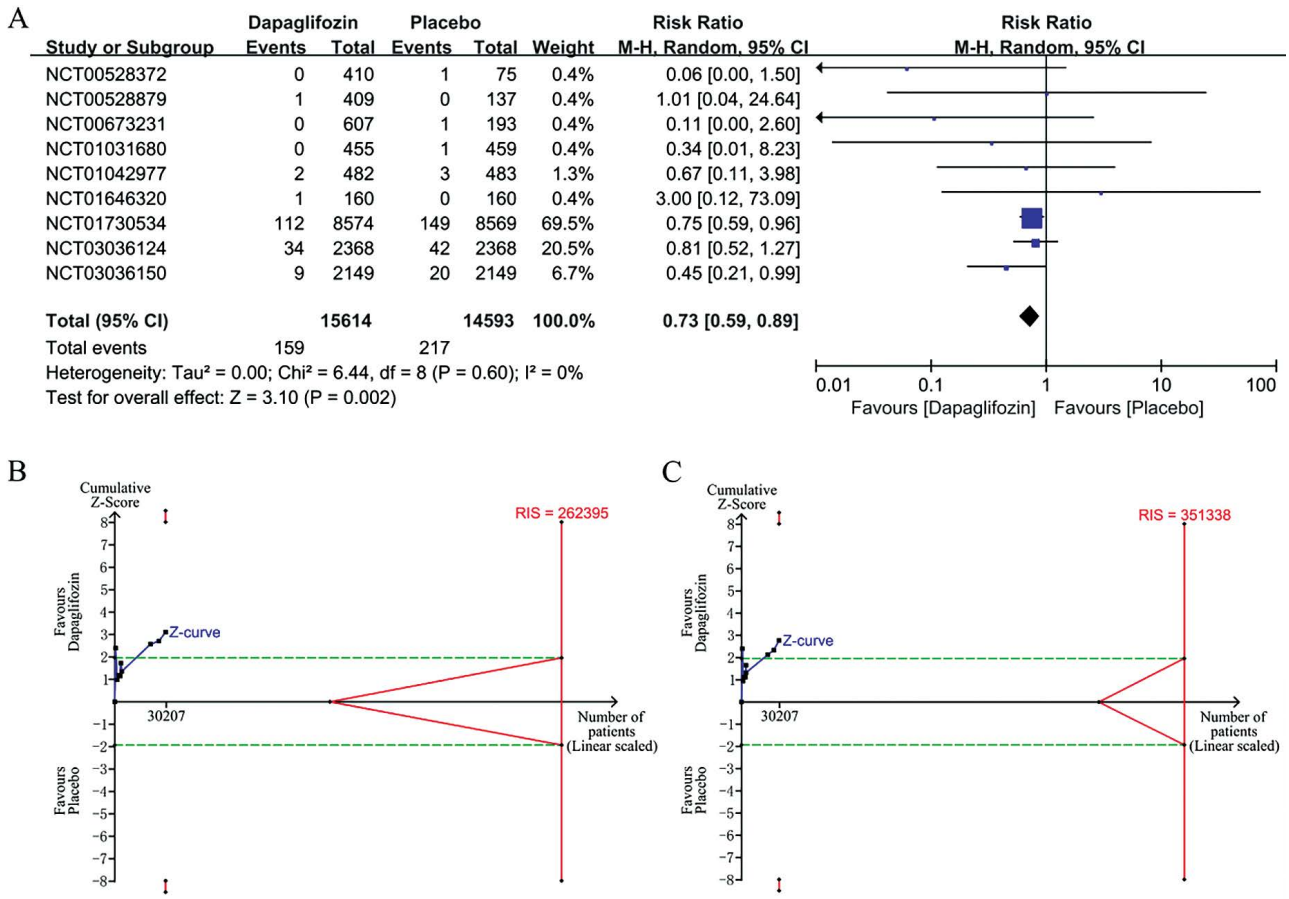
Given the prevalence of AF as the most common arrhythmia encountered in clinical practice, it was crucial to evaluate the efficacy of dapagliflozin in preventing AF. Among the studies included in the meta-analysis, eight [23, 24, 26–31] reported on the incidence of AF. The pooled analysis of these studies showed that dapagliflozin significantly reduced the occurrence of AF compared to placebo (RR = 0.71, 95% CI = 0.57, 0.89, p=0.003, I2<0.001, Figure 4A). However, the Trial Sequential Analysis (TSA) conducted using both DerSimonian-Laird (DL) and Biggerstaff-Tweedie (BT) methods was unable to confirm

Table 1. Characteristics of included studies

Study	Country	NCT		Intervention	Type of patients	No. of patients (M/F)	Mean age, years	Follow-up
		number	Setting					
Wilding et al. (2013)	126 centers worldwide	00673231	Phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled	T: Dapagliflozin 2.5, 5 or 10 mg/d for 24 weeks C: Placebo	T2DM	T: 607 (287/320) C: 193 (95/98)	T: 59.5 ± 8.1a C: 58.8 ± 8.6a	24 weeks
Bailey et al. (2013)	80 sites in 5 countries	00528879	Phase3, multicenter, randomized, parallel-group, double-blind, placebo-controlled	T: Dapagliflozin 2.5, 5 or10 mg/d for 102 weeks C: Placebo	T2DM	T: 409 (215/194) C: 137 (75/62)	T: 53.7 (NA) C: 54.0 (NA)	102 weeks
Leiter et al. (2014)	173 centers in 10 countries	01042977	Phase3, multicenter, randomized, parallel-group, double-blind, age-stratified, placebo-controlled	T: Dapagliflozin 10 mg/d for 24 weeks C: Placebo	T2DM and CVD	T: 480 (321/159) C: 482 (323/159)	T: 63.9 ± 7.6a C: 63.6±7.0a	24 weeks
Bailey et al. (2015)	85 centers in 4 countries	00528372	Phase3, multicenter, randomized, parallel-group, double-blind, placebo-controlled	T: Dapagliflozin 2.5, 5 or 10 mg/d for 102 weeks C: Placebo	T2DM	T: 410 (198/212) C: 75 (31/44)	T:NA C: NA	102 weeks
Cefalu et al. (2015)	141 sites in 9 countries	01031680	Phase3, multicenter, randomized, parallel-group, double-blind, placebo-controlled	T: Dapagliflozin 10 mg/d for 24 weeks C: Placebo	T2DM with high risk of future CVD	T: 455 (309/146) C: 459(315/144)	T: 62.8 ± 7.0s C: 63.0±7.7a	24 weeks
Mathieu et al. (2016)	67 sites in 8 countries	01646320	Phase3, multicenter, randomized, parallel-group, double-blind, placebo-controlled	T: Dapagliflozin 10 mg/d for 52 weeks C: Placebo	T2DM	T: 160(70/90) C: 160(76/84)	T: 55.2 ± 8.6a C: 55.0 ± 9.6a	52 weeks
Wiviott et al. (2019)	882 sites in 33 countries	01730534	Phase3, multicenter, randomized, parallel-group, double-blind, placebo-controlled	T: Dapagliflozin 10 mg/d for 202 weeks C: Placebo	T2DM with or at risk of ASCVD	T: 8582 (5411/3171) C: 8578 (5327/3251)	T: 63.9 ± 6.8a C: 64.0 ± 6.8a	202 weeks
McMurray et al. (2019)	410 centers in 20 countries	03036124	Phase3, multicenter, randomized, parallel-group, double-blind, placebo-controlled	T: Dapagliflozin 10 mg/d for 113.2 weeks C: Placebo	With NYHA class II, III, or IV HF and an EF of 40% or less	T: 2373 (1809/564) C: 2371 (1826/545)	T: 66.2 ± 11.0я C: 66.5±10.8a	113.2 weeks
Heerspink et al. (2020)	386 sites in 21 countries	03036150	Phase3, multicenter, randomized, parallel-group, double-blind, placebo-controlled	T: Dapagliflozin 10 mg/d for 115.2 weeks C: Placebo	CKD* with or without T2DM	T: 2152 (1443/709) C: 2152 (1436/716)	T:61.8± 12.1a C: 61.9 ±12.1'	115.2 weeks

ASCVD, atherosclerotic cardiovascular disease; C, control groups; CKD, chronic kidney disease; CVD, cardiovascular disease; EF, ejection fraction; HF, heart failure; NA, not available; NYHA, New York heart association; T, treatment groups; T2DM, Type 2 diabetes mellitus. a Mean ± SD; * With an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000.

Figure 3. The incidence of AF/AFL



A) Forest plot of the incidence of AF/AFL between the dapagliflozin and the placebo groups.
B) The DL approach used for all trials. A diversity-adjusted information size of 262395 participants was calculated on the basis of an AF/AFL occurrence rate of 1.5% in the placebo group and a RRR of 20%, with α=5% (two-sided), β=20%, I2 =0%. The solid blue line represents the cumulative Z-curve, which crossed the conventional boundary for benefit (dashed green line) but did not cross the trial sequential monitoring boundary for benefit (solid red line).
C) The BT approach used for all trials. A diversity-adjusted information size of 351338 participants was calculated on the basis of an AF/AFL occurrence rate of 1.5% in the placebo group and a RRR of 20%, with α=5% (two-sided), β=20%, I2 =0%. The solid blue line represents the cumulative Z-curve, which crossed the conventional boundary for benefit but did not cross the trial sequential monitoring boundary for benefit.

this finding conclusively. Although the cumulative Z-curve surpassed the conventional boundary for benefit, it did not cross the trial sequential monitoring boundary (Figures 4B and 4C). This suggests that while the initial results are promising, further research is necessary to conclusively determine the effect of dapagliflozin on the prevention of AF.

All-cause mortality

All-cause mortality was reported by seven studies [23, 25, 26, 28–31], with mortality rates of 6.4% in the dapagliflozin group and 7.4% in the placebo group. The aggregated results showed that dapagliflozin significantly reduced the risk of all-cause mortality compared to placebo (RR = 0.90, 95% CI = 0.82, 0.98, p = 0.02, I2 < 0.001, Figure 5A). Nonetheless, TSA did not confirm these outcomes as the cumulative Z-curve crossed the conventional boundary but remained within the trial sequential monitoring boundary (Figures 5B and 5C).

Publication bias

The incidence of AF/AFL among the included trials was examined through a funnel plot (Figure 6). The symmetry observed in the funnel plot suggests the absence of significant publication bias within the included studies. This is further supported by statistical tests for bias detection, with p=0.297 for the Begg's test and P/p=0.090 for the Egger's test, indicating no significant evidence of bias among the studies analyzed.

Discussion

Patients with Type II DM carry a significant and independent risk for developing AF and AFL [8, 32, 33]. Furthermore, there is a well-documented association between DM and the progression of AF/AFL. However, the potential for antihyperglycemic agents (thiazolidinedione, metformin [Met], sulfonylurea [SU], insulin [Insu], dipeptidyl peptidase-4 inhibitor [DPP-4i], glucagon-like peptide-1

ISSN 0022-9040. Кардиология. 2024;64(12). DOI: 10.18087/cardio.2024.12.n2701

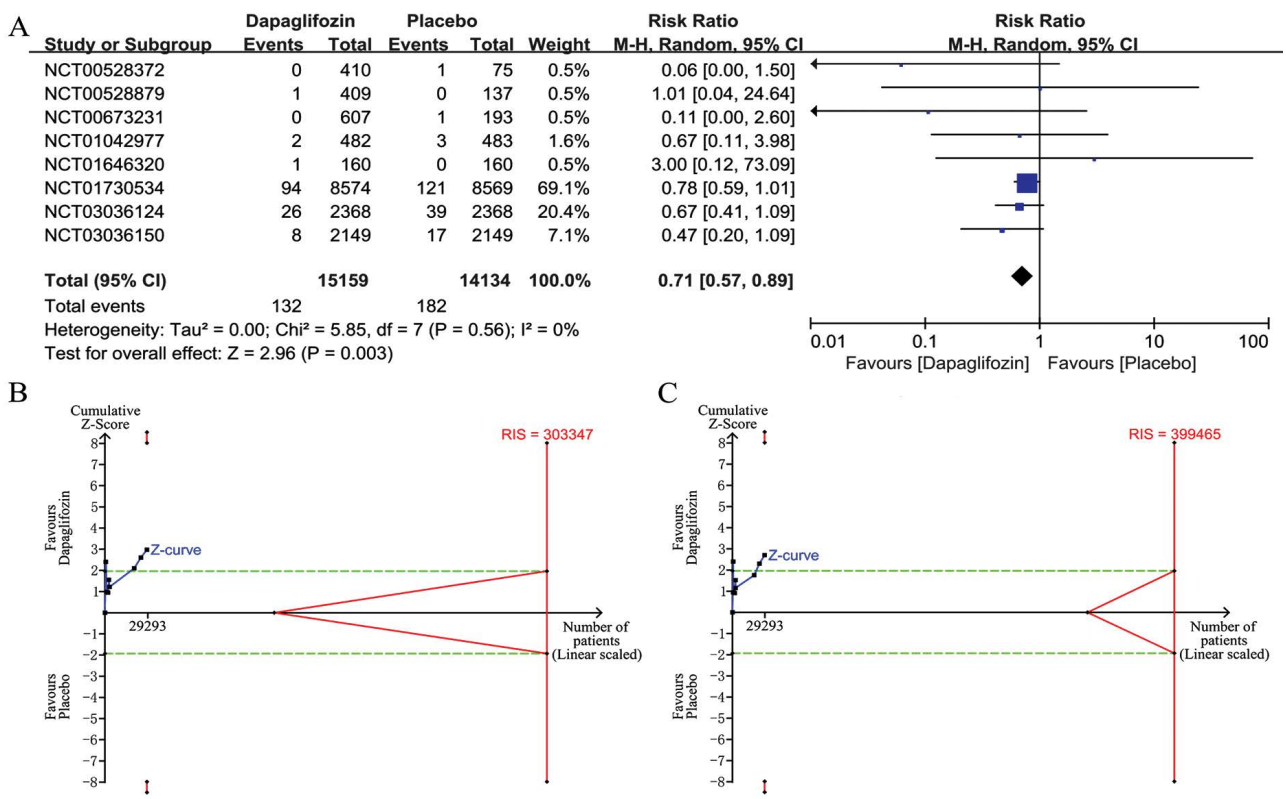
receptor agonist [GLP-1RA], sodium-glucose cotransporter 2 inhibitor [SGLT2i], alpha-glucosidase inhibitor, and non-sulfonylurea [nSU]) to mitigate this risk remains a subject of ongoing investigation [34]. The findings of this meta-analysis indicate that the use of dapagliflozin is associated with a reduced incidence of AF/AFL and all-cause mortality, suggesting that dapagliflozin may significantly lower the risk of new-onset AF. While the specific mechanisms by which dapagliflozin exerts its protective effects against AF are not fully understood, current clinical and research evidence points to potential cardioprotective benefits, including improvements in body mass index and reductions in HbA1c values. This suggests that dapagliflozin may offer a valuable therapeutic option for patients with Type II DM potentially lowering their risk of developing AF/AFL.

The inhibition of sodium-glucose co-transporters (SGLTs) plays a crucial role in glucose reabsorption in the kidneys. Thus, SGLTs are emerging as an innovative therapy for DM [35]. Drugs that inhibit SGLT2 are now recommended for patients with three specific conditions: type II DM, chronic kidney disease, and heart failure with reduced ejection fraction [36]. This therapeutic strategy may partly explain the anti-arrhythmic effects of SGLT-2 inhibitors due to the relationship between hypomagnesemia and an increased risk of supraventricular ectopy and enhanced sinus node automaticity, which in turn could elevate the likelihood of AF/AFL [37].

Dapagliflozin is administered as a once-daily oral dose and functions by blocking the reabsorption of glucose from the glomerular filtrate back into the bloodstream [38]. Beyond its recognized benefits of reducing hospitalizations for heart failure and mitigating adverse renal effects, dapagliflozin has also been shown to decrease the risk of AF/AFL events in patients with type II DM [39]. This evidence supports the multifaceted advantages of dapagliflozin, not only in managing DM and its complications but also in offering cardioprotective effects, particularly in reducing the incidence of arrhythmias, such as AF and AFL.

Preventing AF and AFL in high-risk populations, such as those with DM and heart failure, is a crucial and ongoing effort aimed at mitigating symptoms like stroke and exacerbation of heart failure. This is in addition to basic therapy, including an-

Figure 4. The incidence of AF

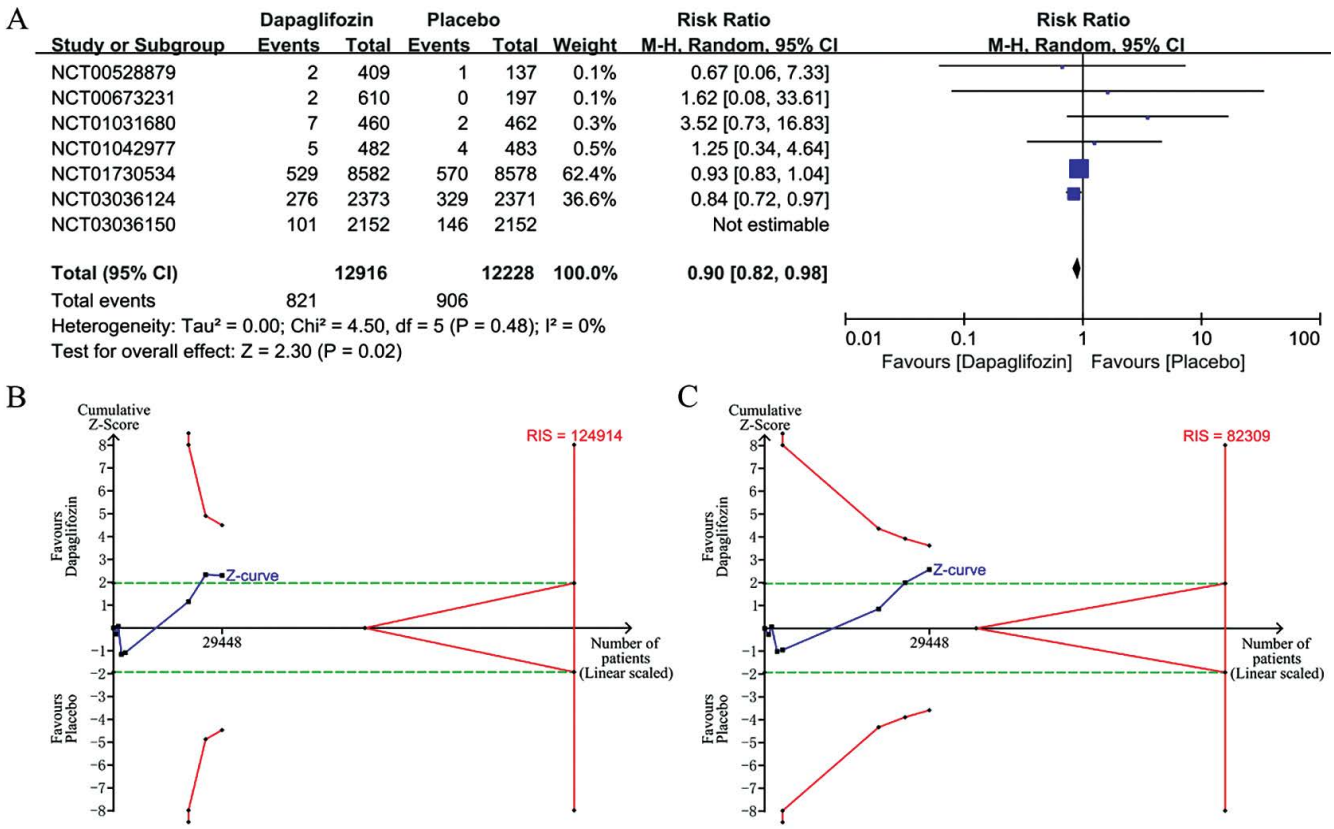


A) Forest plot of the incidence of AF between the dapagliflozin and the placebo groups.

B) The DL approach used for all trials. A diversity-adjusted information size of 303347 participants was calculated on the basis of an AF occurrence rate of 1.3% in the placebo group and a RRR of 20%, with α=5% (two-sided), β=20%, I2 =0%. The solid blue line represents the cumulative Z-curve, which crossed the conventional boundary for benefit (dashed green line) but did not cross the trial sequential monitoring boundary for benefit (solid red line).

C) The BT approach used for all trials. A diversity-adjusted information size of 399465 participants was calculated on the basis of an AF occurrence rate of 1.3% in the placebo group and a RRR of 20%, with α=5% (two-sided), β=20%, I2 =0%. The solid blue line represents the cumulative Z-curve, which crossed the conventional boundary for benefit but did not cross the trial sequential monitoring boundary for benefit.

Figure 5. The all-cause mortality occurrence

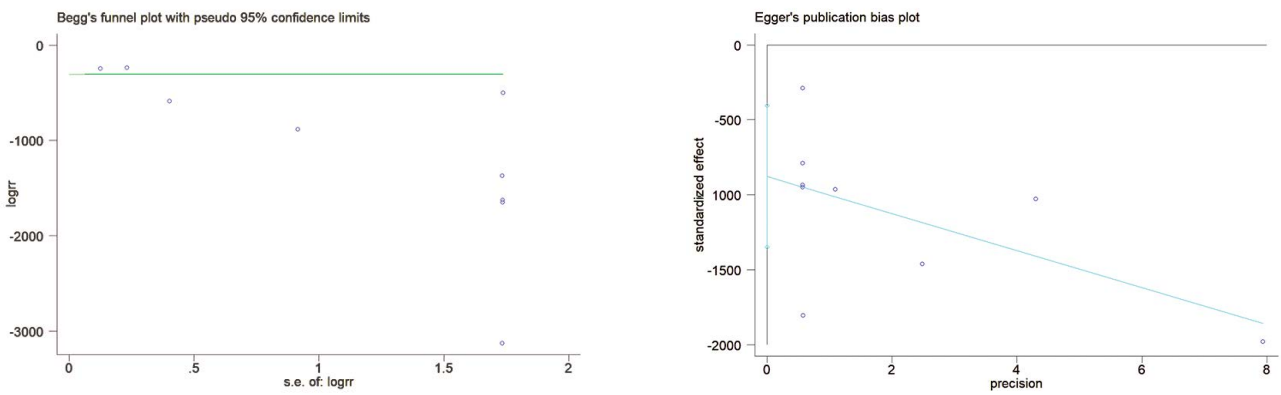


A) Forest plot about the all-cause mortality occurrence with respect to the dapagliflozin and the placebo.
B) The DL approach used for all trials. A diversity-adjusted message size of about 124,914 patients was calculated on the basis of 7.4% mortality rate in the placebo and 20% RRR, with 5% α, 20% β, 0% I2. The cumulative Z-curve is indicated by the solid blue line and exceeded the conventional benefit boundary (dashed green line) but did not overstep the trial sequential monitoring benefit boundary (solid red line).
C) The BT approach used for all trials. A diversity-adjusted message size of 82,309 patients were counted with regard of a 7.4% mortality rate within the placebo and a 20% RRR, with 5% α, 20% β, 0% I2. The cumulative Z-curve has an identical explanation as in panel B).

giotensin-converting enzyme inhibitors, angiotensin receptor antagonists, mineralocorticoid receptor antagonists, and β-blockers [37]. The cumulative incidence of AF was 2.2% in the general population and 3.1% among individuals with DM, with a median time from the onset of DM to the development of AF of 4.79 yrs (interquartile range 2.01 to 8.75 yrs) [10]. SGLT2 inhibitors may offer specific benefits in reducing the risk of AF/AFL in the susceptible type II DM population, regardless of age, body weight, HbA1c levels, and baseline systolic blood pressure [40]. These benefits are partially attributed to the pharmacological effects of SGLT2 inhibitors, which include reductions in HbA1c, body weight, blood pressure, and the risk of heart failure [40].

An earlier, comprehensive meta-analysis encompassing 33 trials and involving 66,685 patients demonstrated that the use of SGLT2 inhibitors was associated with a 19.3%

Figure 6. Funnel plot for AF/AFL



ISSN 0022-9040. Кардиология. 2024;64(12). DOI: 10.18087/cardio.2024.12.n2701

reduction in serious adverse events related to AF/AFL, lower than that observed with placebos. Notably, participants treated with dapagliflozin exhibited the lowest rate of serious adverse events concerning the occurrence of AF/AFL [41]. The findings from our meta-analysis reinforce the notion that dapagliflozin significantly reduces the incidence of AF/AFL compared to placebo, thus highlighting its potential as an effective therapeutic option for patients at high risk of these conditions.

The current meta-analysis has some limitations. While all studies included were assessed for bias, there remains a particular concern regarding the risk of bias due to incomplete blinding of participants and personnel. Additionally, for-profit bias could potentially have influenced the interpretation of the results. The long-term effects of dapagliflozin remain uncertain, as there are no trials with extended follow-up periods available for analysis. Moreover, the integrity and rigor of this analysis may be compromised by the inclusion of studies with limited sample sizes and short follow-up durations, which could affect the robustness and generalizability of the findings.

In conclusion, our analysis indicates a significantly reduced risk of AF and AFL among individuals treated with dapagliflozin, regardless of their DM status. However, these findings should be interpreted with caution, as further investigation with additional randomized clinical trials is necessary to fully understand the clinical implications of dapagliflozin treatment. This cautionary approach will help ensure that the benefits of dapagliflozin, particularly in reducing the incidence of AF/AFL, are accurately assessed and understood in the context of its broader clinical effects.

Data Availability

The experimental data used to support the findings of this study are available from the corresponding author upon request.

Funding

This paper is funded by the key scientific and technological research project of Hebei Province, comparative research on post-stroke re treatment of patients with atrial fibrillation (20191062).

No conflict of interest is reported.

The article was received on 06/05/2024

REFERENCES

1. Baccaglini L, Kusi Appiah A, Ray M, Yu F. US adults with diabetes mellitus: Variability in oral healthcare utilization. PLOS ONE. 2021;16(5):e0251120. DOI: 10.1371/journal.pone.0251120
2. Wang L, Peng W, Zhao Z, Zhang M, Shi Z, Song Z et al. Prevalence and Treatment of Diabetes in China, 2013-2018. JAMA. 2021;326(24):2498–506. DOI: 10.1001/jama.2021.22208
3. Fangel MV, Nielsen PB, Kristensen JK, Larsen TB, Overvad TF, Lip GYH et al. Glycemic Status and Thromboembolic Risk in Patients With Atrial Fibrillation and Type 2 Diabetes Mellitus: A Danish Cohort Study. Circulation: Arrhythmia and Electrophysiology. 2019;12(5):e007030. DOI: 10.1161/CIRCEP.118.007030
4. Kumar S, Lim E, Covic A, Verhamme P, Gale CP, Camm AJ et al. Anticoagulation in Concomitant Chronic Kidney Disease and Atrial Fibrillation. Journal of the American College of Cardiology. 2019;74(17):2204–15. DOI: 10.1016/j.jacc.2019.08.1031
5. Hu W-S, Lin C-L. Comparison of New-Onset Diabetes Mellitus among Patients with Atrial Fibrillation or Atrial Flutter. Korean Circulation Journal. 2020;50(6):527–32. DOI: 10.4070/kcj.2019.0367
6. Zapata J, Paamoni A, Rinard B, Abdou A, Zimmer D, Letherer CC. The Watchman device for preventing stroke in patients with atrial fibrillation. JAAPA. 2021;34(10):33–8. DOI: 10.1097/01.JAA.0000769672.18363.3f
7. Chen Y. Different implication in dementia between patients with atrial flutter and atrial fibrillation: a national cohort study. EP Europace. 2021;23(Suppl 3):euab116.160. DOI: 10.1093/europace/euab116.160
8. Movahed M-R, Hashemzadeh M, Mazen Jamal M. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. International Journal of Cardiology. 2005;105(3):315–8. DOI: 10.1016/j.ijcard.2005.02.050
9. Zhou L, Liu Y, Wang Z, Liu D, Xie B, Zhang Y et al. Activation of NADPH oxidase mediates mitochondrial oxidative stress and atrial remodeling in diabetic rabbits. Life Sciences. 2021;272:119240. DOI: 10.1016/j.lfs.2021.119240
10. Pallisgaard JL, Schjerning A-M, Lindhardt TB, Procida K, Hansen ML, Torp-Pedersen C et al. Risk of atrial fibrillation in diabetes mellitus: A nationwide cohort study. European Journal of Preventive Cardiology. 2016;23(6):621–7. DOI: 10.1177/2047487315599892
11. Mishra V, Nayak P, Sharma M, Albutti A, Alwashmi ASS, Aljasir MA et al. Emerging Treatment Strategies for Diabetes Mellitus and Associated Complications: An Update. Pharmaceutics. 2021;13(10):1568. DOI: 10.3390/pharmaceutics13101568
12. Henríquez-Tejo R, Cartes-Velásquez R. Psychosocial impact of type 1 diabetes mellitus in children, adolescents and their families. Literature review. Revista chilena de pediatría. 2018;89(3):391–8. DOI: 10.4067/S0370-41062018005000507
13. Kaur P, Behera BS, Singh S, Munshi A. The pharmacological profile of SGLT2 inhibitors: Focus on mechanistic aspects and pharmacogenomics. European Journal of Pharmacology. 2021;904:174169. DOI: 10.1016/j.ejphar.2021.174169
14. Nicholson MK, Ghazal Asswad R, Wilding JP. Dapagliflozin for the treatment of type 2 diabetes mellitus – an update. Expert Opinion on Pharmacotherapy. 2021;22(17):2303–10. DOI: 10.1080/14656566.2021.1953471
15. Tadic M, Cuspidi C. Type 2 diabetes mellitus and atrial fibrillation: From mechanisms to clinical practice. Archives of Cardiovascular Diseases. 2015;108(4):269–76. DOI: 10.1016/j.acvd.2015.01.009
16. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Medicine. 2009;6(7):e1000097. DOI: 10.1371/journal.pmed.1000097
17. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. Journal of Clinical Epidemiology. 2008;61(8):763–9. DOI: 10.1016/j.jclinepi.2007.10.007
18. Liu C, Mao Z, Kang H, Hu J, Zhou F. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: a meta-analysis with trial sequential analysis of random-

ized controlled trials. Critical Care. 2016;20(1):144. DOI: 10.1186/s13054-016-1299-0
19. Liu C, Lu G, Wang D, Lei Y, Mao Z, Hu P et al. Balanced crystalloids versus normal saline for fluid resuscitation in critically ill patients: A systematic review and meta-analysis with trial sequential analysis. The American Journal of Emergency Medicine. 2019;37(11):2072–8. DOI: 10.1016/j.ajem.2019.02.045
20. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60. DOI: 10.1136/bmj.327.7414.557
21. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Medical Research Methodology. 2014;14(1):135. DOI: 10.1186/1471-2288-14-135
22. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Medical Research Methodology. 2005;5(1):13. DOI: 10.1186/1471-2288-5-13
23. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Medicine. 2013;11(1):43. DOI: 10.1186/1741-7015-11-43
24. Bailey CJ, Morales Villegas EC, Woo V, Tang W, Ptaszynska A, List JF. Efficacy and safety of dapagliflozin monotherapy in people with Type 2 diabetes: a randomized double-blind placebo-controlled 102-week trial. Diabetic Medicine. 2015;32(4):531–41. DOI: 10.1111/dme.12624
25. Cefalu WT, Leiter LA, De Bruin TWA, Gause-Nilsson I, Sugg J, Parikh SJ. Dapagliflozin's Effects on Glycemia and Cardiovascular Risk Factors in High-Risk Patients With Type 2 Diabetes: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study With a 28-Week Extension. Diabetes Care. 2015;38(7):1218–27. DOI: 10.2337/dc14-0315
26. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F et al. Dapagliflozin in Patients with Chronic Kidney Disease. New England Journal of Medicine. 2020;383(15):1436–46. DOI: 10.1056/NEJMoa2024816
27. Mathieu C, Herrera Marmolejo M, González González JG, Hansen L, Chen H, Johnsson E et al. Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52 weeks in patients with type 2 diabetes. Diabetes, Obesity and Metabolism. 2016;18(11):1134–7. DOI: 10.1111/dom.12737
28. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. New England Journal of Medicine. 2019;381(21):1995–2008. DOI: 10.1056/NEJMoa1911303
29. Wilding JPH, Woo V, Rohwedder K, Sugg J, Parikh S, for the Dapagliflozin 006 Study Group. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. Diabetes, Obesity and Metabolism. 2014;16(2):124–36. DOI: 10.1111/dom.12187
30. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2019;380(4):347–57. DOI: 10.1056/NEJMoa1812389
31. Leiter LA, Cefalu WT, De Bruin TWA, Gause-Nilsson I, Sugg J, Parikh SJ. Dapagliflozin Added to Usual Care in Individuals with Type 2 Diabetes Mellitus with Preexisting Cardiovascular Disease: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with a 28-Week Extension. Journal of the American Geriatrics Society. 2014;62(7):1252–62. DOI: 10.1111/jgs.12881
32. Alwafi H, Wong ICK, Banerjee A, Mongkhon P, Whittlesea C, Naser AY et al. Epidemiology and treatment of atrial fibrillation in patients with type 2 diabetes in the UK, 2001–2016. Scientific Reports. 2020;10(1):12468. DOI: 10.1038/s41598-020-69492-z
33. Creta A, Providência R, Adragão P, De Asmundis C, Chun J, Chierchia G et al. Impact of Type-2 Diabetes Mellitus on the Outcomes of Catheter Ablation of Atrial Fibrillation (European Observational Multicentre Study). The American Journal of Cardiology. 2020;125(6):901–6. DOI: 10.1016/j.amjcard.2019.12.037
34. Shi W, Zhang W, Zhang D, Ren G, Wang P, Gao L et al. Comparison of the effect of glucose-lowering agents on the risk of atrial fibrillation: A network meta-analysis. Heart Rhythm. 2021;18(7):1090–6. DOI: 10.1016/j.hrthm.2021.03.007
35. Chao EC, Henry RR. SGLT2 inhibition — a novel strategy for diabetes treatment. Nature Reviews Drug Discovery. 2010;9(7):551–9. DOI: 10.1038/nrd3180
36. Zhao L-M, Ding L-L, Zhan Z-L, Qiu M. SGLT2 inhibitors should be recommended in patients with one or more of the three diseases: type 2 diabetes, chronic kidney disease, and HFrEF. European Journal of Internal Medicine. 2021;87:102–3. DOI: 10.1016/j.ejim.2021.03.001
37. Granger CB, Mahaffey KW. Preventing Atrial Fibrillation With Treatments for Diabetes Mellitus. Circulation. 2020;141(15):1235–7. DOI: 10.1161/CIRCULATIONAHA.120.045864
38. Komoroski B, Vachharajani N, Feng Y, Li L, Kornhauser D, Pfister M. Dapagliflozin, a Novel, Selective SGLT2 Inhibitor, Improved Glycemic Control Over 2 Weeks in Patients With Type 2 Diabetes Mellitus. Clinical Pharmacology & Therapeutics. 2009;85(5):513–9. DOI: 10.1038/clpt.2008.250
39. Zelniker TA, Bonaca MP, Furtado RHM, Mosenzon O, Kuder JF, Murphy SA et al. Effect of Dapagliflozin on Atrial Fibrillation in Patients With Type 2 Diabetes Mellitus: Insights From the DECLARE-TIMI 58 Trial. Circulation. 2020;141(15):1227–34. DOI: 10.1161/CIRCULATIONAHA.119.044183
40. Li W, Chen X, Xu L, Li Y, Luo B. SGLT2 inhibitors and atrial fibrillation in type 2 diabetes: a systematic review with meta-analysis of 16 randomized controlled trials. Cardiovascular Diabetology. 2020;19(1):130. DOI: 10.1186/s12933-020-01105-5
41. Li D, Liu Y, Hidru TH, Yang X, Wang Y, Chen C et al. Protective Effects of Sodium-Glucose Transporter 2 Inhibitors on Atrial Fibrillation and Atrial Flutter: A Systematic Review and Meta- Analysis of Randomized Placebo-Controlled Trials. Frontiers in Endocrinology. 2021;12:619586. DOI: 10.3389/fendo.2021.619586

ISSN 0022-9040. Кардиология. 2024;64(12). DOI: 10.18087/cardio.2024.12.n2701