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ORIGINAL RESEARCH

Tirzepatide and the Incidence of Atrial Fibrillation in Adults With Overweight or Obesity: An Updated Meta-Analysis of Randomized Controlled Trials

Ensieh S. Mansouri, MD; Flavia Queiroga, MD; Lucas Mendes Barbosa; Anne K. Azevedo, MD; Webster Donaldy, MD; Mohammad Jafar Mirbolouk, MD; Camila V. Blair, MD; André Rivera, MD; Iuri Ferreira Felix, MD; Marconi Abreu, MD; Abhishek J. Deshmukh, MBBS; Christopher V. DeSimone, MD, PhD

BACKGROUND: Tirzepatide is a dual agonist for glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, with proven efficacy in weight loss and improvement in cardiovascular outcomes. However, the effects of tirzepatide on the incidence of atrial fibrillation in patients with overweight or obesity remain unclear.

METHODS: PubMed, Embase, and Cochrane Library were searched for randomized controlled trials comparing tirzepatide versus placebo for individuals with overweight or obesity. Odds ratios (ORs) with 95% credible intervals (CrIs) were pooled using a Bayesian binomial-normal hierarchical model, appropriate for rare-event outcomes.

RESULTS: Our meta-analysis included 10 randomized controlled trials, including 6515 individuals, of whom 4491 (68.9%) were randomized to tirzepatide. The pooled OR was 2.20 (95% CrI, 0.81–6.75) for atrial fibrillation, 2.16 (95% CrI, 0.90–5.87) for atrial arrhythmia, and 1.84 (95% CrI, 1.04–3.90) for any arrhythmia.

CONCLUSIONS: Tirzepatide was not associated with atrial fibrillation or atrial arrhythmia. Although higher odds of overall arrhythmias were observed, event rates were low and the findings should be interpreted cautiously.

Key Words: arrhythmia ■ atrial fibrillation ■ glucagon-like peptide-1 ■ obesity ■ tirzepatide

Approximately 40% of individuals in the United States live with obesity.[1] Excess adipose tissue has been associated with increased systemic inflammation and contributes to cardiac remodeling, which may promote atrial fibrillation (AF).[2,3] Obesity is a well-established risk factor for cardiovascular disease, including AF, primarily because of its proinflammatory effects and association with other comorbidities.[4,5]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as effective therapies for weight loss and cardiovascular risk reduction.[6] Nonetheless, concerns persist about their potential arrhythmogenic effects, possibly because of glucagon-like peptide-1 (GLP-1) receptor expression in the sinoatrial node and ventricular cardiomyocytes, where they modulate β-adrenoceptor stimulation and may influence cardiac excitability.[7,8] Despite these concerns, prior studies

Correspondence to: Ensieh S. Mansouri, MD, Department of Internal Medicine, Ziaeian Hospital, Tehran University of Medical Services, Abuzar Street, opposite Tehran Municipality District 17, Tehran, Iran, 14557-35631. Email: encyesaadaat@yahoo.com and Christopher V. DeSimone, MD, PhD, Department of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN, 55905. Email: desimone.christopher@mayo.edu

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RESEARCH PERSPECTIVE

What Is New?

- This updated meta-analysis of randomized trials evaluated the incidence of atrial fibrillation and arrhythmias in adults with overweight or obesity treated with tirzepatide. Tirzepatide was not associated with atrial fibrillation or atrial arrhythmia. Although higher odds of overall arrhythmias were observed, event rates were low and the findings should be interpreted cautiously.

What Are the Clinical Implications?

- Future studies should evaluate arrhythmia outcomes with systematic monitoring and adjudication to better define the arrhythmic safety profile of tirzepatide.
- Additional research should explore whether incretin-based therapies differ in their effects on arrhythmias and whether these effects are related to metabolic changes or direct cardiac electrophysiologic mechanisms.

Nonstandard Abbreviations and Acronyms

CrI	credible interval
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist

suggest that semaglutide may reduce the incidence of atrial and ventricular arrhythmias compared with a placebo.[9,10] In contrast, dulaglutide may increase the risk of AF.[11] In contrast to semaglutide, tirzepatide is a GLP-1/glucose-dependent insulinotropic polypeptide dual-receptor agonist. Tirzepatide has demonstrated superior glycemic control and weight reduction compared with semaglutide.

Tirzepatide is highly effective even at lower doses and remains well tolerated at higher doses with gradual titration. Chronic administration of tirzepatide has resulted in weight loss ranging from 16% to 25% in individuals with and without diabetes.[12] Additionally, glucose-dependent insulinotropic polypeptide receptor activation in the myocardium has been associated with reduced cardiomyocyte hypertrophy, attenuation of cardiac fibrosis, and modulation of myocardial fatty acid metabolism.[13,14] However, the effects of tirzepatide on arrhythmic outcomes remain unclear.

Prior meta-analyses found no significant difference in AF incidence with tirzepatide. However, they were limited to active comparators, such as insulin, and focused on patients with diabetes.[15] Since then, additional trials have been published, including studies enrolling patients with overweight and obesity.[3,16–18] Therefore, we conducted an updated systematic review and meta-analysis of randomized controlled trials (RCTs) comparing tirzepatide versus placebo to investigate the incidence of AF in patients with overweight or obesity.

METHODS

Ethics Statement

This study is a systematic review and meta-analysis of previously published studies and uses aggregated, deidentified data. Therefore, institutional review board approval and informed consent were not required.

Data Availability Statement

The corresponding author will share the article's data at a reasonable request.

Study Design and Protocol Registration

This systematic review and meta-analysis were performed and reported following the Cochrane Collaboration Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses check-list).[19,20] The prospective meta-analysis protocol was registered at the International Prospective Register of Systematic Reviews (CRD420250654808).

Data Source and Search Strategy

We systematically searched PubMed, Embase, and Cochrane Library from inception to June 2026. The search terms used included "tirzepatide" and "placebo." The complete search strategy is provided in Table S1. Two authors (E.S.M. and F.Q.) independently screened titles and abstracts and thoroughly evaluated the articles for eligibility based on prespecified criteria. Discrepancies were resolved in a panel discussion with a third author. Moreover, we used backward snowballing (ie, review of references) to identify relevant studies from articles included in the original search. The date of the last search was June 2026.

Eligibility Criteria

There was no restriction concerning the publication date, status, or language. We considered studies eligible for inclusion if they (1) were RCTs; (2) compared tirzepatide versus placebo; (3) included individuals with overweight (body mass index ≥25 kg/

m^2) or obesity (body mass index ≥30 kg/m^2); and (4) reported any prespecified efficacy or safety outcome of interest.

Data Extraction and Outcomes

Three authors (E.S.M., F.Q., and M.J.M.) independently extracted the data for each study using a standardized study form: authors, enrollment period, study publication year, main exclusion criteria, sample size, follow-up period, baseline characteristics, end point definitions, and the methods used to assess the effect of tirzepatide on AF. Any discrepancies were resolved by consensus among the authors after examining the complete text of the article and the eligibility criteria. The outcomes of interest were the incidence of any arrhythmias, atrial arrhythmias, and AF.

Quality Assessment

Two independent authors (E.S.M. and W.D.) assessed the risk of bias in the included RCTs using the Cochrane Risk of Bias tool for randomized trials. Disagreements were resolved between the authors. The quality of the evidence for each outcome was summarized with Grading of Recommendations Assessment, Development, and Evaluation using the GRADEpro GDT software.[21]

Statistical Analysis

Given the low frequency of events, we used a binomial-normal hierarchical model suitable for sparse data with weakly informative priors.[22] Results are reported as odds ratios (ORs) with 95% credible interval (CrIs). Markov chain Monte Carlo sampling was run with 4 chains and 2000 saved iterations (1000 burn-in).

All analyses were performed in R (R Environment version 4.5.0) using the MetaStan package.[22] Further details on models and priors are provided in Supplemental Methods.

In trials with multiple tirzepatide dose arms, intervention groups were combined into a single arm to avoid unit-of-analysis error and maintain a single pairwise comparison with the placebo group, in accordance with Cochrane recommendations.

Race and Ethnicity

The American Heart Association Disparities Research Checklist is provided in Table S2.

RESULTS

Study Selection and Characteristics

Our systematic search yielded 3922 potential studies. After removing duplicates and initial title and abstract screening, 94 full-text articles were retrieved and reviewed in full for possible inclusion. Of these, 85 were excluded, primarily because of lack of relevant outcomes or inadequate study design, whereas a small number were excluded for other reasons, such as being a study protocol or duplicate population. Ten RCTs met all the inclusion criteria and were included in the analysis.[16–18,23–29] Overall, 6515 individuals were included, of whom 4491 (68.9%) were randomized to tirzepatide and 2024 (31.1%) were randomized to the placebo group. Comprehensive details of the study selection are detailed in Figure 1.

In this pooled analysis, mean age was 51 and 53% were women. Mean body mass index varied from 30 to 39 kg/m^2, and most studies had a follow-up duration from 40 to 72 weeks. Across studies reporting these characteristics, 42% of individuals had diabetes, 36% had glycated hemoglobin >7%, and 32% had a glomerular filtration rate <90 mL/min per 1.73 m^2.[16,18,23–25] All included studies were multicenter. The prevalence of diabetes varied widely across studies (0%–100%). Baseline individuals and study characteristics are detailed in Table 1. Arrhythmia definitions and detection methods also varied between studies, with most relying on scheduled 12-lead ECGs at predefined visits for event detection (Table S3).

End Points

The pooled OR was 2.20 (95% CrI, 0.81–6.75) for AF (Figure 2), 1.84 (95% CrI, 1.04–3.90) for any arrhythmia (Figure 3), and 2.16 (95% CrI, 0.90–5.87) for atrial arrhythmia (Figure 4), compared with placebo. Absolute event rates were low in both the tirzepatide and placebo groups across all outcomes (Table 2).

Quality Assessment

Individual RCT appraisal is detailed in Figure 5. The Cochrane Collaboration Risk of Bias tool for randomized trials identified 4 RCTs with some concerns for bias and 6 RCTs at low risk of bias. Funnel plot analysis for the primary efficacy end point detected no evidence of publication bias (Figure S1), with a symmetric distribution of study weights around the pooled estimate.

Grading of Recommendations Assessment, Development, and Evaluation Assessment

The certainty of the evidence for both AF and all arrhythmias was rated as moderate. The rating was downgraded because arrhythmias were captured as adverse events rather than prespecified outcomes, and the included trials were not primarily designed to assess arrhythmia incidence. In addition, the relatively

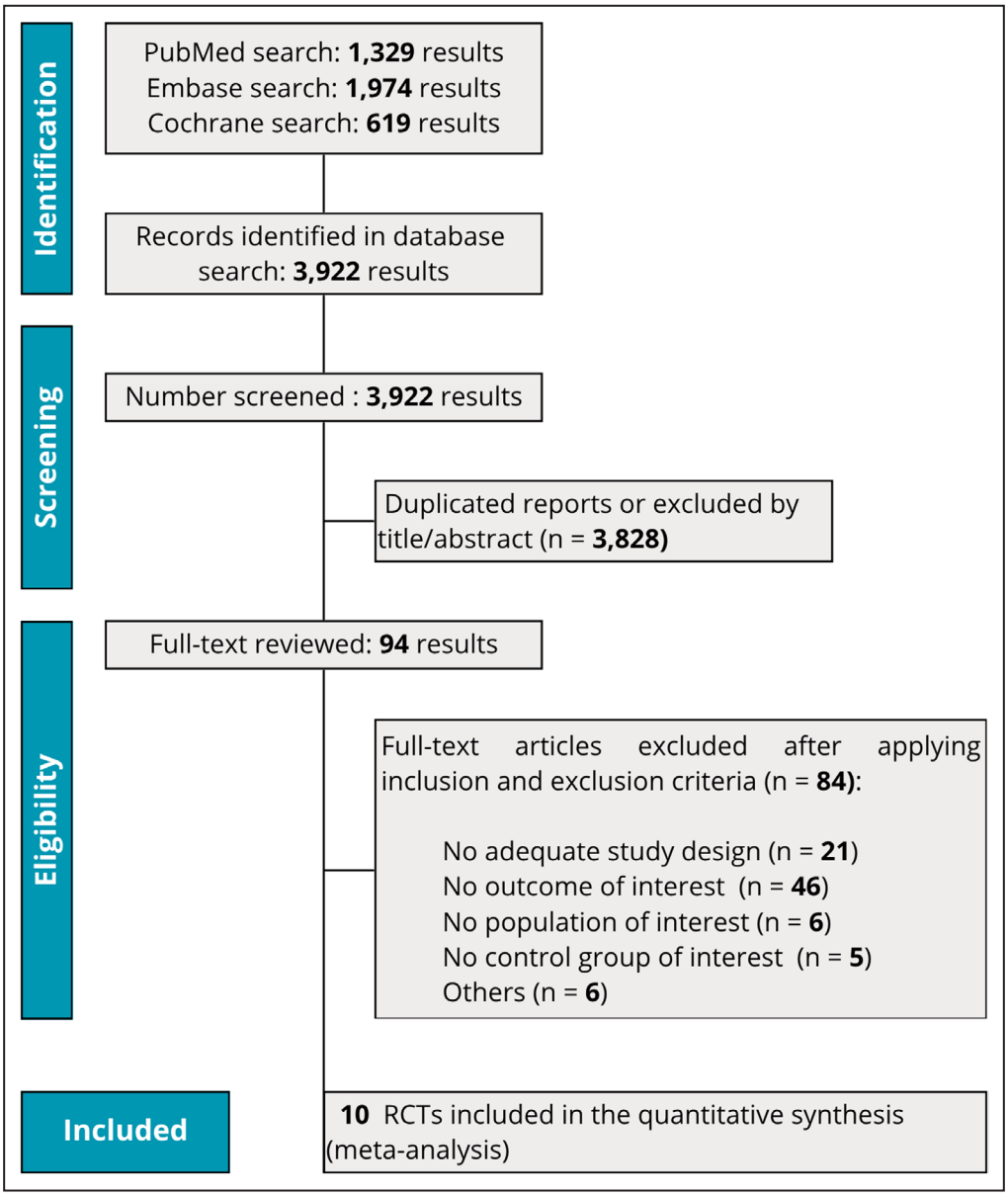

Figure 1. PRISMA flow diagram of study screening and selection.
PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses; and RCT, randomized controlled trial.

low number of events and wide CrIs further limited certainty (Figure S2).

DISCUSSION

This meta-analysis of 10 RCTs involving 6515 individuals assessed the incidence of AF and other arrhythmias in patients with overweight or obesity treated with tirzepatide versus placebo. Although no clear association with AF or atrial arrhythmia was observed, the effect estimates for any arrhythmias suggested higher odds with tirzepatide. Because arrhythmias were not prespecified end points in most trials and event counts were low, these findings should be considered exploratory.

The relationship between obesity and arrhythmias is complex and involves multiple interrelated mechanisms, including systemic inflammation, sympathetic overactivity, myocardial fibrosis, and left atrial remodeling.[5,30] Through weight loss and improved glycemic control, GLP-1 RAs may help mitigate these arrhythmogenic pathways.[31] Recent studies have investigated the direct effects of GLP-1 RAs on arrhythmia risk. Meta-analyses of RCTs have generally shown no significant increase in overall arrhythmia incidence with GLP-1 RAs compared with placebo.[9,32] Recent studies

Table 1. Baseline Characteristics of Included Studies[16–18,23–29]

Study, y	No. of individuals	Mean age, y	Female, %	White individuals, %	Asian individuals, %	Black individuals, %	Diabetes, %	BMI, kg/m^2	eGFR, mL/min per 1.73 m^2	SBP, mm Hg	HbA1c, %	Follow-up, wk
	Tirzepatide/ placebo	Tirzepatide/ placebo	Tirzepatide/ placebo	Tirzepatide/ placebo	Tirzepatide/ placebo	Tirzepatide/ placebo	Overall	Tirzepatide/ placebo	Tirzepatide/ placebo	Tirzepatide/ placebo	Tirzepatide/ placebo	
Rosenstock et al (SURPASS-1) 2021	363/115	54/53	47.3/51.3	34/40	27.3/8	5/4	100	31.9/31.7	94.3/93.4	128/128	7.9/8.1	40
Dahl et al (SURPASS-5) 2022	355/120	61/61	59.4/45.0	80/80	13.2/4.6	2/0	100	33.4/33.2	85.7/84.7	137/140	8.3/8.4	40
Loomba et al (SYNERGY-NASH) 2024	142/48	55/55	57.7/56.2	85/89	8.9/2.6	1/0	NA	36.2/36.0	NA	NA	6.4/6.8	52
Gudzune et al (SURMOUNT-1) 2022	1909/630	45/45	67.4/67.8	71/70	8.0/2.7	8/9	0	37.9/38.2	98.0/98.1	123/123	5.6/5.6	72
Garvey et al (SURMOUNT-2) 2023	623/315	54/54	50.8/50.4	74/79	9.1/4.1	9/7	100	36.1/36.6	96.0/93.5	130/131	8.0/7.9	76
Zhao et al (SURMOUNT-CN) 2024	141/69	35/36	49.6/47.8	NA	NA	NA	100	30.3/30.7	112.9/112.3	120/121	5.6/5.7	52
Frias et al 2018	211/51	57/56	45.9/43.1	80/84	0.9/0.5	11/4	100	32.3/32.4	93.3/95.3	NA	8.2/8.0	26
Malhotra et al (SURMOUNT-OSA) 2024	233/234	49/47	29.6/31.1	68/71	6.9/6.9	13/4	0	39.1/38.6	NA	129/130	5.7/5.6	52
Packer et al (SUMMIT) 2024	364/367	66/65	54.9/52.5	70/70	7.9/9.9	6/4	48	38.3/38.2	64.5/64.3	128/128	NA	104
Kadowaki et al (SURMOUNT-J) 2025	150/75	52/51	41.3/40.0	0/0	66.6/33.3	0/0	0	33.4/33.7	73.6/70.6	126/125	5.7/5.7	72

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; Frias et al., 2018, Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomized, placebo-controlled and active comparator-controlled phase 2 trial; HbA1c, hemoglobin A1c; NA, not available; SBP, systolic blood pressure; SUMMIT, Tirzepatide for heart failure with preserved ejection fraction and obesity; SURMOUNT-1, Association between weight reduction achieved with tirzepatide and quality of life in adults with obesity: results from the SURMOUNT-1 study; SURMOUNT-2, Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes: a double-blind, randomized, multicenter, placebo-controlled, phase 3 trial; SURMOUNT-CN, Tirzepatide for weight reduction in Chinese adults with obesity: the SURMOUNT-CN randomized clinical trial; SURMOUNT-J, Efficacy and safety of once-weekly tirzepatide in Japanese patients with obesity disease: a multicenter, randomized, double-blind, placebo-controlled phase 3 trial; SURMOUNT-OSA, 2024, Tirzepatide for the treatment of obstructive sleep apnea and obesity; SURPASS-1, Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes: a double-blind, randomized, phase 3 trial; SURPASS-5, Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial; and SYNERGY-NASH, Tirzepatide for metabolic dysfunction–associated steatohepatitis with liver fibrosis.

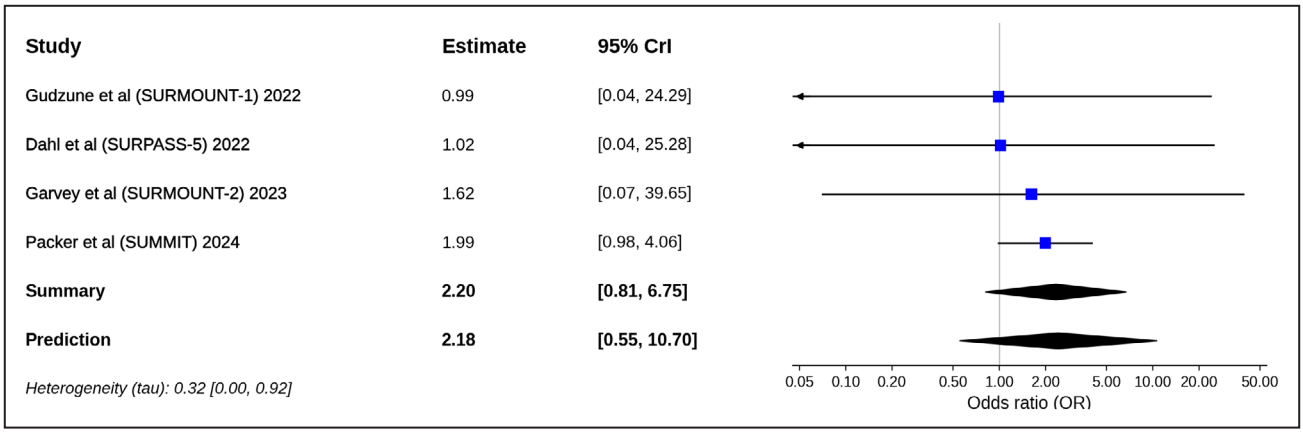

Figure 2. Bayesian meta-analysis of the effects of tirzepatide vs placebo on atrial fibrillation.
CrI indicates credible interval; OR, odds ratio; SUMMIT, Tirzepatide for heart failure with preserved ejection fraction and obesity; SURMOUNT-1, Association between weight reduction achieved with tirzepatide and quality of life in adults with obesity: results from the SURMOUNT-1 study; SURMOUNT-2, Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes: a double-blind, randomized, multicenter, placebo-controlled, phase 3 trial; and SURPASS-5, Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial.

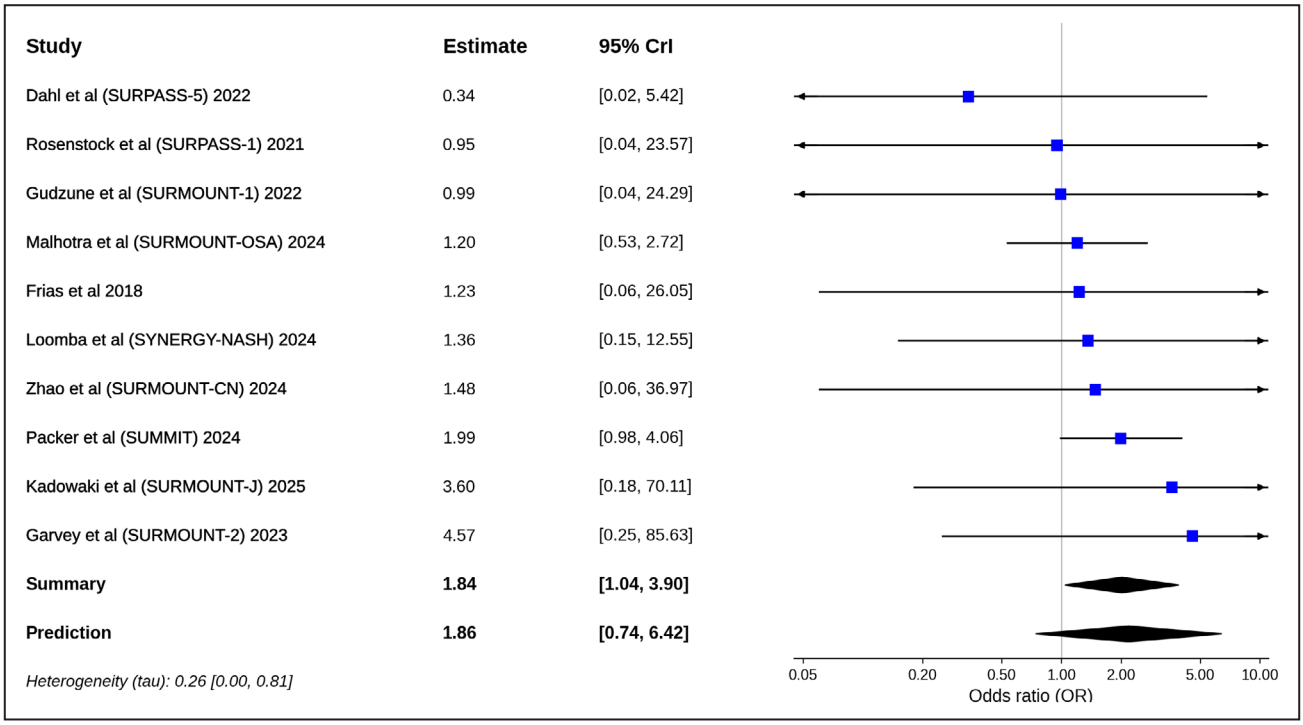

Figure 3. Bayesian meta-analysis of the effects of tirzepatide vs placebo on all arrhythmias.
CrI indicates credible interval; Frias et al., 2018, Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomized, placebo-controlled and active comparator-controlled phase 2 trial; OR indicates odds ratio; SUMMIT, Tirzepatide for heart failure with preserved ejection fraction and obesity; SURMOUNT-1, Association between weight reduction achieved with tirzepatide and quality of life in adults with obesity: results from the SURMOUNT-1 study; SURMOUNT-2, Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes: a double-blind, randomized, multicenter, placebo-controlled, phase 3 trial; SURMOUNT-CN, Tirzepatide for weight reduction in Chinese adults with obesity: the SURMOUNT-CN randomized clinical trial; SURMOUNT-J, Efficacy and safety of once-weekly tirzepatide in Japanese patients with obesity disease: a multicenter, randomized, double-blind, placebo-controlled phase 3 trial; SURMOUNT-OSA, 2024, Tirzepatide for the treatment of obstructive sleep apnea and obesity; SURPASS-1, Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes, a double-bind, randomized, phase 3 trial; SURPASS-5, Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial; and SYNERGY-NASH, Tirzepatide for metabolic dysfunction–associated steatohepatitis with liver fibrosis.

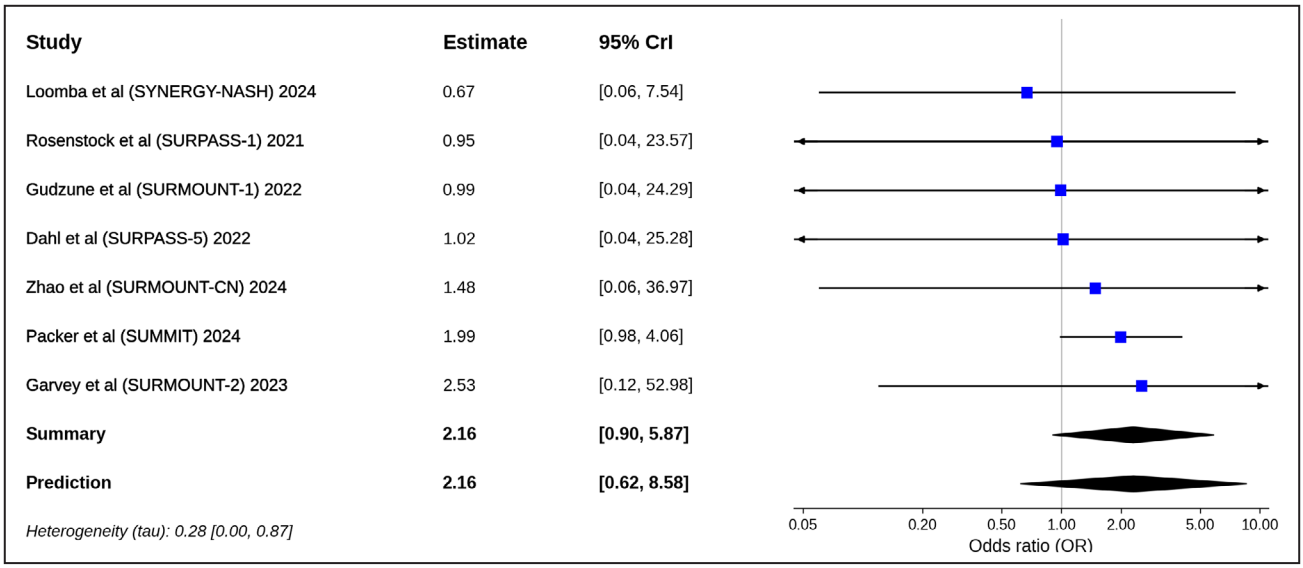

Figure 4. Bayesian meta-analysis of the effects of tirzepatide vs placebo on atrial arrhythmias.
CrI indicates credible interval; OR, odds ratio; SUMMIT, Tirzepatide for heart failure with preserved ejection fraction and obesity; SURMOUNT-1, Association between weight reduction achieved with tirzepatide and quality of life in adults with obesity: results from the SURMOUNT-1 study; SURMOUNT-2, Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes: a double-blind, randomized, multicenter, placebo-controlled, phase 3 trial; SURMOUNT-CN, Tirzepatide for weight reduction in Chinese adults with obesity: the SURMOUNT-CN randomized clinical trial; SURPASS-1, Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes; a double-blind, randomized, phase 3 trial; SURPASS-5, Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial; and SYNERGY-NASH, Tirzepatide for metabolic dysfunction–associated steatohepatitis with liver fibrosis.

have shown a potential reduction in atrial arrhythmias in patients with diabetes and myocardial infarction[33] and individuals with obesity.[34]

In contrast to the literature on selective GLP-1 RAs, our analysis did not demonstrate a clear association between tirzepatide and AF, although the point estimate was numerically higher than unity. This is an interesting finding because GLP-1 receptors are more present in the heart and are known to increase heart rate modestly. Nonetheless, prior meta-analyses have shown a reduction of AF, likely because of their beneficial effects on obesity-related risk factors.[33] Tirzepatide, however, acts as a dual agonist of GLP-1 and glucose-dependent insulinotropic polypeptide receptors. Glucose-dependent insulinotropic polypeptide receptors are less prevalent in cardiac tissue and do not appear to influence heart rate, yet emerging data suggest a potential antiarrhythmic role.[13]

Therefore, tirzepatide's neutral or potentially increasing effect on AF risk may reflect a complex interaction between its dual-receptor targets and the superiority of GLP-1 RAs' effect. Interestingly, dulaglutide, a selective GLP-1 RA, has been associated with a higher incidence of AF.[9,11] This raises the possibility of heterogeneity in arrhythmic risk even within the GLP-1 RA class.

Given tirzepatide's superior effects on weight loss and glycemic control compared with semaglutide and dulaglutide,[35] the lack of benefit in reducing AF risk is unexpected. One possible explanation is that arrhythmic outcomes are influenced not only by traditional risk factor modification but also by distinct pharmacodynamic effects related to receptor selectivity and neurohormonal modulation. These findings highlight the

Table 2. Event Counts and Pooled Bayesian Estimates for Arrhythmia Outcomes

Safety outcome	No. of studies	Tirzepatide events/ patients (%)	Placebo events/ patients (%)	Odds ratio (95% CrI)	Heterogeneity (τ)
Atrial fibrillation	4	26/3251 (0.8)	12/1452 (0.8)	2.20 (0.81–6.75)	0.32 (0–0.92)
All arrhythmias	10	53/4491 (1.2)	25/2024 (1.2)	1.84 (1.04–3.90)	0.26 (0–0.81)
Atrial arrhythmias	7	31/3897 (0.8)	13/1664 (0.8)	2.16 (0.90–5.87)	0.28 (0–0.87)

Odds ratios represent pooled estimates obtained from the Bayesian random-effects meta-analysis. Aggregated event counts are provided for descriptive purposes only and should not be used to calculate crude odds ratios. CrI indicates credible interval.

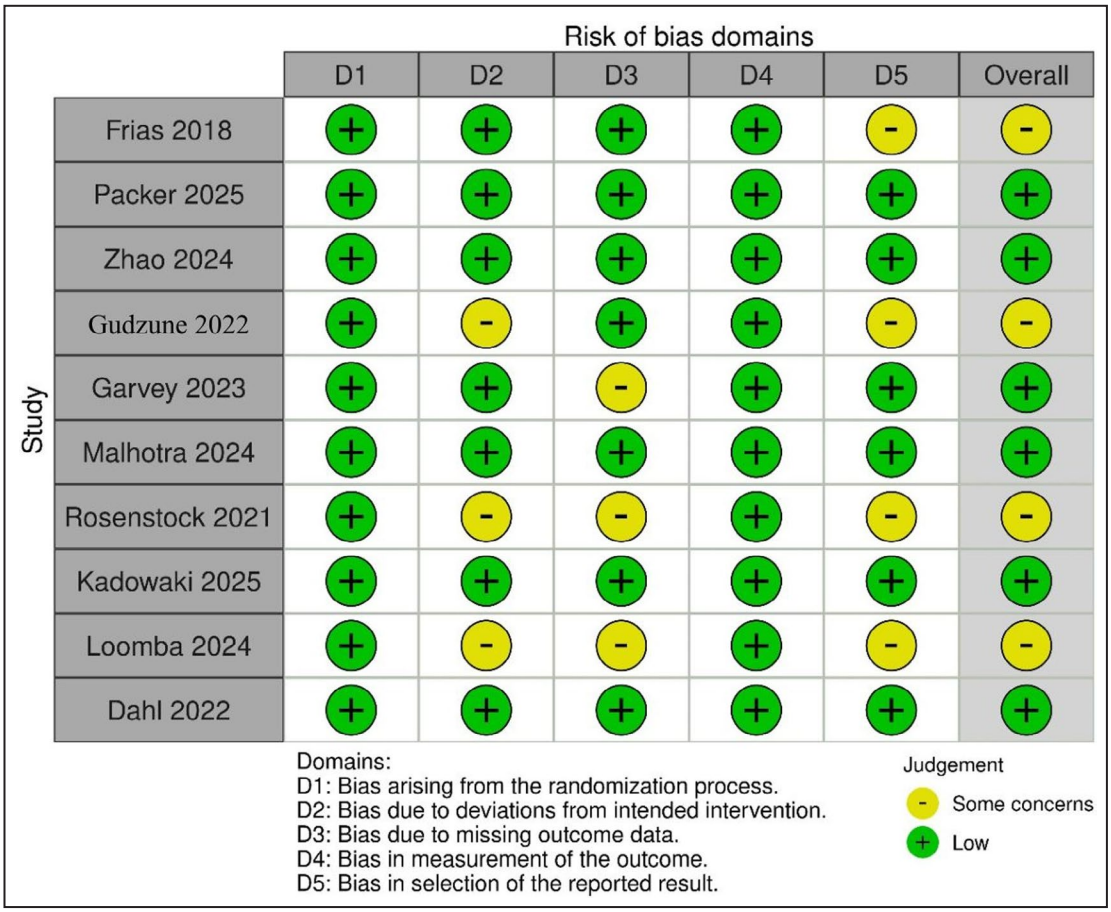

Figure 5. Risk-of-bias assessment of included randomized controlled trials.
Frias et al., 2018, Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomized, placebo-controlled and active comparator-controlled phase 2 trial; SUMMIT, Tirzepatide for heart failure with preserved ejection fraction and obesity; SURMOUNT-1, Association between weight reduction achieved with tirzepatide and quality of life in adults with obesity: results from the SURMOUNT-1 study; SURMOUNT-2, Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes: a double-blind, randomized, multicenter, placebo-controlled, phase 3 trial; SURMOUNT-CN, Tirzepatide for weight reduction in Chinese adults with obesity: the SURMOUNT-CN randomized clinical trial; SURMOUNT-J, Efficacy and safety of once-weekly tirzepatide in Japanese patients with obesity disease: a multicenter, randomized, double-blind, placebo-controlled phase 3 trial; SURMOUNT-OSA, 2024, Tirzepatide for the treatment of obstructive sleep apnea and obesity; SURPASS-1, Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes, a double-bind, randomized, phase 3 trial; SURPASS-5, Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial; and SYNERGY-NASH, Tirzepatide for metabolic dysfunction–associated steatohepatitis with liver fibrosis.

need for mechanistic studies and head-to-head comparisons of incretin-based therapies with arrhythmia-specific end points. Ongoing trials, such as SEMINAL-AF (Semaglutide for Metabolic Intervention and Adipose Loss to Treat Atrial Fibrillation; NCT06499857) and TIRO-AF (Tirzepatide for the Treatment of Obesity in Patients With Atrial Fibrillation; NCT06802081), are expected to clarify the role of tirzepatide in patients with AF.[36,37] Additionally, newer agents, such as the triple hormone receptor agonist retatrutide, may offer further insights into how broader hormonal modulation influences cardiac electrophysiology.[38]

Baseline characteristics varied considerably among trials and may have influenced our findings. Notably, among the limited number of trials reporting AF, event counts were largely derived from higher-risk populations, including the Packer et al. SUMMIT (Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity) trial, which enrolled older individuals with heart failure with preserved ejection fraction.[27] This population differs from the predominantly obesity-based cohorts in the remaining trials and may have contributed disproportionately to the observed estimates. In addition, differences in sex distribution across studies may

have influenced these findings, as trials with varying proportions of female participants or predominantly male cohorts showed heterogeneous point estimates.[26] These considerations further support that the observed pattern should be interpreted within the context of underlying population heterogeneity. Diabetes prevalence differed widely, and because diabetes increases AF risk while concomitant therapies, such as sodium–glucose cotransporter-2 inhibitors, may lower it, this heterogeneity is clinically relevant.[39,40] Other AF risk factors, such as age, sex, kidney dysfunction, obstructive sleep apnea, and differences in follow-up duration, were also unevenly distributed. Most events arose from higher-risk cohorts, whereas obesity-only trials with younger participants contributed few, likely diluting the pattern. Taken together, these patterns suggest that tirzepatide's arrhythmic effects may be context dependent rather than uniform across populations.[41]

Our meta-analysis focuses specifically on this gap by pooling placebo-controlled RCTs that reported arrhythmia outcomes. Compared with the limited AF data in previous studies, our meta-analysis provides an updated synthesis of available evidence with additional 6000 individuals.[15] Despite that, the overall incidence of AF across studies in our meta-analysis was <1%, suggesting that even pooled data may still be limited to detect modest differences in such outcomes.

Limitations

This study has several limitations. Arrhythmia events were typically reported as adverse events rather than prespecified end points and were not captured through systematic assessment. As a result, events were likely underascertained, particularly in asymptomatic individuals, resulting in a low observed event rate and potential misclassification bias. Definitions and detection methods for arrhythmias also varied across trials, and detailed stratifications of arrhythmia subtypes were not available, which limited our ability to assess tirzepatide's effects on specific arrhythmic phenotypes.

Although the estimated heterogeneity was small, the limited number of events indicates limited information to reliably estimate heterogeneity. Moreover, there was clinical variability in terms of population characteristics, follow-up duration, and baseline cardiovascular risk. Subgroup analyses by confounding factors, such as, age, sex, race or ethnicity, or study duration, were not performed because these data were unavailable. Although race or ethnicity and sex were reported in baseline characteristics, the lack of outcome data stratified by these variables limits evaluation of how social determinants of health may modify the association between tirzepatide and AF. Therefore, future studies evaluating tirzepatide should report outcomes stratified by these demographic groups. Additionally, shorter follow-up studies may have missed late-onset arrhythmic events, which may have contributed to detection bias.

Major predictors of AF, such as left ventricular ejection fraction, left atrial dimensions, or valvular disease, were not systematically reported. The absence of these parameters limits our ability to evaluate potential effect modification by cardiac structure or function and restricts the generalizability of our findings. Finally, the overall number of events was small, leading to wide CrIs and uncertainty in the effect estimates. As a result, the absence of a clear association should not be interpreted as definitive evidence of no effect, and a potential increase in arrhythmic events or an effect close to zero with tirzepatide cannot be excluded. Larger, dedicated trials with longer follow-up and prespecified arrhythmia end points are needed to clarify these findings.

CONCLUSIONS

In this meta-analysis of RCTs involving adults with overweight or obesity, tirzepatide was not associated with AF compared with placebo. Although higher odds of overall arrhythmias were observed, absolute event rates were low and the available evidence remains inconclusive.

ARTICLE INFORMATION

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Affiliations

Department of Internal Medicine, Ziaeian Hospital (E.S.M.), Department of Cardiology, Tehran University of Medical Sciences, Tehran, Iran (M.J.M.); Department of Medicine, Emory University, Atlanta, GA (F.Q.); Department of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil (L.M.B.); Department of Medicine, Estácio de Sá University, Juazeiro, Brazil (A.K.A.); Department of Medicine, New York City Health and Hospitals/Harlem, New York, NY (W.D.) Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (C.V.B.); Department of Medicine, Nove de Julho University, São Bernardo do Campo, Brazil (A.R.); Department of Medicine, Mayo Clinic, Rochester, MN (I.F.F.); Division of Endocrinology and Metabolism, University of Texas Southwestern Medical Center, Dallas, TX (M.A.); and Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN (A.J.D., C.V.D.).

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Supplemental Material

Supplemental Methods
Tables S1–S3
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