Reviews in Cardiovascular Medicine

*Rev. Cardiovasc. Med.* **2026**; 27(11): 54203
https://doi.org/10.31083/RCM54203

*Systematic Review*

# Atrial Fibrillation in Patients Treated With Semaglutide: A Systematic Review and Meta-Analysis

Gaetano Marino[1,*], Elvira Graziano[2], Stefania Angela Di Fusco[1], Stefano Aquilani[1], Silvio Fedele[3], Federico Nardi[4], Fabrizio Oliva[5], Domenico Gabrielli[6], Furio Colivicchi[1]

[1]Clinical and Rehabilitation Cardiology Unit, San Filippo Neri Hospital, 00135 Rome, Italy
[2]Department of Medicine and Surgery, University of Siena, 53100 Siena, Italy
[3]Cardiology Unit, Sandro Pertini Hospital, 00157 Rome, Italy
[4]Division of Cardiology, Santo Spirito Hospital, 15033 Casale Monferrato, Italy
[5]De Gasperis Cardiovascular Department, Division of Cardiology, ASST Grande Ospedale Metropolitano Niguarda, 20162 Milan, Italy
[6]Department of Cardio-Thoracic and Vascular Medicine and Surgery, Division of Cardiology, S. Camillo-Forlanini Hospital, 00152 Rome, Italy
*Correspondence: gaetano.marino@aslroma1.it (Gaetano Marino)
Academic Editors: Tong Liu and Chengming Fan
Submitted: 25 May 2026 Revised: 24 July 2026 Accepted: 28 July 2026 Published: 6 November 2026

**Abstract**

**Background:** Obesity and type 2 diabetes mellitus (T2DM) are independent drivers of atrial remodeling and arrhythmogenesis. Semaglutide improves metabolic and inflammatory pathways, potentially mitigating the risk of atrial fibrillation (AF). This meta-analysis aims to evaluate the incidence of AF in patients treated with semaglutide compared with placebo. **Methods:** We systematically pooled data from 15 randomized controlled trials (RCTs) evaluating once-weekly subcutaneous or daily oral semaglutide at various doses versus placebo. The study population consisted of patients with T2DM or overweight/obesity, and in specific trials, these cohorts were further associated with comorbidities such as heart failure with preserved ejection fraction (HFpEF) or chronic kidney disease (CKD). The primary outcome was the incidence of AF. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a random-effects model with inverse-variance weighting. **Results:** A pooled cohort of 34,822 patients with 506 new-onset AF cases was analyzed. Overall, semaglutide did not statistically significantly reduce the risk of new-onset AF compared with placebo (OR 0.86; 95% CI: 0.72–1.03; $p = 0.10$), with no heterogeneity ($I^2 = 0\%$). Subgroup analyses revealed no significant differences in AF risk based on administration route. Similarly, no significant interaction was observed when stratifying by patient population, with a neutral effect in T2DM patients and a non-significant protective trend in overweight or obesity cohorts (OR 0.80; 95% CI: 0.63–1.01; $p = 0.06$). Concomitant sodium-glucose cotransporter 2 inhibitor (SGLT2i) therapy did not modify the treatment effect. Meta-regression revealed no influence of baseline covariates, including treatment duration, publication year, mean participant age, body mass index (BMI), and glycated hemoglobin (HbA1c) levels. Sensitivity analysis showed that the overall effect size was driven by the FLOW trial. When the FLOW trial was omitted from the meta-analysis, the resulting pooled analysis revealed a significant reduction in AF incidence with semaglutide therapy compared to placebo (OR 0.81; 95% CI: 0.67–0.98; $p = 0.03$). **Conclusions:** Semaglutide exhibits a robust cardiovascular safety profile, with no significant increase or decrease in the incidence of AF compared to placebo. An exploratory sensitivity analysis excluding populations with advanced chronic kidney disease suggested a potential protective effect. Given its hypothesis-generating nature, this finding requires cautious interpretation and further confirmation. **The PROSPERO Registration:** CRD420261393817 (https://www.crd.york.ac.uk/PROSPERO/view/CRD420261393817).

**Keywords:** semaglutide; atrial fibrillation; diabetes; obesity; heart failure

## 1. Introduction

Atrial fibrillation (AF) represents the most prevalent cardiac arrhythmia worldwide [1]. Both obesity and type 2 diabetes mellitus (T2DM) are now recognized as independent, potent drivers of atrial remodeling and arrhythmogenesis. From a pathophysiological standpoint, the link among obesity, T2DM, and AF is synergistic. Obesity promotes AF through chronic hemodynamic alterations, including increased total blood volume and cardiac output, which lead to left atrial stretch, enlargement, and subsequent electrical instability. Concurrently, expansion and dysfunction of epicardial adipose tissue (EAT) play a critical paracrine role. Malfunctioning EAT infiltrates the underlying myocardium and secretes proinflammatory cytokines, fostering localized oxidative stress, localized inflammation, and fibro-fatty infiltration of the atrial wall [2,3]. In patients with T2DM, this substrate is further exacerbated by chronic hyperglycemia and insulin resistance. Advanced glycation end-products (AGEs) accumulate within the myocardial matrix, promoting profound structural remodeling via interstitial fibrosis.

Furthermore, diabetes induces electrical remodeling by altering intracellular calcium handling and downregulating connexin proteins, impairing gap junction conduction and creating a highly susceptible substrate for AF [4,5]. Semaglutide, a glucagon-like peptide-1 receptor agonist

**Copyright**: © 2026 The Author(s). Published by IMR Press.
This is an open access article under the CC BY 4.0 license.

**Publisher's Note**: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

(GLP-1RA), represents a cornerstone therapy for T2DM and obesity, improving glycemic control and promoting weight loss. In addition to its primary metabolic actions, semaglutide has demonstrated a spectrum of favorable cardiovascular effects, including antiarrhythmic effects. First, by inducing weight loss and improving glycemic control, semaglutide exerts anti-inflammatory and antioxidant effects, reducing mechanical and metabolic stressors acting on the atria and limiting local fibrosis. Additionally, by improving endothelial function and reducing myocardial stiffness, semaglutide helps stabilize the atrial substrate, potentially halting or reversing structural and electrical remodeling [6]. Therefore, this meta-analysis aims to systematically evaluate the incidence of AF in patients treated with semaglutide compared with placebo, providing a comprehensive assessment of its net arrhythmic safety and potential protective efficacy.

## 2. Methods

### *2.1 Data Source and Search Strategy*

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. The meta-analysis was registered on the International Prospective Register of Systematic Reviews (PROSPERO; registration No. CRD420261393817). A systematic search was conducted across PubMed, Web of Science, Embase, and ClinicalTrials.gov from inception to April 2026. The following search terms were used: "atrial fibrillation", "diabetes", "obesity", "heart failure", and "semaglutide". Boolean operators "AND" and "OR" were used to broaden the search criteria. The search strategy and PRISMA checklist are available in the **Supplementary Material**.

### *2.2 Trial Selection and Eligibility Criteria*

The Population, Intervention, Comparison, Outcomes, Study (PICOS) methodology was used for trial selection [8]. We included only randomized controlled trials (RCTs) that met the following criteria:

a. The study population comprised adults aged ≥18 years with T2DM, overweight or obesity, heart failure with preserved ejection fraction, or chronic kidney disease presenting either as isolated conditions or in various combinations of comorbidities. Eligible studies were included irrespective of the cardiovascular health status of the participant at baseline.

b. RCTs comparing semaglutide versus placebo.

c. Pre-specified and eligible post hoc analyses were included.

d. Trials reporting the following outcome: new-onset AF events.

The exclusion criteria were as follows:

a. Patients with type 1 diabetes.

b. Studies including interventions other than semaglutide.

c. Observational studies, case reports, reviews, non-randomized studies, studies with insufficient data for analysis, and non-human clinical trials.

d. There were no language restrictions, and trials of any sample size, any follow-up duration, and from any country were included.

Two independent reviewers (GM and EG) screened and selected eligible studies. This process involved two phases: in the first phase, search results were screened based on the title and abstract; in the second phase, studies were evaluated by examining the full text and excluding those with insufficient data or unavailable full text. Disagreements were resolved through discussion and consensus. Using an Excel spreadsheet, the following study characteristics were extracted: first author, year of publication, trial name, study design, study duration, number of patients, type of intervention, drug dosage and route of administration, age, percentage of male patients, body mass index (BMI), glycated hemoglobin (HbA1c), and background therapy with sodium–glucose cotransporter 2 inhibitors (SGLT2i).

For the specified outcome, AF incidence was defined as the number of patients who developed AF rather than the total number of events to prevent data skewing by recurrent episodes. Across all included trials, new-onset AF events were identified through adverse event reporting and routinely confirmed by electrocardiogram.

### *2.3 Statistical Analysis*

For each study included in the meta-analysis, effect measures and 95% confidence intervals (CIs) were calculated using the inverse-variance-weighted method. For the dichotomous outcome, the odds ratio (OR) with 95% CI was calculated. The findings were used to generate forest plots. The presence of publication bias was investigated using funnel plots and Egger's linear regression test. Heterogeneity across studies was assessed using "$Tau^2$", "$Chi^2$", and "Higgins and Thompson's $I^2$". Heterogeneity was considered low, moderate, or high if $I^2$ was 25%, 50%, or 75%, respectively [9,10]. Sensitivity analysis using the leave-one-out method was performed to identify any outliers. A random-effects model was applied using the DerSimonian–Laird estimator to synthesize the effect sizes of the studies, assuming inter-study heterogeneity. Subgroup analysis of the main outcome was performed to compare semaglutide versus placebo across specific patient categories, accounting for different routes of administration and concomitant medications. Studies with a single-arm zero event were managed by applying a standard continuity correction of 0.5 added to all cells. To evaluate the robustness of our primary findings and minimize methodological bias related to rare event analysis, we conducted a comprehensive sensitivity analysis using a fixed-effects model. A random-effects meta-regression model was used to explore potential sources of heterogeneity for the primary outcome, consider-

**Table 1. Characteristics of the included trials and the recruited patients.**

| Trials | Population | Total patients (n) | Semaglutide arm | Placebo arm | Age (years, mean) | BMI ($kg/m^2$) | HbA1c (%) | Follow-up (months) | Administration route and dosage | SGLT2i (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| SUSTAIN 6 2016 [12] | T2DM | 3297 | 1648 | 1649 | 64.6 | 32.8 | 8.7 | 27.2 | Subcutaneous injection (0.5 and 1.0 mg) OW | 4.6 |
| PIONEER 6 2019 [13] | T2DM | 3183 | 1591 | 1592 | 66.0 | 32.3 | 8.2 | 16 | Oral 14 mg OD | 9.6 |
| PIONEER 5 2019 [14] | CKD (moderate renal impairment) | 324 | 163 | 161 | 70.0 | 32.4 | 8.0 | 6 | Oral 14 mg OD | N/A |
| STEP 1 2021 [15] | Obesity | 1961 | 1306 | 655 | 46.0 | 37.9 | 5.7 | 17 | Subcutaneous injection (2.4 mg) OW | N/A |
| STEP 2 2021 [16] | Overweight/obesity and T2DM | 1210 | 807 | 403 | 55.0 | 35.7 | 8.1 | 17.2 | Subcutaneous injection (1.0 mg or 2.4 mg) OW | 24.8 |
| STEP 4 2021 [17] | Overweight/obesity | 803 | 535 | 268 | 46.0 | 38.4 | 5.7 | 17 | Subcutaneous injection (2.4 mg) OW | N/A |
| STEP 8 2022 [18]* | Overweight/obesity | 211 | 126 | 85 | 49.0 | 37.5 | 5.5 | 17.2 | Subcutaneous injection (2.4 mg) OW | N/A |
| STEP 6 2022 [19] | Overweight/obesity with or without T2DM | 401 | 300 | 101 | 51 | 31.9 | 6.4 | 17 | Subcutaneous injection (1.7 mg and 2.4 mg) OW | 44.4 |
| SELECT 2023 [20] | Obesity | 17,604 | 8803 | 8801 | 61.6 | 33.35 | 5.78 | 39.8 | Subcutaneous injection (2.4 mg) OW | N/A |
| STEP HFpEF 2023 [21] | HFpEF | 529 | 263 | 266 | 66.6 | 37.0 | N/A | 13.2 | Subcutaneous injection (2.4 mg) OW | 3.6 |
| FLOW 2024 [22] | T2DM/CKD | 3533 | 1767 | 1766 | 66.6 | 32.0 | 7.8 | 40.8 | Subcutaneous injection (1.0 mg) OW | 15.6 |
| PIONEER 4 2019 [23]* | T2DM | 427 | 285 | 142 | 56.0 | 33.0 | 8.0 | 12 | Oral 14 mg OD | 26 |
| STEP 10 2024 [24] | Obesity and prediabetes | 202 | 138 | 64 | 53.0 | 40.1 | 5.9 | 12 | Subcutaneous injection (2.4 mg) OW | N/A |
| STEP HFpEF DM 2024 [25] | Obesity, HFpEF, and T2DM | 616 | 310 | 306 | 69 | 36.9 | 6.9 | 12 | Subcutaneous injection (2.4 mg) OW | 32.8 |
| PIONEER 11 2024 [26] | T2DM | 521 | 390 | 131 | 55.0 | 28.2 | 8.0 | 6.5 | Oral 3 mg, 7 mg and 14 mg OD | 0.03 |

BMI, body mass index; HbA1c, glycated hemoglobin; SGLT2i, sodium–glucose cotransporter 2 inhibitors; T2DM, type 2 diabetes mellitus; CKD, chronic kidney disease; OW, once weekly; OD, once daily; N/A, not available; HFpEF, heart failure with preserved ejection fraction.

*The total sample sizes listed for PIONEER 4 and STEP 8 reflect only the semaglutide and placebo cohorts included in this study; active comparator arms (liraglutide) were excluded in accordance with the study protocol.

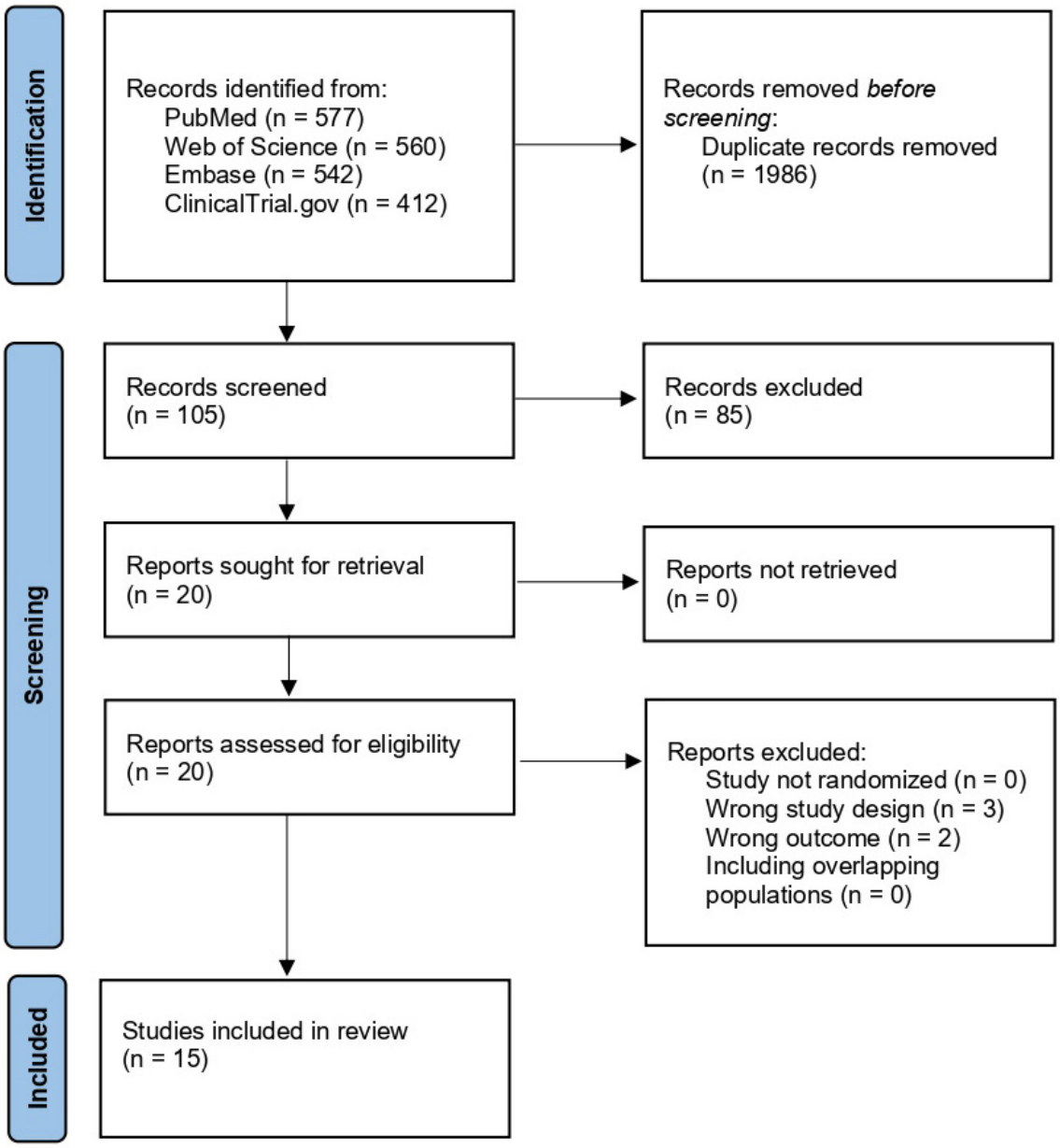



**Fig. 1. Study selection flow diagram**.

ing covariates such as year of publication of the trial, study duration, BMI, age, and HbA1c levels. The regression coefficients and 95% CI were calculated for each covariate; bubble plots were generated to visualize the relationship between the analyzed covariates and the treatment effect size on AF incidence. Statistical significance was set at $p < 0.05$ (two-tailed). Statistical analysis was performed using Review Manager 5.4 software (Cochrane Collaboration, London, UK) and StataSE version 19 (StataCorp LLC, College Station, TX, USA).

### *2.4 Certainty of Evidence*

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was used to assess the quality and strength of the evidence [11]. GRADE uses a structured approach to rate the certainty of the evidence as high, moderate, low, or very low. According to the GRADE method, the quality of evidence is assessed based on several factors, including study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. Two reviewers independently rated the quality of the evidence for each outcome. The GRADEpro Guideline Development Tool (GDT) software version 3.6 (Evidence Prime Inc., Hamilton, ON, Canada) was used to generate an evidence profile table (**Supplementary Material**).

## 3. Results

We identified 2091 articles, of which 1986 were removed as duplicates. In the first screening phase, 105 papers were examined based on the title and abstract. Of

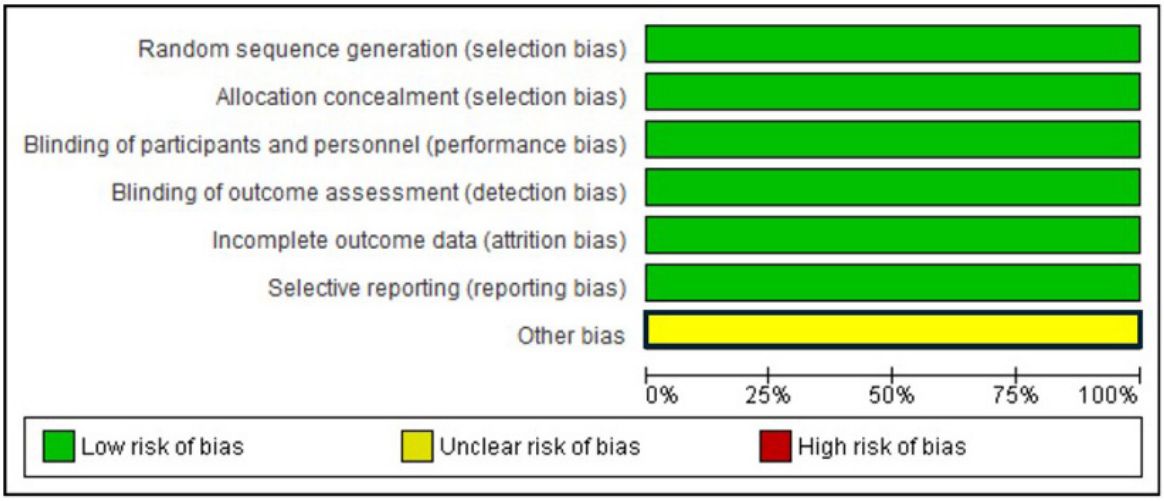



**Fig. 2. Risk of bias assessment of randomized controlled trials (summary plot)**.

these, 85 articles were excluded because they did not meet the inclusion criteria. In the second phase, after full-text evaluation of the 20 articles eligible for inclusion, three were excluded for incorrect study design and two for incorrect outcomes. At the end of this process, 15 clinical trials were included in this systematic review and meta-analysis [12,13,14,15,16,17,18,19,20,21,22,23,24,25,26]. A search flow diagram illustrating the study selection process is shown in Fig. 1. Some included studies are post hoc analyses. The total population recruited consisted of 34,822 patients (18,429 in the drug-treated group and 16,393 in the placebo-treated group). The follow-up duration ranged from 6 to 40.8 months. The characteristics of the included trials and the patient populations are presented in Table 1 (Ref. [12,13,14,15,16,17,18,19,20,21,22,23,24,25,26]).

### *3.1 Risk of Bias and Quality Assessment*

The quality of the included studies was assessed using the Cochrane Risk of Bias tool for randomized controlled trials [27]. The Cochrane Risk of Bias tool is structured into seven domains, potential sources of bias, which were examined by a pair of independent reviewers. The domains identified and evaluated are listed below and illustrated in Table 2 (Ref. [12,13,14,15,16,17,18,19,20,21,22,23,24,25,26]) and Fig. 2:

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other bias.

To mitigate the risk of reporting bias and ensure methodological transparency, the review was conducted in strict adherence to the PRISMA 2020 guidelines. To minimize subjectivity, each stage of data selection and extraction was performed in a double-anonymized manner by two independent reviewers. Both reviewers evaluated the risk of bias, lack of reproducibility of results, lack of generalizability, and degree of imprecision as non-significant and not important. Sensitivity analyses were performed to assess the robustness of the results (leave-one-out). Statistical tests for publication bias (Egger's test) and funnel plots assessing potential publication bias revealed no significant asymmetries (Fig. 3). Specifically, the Egger's test provided no evidence of publication bias for our outcome ($p$ = 0.24). Furthermore, although the funnel plot and Egger's test showed no significant asymmetry, the interpretation of these analyses warrants caution. Testing for publication bias has limited statistical power when fewer than 20 studies are pooled and when evaluating rare event outcomes, making visual and statistical evaluations less reliable in this specific clinical setting.

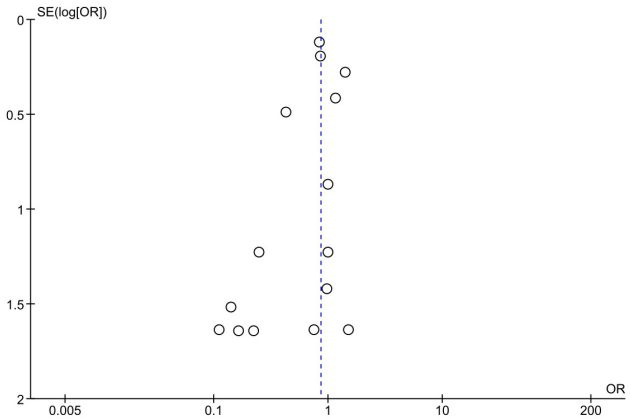



**Fig. 3. Funnel plots assessing publication bias**. y-axis represents study precision (standard error), while the x-axis shows the odds ratio.

**Table 2. Risk of bias assessment of randomized controlled trials (traffic light plot).**

| | D1 | D2 | D3 | D4 | D5 | D6 | Other bias |
|---|---|---|---|---|---|---|---|
| SUSTAIN 6 2016 [12] | + | + | + | + | + | + | + |
| PIONEER 6 2019 [13] | + | + | + | + | + | + | + |
| PIONEER 5 2019 [14] | + | + | + | + | + | + | + |
| STEP 1 2021 [15] | + | + | + | + | + | + | + |
| STEP 2 2021 [16] | + | + | + | + | + | + | + |
| STEP 4 2021 [17] | + | + | + | + | + | + | + |
| STEP 6 2022 [19] | + | + | + | + | + | + | + |
| STEP 8 2022 [18] | + | + | + | + | + | + | + |
| SELECT 2023 [20] | + | + | + | + | + | + | + |
| STEP HFpEF 2023 [21] | + | + | + | + | + | + | + |
| FLOW 2024 [22] | + | + | + | + | + | + | + |
| PIONEER 4 2019 [23] | + | + | + | + | + | + | + |
| STEP 10 2024 [24] | + | + | + | + | + | + | + |
| STEP HFpEF DM 2024 [25] | + | + | + | + | + | + | + |
| PIONEER 11 2024 [26] | + | + | + | + | + | + | + |

D1: random sequence generation (selection bias).
D2: allocation concealment (selection bias).
D3: blinding of participants and personnel (performance bias).
D4: blinding of outcome assessment (detection bias).
D5: incomplete outcome data (attrition bias).
D6: selective reporting (reporting bias).
Other bias.

All included trials were found to have a low risk of bias, and the selected evidence was of moderate quality.

### *3.2 Primary Outcome*

AF Incidence

A total of 237 events were reported in the semaglutide treatment arm and 269 in the placebo arm. The overall pooled analysis demonstrated that semaglutide did not significantly reduce the risk of new-onset AF compared with placebo (OR 0.86; 95% CI: 0.72–1.03; $p$ = 0.10). There was no evidence of statistical heterogeneity among the included studies ($I^2$ = 0%; Fig. 4). Subgroup analysis stratified by administration frequency and route revealed no statistically significant differences in the risk of new-onset AF between semaglutide and placebo. For oral once-daily administration, the pooled OR was 0.53 (95% CI: 0.23–1.24; $p$ = 0.14), encompassing nine events across 2429 patients in the semaglutide arm and 15 events across 2025 patients in the placebo arm. Similarly, for subcutaneous once-weekly administration, semaglutide did not significantly reduce the odds of the outcome compared with placebo (OR 0.88; 95% CI: 0.73–1.06; $p$ = 0.17). Crucially, the test for subgroup differences demonstrated no statistically significant interaction effect between the two administration regimens ($p$ = 0.25; $I^2$ = 23.2%), indicating that the clinical impact of semaglutide on AF incidence did not vary by route of administration. Overall heterogeneity was negligible, with $I^2$ = 0% for both cohorts (Fig. 5a). When stratifying the included trials by patient population, studies focusing on T2DM showed an OR of 0.96 (95% CI: 0.73–1.27; $p$ = 0.77), suggesting a non-significant reduction in AF incidence with semaglutide. Similarly, trials investigating patients with overweight or obesity reported a non-significant trend toward a lower incidence of AF, with an OR of 0.80 (95% CI: 0.63–1.01; $p$ = 0.06). Overall, no significant difference was observed across the entire pooled population (OR 0.86; 95% CI: 0.72–1.03; $p$ = 0.10). The test for subgroup differences confirmed no significant interaction between the two cohorts ($p$ = 0.32), and heterogeneity was $I^2$ = 0% (Fig. 5b). To evaluate whether the effect of semaglutide on AF incidence varied based on background SGLT2i therapy, a further subgroup analysis was performed. The

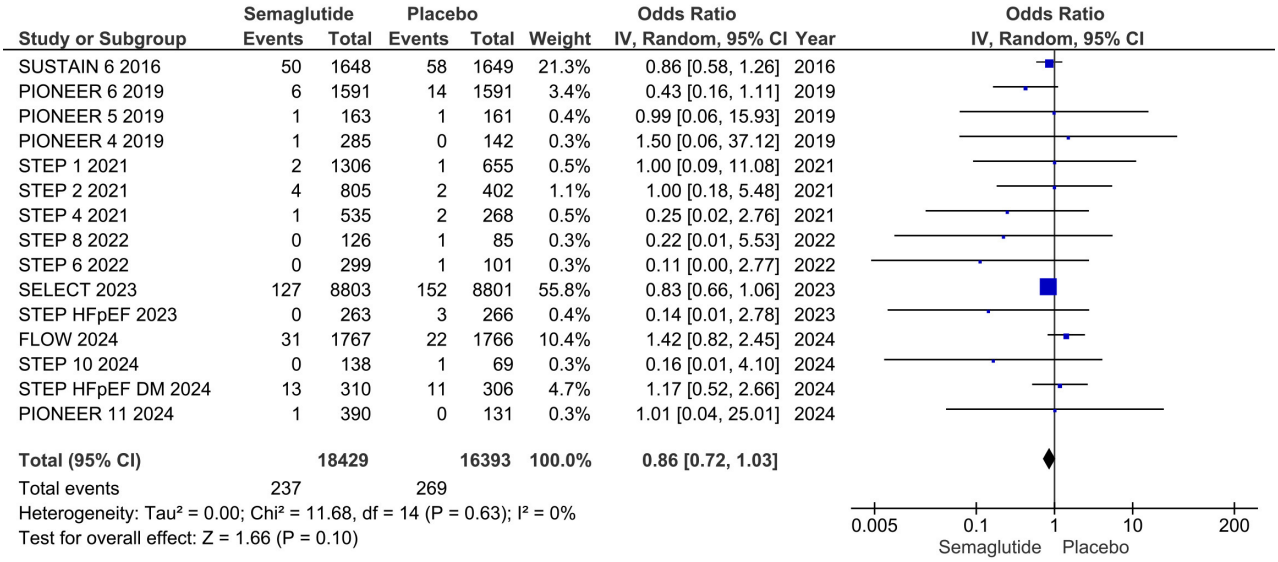



**Fig. 4. Forest plot showing the pooled effect of semaglutide vs. placebo on atrial fibrillation risk**.

analysis demonstrated no significant difference in the incidence of AF between patients receiving semaglutide and those receiving placebo, regardless of SGLT2i treatment. Among patients treated with SGLT2i, semaglutide did not significantly reduce the risk of AF compared with placebo (OR 0.93; 95% CI: 0.68–1.26; $p = 0.62$). Consistently, in the subgroup of patients not receiving an SGLT2i, the risk remained comparable between the two arms (OR 0.81; 95% CI: 0.64–1.03; $p = 0.08$). Importantly, the test for subgroup differences confirmed that the treatment effect was consistent across both groups, showing no significant interaction between semaglutide and SGLT2i therapy ($p = 0.51$). Overall heterogeneity was $I^2 = 0\%$, indicating low heterogeneity (Fig. 5c). Furthermore, to evaluate the robustness of our primary findings under different statistical assumptions and metrics, we performed an additional sensitivity analysis using a fixed-effect model. This supplementary analysis yielded results highly consistent with our primary random-effects OR model, confirming that the choice of effect measure or model selection did not alter the statistical significance or the overall clinical conclusions of our study.

### *3.3 Meta Regression*

To investigate potential sources of heterogeneity and evaluate the impact of moderators on the incidence of AF, random-effects meta-regression analyses were conducted with treatment duration (months), publication year, mean participant age, BMI, and HbA1c levels as covariates. The treatment effect was not significantly moderated by baseline clinical characteristics, including patient age (coefficient: 0.039; 95% CI: –0.016 to 0.089; $p = 0.164$), BMI (coefficient: –0.067; 95% CI: –0.209 to 0.076; $p = 0.361$), or HbA1c levels (coefficient: 0.047; 95% CI: –0.17 to 0.265; $p = 0.670$). Similarly, no significant associations were observed with trial-specific factors, including publication year (coefficient: 0.031; 95% CI: –0.047 to 0.109; $p = 0.438$) and follow-up duration in months (coefficient: 0.012; 95% CI: –0.011 to 0.036; $p = 0.304$). Residual heterogeneity remained very low across all models ($I^2 = 0\%$ for publication year and BMI; $I^2 = 10.42\%$ for age; $I^2 = 11.24\%$ for HbA1c; $I^2 = 11.77\%$ for follow-up duration). This lack of significant residual variance was further confirmed by the test for residual homogeneity, which was consistently non-significant across all evaluated covariates, indicating that no unexplained heterogeneity remained. The high $R^2$ values for age (99.45%) and BMI (99.12%) represent statistical artifacts due to the negligible baseline heterogeneity to be explained rather than a true moderating effect, consistent with the non-significant interaction $p$-value (Fig. 6). Meta-regression analysis was pre-specified to explore the potential impact of relevant clinical covariates on the primary outcome but was performed in the setting of zero statistical heterogeneity. Consequently, these findings are significantly underpowered, strictly exploratory, and should not be used to draw definitive conclusions regarding the effect of covariates.

### *3.4 Sensitivity Analysis*

A leave-one-out sensitivity analysis was conducted to identify outliers. The analysis showed that the overall effect size was driven by the FLOW trial [22]. Notably, when the FLOW trial was omitted from the meta-analysis, the pooled treatment effect of semaglutide on the incidence of AF shifted from non-significant to statistically significant. The resulting pooled analysis revealed a significant reduction in AF incidence with semaglutide therapy compared with placebo (OR 0.81; CI: 0.67–0.98; $p = 0.03$). The remaining trials exhibited complete homogeneity ($I^2 = 0\%$; Fig. 7).

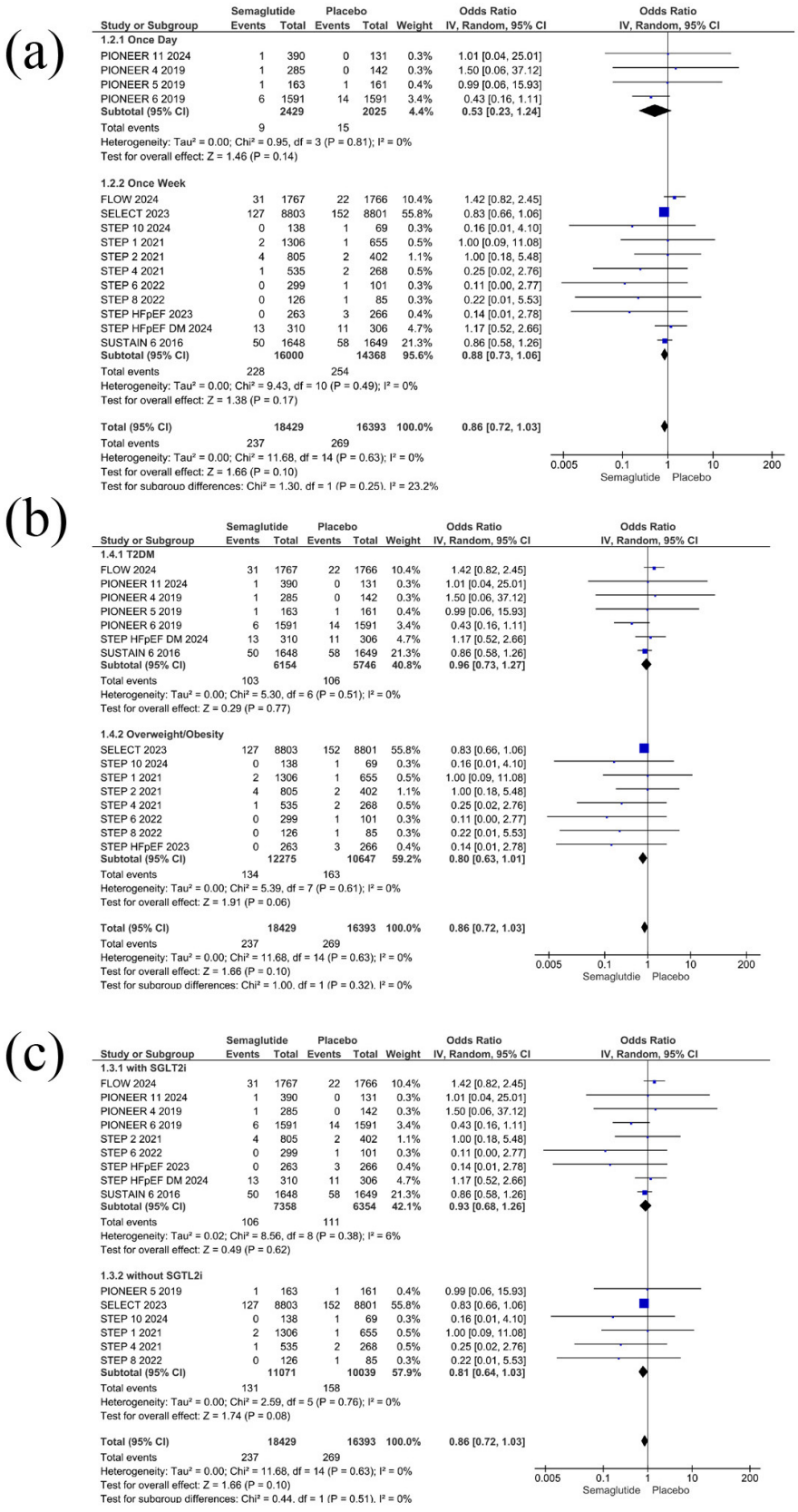



**Fig. 5. Subgroup analysis**. (a) Forest plot of a subgroup analysis comparing different semaglutide administration regimens vs. placebo and the risk of atrial fibrillation. (b) Forest plot of a subgroup analysis assessing the risk of atrial fibrillation with semaglutide vs. placebo based on patient baseline clinical status. (c) Forest plot of subgroup analysis evaluating the risk of atrial fibrillation with semaglutide vs. placebo according to concomitant SGLT2i use.

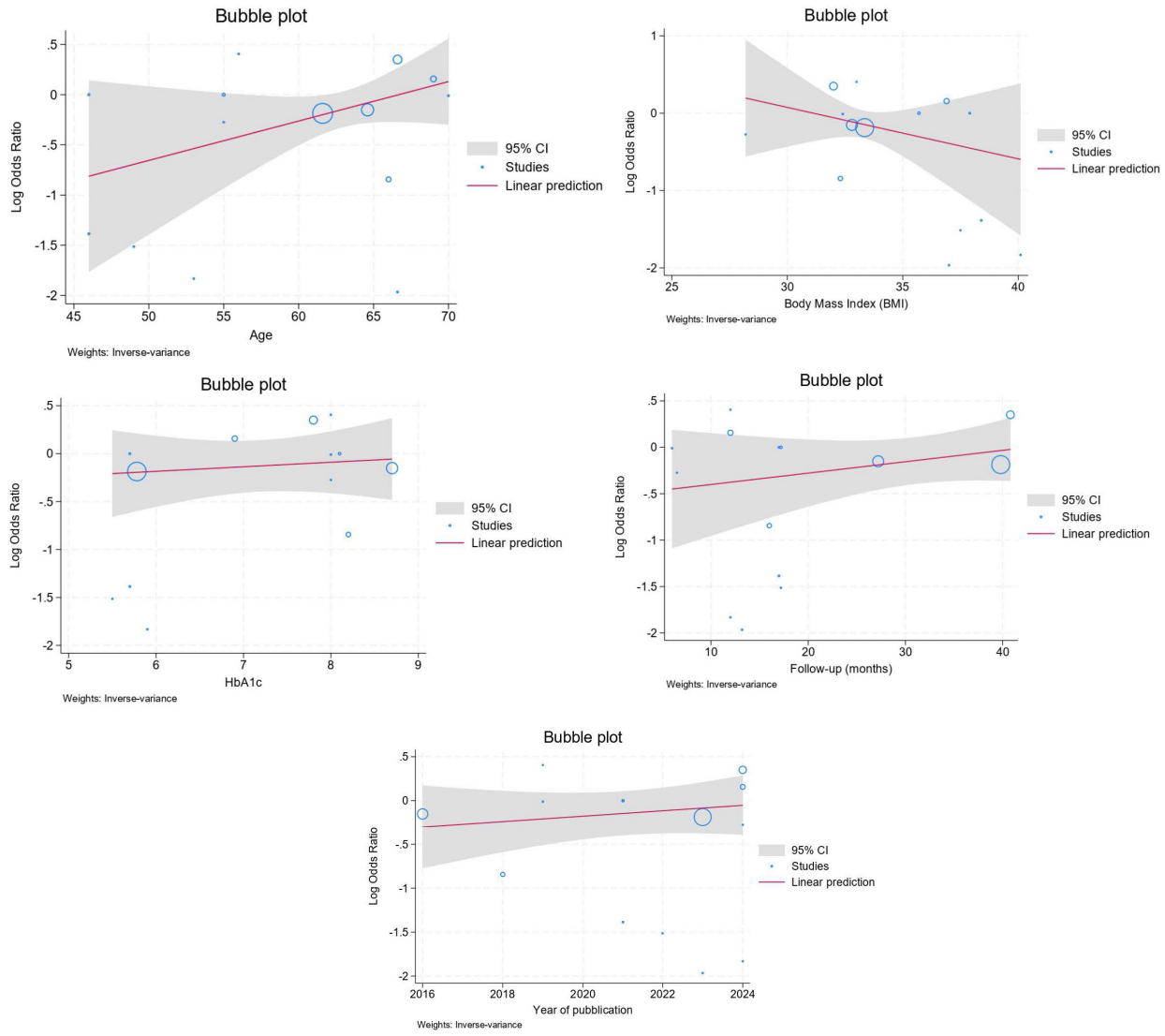



**Fig. 6. Meta-regression bubble plots evaluating the impact of different covariates (age, body mass index, HbA1c, follow up time, year of publication).**

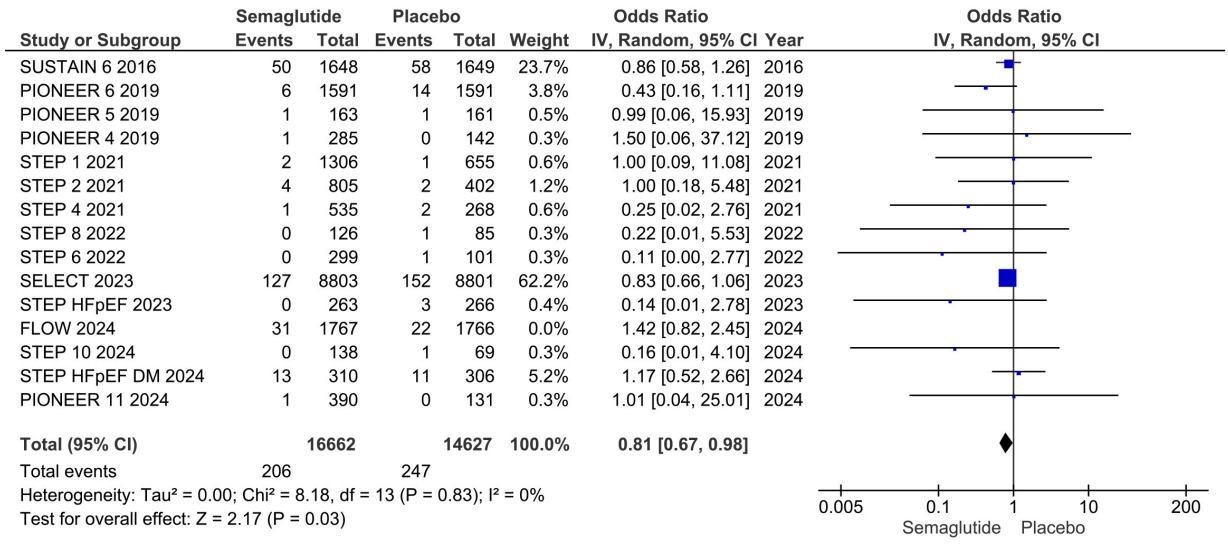



**Fig. 7. Sensitivity analysis forest plot excluding the FLOW trial from the meta-analysis.**

## 4. Discussion

The findings of this comprehensive meta-analysis indicate that the use of semaglutide is not associated with a significant reduction in the incidence of AF compared with placebo. Our overall analysis demonstrated a neutral effect on arrhythmic risk. Notably, statistical heterogeneity across the included trials was negligible ($I^2 = 0\%$), underscoring the remarkable consistency and robustness of these results across the evaluated clinical trials. Interestingly, our primary neutral findings contrast with some recent meta-analyses that reported a statistically significant reduction in incident AF in cohorts treated with semaglutide [28,29]. This apparent discrepancy is influenced by the inclusion of newly published data in our model and by a critical methodological divergence. Specifically, our model restricts its scope to placebo-controlled trials to isolate the absolute electrophysiological effects of semaglutide, thereby excluding other active comparators. When examining the architecture of our meta-analysis, the statistical power and overall pooled estimate are driven by two landmark trials: the SELECT trial [20] and the SUSTAIN 6 trial [12]. Together, these two studies contribute to more than three-quarters of the total analytical weight (77.1%).

To further assess variation in AF incidence, we performed several key subgroup analyses. First, stratifying the data by the frequency and modality of drug administration revealed no significant differences. Second, we evaluated the baseline metabolic phenotype of the target populations, separating patients with T2DM from those who were overweight or obese. In the T2DM subgroup, the drug exhibited a neutral effect; interestingly, in overweight or obese patients, a distinct trend toward a lower incidence of AF was observed, approaching statistical significance. Obesity is a well-known independent driver of atrial remodeling through mechanical, inflammatory, and neurohormonal pathways. Excess adiposity promotes the expansion of EAT, which locally secretes proinflammatory adipokines that promote focal atrial fibrosis, electrical heterogeneity, and structural alterations. Furthermore, obesity leads to diastolic dysfunction, increased left atrial pressure, and atrial stretch [2,3,4,5]. The protective trend observed with semaglutide in this group may be explained by its direct and indirect anti-arrhythmogenic mechanisms [6]. Semaglutide has been shown to reduce epicardial adipose tissue and attenuate its proinflammatory secretory profile, thereby improving endothelial function, lowering systemic oxidative stress, and protecting against calcium-handling abnormalities [30,31]. The fact that this protection was more pronounced in the non-diabetic cohort suggests that in the absence of advanced glucotoxicity and diabetic microvascular damage, the benefits of semaglutide are more effective [32]. The exact biological pathways through which semaglutide might influence AF risk remain to be fully elucidated, and current hypotheses are largely derived from preclinical data. However, because direct mechanistic evidence linking GLP-1 receptor agonists to AF prevention in humans is limited, these underlying mechanisms remain strictly exploratory and require validation in targeted translational studies.

Recent data on the dual Glucose-dependent Insulinotropic Peptide (GIP)/GLP-1 receptor agonist tirzepatide underscore the benefits of potent metabolic modulation. Specifically, these therapies significantly reduce left ventricular mass and EAT volume, thereby mitigating localized inflammation and myocardial wall stress. Crucially, from an electrophysiological standpoint, these agents display a reassuring safety profile. Clinical findings demonstrate no signals of arrhythmogenicity or increased risk of AF. This confirms that the intensive metabolic advantages of incretin-based therapies do not carry unfavorable arrhythmic trade-offs [33]. Furthermore, recent meta-analytic evidence shows that peri- or post-procedural GLP-1 receptor agonist therapy significantly reduces AF recurrence after catheter ablation. This antiarrhythmic benefit is driven by favorable structural and metabolic remodeling, notably through reduced EAT volume and localized inflammation. Consequently, these agents lower atrial stretch and enhance electrical stability, acting as effective upstream adjuncts to support rhythm maintenance [34,35]. Third, we explored the impact of concomitant SGLT2i use. Semaglutide demonstrated a neutral effect on AF incidence in both groups. Finally, our sensitivity analysis yielded a critical and nuanced insight into the data. The sequential exclusion of individual trials revealed that the primary analysis was sensitive to the inclusion of the FLOW trial [22]. Upon removal of this trial, the pooled analysis demonstrated a statistically significant reduction in the incidence of AF compared to placebo. The FLOW trial evaluated patients with T2DM and advanced chronic kidney disease (CKD). These patients exhibit severe underlying cardiac structural remodeling, distinct electrolyte fluctuations, and uremic toxin retention that elevate baseline arrhythmogenic susceptibility, potentially confounding the protective cardiovascular pathways of semaglutide seen in broader populations such as the SELECT cohort [20]. This sensitivity analysis underscores that while the drug is globally neutral, semaglutide might exert an intrinsic protective effect against AF in populations who have not yet transitioned to advanced organ damage.

### *Limitations*

This meta-analysis has some limitations. First, AF was not the primary endpoint in the included trials; this may have led to underreporting or underdetection of asymptomatic or paroxysmal AF episodes across the trial cohorts. However, because AF events across all cohorts were consistently captured as adverse events documented by electrocardiogram, the risk of significant bias from heterogeneous ascertainment methods is minimized. Second, the duration

of follow-up varied across the included trials, which might influence the temporal window required to observe rhythmic outcomes.

## 5. Conclusion

Semaglutide exhibits a robust cardiovascular safety profile, with no significant change in the incidence of AF compared with placebo. Although a leave-one-out sensitivity analysis excluding the FLOW trial suggested a possible 19% risk reduction, this secondary analysis remains exploratory. Consequently, while semaglutide may confer a protective cardiovascular effect against AF, this post hoc finding should not be overinterpreted and warrants validation in subsequent targeted clinical trials.

## Availability of Data and Materials

The data that supporting the findings of this study are openly available in PubMed Central (National Library of Medicine). See the "References" for the specific DOI.

## Author Contributions

GM: Writing—review and editing, Writing—original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. EG: Writing—review and editing, Writing—original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. SADF: Writing—review and editing, Supervision, Methodology. SA: Writing—review and editing, Supervision, Methodology. SF: Writing—review and editing, Supervision, Methodology. FN: Supervision, Conceptualization. FO: Supervision, Conceptualization. DG: Supervision, Conceptualization. FC: Supervision, Conceptualization. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript. Furthermore, all authors have contributed sufficiently to the work and have agreed to be accountable for all aspects of the research.

## Ethics Approval and Consent to Participate

Not applicable.


## Acknowledgment

Not applicable.

## Funding

This research received no external funding.


## Conflicts of Interest

The authors declare no conflicts of interest. Furio Colivicchi and Stefania Angela Di Fusco are members of the Editorial Board of this journal. We declare that neither Furio Colivicchi nor Stefania Angela Di Fusco was involved in the peer-review process for this article or had access to any information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Tong Liu and Chengming Fan.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/RCM54203.

## References


[1] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. European Heart Journal. 2021; 42: 373–498. https://doi.org/10.1093/eurheartj/ehaa612 Erratum in: European Heart Journal. 2021; 42: 507. https://doi.org/10.1093/eurheartj/ehaa798 Erratum in: European Heart Journal. 2021; 42: 546–547. https://doi.org/10.1093/eurheartj/ehaa945 Erratum in: European Heart Journal. 2021; 42: 4194. https://doi.org/10.1093/eurheartj/ehab648

[2] Wong CX, Ganesan AN, Selvanayagam JB. Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions. European Heart Journal. 2017; 38: 1294–1302. https://doi.org/10.1093/eurheartj/ehw045

[3] Sha R, Baines O, Hayes A, Tompkins K, Kalla M, Holmes AP, et al. Impact of Obesity on Atrial Fibrillation Pathogenesis and Treatment Options. Journal of the American Heart Association. 2024; 13: e032277. https://doi.org/10.1161/JAHA.123.032277

[4] Russo I, Frangogiannis NG. Diabetes-associated cardiac fibrosis: Cellular effectors, molecular mechanisms and therapeutic opportunities. Journal of Molecular and Cellular Cardiology. 2016; 90: 84–93. https://doi.org/10.1016/j.yjmcc.2015.12.011

[5] Wang A, Green JB, Halperin JL, Piccini JP Sr. Atrial Fibrillation and Diabetes Mellitus: JACC Review Topic of the Week. Journal of the American College of Cardiology. 2019; 74: 1107–1115. https://doi.org/10.1016/j.jacc.2019.07.020

[6] Masson W, Lobo M, Nogueira JP, Rodriguez-Granillo AM, Barbagelata LE, Siniawski D. Anti-inflammatory effect of semaglutide: updated systematic review and meta-analysis. Frontiers in Cardiovascular Medicine. 2024; 11: 1379189. https://doi.org/10.3389/fcvm.2024.1379189

[7] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical Research Ed.). 2021; 372: n71. https://doi.org/10.1136/bmj.n71

[8] Schiavenato M, Chu F. PICO: What it is and what it is not. Nurse Education in Practice. 2021; 56: 103194. https://doi.org/10.1016/j.nepr.2021.103194

[9] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical Research Ed.). 2003; 327: 557–560. https://doi.org/10.1136/bmj.327.7414.557

[10] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine. 2002; 21: 1539–1558. https://doi.org/10.1002/sim.1186

[11] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical Research Ed.). 2008; 336: 924–926. https://doi.org/10.1136/bmj.39489.470347.AD

[12] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England Journal of

Medicine. 2016; 375: 1834–1844. https://doi.org/10.1056/NEJMoa1607141

[13] Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England Journal of Medicine. 2019; 381: 841–851. https://doi.org/10.1056/NEJMoa1901118

[14] Mosenzon O, Blicher TM, Rosenlund S, Eriksson JW, Heller S, Hels OH, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. The Lancet. Diabetes & Endocrinology. 2019; 7: 515–527. https://doi.org/10.1016/S2213-8587(19)30192-5 Erratum in: The Lancet. Diabetes & Endocrinology. 2019; 7: e21. https://doi.org/10.1016/S2213-8587(19)30246-3

[15] Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. The New England Journal of Medicine. 2021; 384: 989–1002. https://doi.org/10.1056/NEJMoa2032183

[16] Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet. 2021; 397: 971–984. https://doi.org/10.1016/S0140-6736(21)00213-0

[17] Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. JAMA. 2021; 325: 1414–1425. https://doi.org/10.1001/jama.2021.3224

[18] Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. JAMA. 2022; 327: 138–150. https://doi.org/10.1001/jama.2021.23619

[19] Kadowaki T, Isendahl J, Khalid U, Lee SY, Nishida T, Ogawa W, et al. Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial. The Lancet. Diabetes & Endocrinology. 2022; 10: 193–206. https://doi.org/10.1016/S2213-8587(22)00008-0

[20] Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. The New England Journal of Medicine. 2023; 389: 2221–2232. https://doi.org/10.1056/NEJMoa2307563

[21] Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. The New England Journal of Medicine. 2023; 389: 1069–1084. https://doi.org/10.1056/NEJMoa2306963

[22] Perkovic V, Tuttle KR, Rossing P, Mahaffey KW, Mann JFE, Bakris G, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. The New England Journal of Medicine. 2024; 391: 109–121. https://doi.org/10.1056/NEJMoa2403347

[23] Pratley R, Amod A, Hoff ST, Kadowaki T, Lingvay I, Nauck M, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet. 2019; 394: 39–50. https://doi.org/10.1016/S0140-6736(19)31271-1 Erratum in: Lancet. 2019; 394: e1. https://doi.org/10.1016/S0140-6736(19)31519-3

[24] McGowan BM, Bruun JM, Capehorn M, Pedersen SD, Pietiläinen KH, Muniraju HAK, et al. Efficacy and safety of once-weekly semaglutide 2·4 mg versus placebo in people with obesity and prediabetes (STEP 10): a randomised, double-blind, placebo-controlled, multicentre phase 3 trial. The Lancet. Diabetes & Endocrinology. 2024; 12: 631–642. https://doi.org/10.1016/S2213-8587(24)00182-7

[25] Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, Hovingh GK, et al. Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. The New England Journal of Medicine. 2024; 390: 1394–1407. https://doi.org/10.1056/NEJMoa2313917

[26] Wang W, Bain SC, Bian F, Chen R, Gabery S, Huang S, et al. Efficacy and safety of oral semaglutide monotherapy vs placebo in a predominantly Chinese population with type 2 diabetes (PIONEER 11): a double-blind, Phase IIIa, randomised trial. Diabetologia. 2024; 67: 1783–1799. https://doi.org/10.1007/s00125-024-06142-3

[27] Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical Research Ed.). 2011; 343: d5928. https://doi.org/10.1136/bmj.d5928

[28] Saglietto A, Falasconi G, Penela D, Francia P, Sau A, Ng FS, et al. Glucagon-like peptide-1 receptor agonist semaglutide reduces atrial fibrillation incidence: A systematic review and meta-analysis. European Journal of Clinical Investigation. 2024; 54: e14292. https://doi.org/10.1111/eci.14292

[29] Cesaro A, Pastori D, Acerbo V, Biccirè FG, Golino M, Panico D, et al. Reduction of New Onset of Atrial Fibrillation in Patients Treated with Semaglutide: An updated systematic review and meta regression analysis of randomized controlled trials. European Journal of Preventive Cardiology. 2025; zwaf257. https://doi.org/10.1093/eurjpc/zwaf257

[30] Manubolu VS, Lakshmanan S, Kinninger A, Ahmad K, Susarla S, Seok HJ, et al. Effect of Semaglutide on Epicardial Adipose Tissue in Type 2 Diabetes: Insights From the STOP (Semaglutide Treatment effect On coronary atherosclerosis Progression) Randomized Trial. Journal of the American College of Cardiology. 2024; 84: 865–867. https://doi.org/10.1016/j.jacc.2024.05.065

[31] Malavazos AE, Meregalli C, Sorrentino F, Vignati A, Dubini C, Scravaglieri V, et al. Semaglutide therapy decreases epicardial fat inflammation and improves psoriasis severity in patients affected by abdominal obesity and type-2 diabetes. Endocrinology, Diabetes & Metabolism Case Reports. 2023; 2023: 23-0017. https://doi.org/10.1530/EDM-23-0017

[32] Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular Actions and Clinical Outcomes With Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors. Circulation. 2017; 136: 849–870. https://doi.org/10.1161/CIRCULATIONAHA.117.028136

[33] Abdul-Hafez HA, Awashra A, Bdir S, Saife S, Salah Q, Barbarawi M, et al. Tirzepatide and Cardiovascular Outcomes: A Narrative Review of Mechanisms, Efficacy and Implications for Heart Failure Management. Endocrinology, Diabetes & Metabolism. 2026; 9: e70152. https://doi.org/10.1002/edm2.70152

[34] Karakasis P, Fragakis N, Patoulias D, Theofilis P, Kassimis G, Karamitsos T, et al. Effects of Glucagon-Like Peptide 1 Receptor Agonists on Atrial Fibrillation Recurrence After Catheter Ablation: A Systematic Review and Meta-analysis. Advances in Therapy. 2024; 41: 3749–3756. https://doi.org/10.1007/s12325-024-02959-x

[35] Shubietah A, Elgendy MS, Awashra A, Murad MR, Alqudah M, Gowaily I, et al. Effect of GLP-1 Receptor Agonists on Post-Ablation Atrial Fibrillation Recurrence: A Meta-Analysis. Pacing and Clinical Electrophysiology. 2026; 49: 1086–1099. https://doi.org/10.1111/pace.70262