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META-ANALYSIS

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Glucagon-like peptide-1 receptor agonist semaglutide reduces atrial fibrillation incidence: A systematic review and meta-analysis

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Abstract

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are new anti-hyperglycaemic drugs with proven cardiovascular (CV) benefit in diabetic and non-diabetic patients at high CV risk. Despite a neutral class effect on arrhythmia risk, data on semaglutide suggest a possible drug-specific benefit in reducing atrial fibrillation (AF) occurrence.

Objective: To perform a meta-analysis of randomized clinical trials (RCTs) to assess the risk of incident AF in patients treated with semaglutide compared to placebo.

Methods and Results: Ten RCTs were included in the analysis. Study population encompassed 12,651 patients (7285 in semaglutide and 5366 in placebo arms), with median follow-up of 68 months. A random effect meta-analytic model was adopted to pool relative risk (RR) of incident AF. Semaglutide reduces the risk of AF by 42% (RR .58, 95% CI .40–.85), with low heterogeneity across the studies (I^2 0%). At subgroup analysis, no differences emerged between oral and subcutaneous

administration (oral: RR .53, 95% CI .23–1.24, I^2 0%; subcutaneous: RR .59, 95% CI .39–.91, I^2 0%; *p*-value .83). In addition, meta-regression analyses did not show any potential influence of baseline study covariates, in particular the proportion of diabetic patients (*p*-value .14) and body mass index (BMI) (*p*-value .60).

Conclusions: Semaglutide significantly reduces the occurrence of incident AF by 42% as compared to placebo in individuals at high CV risk, mainly affected by type 2 diabetes mellitus. This effect appears to be consistent independently of the route of administration of the drug (oral or subcutaneous), the presence of underlying diabetes and BMI.

KEYWORDS

atrial fibrillation, glucagon-like peptide-1 receptor agonists, overweight, semaglutide

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are new anti-hyperglycaemic drugs which mimic the effects of the endogenous GLP-1, contributing to favourable glycaemic control and weight loss.[1] During the past decade, clinical trials of GLP-1 RAs mainly focused on effects on major adverse cardiovascular events (MACE) in type 2 diabetes mellitus (T2DM) patients beyond their beneficial glycaemic and weight loss effects, showing a 14% MACE reduction in T2DM patients (mostly with established cardiovascular (CV) disease).[2] Interestingly, the recently published SELECT trial demonstrated that semaglutide was also effective in reducing MACE in a population of overweight individuals and pre-existing CV disease without diabetes, laying the basis for its possible use in non-diabetic patients at high CV risk.[3]

Previous large-scale cardiovascular outcome trials (CVOTs) in diabetic patients had raised safety concerns related to an increased arrhythmic risk in patients undergoing GLP-1 RA therapy, which were allayed following results of a meta-analytic analysis demonstrating no difference in terms of atrial arrhythmias, ventricular arrhythmias, as well as sudden cardiac death, between patients on GLP-1 RA and controls.[4] Specific data on semaglutide suggested, instead, a potential protective effect of the drug on the incidence of atrial fibrillation (AF), a common arrhythmia known to be a major driver of morbidity and mortality.[5]

The aim of the present study was therefore to perform a systematic review and meta-analysis summarizing current clinical evidence and assessing the relative risk (RR) of incident AF in patients treated with semaglutide as compared to placebo.

2 | METHODS

This systematic review and meta-analysis was performed in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[6]

2.1 | Search strategy

PubMed/MEDLINE, EMBASE, CENTRAL and ClinicalTrial.gov databases were screened from their inceptions to 10 April 2024, using the following search strategy: "semaglutide AND (randomized OR RCT)".

2.2 | Study selection and quality assessment

Two investigators (AS, MA) independently reviewed the titles/abstracts and studies to determine their eligibility based on the inclusion criteria and extracted all the relevant outcomes of interest. Inclusion criteria were: (a) randomized design; (b) studies that compare semaglutide administration (oral or subcutaneous) versus placebo; and (c) studies that report incident AF episodes as adverse events. Short follow-up duration (less than 24 weeks) and non-English language were considered exclusion criteria. Risk of bias assessment was performed at the study level using the revised Cochrane risk-of-bias tool (RoB2) for RCT (Supplementary Material—Data S1).

2.3 | Data extraction

Two investigators (AS and MA) extracted relevant data, which included study characteristics (study name, registration number, year of publication, population size), baseline features of participants (mean age, male proportion, baseline BMI, glycated haemoglobin [HbA1c]), semaglutide dosage and administration route, and outcome data.

The primary outcome of the study was AF incidence during follow-up, while the secondary outcome was incidence of ischaemic stroke. Considered that arrhythmic events, as well as ischaemic stroke events, were commonly reported as severe adverse events (SAEs), the adverse events section of each study page on ClinicalTrials.gov was checked to collect outcome data, when present. Risk of bias at the study level was assessed using the RoB2 for RCTs[7] (please refer to Supplementary Appendix—Data S1).

2.4 | Statistical analysis

Baseline features of the meta-analytic population are reported as median values between the included studies, together with their interquartile range. To account for the likely heterogeneity across studies, a random effect model (inverse-variance weighting) was adopted. Meta-analysis of RR was performed and the results with the corresponding 95% confidence interval (CI) were reported as a forest plot. Heterogeneity across studies was assessed using the Cochran Q test. Higgins I^2 statistics was used to determine the degree of between-study heterogeneity ($I^2 < 25\%$—low, 25%–50%—moderate and >50%—high degree of heterogeneity). To investigate potential publication bias, Egger test was run to identify asymmetry of funnel plot. A pre-specified subgroup analysis was also performed considering the route of administration of the drug (oral vs. subcutaneous). Finally, meta-regression analysis was performed to assess potential influence of study-specific baseline covariates and of the magnitude of body fat reduction (measured as the study-specific differential weight reduction [kg] and differential waist circumference reduction [cm] between the two treatment arms) on treatment effect for the primary outcome.

p values <.05 were considered statistically significant. Statistical analyses were performed with RStudio version 1.3.959 (Posit PBC, Boston, USA).

3 | RESULTS

Initial search retrieved 2974 results (please refer to Figure 1 for the PRISMA flow diagram). Forty reports were assessed for eligibility and 10 of them finally included in the present systematic review and meta-analysis.[8–17] Figure S1 reports study quality evaluation through RoB2 tool, showing that the majority of included RCTs were

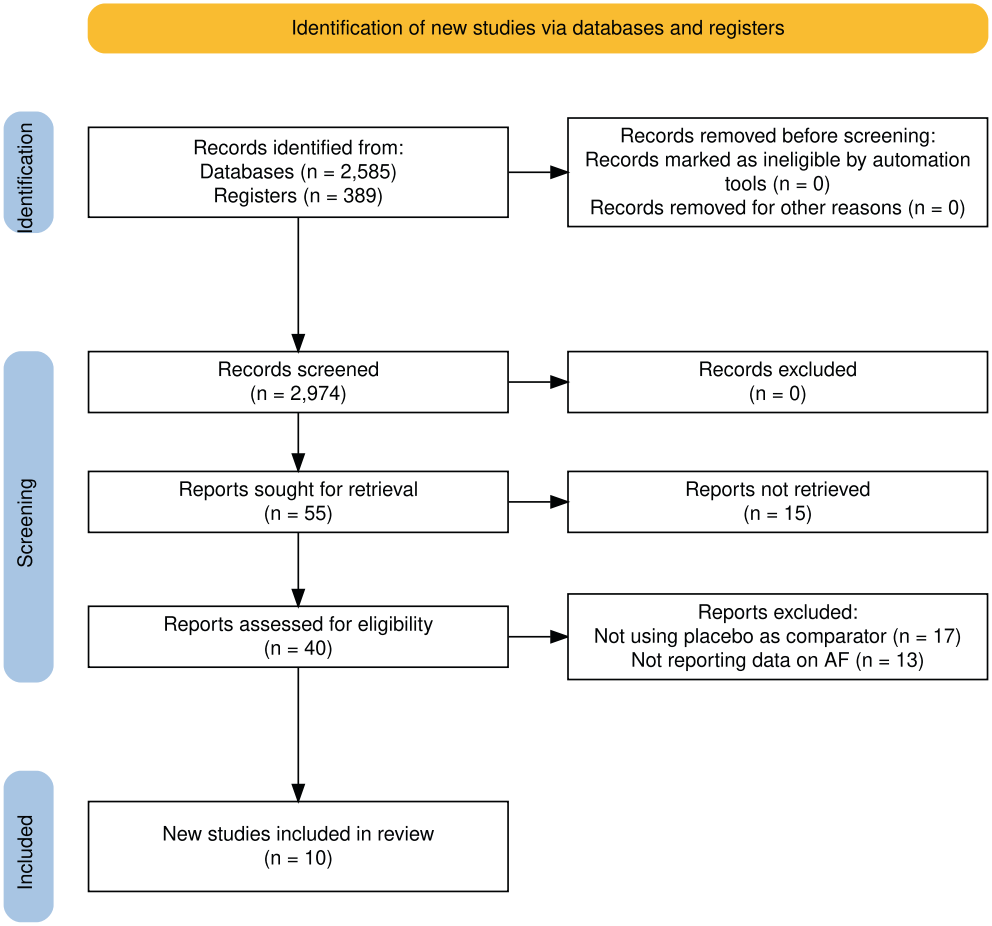

FIGURE 1 Flow chart of the search strategy following PRISMA guidelines.

judged at low risk of bias. Table 1 reports main clinical characteristics of the included studies.

The final study population encompassed 12,651 patients (7285 in the semaglutide and 5366 in the placebo arm, respectively), with a nearly 1:1 male-to-female ratio (males 51% [IQR 45–63]). Median age was 56 years (IQR 51–66 years), while median body mass index (BMI) and glycosylated haemoglobin (HbA1c) were, respectively 33 kg/m^2 (IQR 32–36 kg/m^2) and 8% (IQR 6.2–8.1%). Median follow-up duration was 68 months (IQR 52–68 months). Concerning drug administration route, four studies used oral semaglutide as the intervention arm (total number of patients: 4194), while the remaining six studies used subcutaneous semaglutide (total number of patients: 8457). Pooled incidence rate of AF episodes in the control arm was .86 events per 100 person-years (Figure S2).

Meta-analysis revealed that semaglutide reduces the risk of incident AF episodes by 42% (RR .58, 95% CI .40–.85), with low heterogeneity across the included studies (I^2 0%). The pre-specified subgroup analysis based on administration route did not report any significant difference between oral and subcutaneous (oral semaglutide: RR .53, 95% CI .23–1.24, I^2 0%; subcutaneous semaglutide: RR .59, 95% CI .39–.91, I^2 0%; *p*-value for subgroup differences: .83). Figure 2 displays the meta-analytic forest plot, reporting overall and subgroup (oral and subcutaneous) treatment effect estimates. Funnel plot analysis (Figure S3) did not detect potential risk for publication bias (Egger's test *p*-value: .71). Concerning secondary outcome, for which data was available in 7 out of the 10 included studies, no significant difference emerged between study arms (RR .76, 95% CI .47–1.24, I^2 0%; Figure 3). Moreover, at sensitivity analysis by multivariate meta-analytic approach including both outcomes into the model, results were similar to those of the univariate models separately evaluating primary and secondary outcome (Table S1).

Meta-regression analyses for the primary outcome did not show any potential influence of the following baseline study covariates (Figure 4): follow-up duration (*p*-value .42), male sex (*p*-value .72), age (*p*-value .71), proportion of T2DM patients in each study (*p*-value .14), BMI (*p*-value .60), Hb1AC (*p*-value .49). Similarly, treatment effect appeared to be independent from the achieved magnitude of differential body fat reduction (differential body weight reduction: *p*-value .63; differential waist circumference reduction: *p*-value .15). Table S2 reports study-specific body fat reduction metrics.

4 | DISCUSSION

The main findings of the present systematic review and meta-analysis (Graphical Abstract) are:

1. in a meta-analytic population constituted by overweight individuals mainly affected by T2DM GLP-1 RA semaglutide significantly reduces the occurrence of incident AF episodes (−42%) along a median follow-up of 68 months;
2. the meta-analytic estimate did not show heterogeneity across the included RCTs (I^2 0%);
3. the reduction in incident AF episodes appears to be independent from the administration route of the drug (oral vs. subcutaneous); and
4. baseline clinical variables, as well as the magnitude of fat reduction, did not influence the extent of drug effect; notably the treatment effect appeared to be independent from BMI and presence of T2DM.

In the past few years, obesity has clearly emerged as an independent risk factor for the development of AF, as documented by an additional 25% risk of incident AF for every five-unit increase in BMI.[18,19] Moreover, scientific evidence has accumulated demonstrating how excessive body weight is related to sub-optimal results of AF catheter ablation and how weight loss, in a dose-dependent fashion, reduces long-term recurrences after ablation and AF severity and burden in unselected cohort of AF patients.[20–24]

Different mechanisms have been proposed to explain how overweight/obesity contribute to risk, progression and severity of AF.[25,26] Obesity might be closely related to systemic conditions such as hypertension, obstructive sleep apnoea syndrome, diabetes, as well as might involve an increased local epicardial[27,28] and intramyocardial[29,30] fat content. Additionally, in obese individuals, the white adipose tissue (WAT), that includes the epicardial adipose tissue, undergoes profound changes; it expands, becomes dysfunctional and develops a low-grade inflammatory state.[31] These systemic and local changes in turn promote inflammation and oxidative stress, potentially leading to structural remodelling, left atrial enlargement and electrical remodelling, ultimately causing and perpetuating AF. Interestingly enough, activating the thermogenic brown adipose tissue (BAT) and browning of WAT are both under active study as appealing therapeutic interventions for the prevention and re-versal of obesity; GLP-1 mediated pathways (central and peripheral) are actively involved in this process.[32]

Among the different GLP-1 RAs, semaglutide was shown to have the highest efficacy in reducing body weight.[33] This is most likely due to an additional direct effect on the arcuate nucleus of the hypothalamus, affecting the activity of neural pathways involved in food intake, reward and energy expenditure, including centrally mediated BAT activation and promotion of WAT browning.[34,35] This peculiarity might explain why semaglutide,

TABLE 1 Details of the studies included in the present systematic review and meta-analysis.

Study	Year	ID clinical trial	Description	Population (*n*)	Semaglutide arm (*n*)	Placebo arm (*n*)	DM (%)	Males (%)	Age (years)	BMI (kg/m^2)	Hb1AC (%)	Follow-up (months)	Administration	Dosage
PIONEER 4	2019	NCT02863419	T2DM	427[a]	285	142	100	52	56	33	8	52	Oral	14 mg daily
PIONEER 5	2019	NCT02827708	T2DM and moderate renal impairment	324	163	161	100	48.1	70	32.4	8	26	Oral	14 mg daily
PIONEER 6	2019	NCT02692716	T2DM with high CV risk	3182	1591	1591	100	68.4	66	32.3	8.2	68	Oral	14 mg daily
PIONEER 11	2023	NCT04109547	T2DM	521	390	131	100	63.7	52	n.r.	n.r.	26	Oral	3/7/14 mg daily
SUSTAIN 6	2016	NCT01720446	T2DM	3297	1648	1649	100	60.7	64,6	32.8	8.7	104	Subcutaneous	5/1 mg weekly
STEP 1	2021	NCT03548935	Overweight or obese, without T2DM	1961	1306	655	0	24.9	46	37.8	5.7	68	Subcutaneous	2.4 mg weekly
STEP 2	2021	NCT03552757	T2DM, overweight or obese	1207	805	402	100	49.1	55	35.7	8.1	68	Subcutaneous	1/2.4 mg weekly
STEP 4	2021	NCT03548987	Overweight or obese, w/o T2DM	803	535	268	0	21	46	34.1	5.4	68	Subcutaneous	2.4 mg weekly
STEP 6	2022	NCT03811574	Overweight or obese, possible T2DM	400	299	101	25	63.1	51	31.9	6.4	68	Subcutaneous	1.7/2.4 mg weekly
STEP HFpEF	2023	NCT04788511	LVEF >45%, NYHA class II-IV, no T2DM	529	263	266	0	43.9	69	37	n.r.	52	Subcutaneous	2.4 mg weekly

Abbreviations: CV, cardiovascular; LVEF, left ventricular ejection fraction; n.r., not reported; T2DM, type 2 diabetes mellitus.

[a]Here reported as the sum of semaglutide and placebo arm, without considering the additional patients from the liraglutide arm (total number of patients in the study: 711).

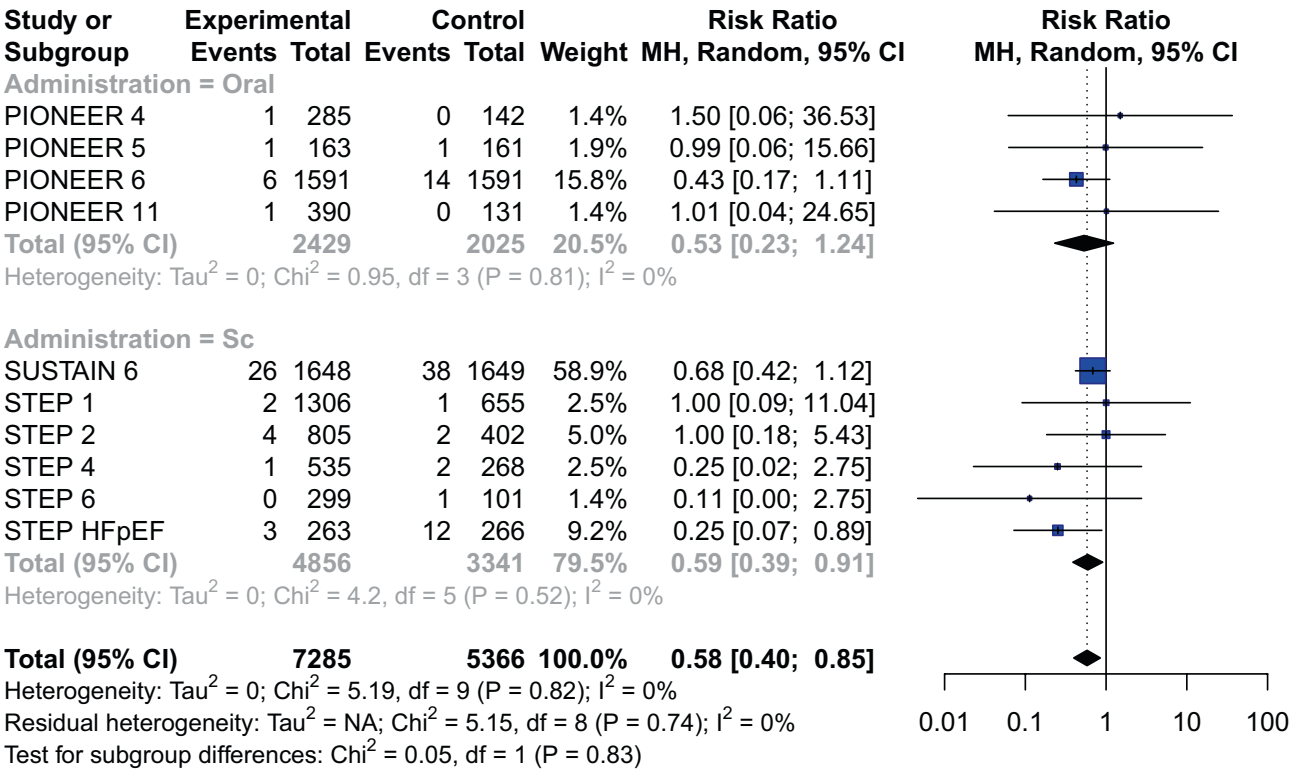

FIGURE 2 Forest plot for AF occurrence comparing semaglutide vs placebo arms, also providing the estimates for subgroups based on drug administration route (oral or subcutaneous).

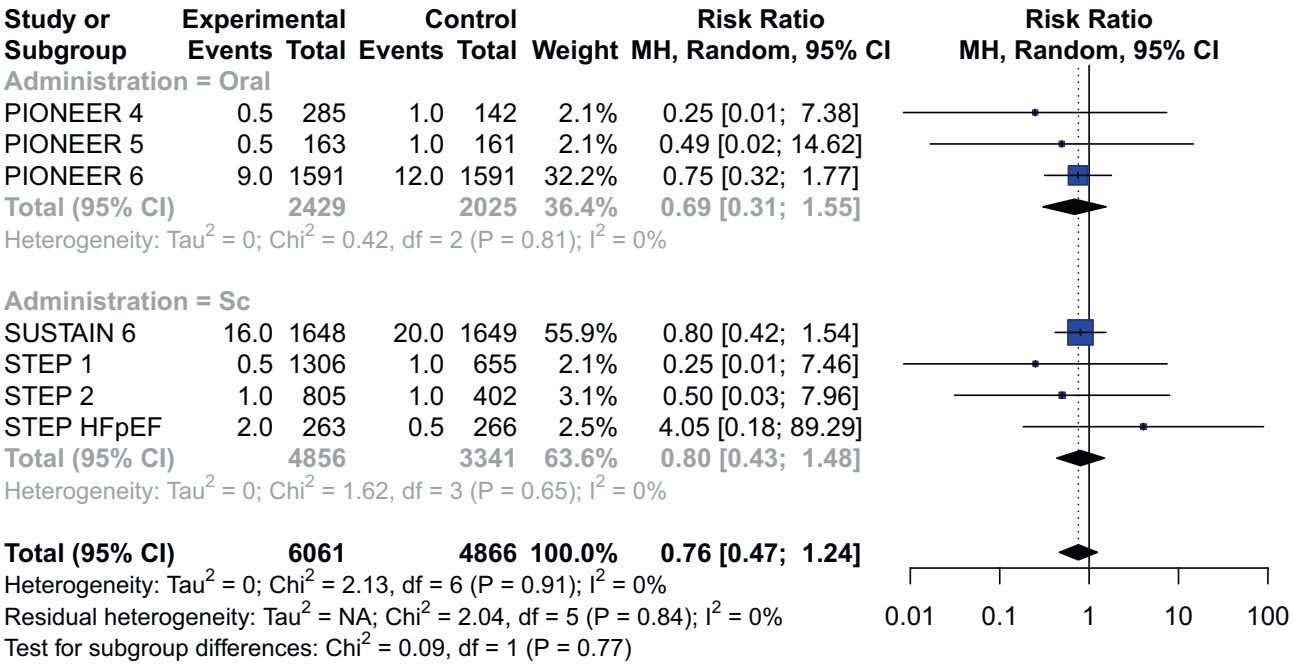

FIGURE 3 Forest plot for ischaemic stroke occurrence comparing semaglutide vs placebo arms, also providing the estimates for subgroups based on drug administration route (oral or subcutaneous).

differently to other GLP-1 RAs appearing neutral in terms of risk of incident AF, reduces the risk of AF in overweight individuals. It should also be kept in mind that semaglutide is the only GLP-1 RA with an oral formulation available, potentially reaching similar pharmacological effects with a greater compliance. Of note, it should be highlighted that semaglutide has shown more effective in improving metabolic status than the other GLP-1 RAs,[36] and this

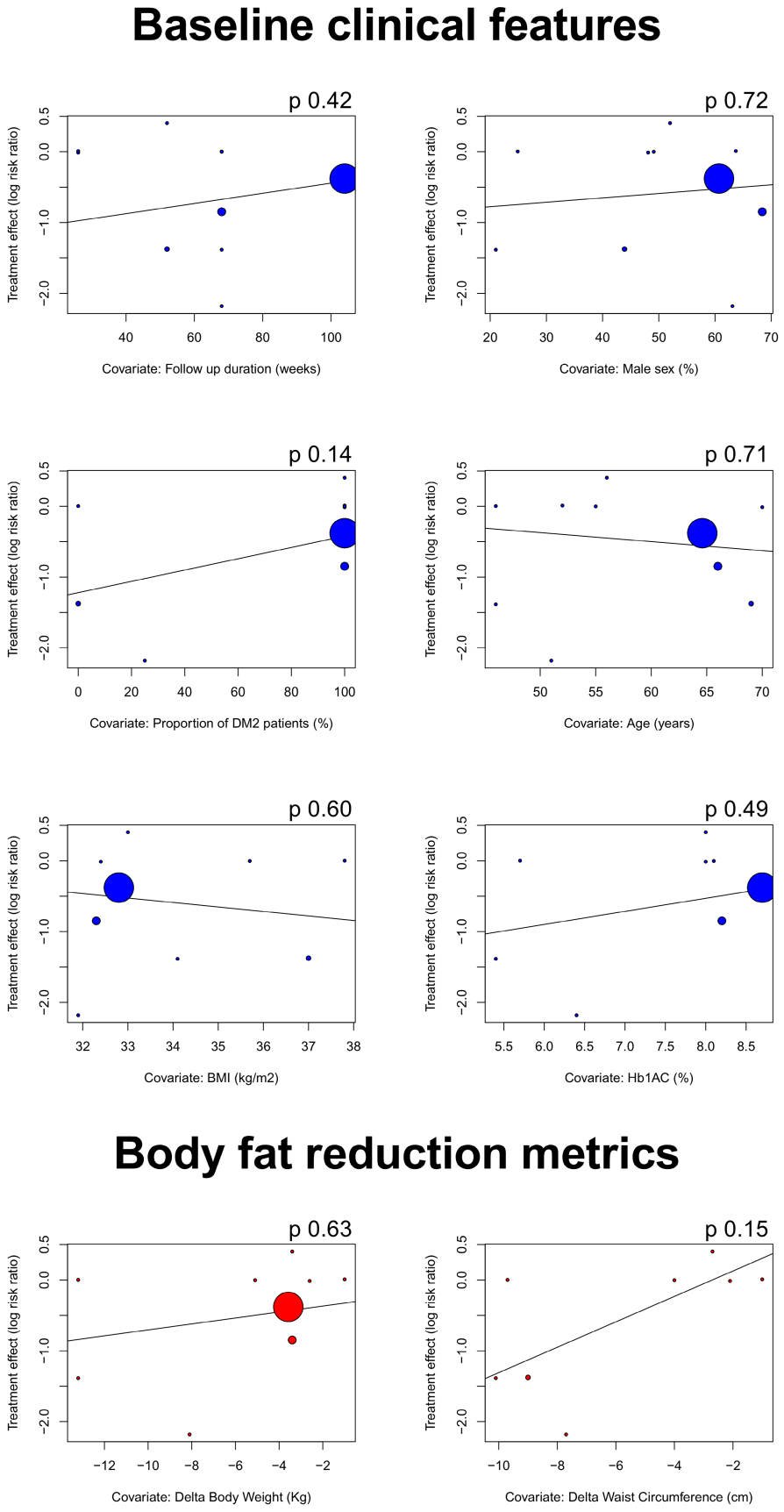

FIGURE 4 Meta-regression bubble plots for study-level clinical features and body fat reduction metrics.

peculiarity might be one of the potential players, adjunctive to weight loss, of the AF protection effect. The relevance of metabolic status has been thoroughly discussed over recent years, particularly because it has been used to explain, at least partly, the so-called 'obesity paradox'—the phenomenon whereby overweight and mildly obese patients with established CV disease have apparently better short- and moderate-term prognoses compared with leaner patients—also claimed for AF patients.[37,38] Likely, it is rather the complex interplay between adipose tissue (only grossly described by BMI, not able to discriminate between subcutaneous and visceral fat) and metabolic status that determines the CV risk of a specific individual.

Interestingly, since no significant association between the percentage of diabetic patients of the included studies and the meta-analytic risk estimate emerged, the present results suggest that drug effect is likely maintained in non-diabetic individuals. The target population for the drug might therefore be larger than the diabetic population. Of note, one of the included studies, the STEP HFpEF trial, enrolled a population of overweight patients without T2DM and with heart failure with preserved ejection fraction, demonstrating that in a higher AF risk population (incidence rate of AF was higher compared to that in cohorts of non-HF patients with T2DM, please refer to Figure S2) semaglutide has high efficacy in preventing incident AF episodes (study-specific treatment estimate: RR .25 [95 CI .07–.89]). This translates into a study-specific NNT to prevent an AF episode of 30 (at 1 year), compared to an overall meta-analytic NNT of 357. Albeit the overall meta-analytic population was characterized by low risk of incident AF (incidence rate of .86 per 100 person-year) and resulted in a relatively high NNT, the effect appears to be consistent (and, at least numerically, potentially stronger) in a higher-risk subpopulation, such as that of STEP-HFpEF (incidence rate of 4.25 per 100 person-year). Altogether, these findings provide interesting potential clinical applications, such as considering to prescribe semaglutide in T2DM or overweight individuals without known AF to reduce the risk of experiencing the arrhythmia and its potential consequences. No statistically significant differences were found in ischaemic stroke occurrences between semaglutide and placebo group, however secondary outcome analysis is limited by a very low incidence rate of the outcome, not permitting adequate power and therefore not excluding that in higher risk populations these differences could have reached statistical significance also for ischaemic stroke, the most feared AF consequence. Future specifically designed clinical trials are needed to support the potential use of semaglutide as a new upstream therapy for preventing AF in T2DM and/or overweight individuals, particularly assessing how to select patients who will benefit most from the drug in terms of AF prevention.

Finally, despite the meta-regression analyses not showing a relationship between absolute weight reduction and treatment effect, the magnitude of differential body fat reduction showed a trend, albeit not statistically significant, of an increased treatment effect when a higher reduction in waist circumference was achieved, potentially suggesting that a key driver in reducing AF risk is central obesity (visceral adipose tissue). Closing the circle, visceral adiposity has been associated with epicardial adipose tissue inflammation and dysfunction, both involved in AF promotion.[39] Of note, a recent study performing Mendelian randomization analysis showed that genetically determined central obesity, as denoted by waist circumference, hip circumference and trunk fat mass, was associated with an increased risk of AF.[40] This association still remained significant even after adjusting for potential mediators such as hypertension, diabetes, BMI, body fat percentage and sleep apnea.

4.1 | Limitations

There are some limitations to our systematic review and meta-analysis. First, AF episodes reported as SAE in the included trials are likely clinically relevant symptomatic episodes, thus virtually excluding possible asymptomatic episodes that could have been detected in dedicated trials implementing ad-hoc monitoring strategies to assess AF occurrence (e.g. periodic ECG Holter monitoring). Second, due to the limited number of included studies and that some studies provided limited contribution to the pooled estimates, we cannot exclude that meta-regression analyses were underpowered to detect potential significant causes of heterogeneity among the baseline clinical covariates. Moreover, even though we did not apparently detect heterogeneity across studies, we cannot exclude that the computed I^2 index might be due to the low number of events in the majority of the studies, rather than indicating a real absence of heterogeneity of the investigated outcomes. Finally, the lack of a deeper cardiac phenotyping of the included patients prevents from being able to perform specific meta-regression analysis based on specific cardiological features (e.g. left ventricular ejection fraction, baseline prevalence of AF).

5 | CONCLUSION

The GLP-1 RA semaglutide significantly reduces the occurrence of incident AF episodes by 42% as compared to placebo in overweight individuals mainly affected by T2DM; this effect appears to be consistent across the different randomized trials included in the present study and independent of (1) the administration route of the drug (oral or subcutaneous), (2) the presence of underlying T2DM, and (3) BMI. Altogether, these findings

potentially lay the basis for broadening the use of the drug in overweight individuals, even without a concomitant diagnosis of diabetes, to reduce the risk of incident AF. Future dedicated trials should be designed to address this hypothesis.

AUTHOR CONTRIBUTIONS

A.Saglietto and M.A. designed the study. A.Saglietto, G.F., D.P., P.F. retrieved the studies. A.Saglietto performed the analysis. All the authors (A.Saglietto, G.F., D.P., P.F., A.Sau, F.S.N., V.D., D.C., F.G., A.B., G.M.D.F. and M.A.) critically analysed the results of the analysis. All the authors (A.Saglietto, G.F., D.P., P.F., A.Sau, F.S.N., V.D., D.C., F.G., A.B., G.M.D.F. and M.A.) wrote the manuscript and approved its submission.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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