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GLP-1 Receptor Agonists and Risk of Cardiac Arrhythmias: A Multi-Cohort Analysis of Atrial Fibrillation and Bradycardia in Diabetic Patients

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Abstract

Background. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been a cornerstone of type 2 diabetes and obesity treatment but the impact on cardiac rhythm is still not clear. Due to hyperactivity of the heart during rest, an increased risk of tachyarrhythmia was a concern with GLP-1RAs, but more recent information indicates potential protection against atrial fibrillation (AF). There is little evidence to support bradycardia. This is a narrative review, summarizing available randomized, observational, genetic, and mechanistic evidence in the field of GLP-1RAs and arrhythmias in diabetes from 2023 to 2026.

Methods. Searches were conducted in October 2026. The findings were presented by study design and the type of arrhythmia and published effects estimates were presented across without re-pooling.

Results. Meta-analyses of trials of semaglutide show a reduction in AF (RR 0.58, 95% CI 0.40–0.85) while 30 trials of all GLP-1RAs did not show a significant difference (OR 0.94, 95% CI 0.86–1.04). The overall AF risk was not significantly different in a matched cohort of 80,948 pairs (OR 0.96), but was reduced with ≥5% weight loss (OR 0.83). A Mendelian randomization study indicated lower odds of AF (0.78) that was not independent of BMI or diabetes. This is because the increases in heart-rate are agent-dependent and result from a direct sinus node action, and trial data did not indicate more sinus node dysfunction.

Conclusions. GLP-1RAs seem to be rhythm safe in diabetes, and may have a possibly weight-related decrease in AF. But the endpoints were not prespecified and some confounding; studies specifically designed for monitoring rhythms are required.

Introduction

Cardiac arrhythmias are one of the most common morbidity causes in people with diabetes. The epidemiology of AF has been reviewed extensively, as has the

clinical complications of AF, with a significant burden of stroke, heart failure, and hospitalization (Bizhanov et al., 2023). T2DM increases the risk of AF, ventricular arrhythmia and sudden cardiac arrest and prediabetes has also been associated with poorer rhythm and cerebrovascular outcomes in patients with AF (Batta & Hatwal, 2024; Desai et al., 2024; Zhang et al., 2025). Diabetes is often associated with obesity, hypertension, heart failure and coronary disease, all of which play a role in atrial substrate formation in its own right (Batta et al., 2023; Van Gelder et al., 2024).

GLP-1 receptor agonists (GLP-1RAs) simulate an incretin hormone that increases glucose-dependent insulin secretion, delays gastric emptying, and decreases appetite, and result in clinically significant glycemic and weight reduction. In addition to metabolic control, the class can also reduce major adverse cardiovascular events and has been given pleiotropic functions in heart failure, kidney disease and inflammation (Drucker, 2024; Ussher & Drucker, 2023). With the spread of drug use from specialist diabetes care to primary care and obesity medicine, clinicians are more frequently considering the safety, neutrality or benefit of these drugs for cardiac rhythm.

The question is a two-way one. At the opposite end, GLP-1RAs have a proven effect on increasing resting heart rate, and the sinus node itself contains the GLP-1 receptor (Lubberding et al., 2024). If the heart rate is increased, it raises the possibility of a tachyarrhythmia, especially in those with structural heart disease. Conversely, the loss of weight, better glycaemic control, a decrease in blood pressure and inflammation should, in theory, diminish the substrate for AF in principle, and multiple preclinical and clinical studies have suggested antiarrhythmic effects (Bohne et al., 2023; Chan et al., 2023; Zhong et al., 2024). Despite the clinical relevance of whether GLP-1RAs impact on the function of the pacemaker, atrioventricular (AV) conduction and sinus node dysfunction, the subject of whether there is an effect from GLP-1RAs has not been the focus of much attention as it has been for tachycardia.

Since 2023 there are a number of developments that warrant a new synthesis. Meta-analyses limited to semaglutide, obesity trial meta-analyses of dual and triple incretin agonists, large propensity-matched cohort studies, a drug-target Mendelian randomization analysis, and mechanistic studies of the sinus node have all been published. Their findings are not entirely agreed. In some pooled analyses, there was a significant decrease in AF, while others showed no significant differences and genetic analyses indicated possible benefit that was lost upon modelling for BMI and diabetes. These results must be reconciled, and attention needs to be paid to the design, population, comparison, endpoint determination, and metric used.

The purpose of this review was to: (a) summarize mechanisms by which GLP-1RAs could affect cardiac electrophysiology; (b) review the evidence from randomized trials, observational cohorts, and genetic studies of AF; (c) review evidence for effects on ventricular arrhythmia, cardiac arrest, bradyarrhythmia, sinus node dysfunction, and heart rate; and (d) suggest clinical implications and research priorities. The emphasis is on individuals with diabetes, but data from the obesity population is used when it supports the diabetic population.

The structure of the article is as follows: The following section outlines methods used to identify and present evidence. Mechanisms, AF evidence from RCTs and cohort and genetic studies, VA and cardiac arrest, and bradycardia and heart rate are reviewed in subsequent sections. The results are then reconciled and clinical implications, limitations, and future directions are discussed.

Methods of the Review

Design and Reporting

This is a narrative review in a structured method of evidence selection and presentation. It does not include a systematic review and was not registered and no formal risk-of-bias instrument was used. The narrative design is adopted because there is no quantitative pooling, due to the diversity of outcomes, metrics, and study design. All effect sizes presented here were taken from the main reports or from the abstracts

or full-text summaries presented to the reviewer, and are explained in the terms used by the reports.

Search Strategy and Eligibility

In October 2026, targeted searches were conducted using web-based interfaces to bibliographic databases and publisher websites. The search terms included GLP-1 receptor agonist, semaglutide, liraglutide, and tirzepatide with atrial fibrillation, arrhythmia, bradycardia, sinus node, heart rate, cardiac arrest. The publications targeted were those from January 2023 to October 2026 to ensure the synthesis is based on the latest evidence. Meta-analyses of randomized trials, cohort studies with an active comparator, genetic association studies, mechanistic studies of cardiac electrophysiology, clinical guidelines, and narrative reviews that provided context for the evidence were included. The recent publications summarizing the earlier landmark analyses are the only ones used to refer to them.

Evidence Organization and Presentation

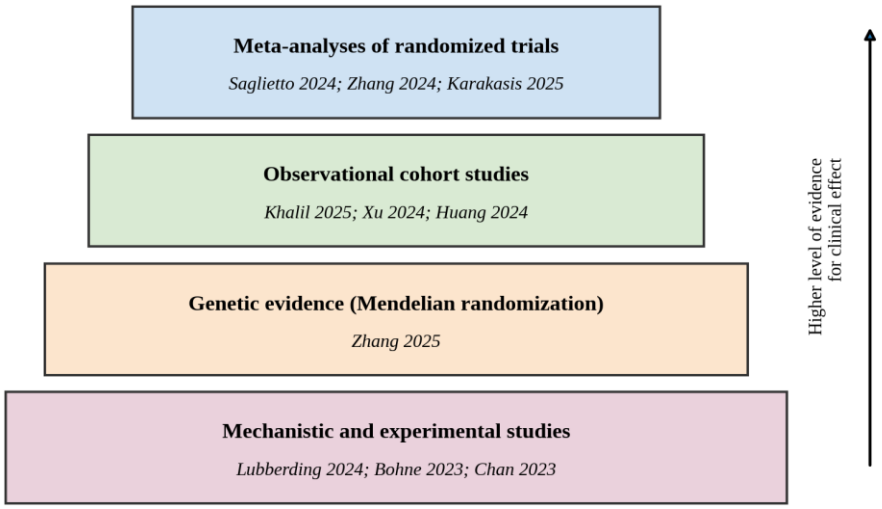
The sources were divided into four tiers based on design; meta-analyses of randomized trials, observational cohorts, genetic evidence, and mechanistic experiments (Figure 1). For each tier, estimates of the same arrhythmia were compared. Effect estimates are presented as reported (RR or OR, HR or MD) and not transformed as the measures are not interchangeable. Published estimates are thus presented concurrently in the forest-style graph and should not be interpreted as a pooled analysis in this article. Certainty ratings for the summary tables are not formal GRADE assessments, but rather qualitative judgements made by the reviewers based on their design, consistency, directness and precision.

Interpreting Rhythm Endpoints

Interpretation of outcomes by rhythm is different than mortality or hospitalization. AF may be asymptomatic and paroxysmal, and so the likelihood of an episode being recorded is related to the frequency of examinations. Similarly, the incidence of AF observed in trials in which it is identified on adverse-event forms is influenced by how often it is being monitored, and the same is true for bradyarrhythmia, which may only be identified if symptoms require an electrocardiogram. Clicking on relative effect should be interpreted in conjunction with absolute event rates. Even a statistically significant relative difference between the groups in the VHVA cohort (4.1% versus 4.3%) would represent a small absolute difference over the course of observation. Finally, composite rhythm outcomes involve events that are heterogeneous in terms of rhythm or mechanism; for example, "Reduced Risk of Sinus Node Dysfunction" is a composite outcome for sick sinus syndrome, sinus arrest, sinus pause, and sinoatrial block.

Figure 1

Hierarchy of Evidence Sources Used in This Review

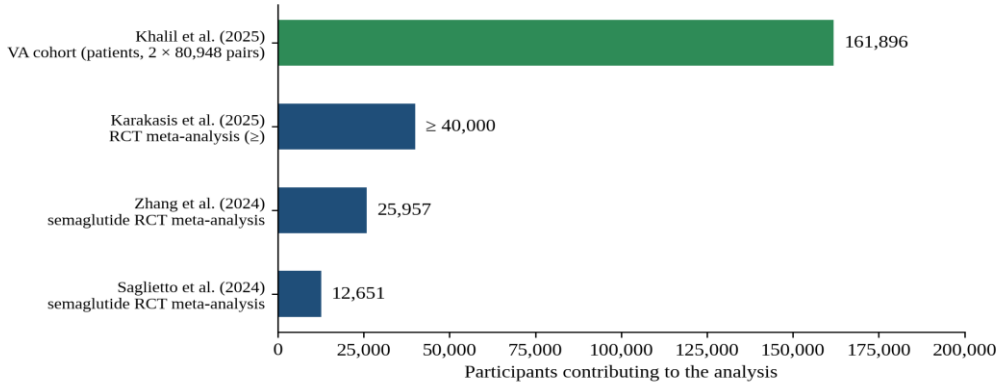


Scale of the Evidence Base

The sources are very variable in size. Meta-analyses of randomized trial studies have fewer numbers, but higher protection against confounding, at the extremes, whereas cohort studies have the largest numbers (Figure 2). As summarized by Zhang et al. (2025), a meta-analysis of semaglutide trials involved approximately 12,651 participants, and another analysis of semaglutide trials, summarized by Zhang et al., 2024, included 21 trials with 25,957 participants. Recently, a meta-analysis was included with over 40,000 randomized participants in overweight and obesity (Karakasis et al., 2025). Khalil et al. (2025) matched the cohort of veterans to 80,948 pairs of users of GLP-1RA and dipeptidyl peptidase-4 inhibitors (DPP4Is).

Figure 2

Participants Contributing to Key Analyses of GLP-1 Receptor Agonists and Atrial Fibrillation



Note. Data are from Khalil et al. (2025; 2 × 80,948 matched pairs), Karakasis et al. (2025; shown as a lower bound), and Zhang et al. (2024) and Saglietto et al. (2024), both as summarized by Zhang et al. (2025).

Pharmacology and Electrophysiological Mechanisms

Cardiac GLP-1 Receptor Biology

Pharmaceutical GLP-1RAs are designed to last much longer than the native GLP-1 (Ussher & Drucker, 2023). The class (Ussher & Drucker, 2023) has cardiovascular effects that are mediated through GLP-1 receptors in the heart, vasculature, and kidney, as well as indirect mechanisms that are mediated by weight loss, glycemic control, and blood pressure (Ussher & Drucker, 2023). For rhythm the relevance is that receptors are located in the sinoatrial region, thus the drug can have a direct effect on the pacemaker as well as systemic and autonomic effects.

The Sinus Node and Heart Rate

The best mechanistic evidence is of the chronotropic effect. When GLP-1 was infused into pigs with an integrated study, there was a consistent increase in heart rate in the isolated perfused heart that was GLP-1 receptor dependent, while the inactive GLP-1(9-36) metabolite did not (Lubberding et al., 2024). Receptor expression was localized in single-nucleus RNA sequencing in sinus node cells. In isolated sinus node preparations, GLP1 reduced the action potential cycle length of pacemaker cells and advanced the site of earliest activation. The authors found that the effect was not mediated by autonomic innervation, but rather due to calcium clock signaling; thus, they suggested that interventions that target the pacemaker calcium clock may be useful for reducing heart rate in individuals treated with GLP-1RAs (Lubberding et al., 2024).

The finding is of clinical significance. The increased rate is a pharmacodynamic effect of the drug and not a sign of sympathetic overactivity if it is intrinsic to the sinus node. This also means that any improvement gained from weight loss or decreased inflammation will be accompanied by a corresponding increase in the sinus rate – not the other way around. The converse (whether an agent which speeds up the pacemaker has an ability to unmask or even aggravate bradyarrhythmia) is not directly substantiated by mechanistic evidence; indeed, the direction of its pacemaker effect is opposite.

Atrial Electrophysiology and Remodeling

Mechanistic studies indicate that GLP-1 signaling could be a protective effect on the atrium. In the mouse T2DM model, GLP-1 prevented AF and decreased atrial remodeling (Bohne et al., 2023), an effect commented upon as a potential pathway to AF prevention in diabetes by Stoll & Lo, 2023. The relevance of this is that cellular work shows that GLP-1 receptor activation inhibit pulmonary vein arrhythmogenesis and control calcium homeostasis (Chan et al., 2023), which is especially important given that pulmonary vein triggers are the main triggers of AF. There have been also reviews regarding the improvement of myocardial metabolism in the context of AF (Zhong et al., 2024).

Systemic and Metabolic Pathways

The beneficial effect of GLP-1RAs on mitochondrial function and oxidative stress in the cardiovascular system could decrease cellular damage and metabolic load (Luna-Marco et al., 2024). Additionally, they have protective effects on neurons, immune cells and various organs that have receptors, which reduce systemic and local inflammation and promote endothelial function (Drucker, 2024). Clinical data has shown that the risk of AF was dependent on weight loss or not, a measure that is probably the most important systemic mediator (Khalil et al., 2025). Figure 3 shows the relationship of these pathways to outcomes of heart rate and AF and Table 1 summarizes the pathways and the nature of the evidence supporting each.

Figure 3

Proposed Pathways Linking GLP-1 Receptor Agonists to Heart Rate and Atrial Fibrillation

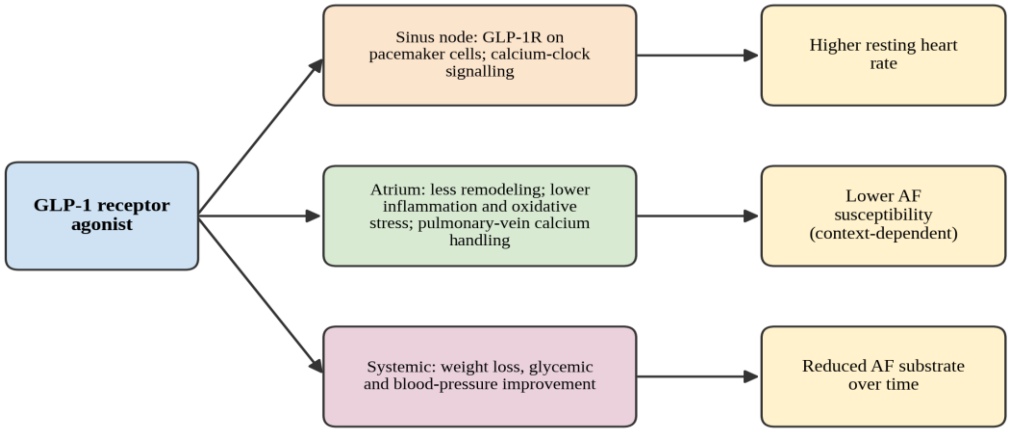


Table 1

Proposed Mechanisms Linking GLP-1 Receptor Agonists to Cardiac Rhythm

Pathway	Proposed rhythm effect	Evidence type	Key source
Direct sinoatrial action	Faster pacemaker firing through calcium-clock changes; higher resting heart rate	Pig perfused heart, isolated sinus node, single-nucleus RNA sequencing	Lubberding et al. (2024)
Autonomic balance	Chronotropic effect persists independent of autonomic innervation	Preclinical	Lubberding et al. (2024)
Pulmonary vein calcium handling	Reduced pulmonary vein arrhythmogenesis	Cellular and preclinical	Chan et al. (2023)
Diabetic atrial remodeling	Less AF and less atrial remodeling in diabetic mice	Animal model	Bohne et al. (2023); Stoll & Lo (2023)
Myocardial metabolism and mitochondria	Improved metabolism, lower oxidative stress and cellular injury	Narrative reviews	Zhong et al. (2024); Luna-Marco et al. (2024)
Inflammation and endothelium	Lower systemic and local inflammation; better endothelial function	Narrative review	Drucker (2024); Ussher & Drucker (2023)
Weight loss	Lower AF incidence in patients losing at least 5% of body weight	Observational cohort	Khalil et al. (2025)

From Bench to Bedside

The majority of the mechanistic observations have been made in animal or isolated-tissue models. High resolution electrophysiology studies of the pig heart and isolated sinus node studies (Lubberding et al., 2024) provide a means to understand the physiology of the human heart, but the heart rate, ion-channel expression, and receptor

density in these other species do not necessarily match that of humans, and so can limit direct translation to humans. The mouse model of diabetic atrial remodeling is an excellent model of T2DM, but is not a model of multimorbidity of human patients (Bohne et al., 2023), and cellular results on calcium handling in pulmonary veins are informative about the potential triggers of an arrhythmia, but do not establish clinical antiarrhythmic efficacy (Chan et al., 2023). In this review, mechanistic evidence is therefore used to provide explanations for observations and to generate hypotheses, not to estimate clinical effect and is thus ranked at the lowest tier in Figure 1.

Implications of the Mechanisms

Mechanisms foresee a dissociation between rate and rhythm. A direct sinus effect raises heart rate, regardless of baseline rhythm risk, while weight loss, anti-inflammatory and metabolic effects and maybe improved calcium handling are known to provide atrial protection. This dissociation may help to account for observed trial effects such as the fact that although a trial might report a slight increase in heart rate, it may not report an increase in AF, and that apparent decreases in AF may be larger if weight loss is larger. It also cautions against the risk of drawing clinical conclusions about arrhythmia risk based solely on a change in mean heart rate.

Atrial Fibrillation: Evidence From Randomized Trials

Semaglutide Trials

There is the most randomized evidence on semaglutide in the context of AF. A systematic review and meta-analysis of 10 RCTs, which included 132,940 individuals with overweight or obesity, demonstrated that semaglutide notably reduced incident AF by 42% (relative risk 0.58, 95% CI 0.40–0.85) with no observed heterogeneity ($I^2 = 0\%$) (Saglietto et al., 2024). It was deemed to be consistent across trials, independent of the route of administration (oral versus subcutaneous), presence of T2DM, and the body mass index in populations at high cardiovascular risk and predominantly influenced by T2DM (Saglietto et al., 2024). Another meta-analysis of 21 randomized trials in T2DM, obesity or overweight also found a reduction in AF in patients taking semaglutide (Zhang et al., 2024, summarized by Zhang et al., 2025).

Two cautions apply. First, AF in these trials was typically reported as an adverse event instead of a prespecified endpoint, which was systematically monitored. A recent synthesis of randomized trials using fixed-effect inverse-variance pooling reaffirmed that none of the individual trials was powered for AF events, and observed a directionally consistent but not statistically significant pooled risk ratio of 0.87 (95% CI 0.64–1.17) without heterogeneity ("Association Between Glucagon-Like Peptide-1 [GLP-1] Receptor Agonists and Atrial Fibrillation Adverse Events," 2026). Second, the estimate of the semaglutide is based on few event-sparse trials, and the confidence interval is broad and the point estimate may not be precise.

Class-Wide and Obesity Trials

The benefits of using semaglutide is less obviously. In adults with overweight or obesity, a meta-analysis of more than 40,000 participants of randomized trials demonstrated a 18% reduction in risk for AF with GLP-1RAs and incretin co-agonists compared to placebo with minimal heterogeneity across studies and no differences among single, dual, or triple-receptor agonists, consistent with a class-wide effect (Karakasis et al., 2025). However, a meta-analysis of 30 randomized trials and eight retrospective observational studies at the conference level did not show a significant decrease in atrial arrhythmias (OR 0.94, 95% CI 0.86–1.04, $p = 0.23$) but did suggest a modest decrease in AF risk (HR 0.93, 95% CI 0.89–0.97, $p = 0.001$), and the investigators' final conclusion was that GLP-1RAs do not significantly reduce the incidence of AF (Effect of Glucagon-Like Peptide-1 Receptor Agonists on Atrial Fibrillation Incidence, 2025). Another meta-analysis of 13 studies in overweight and obese non-diabetic individuals found no effect (de Oliveira Almeida et al., 2024, cited in Zhang et al., 2025).

The seemingly contradictory findings of these studies are due to different populations (diabetes vs. obesity), agents included, statistical model used, and the definition of outcome. Details of the comprehensive summaries are provided in Table 2 and the central estimates are compared in Figure 4. Point estimates for AF are all below 1.0 across designs with some confidence intervals touching or crossing 1.0 in several analyses, as displayed in the graph.

Table 2

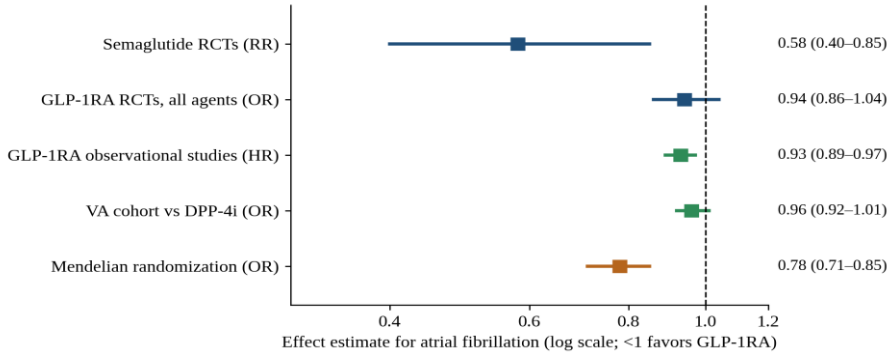
Characteristics and Main Findings of Key Studies on GLP-1 Receptor Agonists and Atrial Fibrillation

Study	Design	Population or comparator	Size	Main AF finding
Saglietto et al. (2024)	Meta-analysis, 10 RCTs	Semaglutide vs. placebo	About 12,651*	RR 0.58 (0.40–0.85); $I^2 = 0\%$
Zhang et al. (2024)	Meta-analysis, 21 RCTs	Semaglutide; T2DM, obesity or overweight	25,957*	Lower AF with semaglutide*
Karakasis et al. (2025)	Meta-analysis of RCTs	GLP-1RA and co-agonists vs. placebo; overweight or obesity	> 40,000	18% lower AF risk; no difference by receptor class
Conference abstract (2025)	Meta-analysis, 30 RCTs and 8 observational studies	GLP-1RA vs. placebo or other agents	Not stated	RCTs: OR 0.94 (0.86–1.04); observational: HR 0.93 (0.89–0.97)
Khalil et al. (2025)	Propensity-matched cohort	Veterans with diabetes; GLP-1RA vs. DPP-4i	80,948 pairs	OR 0.96 (0.92–1.01); ≥ 5% weight loss OR 0.83 (0.78–0.89)
Xu et al. (2024)	Real-world cohort	US adults with diabetes	Not retrieved	Reduced AF risk*
Huang et al. (2024)	Global retrospective cohort	Obesity without T2DM	Not retrieved	Lower AF and arrhythmia risk*
Karakasis et al. (2024)	Meta-analysis	Patients after AF catheter ablation	Not retrieved	Reduced recurrence at 12 months*
Zhang et al. (2025)	Two-sample drug-target MR	Genetic proxies of GLP1R; 50,743 AF cases	261,395 (cases + controls)	OR 0.78 (0.71–0.85); null after BMI and T2DM adjustment

Note. AF = atrial fibrillation; BMI = body mass index; DPP-4i = dipeptidyl peptidase-4 inhibitor; HR = hazard ratio; MR = Mendelian randomization; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; T2DM = type 2 diabetes mellitus. *As summarized by Zhang et al. (2025). The conference abstract is cited as "Effect of Glucagon-Like Peptide-1 Receptor Agonists on Atrial Fibrillation Incidence" (2025).

Figure 4

Published Effect Estimates for Atrial Fibrillation Across Study Designs



Note. Estimates are shown as reported; the metrics are not interchangeable and were not pooled. Data are from Saglietto et al. (2024), Khalil et al. (2025), Zhang et al. (2025), and the conference abstract "Effect of Glucagon-Like Peptide-1 Receptor Agonists on Atrial Fibrillation Incidence" (2025; two rows). Bars show 95% confidence intervals. DPP-4i = dipeptidyl peptidase-4 inhibitor; HR = hazard ratio; OR = odds ratio; RR = relative risk.

Arrhythmia as a Safety Outcome in Diabetes Trials

Safety analyses have directly assessed this issue as earlier cardiovascular outcomes trials in diabetes raised this safety concern, which was subsequently addressed by meta-analysis (Saglietto et al., 2024). In people with diabetes, cardiovascular outcome trials (CVOTs) have been conducted and evaluated via meta-analysis, which showed no significant difference in the incidence of major cardiac arrhythmias among GLP-1RAs (Al-Sadawi et al., 2023; Boulmpou et al., 2023). The randomized evidence on harm is therefore reassuring and is suggestive, but not definitive, on benefit, when combined with the obesity analysis.

Interpretation of the Randomized Evidence

Randomized comparisons provide the highest degree of control for confounding, but may be of limited utility for rhythm outcomes because of the difficulty of ascertaining the outcomes. Both paroxysmal and asymptomatic AF may have been underdiagnosed, since trials generally used spontaneous reporting or electrocardiograms that were recorded for other purposes. Non-differential misclassification may also underestimate the true effects (bias towards the null), while differential surveillance such as increased contact in cardiology may induce apparent differences. The semaglutide estimate could also be influenced by the greater weight loss seen with this agent. These findings should therefore be interpreted as hypothesis-generating rather than hypothesis-confirming and should be interpreted in the light of these limitations.

Atrial Fibrillation: Cohort and Genetic Evidence

Active-Comparator Cohort Studies

Cohort studies are subject to confounding and surveillance bias and have many numbers.The cohort studies have many numbers and are subject to surveillance bias and confounding. The Researchers at the VA compared new users of GLP-1RAs to new users of another active comparator with a neutral expected effect on AF, dipeptidyl peptidase-4 inhibitors (DPP4Is) (Khalil et al., 2025). The investigators matched 80,948 users of GLP-1RA with 217,668 users of a comparator on 88 characteristics, with 116,235 of these users in each group. There was no effect observed with the composite AF outcome (4.1% vs 4.3% for GLP-1RA vs comparator group, respectively; odds ratio 0.96, 95% CI 0.92–1.01), and stratification by duration of the use did not change this result (Khalil et al., 2025).

The most informative findings were the heterogeneity by weight change. Patients who lost at least 5% of their weight had significantly lower AF incidence (odds

ratio 0.83, 95% CI 0.78-0.89) while those who lost no weight or weight gained showed no differences (odds ratio 1.05, 95% CI 0.97-1.12) (Khalil et al., 2025). This pattern, depicted in Figure 5A, is also consistent with weight loss as an effect modifier or mediator, and is similar to the well-established association between adiposity and AF burden. It is not an indicator of mediation because weight loss following treatment is a post-baseline measure, which could be associated with the weight loss behavior and adherence.

Other studies in the real-world show positive correlations. As previously reported by Zhang et al. (2025), a study in adults with diabetes in the United States showed that use of GLP-1RAs was associated with a lower risk of AF, while a global retrospective cohort that was part of a federated research network showed a lower risk of AF and arrhythmia among individuals with obesity without diabetes (Huang et al., 2024). In people with obesity (with and without diabetes), GLP-1RA use was more than 65% lower at one and three years for cardiac arrest (Jaiswal et al., 2025). The results are positive but could be biased for the healthy user and indication, because patients taking these drugs might have different access, adherence and risk factors at baseline.

Bias in Observational Rhythm Studies

There are several biases involved when comparing GLP-1RA users to other patients observed. Compared to a non-user comparator group, using an active comparator group, such as the Veterans Health Administration cohort that received dipeptidyl peptidase-4 inhibitors, limits confounding by indication and healthy user effects (Khalil et al., 2025). Matching with 88 baseline characteristics further enhances the balance, but there are unmeasured factors like diet, physical activity and socioeconomic status that cannot be matched. Prescribing changes and available agents are likely to have occurred over the 15 fiscal years studied (2006–2021). Stratifying by achieved weight loss is difficult, as patients who lose weight may be more likely to be compliant, more likely to be engaged in therapy or baseline healthier, and therefore the association is hypothesis-generating. Large electronic cohorts (Huang et al., 2024, summarised by Zhang et al., 2025) are available but a reliance on diagnostic codes leads to misclassification of AF and cardiac arrest. The agreement of the estimates from the different designs on a slight reduction in risk is encouraging, but can't be ruled out that the effect is due to weight and metabolic status, not to the drug.

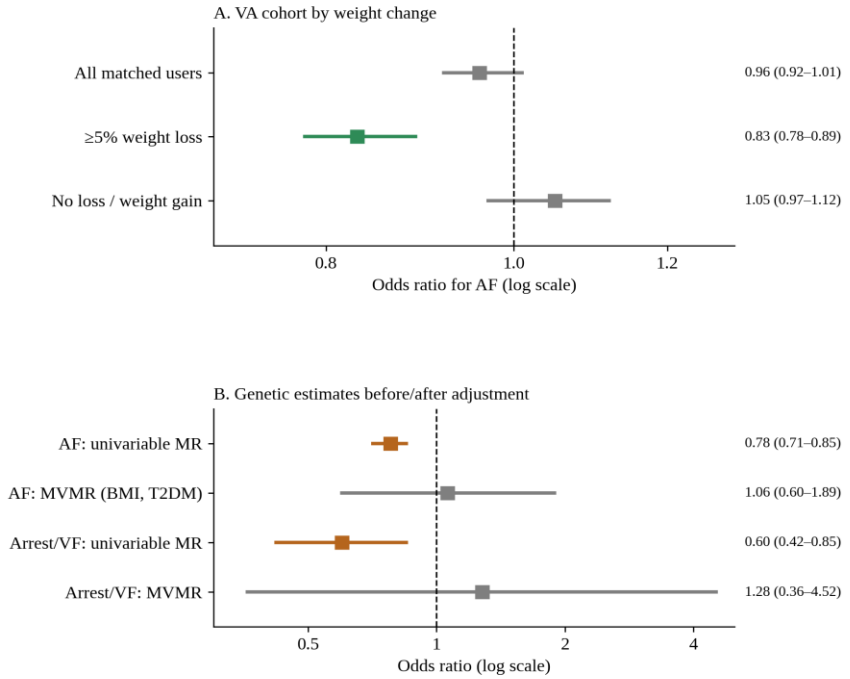
Mendelian Randomization

However, drug-target Mendelian randomization uses the genetic variants that affect the expression of the target gene as proxies for lifetime exposure and is less susceptible to confounder and reverse causation. To ensure valid associations with lower T2DM risk (odds ratio 0.90, 95% CI 0.86–0.96) and lower BMI (Zhang et al., 2025), 12 independent cis-expression variants were used for a two-sample analysis at the GLP1R locus. The association between genetically proxied GLP-1RA activity and a reduced risk of AF (odds ratio 0.78; 95% CI 0.71–0.85; AF outcome data in 50,743 cases and 210,652 controls) and of cardiac arrest and ventricular fibrillation (odrs 0.60; 95% CI 0.42–0.85) was not heterogeneous and did not show horizontal pleiotropy (Zhang et al., 2025).

There are important qualifiers to this result. No information was provided by the Bayesian colocalization analysis, nor did any statistically significant association between GLP1R expression and either arrhythmia or cardiac arrest and/or ventricular fibrillation emerge in multivariable analyses in which body mass index and T2DM accounted for variability (Zhang et al., 2025). They pointed out that the multivariable analysis was limited by the small number of shared instruments as well as the lack of independence due to the collinearity of BMI and T2DM, which should not be the basis for overinterpreting the loss of association. The estimates in Figure 5B were adjusted, with a similar pattern emerging that supports a mediating role for adiposity and glycemia, and were limited to individuals of European ancestry (Zhang et al., 2025).

Figure 5

Weight Change and Genetic Adjustment Modify the Association Between GLP-1 Receptor Agonists and Arrhythmia



Note. Panel A is from Khalil et al. (2025) and Panel B from Zhang et al. (2025). Bars show 95% confidence intervals. MR = Mendelian randomization; MVMR = multivariable MR adjusted for body mass index and type 2 diabetes; VF = ventricular fibrillation.

Perioperative and Post-Ablation Settings

There are two other settings that offer supportive evidence. A meta-analysis of GLP-1RA use in patients undergoing AF catheter ablation demonstrated a decreased risk of AF recurrence at 12-month follow-up, primarily based on the studies from the USA (Karakasis et al., 2024). A recent narrative review of observational studies in cardiac surgery identified associations of GLP-1RA use with reduced post-operative AF after CABG, discussed the findings of the GLOBE randomized trial, and summarized the results of a trial in TAVR that is currently running ("GLP-1 Receptor Agonists in Cardiac Surgery," 2026). In these contexts, the AF endpoints are well-defined, with intensive monitoring and preliminary conclusions.

Ventricular Arrhythmia and Cardiac Arrest

Ventricular arrhythmia and sudden cardiac death are less frequent than AF and not as informative in trials. According to Zhang et al. (2025), reviews of glucose-lowering agents have been generally neutral regarding these outcomes, attributing GLP-1RAs to a neutral or negligible effect. Meta-analyses of five RCTs have similarly found no significant difference in cardiovascular outcomes, including ventricular arrhythmia or sudden cardiac death, among patients with T2DM using GLP-1RAs (Al-Sadawi et al., 2023); similarly, pooled data from cardiovascular outcome trials has failed to show significant difference in major arrhythmias (Boulmpou et al., 2023).

There is a suggestion that it may be helpful from an observational and a genetic perspective. The cohort of patients with obesity had significantly reduced risk of cardiac arrest over 1 year, as well as over 3 years (Jaiswal et al., 2025) and genetically proxied GLP-1RA activity showed reduced risk of cardiac arrest and ventricular fibrillation (Zhang et al., 2025). After adjustment, however, the genetic estimate was reduced, the cohort was not limited to diabetes and the absolute number of events was low. One plausible indirect pathway is via coronary disease and heart failure, as AF is also linked to increased risk of ventricular arrhythmia and cardiac arrest (Fawzy et al., 2023) and

coronary disease to both AF and ventricular fibrillation (Batta et al., 2023; Zhang et al., 2025). The evidence from these together suggests neutrality in trials and possible benefit in observational and genetic analyses; this is of low certainty.

Bradycardia, Sinus Node Function, and Heart Rate

Heart-Rate Effects Differ by Agent and Dose

The increase in resting heart rate with GLP-1RAs has been quantified in a recent pairwise and network meta-analysis of 26-week or longer randomized trials in individuals with overweight or obesity but no diabetes ("Effect of Glucagon-Like Peptide-1 Receptor Agonists on Heart Rate," 2026). The mean difference in heart rate between each intervention and placebo was significantly the greatest for Orforglipron 36 mg compared to the others (see Figure 6A), and the smallest for tirzepatide 5 mg (see Figure 6B). The review had reported that previous research also had linked GLP-1RAs for T2DM to a rise in heart rate. Due to the data collected from non-diabetics, extrapolation to diabetes patients is advised but caution is required given the common receptor mechanism, dose and agent gradient (Lubberding et al., 2024).

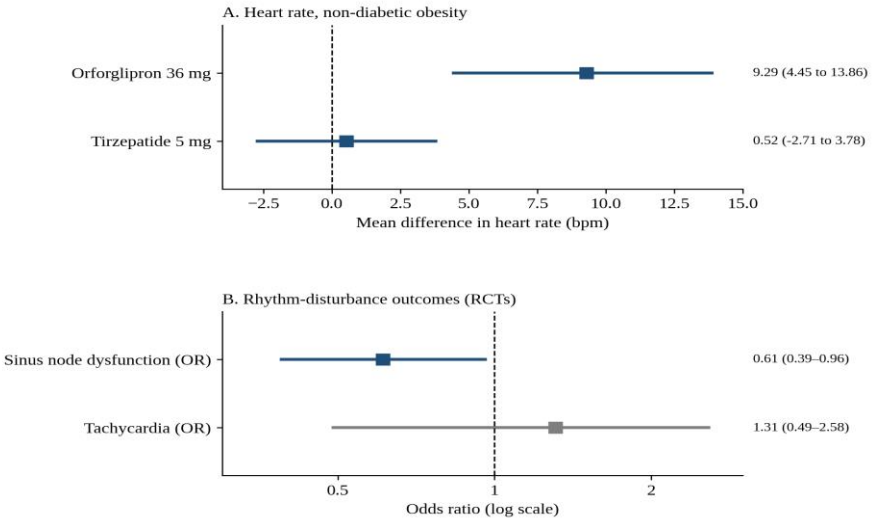
Bradyarrhythmia and Sinus Node Dysfunction

There is little direct evidence for bradycardia and it is primarily abstract. The systematic review of randomised trials was presented at a large cardiology conference and was a review of sick sinus syndrome, sinus arrest, sinus pause, sinoatrial block, sinus node dysfunction, tachycardia and premature atrial or ventricular contractions. Sinus node dysfunction, as a composite outcome, was associated with a 39% reduced risk with GLP-1RAs (odds ratio 0.61, 95% CI 0.39–0.96, p = 0.03), while tachycardia was not significantly associated (odds ratio 1.31, 95% CI 0.49–2.58, p = 0.78) ("Reduced Risk of Sinus Node Dysfunction," 2026) (Figure 6B). The authors reported that GLP-1RAs had no effect on tachycardia or premature contraction arrhythmias, but had a beneficial effect on sinus node dysfunction.

The results are subject to interpretation. They come from an abstract lacking in methodological detail, and the number of events is small in trials for bradyarrhythmia, and inconsistent reporting of conduction disturbances in trials. The outcome is still consistent with the mechanistic data, since a drug that is more likely to increase the firing rate of the pacemaker would be less likely to be associated with a slowing of the pacemaker (Lubberding et al., 2024). No study reported on in this review reported evidence for increased high-grade atrioventricular block or pacemaker implantation with GLP-1RAs. Evidence thus far on bradycardia is therefore reassuring but sparse and has not been studied in dedicated electrocardiographic or ambulatory monitoring studies of diabetic populations.

Figure 6

Heart-Rate and Rhythm-Disturbance Estimates for GLP-1 Receptor Agonist Therapy



Note. Panel A is from a network meta-analysis in non-diabetic overweight or obesity ("Effect of Glucagon-Like Peptide-1 Receptor Agonists on Heart Rate," 2026). Panel B is from a conference-abstract meta-analysis of randomized trials ("Reduced Risk of Sinus Node Dysfunction," 2026) and is preliminary. Bars show 95% confidence intervals.

Special Populations

Not all patients are suitable for this treatment. The older diabetics may be at greater risk for conduction disease, and the limited bradyarrhythmia information outlined above may not reflect the experience of all diabetics, so caution should be exercised in patients with known sinus node disease or atrioventricular block. People with obesity but not diabetes were the focus of the network meta-analysis of heart rate and of the class-wide AF analysis (Karakasis et al., 2025; "Effect of Glucagon-Like Peptide-1 Receptor Agonists on Heart Rate," 2026), and their risk profile differs from that of the diabetic patients who are the focus of this review, so findings may extrapolate only partly. Patients with cardiac surgery or undergoing AF ablation are a high-risk population where endpoints of rhythm are closely monitored, and the clinical evidence is encouraging, but mostly observational (Karakasis et al., 2024; "GLP-1 Receptor Agonists in Cardiac Surgery," 2026). The genetic evidence comes from individuals of European ancestry (Zhang et al., 2025), so it is not clear to what extent it applies to other ancestries. The lack of evidence of harm in each group should not be taken as evidence of safety in rare conditions, such as high grade conduction block.

Summary of the Rhythm Evidence

Table 3 combines the data by arrhythmia type with the qualitative certainty ratings of the reviewers. The strongest signal relates to AF where the direction of change is favourable or neutral, with the possibility of a favourable direction but low certainty in the case of cardiac arrest. Heart-rate increase has been documented and is dependent upon the agent. Data on bradyarrhythmias are the least available.

Table 3

Summary of Evidence by Arrhythmia Type

Outcome	Direction of evidence	Certainty	Key sources
AF incidence	Neutral to lower; estimates vary by agent, population and design	Low to moderate	Saglietto et al. (2024); Karakasis et al. (2025); Khalil et al. (2025)
AF recurrence after ablation	Lower recurrence at 12 months	Low	Karakasis et al. (2024)

Outcome	Direction of evidence	Certainty	Key sources
Postoperative AF	Lower in observational cardiac-surgery data; randomized evidence emerging	Low	"GLP-1 Receptor Agonists in Cardiac Surgery" (2026)
Ventricular arrhythmia and sudden death	Neutral in trial meta-analyses	Low	Al-Sadawi et al. (2023); Boulmpou et al. (2023)
Cardiac arrest	Lower in a cohort and genetic analysis; attenuated after adjustment	Low	Jaiswal et al. (2025); Zhang et al. (2025)
Sinus node dysfunction and bradyarrhythmia	Lower odds in a trial meta-analysis (abstract); no signal of harm	Very low	"Reduced Risk of Sinus Node Dysfunction" (2026)
Heart rate and tachycardia	Agent- and dose-dependent rise in rate; no significant excess of tachycardia events	Moderate	Lubberding et al. (2024); "Effect of Glucagon-Like Peptide-1 Receptor Agonists on Heart Rate" (2026)

Reconciling Discordant Findings

The overarching question is why estimates of the impact of pooled AF have been as low as 42% reduction and as high as no effect. There are a number of possible explanations that can be advanced – and these suggestions are not mutually mutually exclusive.

Differences in Agent and Population

The analyses that were included in the semaglutide meta-analyses were mostly conducted on high-risk populations with T2DM, resulting in the strongest estimates (Saglietto et al., 2024), while analyses combining agents, populations with obesity but no diabetes, and trials of short duration tended to weaken any effect (Zhang et al., 2025). There is a great variation in weight loss observed between agents and doses, and, if weight loss is a key factor in the AF benefit, then agents with minimal weight loss would demonstrate less benefit. This is consistent with the class-wide reduction reported in obesity trials, where weight loss is the main intervention target (Karakasis et al., 2025). There is a neutral AF effect in people with obesity and without diabetes (de Oliveira Almeida et al., 2024, as cited in Zhang et al., 2025), suggesting that baseline risk of AF (in diabetes) may have a role in the absolute and relative benefit.

Endpoint Ascertainment and Statistical Power

AF is a condition that doesn't necessarily cause symptoms and can come and go. Studies based on adverse event reporting only identify clinically apparent or occurrences that were recorded as an adverse event; the number of events per study is low. Pooling is therefore subject to small-study effects, selective reporting and to choice of fixed-effect versus random-effects model. The synthesis by fixed-effect pooling reported a non-significant result with a point estimate in the same direction as the class-wide analysis, while the 30-trial analysis reported a null result in a different metric ("Association Between Glucagon-Like Peptide-1 [GLP-1] Receptor Agonists and Atrial Fibrillation Adverse Events," 2026; "Effect of Glucagon-Like Peptide-1 Receptor Agonists on Atrial Fibrillation Incidence," 2025). If you read it straight, then

you are favoring benefits at the point estimate and may be seeing no effect in your confidence interval.

Mediation by Weight and Metabolic Control

The weight-stratified cohort result and the reduction in genetic estimates following the adjustment for BMI and T2DM are consistent with a mediation model (Khalil et al., 2025; Zhang et al., 2025). In this model, GLP-1RAs act indirectly on AF through their effects on decreasing adiposity, glycemia, and blood pressure and inflammation without a large direct effect on the myocardium. There is a practical corollary to this interpretation: the benefit would be more likely to be seen in patients who respond metabolically and less in those who don't. It also works with the above stated limitation of the genetic analysis which was unable to distinguish the effects of the drug target from the effects of adiposity and diabetes.

Heart Rate Versus Arrhythmia

There is no randomized evidence of excess arrhythmia with increases in resting HR. The sinus node effect does not seem to reflect sympathetic overactivity or atrial irritability (Lubberding et al., 2024), but instead is likely a direct receptor-mediated pharmacodynamic effect. There are no excessive numbers of tachycardia events in trial-level analyses, and in fact, there is a reduced risk of sinus node dysfunction (Trial Level Analysis – "Reduced Risk of Sinus Node Dysfunction," 2026). However, it is possible that some vulnerable subgroups like those with heart failure or structural heart disease, may be different, which existing analyses cannot answer due to the fact that cardiac substrate is rarely stratified in rhythm outcomes.

Heterogeneity of Metrics

Lastly, the effect sizes in Figure 4 are presented as relative risks, odds ratios and hazard ratios from various populations. Odds ratios overestimate risk reductions when events are common, hazard ratios are dependent on the length of follow-up and on censoring, and cohort estimates account for residual confounding. The graph should then be used as a map of direction and precision rather than as a quantitative total.

Clinical Implications

Safety of Prescribing

Considering all available evidence, GLP-1RAs should not be withheld from people with diabetes because of the risk of arrhythmia. Randomized safety analyses revealed no increased risk of major arrhythmias or sudden cardiac death (Al-Sadawi et al., 2023; Boulmpou et al., 2023), and there was neither a signal nor an increased risk of AF, and no signal for bradyarrhythmia. The rise in heart rate (small or many beats per minute; depending on the agent and dose – "Effect of Glucagon-Like Peptide-1 Receptor Agonists on Heart Rate," 2026) should be expected and discussed with the patient; otherwise, they could be a reason for premature withdrawal.

Alignment With Guidelines

Focus on the metabolic influences of AF is supported as per current guidance. The 2024 European Society of Cardiology (ESC) guideline identifies hypertension, heart failure, T2DM and obesity as risk factors that contribute to AF onset and progression (Van Gelder et al., 2024); the 2023 American College of Cardiology and the American Heart Association (ACC/AHA) guideline considers risk-factor management as part of comprehensive AF care (Joglar et al., 2024). GLP-1RAs are recommended by the American Diabetes Association Standards of Care for individuals with T2DM who have a heart failure with preserved ejection fraction (HFpEF) and other cardiometabolic comorbidities, such as obesity (American Diabetes Association Professional Practice Committee, 2025). Until now, there are no guidelines recommending the use of GLP-1RAs as a specific treatment for AF prevention, and the evidence reviewed here is not yet adequate for this purpose.

Communicating With Patients

The rate effect is a predictable pharmacodynamic effect and this can help to avoid unnecessary alarm by anticipatory counseling. Patients can be informed that a

slight increase in resting pulse can be seen, this depends on the agent and dose ("Effect of Glucagon-Like Peptide-1 Receptor Agonists on Heart Rate", 2026), and that current evidence does not indicate that it is indicative of a dangerous arrhythmia (Lubberding et al., 2024). They should be asked if their palpitations, lightheadedness, or fainting were sustained, which should be evaluated as any other rhythm disorder. In patients with existing AF, the drug should not be marketed as an antiarrhythmic therapy since this has not yet been established and in some patients plans for rate control may need to be reassessed if resting rate increases. Patients who experience significant weight loss should also be reminded that weight loss can affect BP, medication needs and risk of rhythm, so cardiometabolic therapy should be reassessed periodically.

A Pragmatic Monitoring Framework

An approach that has been found to be pragmatic is as follows: review the risk of rhythm before initiating treatment, treat for the indicated rhythm disorder, and monitor resting HR and symptoms. Routine electrocardiograms and/or ambulatory monitoring should be performed in patients with persistent, unexplained increased rates, palpitations, or syncope; if ambulatory monitoring is performed, documented AF should be treated in accordance with guideline-directed therapy. The figure 7 is a conceptual synthesis by the reviewer, and is not derived from any guideline. The other clinical considerations are presented in Table 4, along with research needs.

Figure 7

Conceptual Framework for Rhythm Surveillance in Patients Starting a GLP-1 Receptor Agonist

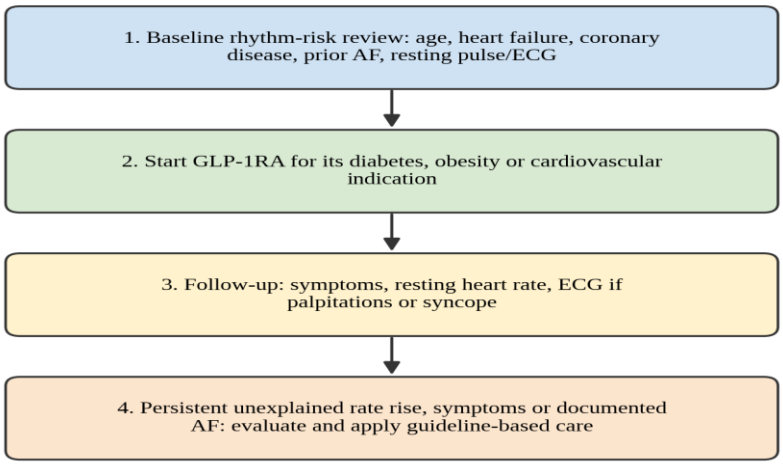


Table 4

Clinical Considerations and Research Priorities

Domain	Current position	Research priority
Patient selection	Hypertension, heart failure, T2DM and obesity contribute to AF (Van Gelder et al., 2024); GLP-1RA indications follow diabetes standards (American Diabetes Association Professional Practice Committee, 2025)	Trials in high AF-risk groups with prespecified rhythm outcomes
Rhythm ascertainment	Trials were not powered for AF and relied largely on adverse-event reporting ("Association Between Glucagon-Like Peptide-1 [GLP-1] Receptor Agonists and Atrial Fibrillation Adverse Events," 2026)	Continuous or implantable rhythm monitoring

Domain	Current position	Research priority
Heart rate	Rise varies by agent and dose ("Effect of Glucagon-Like Peptide-1 Receptor Agonists on Heart Rate," 2026)	Long-term ambulatory data and mechanistic studies in humans
Bradycardia and conduction	Sparse; abstract-level data suggest no harm ("Reduced Risk of Sinus Node Dysfunction," 2026)	Full-text pooled analyses; pacemaker and block outcomes in older patients
Perioperative use	Observational and early randomized data in cardiac surgery ("GLP-1 Receptor Agonists in Cardiac Surgery," 2026)	Completed randomized trials in surgery and ablation
Mediation	Benefit appears tied to weight loss (Khalil et al., 2025; Zhang et al., 2025)	Formal mediation analysis of weight, glycemia and blood pressure

Note. AF = atrial fibrillation; T2DM = type 2 diabetes mellitus.

Summary of Principal Findings

There are four salient findings. The direction of the AF estimate is favorable or neutral in all designs, ranging from a relative risk of 0.58 in semaglutide trials (Saglietto et al., 2024) to an odds ratio of 0.96 in the largest cohort (Khalil et al., 2025); the analyses that reach statistical significance are those in semaglutide, class-wide obesity, observational, and genetic data. Second, its apparent benefit is limited to weight loss, and is not seen in estimates of genes that are corrected for adiposity and diabetes (Khalil et al., 2025; Zhang et al., 2025). Third, with GLP-1 receptor agonists, there is no excess of tachyarrhythmia and a direct sinus node mechanism for increases in resting heart rate, that exist to a greater degree with some agents than others (Lubberding et al., 2024; "Effect of Glucagon-Like Peptide-1 Receptor Agonists on Heart Rate," 2026). Fourth, there is sparse evidence, and no evidence that suggests harm, for bradyarrhythmia ("Reduced Risk of Sinus Node Dysfunction," 2026).

Strengths and Limitations

There are a number of strengths to this review. It focuses on evidence within the period of 2023 - 2026, includes all significant designs, and does not convert reported effect metrics. It also incorporates mechanistic information on the sinus node, which is not typically correlated with clinical rhythm results, and it treats bradycardia directly, in contrast with most current reviews.

These restrictions are significant. First, the review was narrative, and was not registered, and the screening and the use of formal risk-of-bias tools were not performed in a dual independent way, so this may be a problem of incompleteness of the selection of sources. Second, several effect estimates such as the result for sinus node dysfunction and the 30-trial analysis are from abstracts, and could be updated when the studies are published. Third, certain information about the cohorts and trials was only summarized in later papers, so it is subject to the possible errors of the summarizing source. Fourth, certainty ratings are qualitative. Fifth, this article uses the term multi-cohort analysis but did not include a new patient-level analysis, it was rather a combination of several published cohorts. Last, there is limited evidence for bradycardia and publication bias for positive results cannot be ruled out.

Future Directions

The next priorities for research are listed. The most obvious need is randomized trials with AF as a prespecified outcome, preferably with continuous or implantable rhythm monitoring, which would eliminate the lack of certainty due to adverse-event reporting. The beneficial effect of the drugs could be distinguished from the beneficial

effect of weight, glycemia and blood pressure, by conducting mediation analyses. There is a lack of information on conduction and bradyarrhythmia (including AV block) in older people with diabetes, and this is an area of interest for prospective studies of pacemaker implantation and AV block.

Mechanistically, human electrophysiological studies should evaluate if the calcium-clock mechanism observed in animal sinus node tissue exists in humans and whether increases in rate are lessened over time in humans (Lubberding et al., 2024). A upcoming trial of transcatheter aortic valve replacement (TAVR) has been described and with other studies during the perioperative and post-ablation periods, will help clarify the role of GLP-1RAs as adjunctive antiarrhythmic treatment. Lastly, standardization of the reporting of outcomes for heart rate, heart rhythm, and weight change across future trials of dual and triple incretin agonists would enable direct comparisons between the agents, like those shown in the heart-rate differences between orforgliron and tirzepatide.

Going forward, results of syntheses should be presented with clear definitions, be prespecified by subgroup (agent, diabetes status, and baseline cardiac disease), and include both absolute and relative effects. Time-to-event modelling with consistent censoring could be used via individual patient data meta-analysis, and sponsors could provide adjudicated rhythm data from completed trials. Pharmacovigilance databases can be used to complement trials for rare conduction events, but with due consideration of reporting bias.

Conclusion

The evidence published from 2023 to 2026 shows that GLP-1RAs are safe to use in people with diabetes, electrophysiologically speaking. The effect is agent- and dose-dependent, and occurs directly on the sinus node, which does not lead to the development of more tachyarrhythmia, and the trial data do not indicate more sinus node dysfunction. Semaglutide meta-analyses, class-wide analyses of obesity, and observational and genetic studies suggest reduced risk for AF, but some confidence intervals overlap with no effect and there is a relationship between benefit and weight loss and metabolic improvement. Evidence of bradycardia and conduction disease is sparse and needs to be enriched. It is safe to prescribe GLP-1RAs for the approved indications without reservations or concerns about arrhythmia benefits, and the antiarrhythmic effect is potentially possible, but yet to be proven, pending on trials specifically powered for a rhythm endpoint. The practical take-home messages to people with diabetes are that the metabolic and cardiovascular effects of GLP-1RAs can be achieved without any adverse impact on rhythm, and that benefit of effective weight and glycemic control is a potential additional benefit of GLP-1RAs, not an independent one.

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