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RESEARCH

Disproportionality analysis of ventricular extrasystoles reported with semaglutide in VigiBase and the FDA Adverse Event Monitoring System

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Abstract

Semaglutide is widely used to treat type 2 diabetes and obesity and to reduce cardiovascular risk. However, its association with cardiac rhythm-related adverse-event reporting in routine clinical practice remains incompletely characterized. To investigate cardiovascular and rhythm-related adverse-event reporting associated with semaglutide, with a focus on ventricular extrasystoles, we conducted a disproportionality analysis of individual case safety reports from VigiBase and the FDA Adverse Event Monitoring System (AEMS; formerly the FDA Adverse Event Reporting System [FAERS]). Reports were included when semaglutide was recorded as a suspected drug, according to database-specific criteria. Cardiovascular outcomes were identified using Medical Dictionary for Regulatory Activities Preferred Terms. Reporting odds ratios (RORs) and 95% confidence intervals (CIs) were calculated. A cross-database reporting signal was defined as at least three semaglutide-associated reports and a lower 95% CI bound exceeding 1 in each database. After deduplication and application of the predefined inclusion criteria, 1980 semaglutide-associated cardiovascular reports from VigiBase and 1754 from AEMS were included. Among the screened cardiovascular and rhythm-related preferred terms, ventricular extrasystoles was the only term that met the prespecified signal criterion in both databases. Ventricular extrasystoles, clinically corresponding to premature ventricular contractions, showed disproportionate reporting in VigiBase (ROR 1.77, 95% CI 1.31–2.40) and AEMS (ROR 1.37, 95% CI 1.00–1.88; unrounded lower CI bound > 1). Ventricular extrasystoles showed a consistent disproportionality signal across VigiBase and AEMS. Although spontaneous reporting data cannot establish incidence, causality, or prognostic significance, this finding warrants prospective investigation using systematic electrocardiographic assessment and ambulatory rhythm monitoring.

Keywords Semaglutide · Ventricular extrasystoles · Premature ventricular contractions · Pharmacovigilance · AEMS · VigiBase

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), including semaglutide, have transformed the management of type 2 diabetes and obesity by improving glycaemic control, promoting sustained weight loss, and reducing cardiovascular risk (Drucker 2022; Eberly et al. 2021; Gudzune and Kushner 2024; Kelly et al. 2024). Large randomized clinical trials have shown that semaglutide improves not only metabolic outcomes but also cardiovascular outcomes. In a pivotal trial involving more than 17,000 overweight or obese patients with established cardiovascular disease (CVD), once-weekly semaglutide reduced the risk of major adverse cardiovascular events, including myocardial infarction, stroke, and cardiovascular death, by 20% over a median

Daobin Wu and Rongying Yang contributed equally to this work.

Key points
- Ventricular extrasystoles emerged as a reproducible rhythm-related disproportionality finding associated with semaglutide across both VigiBase and AEMS.
- This signal was modest in magnitude but rhythm-specific, and sensitivity analyses suggested that it was not primarily explained by co-reported gastrointestinal adverse events.
- These findings identify ventricular ectopy as a focused safety question that warrants prospective evaluation using electrocardiographic assessment and ambulatory rhythm monitoring.

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follow-up of 33 months (Lincoff et al. 2023). Subsequent studies extended these benefits to patients with atherosclerotic CVD and to those with mildly reduced or preserved ejection fraction, demonstrating reductions in cardiovascular death, worsening heart failure, and heart failure-related hospitalization (Deanfield et al. 2024; Kosiborod et al. 2024). Consistent with these findings, meta-analyses of randomized controlled trials have reported no increased risk of atrial or ventricular arrhythmias with semaglutide treatment (Cesaro et al. 2025; Wu et al. 2022; Zhang et al. 2024).

Despite these established cardiometabolic benefits (Harris 2023; Solomon et al. 2024), the safety profile of semaglutide continues to evolve as its use expands rapidly in both diabetic and non-diabetic populations. Gastrointestinal (GI) adverse events, including nausea, vomiting, delayed gastric emptying, biliary disease, pancreatitis, and gastroparesis, are among the most commonly reported complications (Osei et al. 2024; Sodhi et al. 2023). In addition to their direct clinical effects, GI disturbances may influence gut microbial composition, bile acid metabolism, intestinal barrier function, and circulating metabolites with potential cardiovascular relevance. For example, trimethylamine-N-oxide has been associated with arrhythmogenesis and adverse cardiovascular outcomes, whereas reductions in protective short-chain fatty acids may contribute to systemic inflammation and autonomic imbalance. Through the gut-heart axis, these changes could theoretically influence myocardial electrical stability (Abdulrahim et al. 2025; Gao et al. 2024; Huang et al. 2023; Snelson et al. 2025).

Concerns have therefore emerged regarding possible cardiac rhythm disturbances in patients receiving GLP-1RAs. Ventricular extrasystoles, clinically corresponding to premature ventricular contractions, are common in the general population and are often benign in individuals without structural heart disease. However, they may cause symptoms, reflect myocardial or autonomic dysfunction, and, in susceptible patients, coexist with or precede more clinically significant ventricular arrhythmias (Dukes et al. 2015; Konemann et al. 2023). Ventricular ectopy has not been systematically evaluated as an independent safety outcome in most large randomized trials of semaglutide, where arrhythmic events were infrequent and were often incorporated into broader composite cardiovascular endpoints.

Real-world pharmacovigilance databases complement randomized trials by enabling the detection of rare or unexpected adverse drug reaction signals across large and heterogeneous populations. However, evidence regarding semaglutide-associated ventricular extrasystoles in routine clinical practice remains limited. To address this gap, we conducted a pharmacovigilance signal-detection study using VigiBase and AEMS. This study was designed to identify disproportionality signals and generate hypotheses, not to estimate incidence, comparative clinical risk, or causality.

Methods

Study design

We conducted a two-stage pharmacovigilance signal-detection study using VigiBase and AEMS. Cardiovascular and rhythm-related outcomes were identified using a prespecified MedDRA Preferred Term-based approach. The complete PT inventory, clinical grouping, rhythm-related classification, and analytic role are provided in Supplementary Table S1. A validated SMQ-based sensitivity analysis was not performed in the present study. Therefore, the analysis should be interpreted as an exploratory PT-based disproportionality screen.

Data sources

This study was designed to evaluate cardiovascular adverse event reports associated with semaglutide using two major pharmacovigilance systems: the FDA Adverse Event Monitoring System (AEMS; formerly the FDA Adverse Event Reporting System, FAERS) (Zhang et al. 2023; FDA n.d.) and the World Health Organization global database of individual case safety reports, VigiBase (Igawa et al. 2024; WHO n.d.). AEMS is a publicly accessible database that collects spontaneous safety reports from patients, healthcare professionals, and pharmaceutical companies in the United States. VigiBase, developed and maintained by the Uppsala Monitoring Centre, is the world's largest pharmacovigilance database and aggregates individual case safety reports from more than 130 countries.

To capture post-marketing experience with semaglutide, we extracted data from the launch of Ozempic®, the first marketed semaglutide formulation, to the latest available data cutoff. VigiBase data covered December 2017 to November 2025, and AEMS data covered the first quarter of 2017 to the third quarter of 2025. Because many VigiBase reports originate from national pharmacovigilance systems, including the United States, some overlap with AEMS reports is possible. Therefore, AEMS and VigiBase should not be regarded as fully independent case sources for this study. Rather, they represent partially overlapping but methodologically distinct pharmacovigilance systems, with different reporting pathways, data structures, deduplication procedures, and curation processes. Accordingly, our dual-database approach was used to assess the consistency of disproportionality signals across two major safety-reporting systems, rather than to provide independent epidemiological replication.

The data of VigiBase was obtained from the Uppsala Monitoring Centre (UMC) in a duplicate-free form. UMC

used the "vigiMatch" machine learning model, which predicts suspected duplicate case reports by comparing patient age, gender, onset date, summaries of all dates in the report, adverse events, drugs/vaccines, and an external indicator flag (when the case identifier in a report matches the sending party's report ID or the global unique case identifier in another report). After identifying the duplicates, a complete linkage clustering is applied to select the main report with the highest vigiGrade integrity score.

For AEMS, the data were obtained from the FDA in their original form and were de-duplicated according to the methods recommended by the FDA. Records were sorted by CASEID, FDA_DT, and PRIMARYID. For each CASEID, only the record with the latest FDA_DT was retained. If the CASEID and FDA_DT were the same, the record with the highest PRIMARYID was retained. This method preserves the latest complete version of each case and removes subsequent reports that would increase the case count if retained. After de-duplication, literature cases were retained as separate cases. Since AEMS and VigiBase are two independent reporting systems with different data structures and overlapping but not fully identical reporting sources, no additional cross-database de-duplication operations were performed.

Case identification and cohort construction

A standardized data-processing workflow was applied to both databases. The exposure cohort was identified using the generic name "semaglutide" and all marketed brand names, including Ozempic®, Rybelsus®, and Wegovy®. Reports were included in the semaglutide-exposed group only when semaglutide was coded as the primary suspected drug in AEMS or as a suspected drug in VigiBase, thereby reducing potential misclassification from concomitant therapies.

Cardiovascular outcomes were identified using the Medical Dictionary for Regulatory Activities (MedDRA, version 28.0) (Medical dictionary for regulatory activities n.d.). All adverse event terms were mapped to standardized preferred terms and system organ classes. Reports were classified as cardiovascular cases when at least one reported adverse event matched a predefined cardiovascular term. Key covariates, including age, sex, indication for use, and dosage, were extracted and harmonized across databases to support descriptive and subgroup analyses.

Outcome definitions

Cardiovascular adverse events were identified using MedDRA version 28.0 preferred terms. Before analysis, all selected preferred terms were classified into prespecified clinical categories: major cardiovascular events, major rhythm-related events, conduction disorders, ventricular ectopy, atrial arrhythmias, and other cardiac symptoms. Ventricular extrasystoles was analyzed as the MedDRA preferred term corresponding clinically to premature ventricular contractions. Palpitations and sinus tachycardia were treated as symptom-level rhythm-related terms rather than major arrhythmias.

To improve transparency and reproducibility, the complete list of included MedDRA preferred terms and their prespecified clinical classifications is provided in Supplementary Table S1. When multiple cardiovascular preferred terms were reported in the same case, the case was classified according to a prespecified hierarchy: cardiac arrest or fatal arrhythmic events; ventricular tachyarrhythmias; major cardiovascular events; atrial arrhythmias or conduction disorders; ventricular extrasystoles; and symptom-level rhythm-related terms. This hierarchy was used only to describe event structure and did not imply clinical severity at the individual-patient level.

In this manuscript, the MedDRA preferred term "ventricular extrasystoles" was used for signal detection, whereas the clinically equivalent term premature ventricular contractions (PVCs) was used when discussing clinical interpretation.

Because the primary objective was to evaluate rhythm-related safety signals associated with semaglutide, subsequent analyses focused on arrhythmia-related preferred terms, particularly ventricular extrasystoles. Broader cardiovascular preferred terms were retained only for exploratory signal screening and contextualization of the overall cardiovascular reporting profile.

Data cleaning and standardization

The data of VigiBase was obtained from the Uppsala Monitoring Centre (UMC) as a deduplicated extract of individual case safety reports. UMC used the "vigiMatch" machine learning model, which predicts suspected duplicate case reports by comparing patient age, gender, onset date, summaries of all dates in the report, adverse events, drugs/vaccines, and an external indicator flag (when the case identifier in a report matches the sending party's report ID or the global unique case identifier in another report). After identifying the duplicates, a complete linkage clustering is applied to select the main report with the highest vigiGrade integrity score.

For AEMS, the data was obtained from the FDA in its original form and was de-duplicated according to the methods recommended by the FDA. Records were sorted by CASEID, FDA_DT, and PRIMARYID. For each CASEID, only the record with the latest FDA_DT was retained. If the CASEID and FDA_DT were the same, the record with the highest PRIMARYID was retained. This method preserves the latest complete version of each case and removes subsequent reports that would increase the case count if retained. After de-duplication, literature

cases were retained as separate cases (Supplementary Table S2). Since AEMS and VigiBase are separate pharmacovigilance systems with different data structures and overlapping but not fully identical reporting sources, no additional cross-database de-duplication operations were performed.

When multiple cardiovascular preferred terms were reported in a single case, the event was classified according to a predefined severity-first rule, assigning the case to the most clinically severe event category. GI adverse events reported after semaglutide use were also extracted to explore potential co-reporting with cardiovascular events. These included reports classified under the MedDRA system organ class "Gastrointestinal disorders", as well as the 30 most frequently reported gastrointestinal preferred terms and their corresponding case counts. The overall data-processing workflow is shown in Fig. 1.

Statistical methods

Baseline characteristics were summarized as frequencies and percentages for categorical variables and as means with standard deviations or medians with interquartile ranges for continuous variables. Group comparisons were performed using the chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables, as appropriate.

For signal detection, disproportionality analysis was performed using the reporting odds ratio (ROR) (Bate and Evans 2009). A pharmacovigilance signal was defined a priori as at least three reports with a lower bound of the 95% confidence interval of the ROR exceeding 1 in both databases. The ROR compares the reporting odds of a specific adverse event for semaglutide with that for all other drugs in the database. It was calculated as (Pace and Multani 2018):

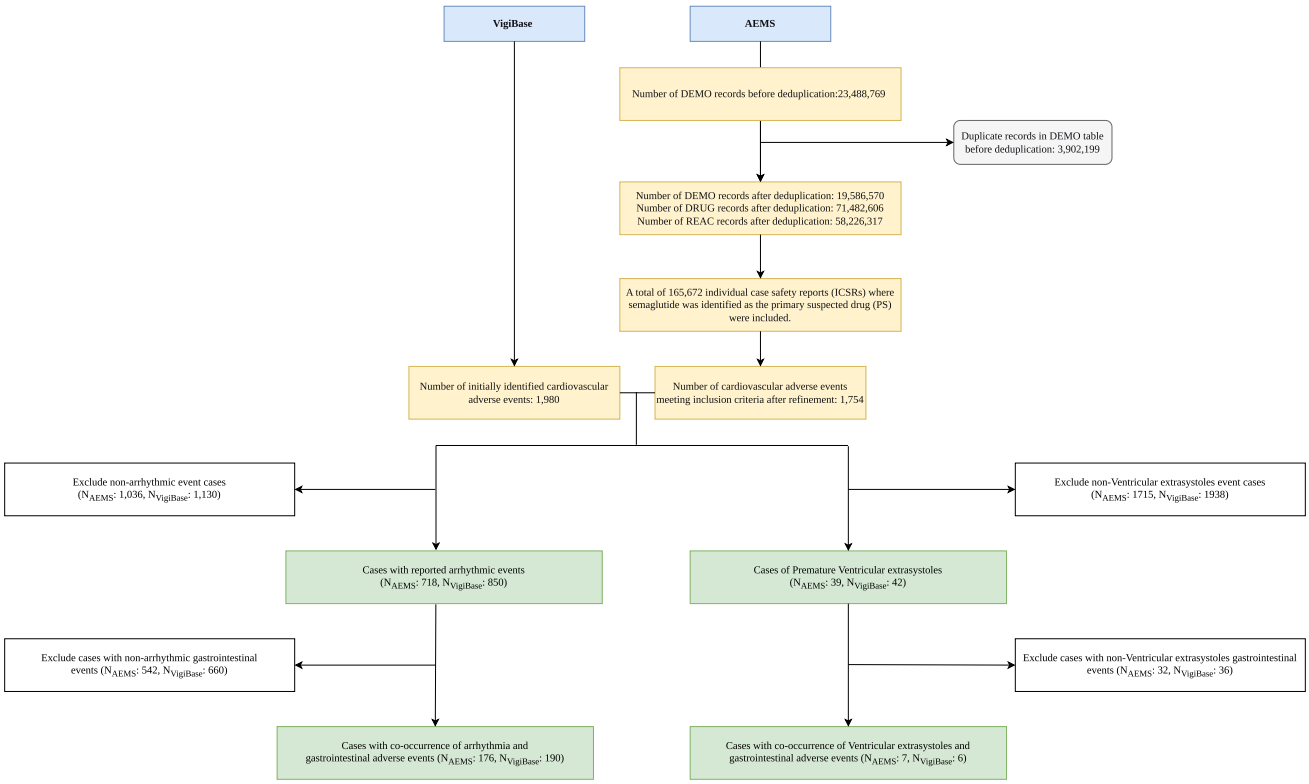


Fig. 1 Flowchart of semaglutide-associated cardiovascular and arrhythmia reports in VigiBase and AEMS. The flowchart shows the selection of adverse event reports related to semaglutide from VigiBase and AEMS. After deduplication and application of the predefined inclusion criteria, 1980 semaglutide-associated cardiovascular reports were identified in VigiBase and 1754 in AEMS. After exclusion of non-arrhythmia events, 850 arrhythmia reports in VigiBase and 718 in AEMS were retained. Among these, arrhythmia and gastrointestinal adverse events were co-reported in 190 VigiBase reports and 176 AEMS reports. Ventricular extrasystoles, clinically corresponding to premature ventricular contractions, were identified in 42 VigiBase reports and 39 AEMS reports, of which 6 and 7 reports, respectively, also included gastrointestinal adverse events. Abbreviations: AEMS, FDA Adverse Event Monitoring System; PVCs, premature ventricular contractions; VigiBase, WHO global database of individual case safety reports

$$ROR = \frac{(a/b)}{(c/d)}$$

where a is the number of reports of a specific adverse reaction with semaglutide, b is the number of reports for semaglutide without that reaction, c is the number of reports of the same reaction with other drugs, and d is the number of reports for other drugs without that reaction. The ROR is a disproportionality metric that quantifies whether a drug-event pair is reported more frequently than expected relative to the reporting background in the database. It does not estimate incidence, absolute risk, relative clinical risk, or causal effect. Therefore, all ROR-based findings were interpreted as pharmacovigilance disproportionality findings.

All analyses were performed using R software (version 4.5.0), and figures were generated using GraphPad Prism (version 10.1.2). A two-sided P value < 0.05 was considered statistically significant.

Descriptive, subgroup, and sensitivity analyses

Demographic and clinical characteristics were summarized as means with standard deviations or medians with interquartile ranges for continuous variables and as frequencies with percentages for categorical variables. Reported indications for semaglutide use were harmonized into prespecified clinical categories, including diabetes, weight management, unknown or unspecified indication, and other indications, before subgroup analyses (Supplementary Table S3).

Subgroup and bias-related sensitivity analyses were conducted according to these clinical categories. To address potential confounding by indication and channeling bias, comparator analyses were performed using clinically relevant cardiometabolic therapies. Metformin was selected as a first-line glucose-lowering therapy for type 2 diabetes (Pernicova and Korbonits 2014), and therefore served as a diabetes-related reporting background. Dulaglutide was selected as another GLP-1 receptor agonist to assess whether the ventricular extrasystoles signal might reflect a GLP-1RA class effect rather than a semaglutide-specific signal (Scott 2020). Insulin glargine was selected as an injectable glucose-lowering therapy commonly used in patients with more advanced type 2 diabetes (Dahl et al. 2022), thereby providing a secondary exploratory comparator related to diabetes severity, injectable therapy, and higher baseline cardiovascular risk. Atorvastatin was included only as a supplementary cardiometabolic comparator because it is frequently prescribed to patients with cardiovascular risk factors (Galicia-Garcia et al. 2020). However, because it does not share the same therapeutic indication as semaglutide, this comparison was considered exploratory and interpreted cautiously.

Subgroup analyses used the relative risk ratio (RR) as the primary association metric. Statistical comparisons were performed using chi-square tests, Wilcoxon rank-sum tests, Kruskal-Wallis tests, or Fisher's exact tests, as appropriate. Homogeneity of odds ratios across strata was assessed using the Breslow-Day test. The null hypothesis was that the stratum-specific odds ratios were equal, and the test statistic was evaluated against a chi-square distribution with $k - 1$ degrees of freedom, where k denotes the number of strata. The corresponding P values are reported as P for interaction in the subgroup plots and represent tests of heterogeneity on the odds-ratio scale. These analyses were exploratory.

Association between gastrointestinal events and arrhythmias

We assessed whether gastrointestinal (GI) events and arrhythmias were co-reported within the same individual case safety report (ICSR). GI events were defined as reports classified under the MedDRA System Organ Class (SOC) "Gastrointestinal disorders", and arrhythmias were defined as reports classified under the High Level Group Term (HLGT) "Cardiac arrhythmias". For each database, a two-by-two contingency table was constructed. The exposed group comprised reports containing at least one GI event, and the unexposed group comprised reports without GI events. The case group comprised reports containing at least one arrhythmia event, and the control group comprised reports without arrhythmia events. Cells were defined as follows: a, GI event and arrhythmia; b, GI event without arrhythmia; c, no GI event with arrhythmia; d, no GI event and no arrhythmia. The odds ratio (OR) was calculated as $(a \times d)/(b \times c)$, and the relative risk (RR) was calculated as $[a/(a+b)]/[c/(c+d)]$, both with 95% confidence intervals. The null hypothesis was that GI events and arrhythmia reporting were independent; the alternative hypothesis was that an association exists. Statistical comparisons were performed using the chi-square test or Fisher's exact test, as appropriate. A two-sided P value < 0.05 was considered statistically significant. This analysis was exploratory and hypothesis-generating.

Ethics statement

AEMS and VigiBase are publicly available or accessible upon request as anonymized pharmacovigilance databases. All personal identifiers are removed. In accordance with the Declaration of Helsinki and prevailing research ethics guidelines, studies based exclusively on such de-identified secondary data do not require institutional ethics approval or informed consent (Goodyear et al. 2007).

Reporting standards

The design, analysis, and reporting of this study followed the "Guidelines for the Analysis of Disproportionate Adverse Drug Reaction Reports in Pharmacovigilance Databases" (READUS-PV) (Fusaroli et al. 2024a; Fusaroli et al. 2024b; READUS-PV n.d.).

Results

Study population and exploratory cardiovascular screening

After deduplication and application of the predefined inclusion criteria, 1754 semaglutide-associated cardiovascular reports from AEMS and 1980 reports from VigiBase were included in the final analytic dataset (Supplementary Table S4 and Table S5). The most frequently reported cardiovascular events included atrial fibrillation, palpitations, tachycardia, and myocardial infarction.

We performed an exploratory disproportionality screening of selected cardiovascular and rhythm-related MedDRA preferred terms to contextualize the overall cardiovascular reporting profile of semaglutide. Figure 2A summarizes the reporting odds ratio point estimates for these selected terms across AEMS and VigiBase, while Fig. 2B and C show the corresponding semaglutide-associated report counts in AEMS and VigiBase, respectively. Signal status was determined according to the prespecified ROR-based criterion and is summarized in Supplementary Table S4. In this screening, ventricular extrasystoles was the only preferred term that met the prespecified signal criterion in both databases. Several additional preferred terms met the signal criterion in AEMS only and were therefore interpreted as exploratory database-specific findings. Accordingly, ventricular extrasystoles was selected for focused characterization.

Structural distribution of cardiovascular events

To examine the hierarchical structure of reported cardiovascular events, we constructed Sankey diagrams based on MedDRA classifications, tracing reports from the system organ class (SOC) "Cardiac disorders" to higher-level group terms (HLGTs), higher-level terms (HLTs), and preferred terms (PTs). In VigiBase, most selected reports (90.3%) mapped to the HLGT category "Cardiac arrhythmias", whereas a smaller proportion mapped to the "coronary artery disease" branch. In AEMS, the largest proportion of selected reports (78.1%) mapped to "cardiac disorders, signs and symptoms not elsewhere classified", with fewer reports assigned to arrhythmia-related branches.

Despite these structural differences, both databases contained arrhythmia-related categories at the HLT and PT levels (Fig. 2D and E). These Sankey diagrams describe the MedDRA hierarchy and reporting distribution of selected cardiovascular terms, rather than defining cross-database signal status. According to the prespecified ROR-based signal criterion, ventricular extrasystoles was the only preferred term that met the signal threshold in both VigiBase and AEMS and was therefore selected for focused characterization.

Exploratory analysis of gastrointestinal events and arrhythmias

Because semaglutide is commonly associated with GI adverse events, such as nausea, vomiting, and diarrhoea (Ahmann et al. 2018; Liu et al. 2022), we explored whether GI events were co-reported with arrhythmias. In the AEMS SOC-level analysis, GI events were the most frequently reported adverse events among semaglutide users and showed disproportionate reporting (ROR 3.89, 95% CI 3.85-3.94; Fig. 3A). Among the 30 most frequently reported GI preferred terms, 28 showed positive disproportionality signals (Fig. 3B; Supplementary Table S6).

In contrast, cardiovascular events at the SOC level showed reduced reporting frequency relative to other drugs (ROR 0.46, 95% CI 0.44–0.48). This finding is consistent with the established cardiovascular benefits of semaglutide observed in randomized trials (Lincoff et al. 2023; McGuire et al. 2025), although SOC-level results should be interpreted cautiously because they combine heterogeneous cardiovascular outcomes.

Baseline characteristics of arrhythmia and GI co-reporting groups

Baseline characteristics are shown in Table 1 for VigiBase and Table 2 for AEMS. In both databases, patients with arrhythmia reports and those with combined arrhythmia and GI reports were broadly similar to the overall semaglutide-associated adverse-event population. Women predominated overall, accounting for 58.0% of AEMS reports and 60.0% of VigiBase reports, whereas the proportion of men was higher among arrhythmia reports, accounting for 43.0% in AEMS and 41.0% in VigiBase.

In AEMS, patients with combined arrhythmia and GI events tended to be older, with a mean age of 60.9 years and 50.0% aged $\geq$ 60 years, compared with 32.0% in VigiBase. Most reports originated from the Americas, followed by Europe, and reporting increased over time, paralleling the rapid global uptake of semaglutide. Weight

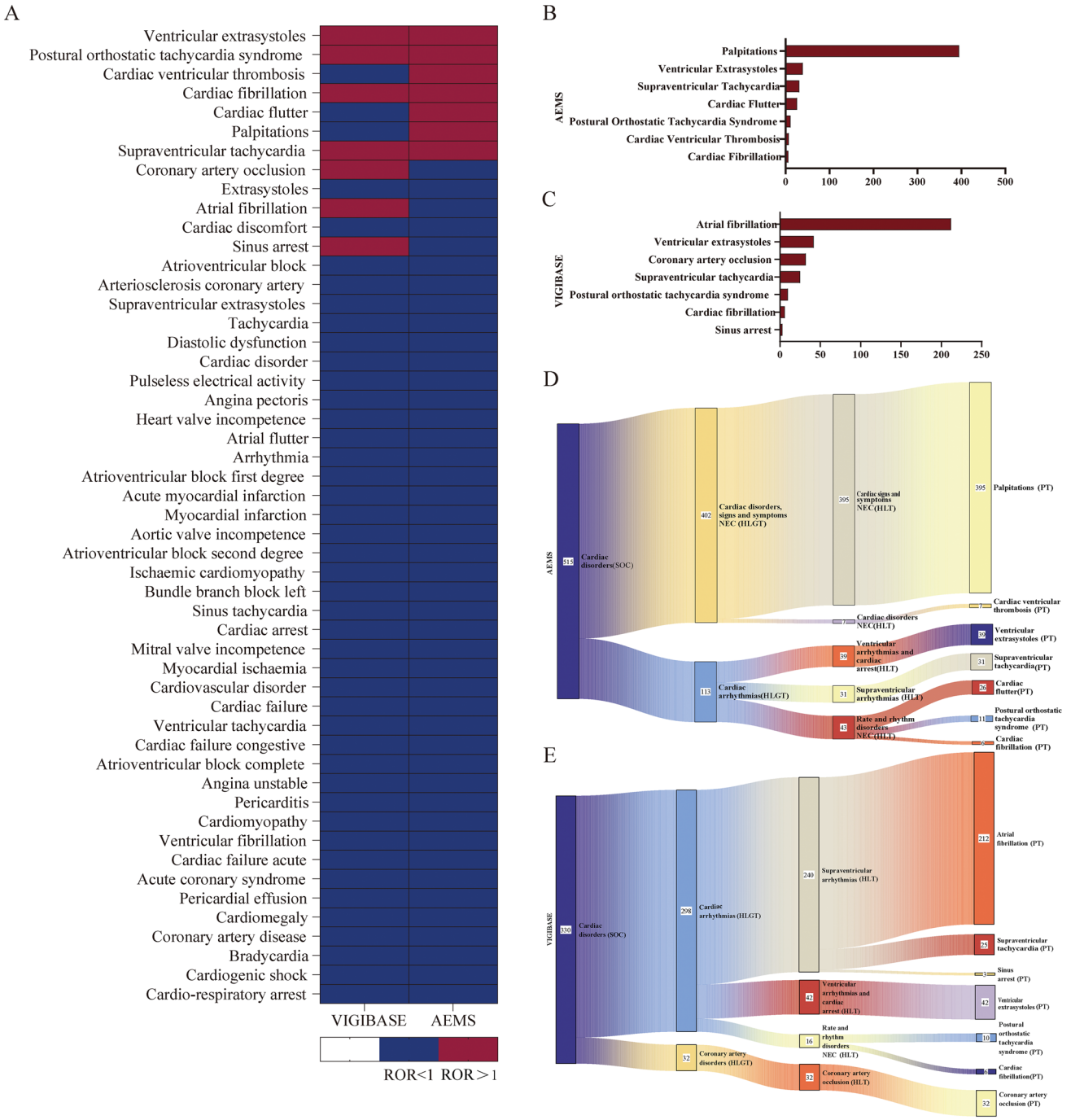


Fig. 2 Exploratory cardiovascular signal screening and MedDRA-based classification of semaglutide-associated reports. **A** The heatmap shows the point estimates of the reporting odds ratio (ROR) of cardiovascular adverse events associated with semaglutide in VigiBase and AEMS. **B** and **C** The bar charts display semaglutide-associated report counts for selected cardiovascular and rhythm-related preferred terms with ROR point estimates > 1 in AEMS and VigiBase, respectively. **D** The sankey diagram in AEMS shows the hierarchical classification of semaglutide-associated cardiovascular reports based on MedDRA terms, from system organ class (SOC) to higher-level group terms (HLGT), higher-level terms (HLT), and preferred terms (PT), with the width of the nodes proportional to the number of reports. The largest branch in AEMS is "Cardiac diseases, signs and symptoms, unclassified" (HLGT). **E** The sankey diagram for VigiBase uses the same MedDRA hierarchy structure and the same node sequence. The largest branch in VigiBase is "Cardiac arrhythmias" (HLGT). Figures D and E are directly comparable, facilitating cross-database comparisons. These exploratory analyses are used to place the overall cardiovascular report situation in a specific context and identify signals related to heart rhythm for subsequent focused analysis. Abbreviations: AEMS, US Food and Drug Administration Adverse Event Monitoring System; HLGT, higher-level group term; HLT, higher-level term; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; ROR, reporting odds ratio; SOC, system organ class; VigiBase, World Health Organization Global Database of Individual Case Safety Reports

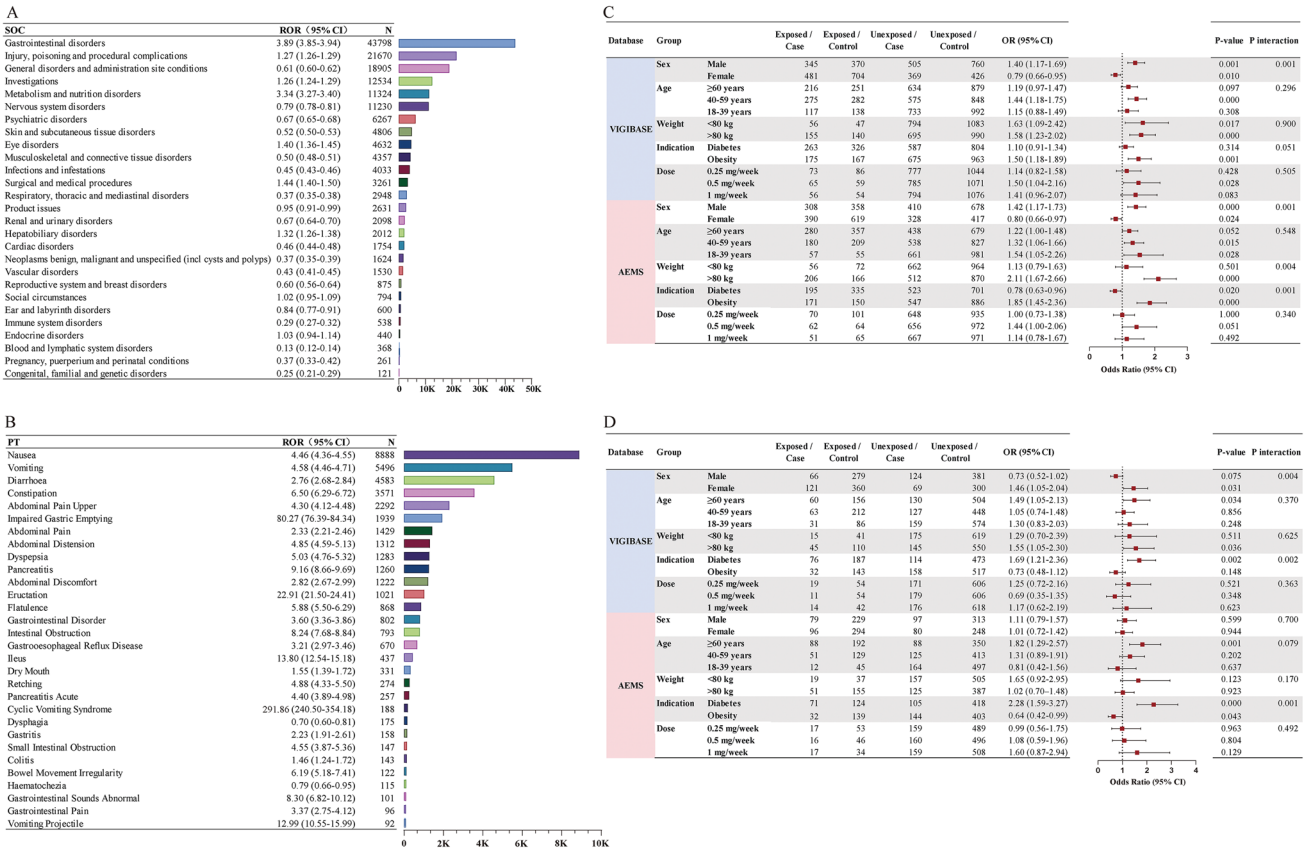


Fig. 3 Gastrointestinal adverse events and exploratory subgroup analyses of arrhythmia reports. **A** Reporting odds ratios (RORs) with 95% confidence intervals (CIs) for semaglutide-associated adverse events by System Organ Class (SOC) in AEMS. The bar chart on the right shows the corresponding number of reports for each SOC. **B** RORs with 95% CIs for the 30 most frequently reported gastrointestinal (GI) preferred terms (PTs) associated with semaglutide. The bar chart on the right shows the corresponding number of cases. **C** Exploratory subgroup analyses of arrhythmia reports in VigiBase and AEMS. **D** Exploratory subgroup analyses of reports co-reporting arrhythmia and GI adverse events in both databases. For each subgroup analysis (C and D), a separate two-by-two contingency table was constructed. The exposed group comprised reports belonging to the given subgroup, and the unexposed group comprised the remaining reports within the corresponding semaglutide-associated analysis cohort in the same database. For panel C, the case group comprised reports of arrhythmia, and the control group comprised reports of other adverse events. For panel D, the case group comprised reports of arrhythmia co-reported with GI events, and the control group comprised reports of other adverse events. Cells were defined as follows: a, exposed/case; b, exposed/control; c, unexposed/case; d, unexposed/control. The OR was calculated as (a/c)/(b/d) with 95% CIs. These analyses are exploratory and should be interpreted cautiously because of missing data, small numbers in some strata, and potential reporting bias

management was more frequently reported as an indication among arrhythmia cases than in the overall dataset, accounting for 24.0% of AEMS reports and 21.0% of VigiBase reports. Serious outcomes were more common among arrhythmia cases in VigiBase than in the overall population, with a similar pattern observed in AEMS.

Exploratory subgroup analyses of arrhythmia reports

Subgroup analyses of arrhythmia reports are shown in Fig. 3C and Supplementary Table S7. In VigiBase, arrhythmia reporting was higher among males, individuals aged 40–59 years, and patients with overweight or obesity. The 0.5 mg/week dose showed a positive association, whereas 0.25 mg/week and 1.0 mg/week did not. In AEMS, similar but stronger patterns were observed, with higher reporting among males, individuals aged 18-59 years, patients weighing > 80 kg, and those using semaglutide for obesity. By contrast, diabetes as the indication for semaglutide use was associated with lower arrhythmia reporting in AEMS.

Overall, arrhythmia reporting appeared to cluster in males, younger or middle-aged adults, and individuals with overweight or obesity. However, these subgroup findings should be considered exploratory because of missing data, potential reporting bias, and small numbers in some strata.

Table 1 Population demographics and clinical features of semaglutide-associated cardiovascular adverse events in the VigiBase database

Characteristic	Patients, No. (%)		
	ALL[a] (*N* = 1980)	CA[b] (*N* = 850)	CA & GI[c] (*N* = 190)
Sex (%)			
Female	1185 (60%)	481 (57%)	121 (64%)
Male	715 (36%)	345 (41%)	66 (35%)
Missing	80 (4%)	24 (3%)	3 (2%)
Age (years)			
Mean (SD)	55.8 (14.7)	53 (18.1)	56.2 (14.9)
Age group (%)			
≥ 60	467 (24%)	216 (25%)	60 (32%)
18–39	255 (13%)	117 (14%)	31 (16%)
40–59	557 (28%)	275 (32%)	63 (33%)
Other	701 (35%)	242 (28%)	36 (19%)
Country (%)			
Africa	9 (0%)	3 (0%)	0 (0%)
Americas	1113 (56%)	460 (54%)	119 (63%)
Asia	62 (3%)	28 (3%)	2 (1%)
Europe	753 (38%)	343 (40%)	69 (36%)
Oceania	43 (2%)	16 (2%)	0 (0%)
Received year (%)			
2019	82 (4%)	42 (5%)	13 (7%)
2020	91 (5%)	42 (5%)	10 (5%)
2021	159 (8%)	63 (7%)	10 (5%)
2022	197 (10%)	86 (10%)	17 (9%)
2023	373 (19%)	163 (19%)	39 (21%)
2024	598 (30%)	250 (29%)	57 (30%)
2025	480 (24%)	204 (24%)	44 (23%)
Outcome (%)			
Non-serious	709 (36%)	269 (32%)	63 (33%)
Serious	1271 (64%)	581 (68%)	127 (67%)
Indication (%)			
Diabetes	589 (30%)	263 (31%)	76 (40%)
Weight management	342 (17%)	175 (21%)	32 (17%)
Product used for unknown indication	550 (28%)	209 (25%)	33 (17%)
Other	499 (25%)	203 (24%)	49 (26%)

[a]All cardiovascular adverse events following semaglutide use

[b]All arrhythmic adverse reactions occurring after semaglutide use

[c]Cases of dual arrhythmia and gastrointestinal adverse events following semaglutide treatment

Composite arrhythmia and gastrointestinal events

Exploratory subgroup analysis of co-reported arrhythmia and gastrointestinal events is shown in Fig. 3D and Supplementary Table S8. Diabetes was associated with combined arrhythmia and GI event reporting in both databases (VigiBase RR 1.49; AEMS RR 1.81). Obesity as the indication for semaglutide use was not associated with increased composite reporting. Among semaglutide-associated arrhythmia reports, age ≥60 years was associated with higher odds of GI co-reporting in VigiBase (OR 1.49, 95% CI 1.05–2.13; P = 0.034) and AEMS (OR 1.82, 95% CI 1.29–2.57; P = 0.001), respectively. Female sex and body weight >80 kg were associated with higher odds of GI co-reporting in VigiBase; neither association reached statistical significance in AEMS.

Exploratory gastrointestinal co-reporting analysis

Among 1754 AEMS reports, 475 involved GI events and 718 involved arrhythmias (Supplementary Table S9). GI events were negatively associated with arrhythmia reporting in AEMS (OR 0.80, 95% CI 0.64–0.99; RR 0.87, 95%

Table 2 Population demographics and clinical features of semaglutide-associated cardiovascular adverse events in the FDA Adverse Event Monitoring System (AEMS)

Characteristic	Patients, No. (%)		
	ALL[a] ($N=1754$)	CA[b] ($N=718$)	CA & GI[c] ($N=176$)
Sex (%)			
Female	1009 (58%)	390 (54%)	96 (55%)
Male	666 (38%)	308 (43%)	79 (45%)
Missing	79 (5%)	20 (3%)	1 (1%)
Age (years)			
Mean (SD)	59.8 (14.4)	58.9 (14.7)	60.9 (14.3)
Age group (%)			
≥60	637 (36%)	280 (39%)	88 (50%)
18–39	112 (6%)	57 (8%)	12 (7%)
40–59	389 (22%)	180 (25%)	51 (29%)
Other	616 (35%)	201 (28%)	25 (14%)
Country (%)			
Africa	3 (0%)	2 (0%)	0 (0%)
Americas	1310 (75%)	503 (70%)	135 (77%)
Asia	79 (5%)	29 (4%)	3 (2%)
Europe	290 (17%)	152 (21%)	32 (18%)
Oceania	33 (2%)	13 (2%)	2 (1%)
Received year (%)			
2019	51 (3%)	25 (3%)	12 (7%)
2020	68 (4%)	30 (4%)	9 (5%)
2021	129 (7%)	43 (6%)	8 (5%)
2022	133 (8%)	61 (8%)	13 (7%)
2023	295 (17%)	125 (17%)	30 (17%)
2024	496 (28%)	216 (30%)	57 (32%)
2025	565 (32%)	213 (30%)	47 (27%)
Outcome (%)			
Non-serious	861 (49%)	393 (55%)	107 (61%)
Serious	604 (34%)	263 (37%)	69 (39%)
Indication (%)			
Diabetes	530 (30%)	195 (27%)	71 (40%)
Weight management	321 (18%)	171 (24%)	32 (18%)
Product used for unknown indication	690 (39%)	269 (37%)	49 (28%)
Other	213 (12%)	83 (12%)	24 (14%)

[a]All cardiovascular adverse events following semaglutide use

[b]All arrhythmic adverse reactions occurring after semaglutide use

[c]Cases of dual arrhythmia and gastrointestinal adverse events following semaglutide treatment

CI 0.77–1.00; $P=0.044$). A similar pattern was observed in VigiBase (OR 0.74, 95% CI 0.60–0.90; RR 0.83, 95% CI 0.74–0.95; $P=0.004$).

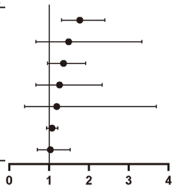
Focused analysis of ventricular extrasystoles

Among the rhythm-related preferred terms identified during exploratory screening, ventricular extrasystoles showed the most consistent disproportionality finding across both databases. Therefore, this preferred term was selected for focused descriptive characterization. This selection was intended to further characterize the observed reporting pattern and should not be interpreted as confirmation of a prespecified clinical risk.

Compared with all other drugs, semaglutide was associated with disproportionate reporting of ventricular extrasystoles in VigiBase (ROR 1.77, 95% CI 1.31–2.40) and AEMS (ROR 1.37, 95% CI 1.00–1.88; Fig. 4A and B).

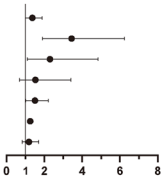
A

AEs	ROR	95% LCI	95% UCI
Ventricular extrasystoles	1.77	1.31	2.40
Cardiac fibrillation	1.49	0.67	3.33
Coronary artery occlusion	1.36	0.96	1.92
Postural orthostatic tachycardia syndrome	1.26	0.67	2.33
Sinus arrest	1.19	0.38	3.69
Atrial fibrillation	1.07	0.93	1.22
Supraventricular tachycardia	1.03	0.70	1.53



B

AEs	ROR	95% LCI	95% UCI
Ventricular Extrasystoles	1.37	1.00	1.88
Postural orthostatic tachycardia syndrome	3.44	1.90	6.23
Cardiac Ventricular Thrombosis	2.30	1.10	4.84
Cardiac Fibrillation	1.53	0.69	3.41
Cardiac Flutter	1.51	1.02	2.21
Palpitations	1.26	1.14	1.40
Supraventricular Tachycardia	1.19	0.84	1.70



C

Database	Group		Exposed / Case	Exposed / Control	Unexposed / Case	Unexposed / Control	OR (95% CI)	P-value	P interaction
VIGIBASE	Sex	Male	18	697	24	1241	1.34 (0.72-2.48)	0.359	0.258
		Female	23	1162	19	776	0.81 (0.44-1.49)	0.497	
	Age	≥60 years	5	462	37	1476	0.43 (0.17-1.10)	0.106	0.003
		40-59 years	18	539	24	1399	1.95 (1.05-3.62)	0.049	
		18-39 years	12	243	30	1695	2.79 (1.41-5.52)	0.003	
	Weight	<80 kg	4	99	38	1839	1.96 (0.68-5.59)	0.202	0.932
		>80 kg	11	284	31	1654	2.07 (1.03-4.16)	0.038	
	Indication	Diabetes	12	577	30	1361	0.94 (0.48-1.86)	0.866	0.222
		Obesity	11	331	31	1607	1.72 (0.86-3.46)	0.122	
	Dose	0.25 mg/week	4	229	38	1709	0.79 (0.28-2.22)	0.830	0.245
		0.5 mg/week	6	196	36	1742	1.48 (0.62-3.56)	0.531	
		1 mg/week	14	361	28	1577	2.18 (1.14-4.19)	0.027	
AEMS	Sex	Male	21	645	18	1070	1.94 (1.02-3.66)	0.039	0.003
		Female	16	993	23	722	0.51 (0.27-0.96)	0.035	
	Age	≥60 years	10	627	29	1088	0.60 (0.29-1.24)	0.217	0.001
		40-59 years	10	379	29	1336	1.22 (0.59–2.52)	0.599	
		18-39 years	10	102	29	1613	5.45 (2.59–11.50)	0.000	
	Weight	<80 kg	3	125	36	1590	1.06 (0.32-3.49)	0.760	0.237
		>80 kg	15	357	24	1358	2.38 (1.23-4.58)	0.014	
	Indication	Diabetes	12	518	27	1197	1.03 (0.52-2.04)	0.939	0.824
		Obesity	8	313	31	1402	1.16 (0.53-2.54)	0.718	
	Dose	0.25 mg/week	7	301	32	1414	1.03 (0.45-2.35)	0.949	0.887
		0.5 mg/week	6	239	33	1476	1.12 (0.47-2.71)	0.980	
		1 mg/week	8	274	31	1441	1.36 (0.62-2.98)	0.588	

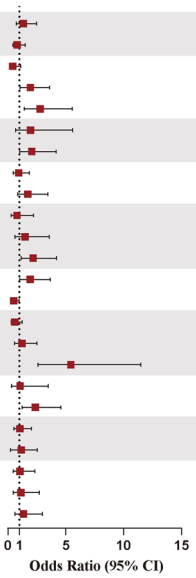


Fig. 4 Focused analysis of ventricular extrasystoles reported with semaglutide. **A** and **B** Forest plots showing reporting odds ratios (RORs) and 95% confidence intervals (CIs) for selected cardiovascular adverse events associated with semaglutide in VigiBase and AEMS, respectively. Point estimates are shown with horizontal lines indicating 95% CIs. A positive disproportionality signal was defined as at least three reports with the lower bound of the 95% CI of the ROR greater than 1. **C** Exploratory subgroup analyses of semaglutide-associated ventricular extrasystoles across VigiBase and AEMS. Ventricular extrasystoles showed consistent disproportionate reporting in both databases and were therefore selected for focused analysis. Abbreviations: CI, confidence interval; AEMS, FDA Adverse Event Monitoring System; ROR, reporting odds ratio; VigiBase, WHO global database of individual case safety reports

Characteristics of ventricular extrasystole cases

Demographic and clinical features of ventricular extrasystoles cases are summarized in Supplementary Table S10. In both databases, patients were predominantly middle-aged, with mean ages of 49.5 years in VigiBase and 51.8 years in AEMS, and were generally overweight or obese, with mean body weight near or above 100 kg. Sex distribution differed slightly, with a female predominance in VigiBase (55.0%) and a male predominance in AEMS (54.0%). Most reports originated from the Americas, and reporting increased markedly after 2023. The median dose was approximately 1.0 mg/week, administered mainly by subcutaneous injection. The main reported indications were type 2 diabetes and weight management.

Relationship between ventricular extrasystoles and GI events

No positive association was found between ventricular extrasystoles and GI events (Supplementary Table S9). In AEMS, GI events were reported in 17.9% of ventricular extrasystoles cases compared with 24.7% of non-ventricular extrasystoles cases (OR 0.67, 95% CI 0.29–1.52; $P = 0.331$). Similar findings were observed in VigiBase, where GI events were reported in 14.3% of ventricular extrasystoles cases and 25.9% of non-ventricular extrasystoles cases (14.3% vs 25.9%; OR 0.48, 95% CI 0.20–1.14; $P = 0.089$).

Exploratory subgroup analyses of ventricular extrasystoles

Subgroup analyses of ventricular extrasystoles are shown in Fig. 4C and Supplementary Table S11. In VigiBase, reporting was higher among patients aged 18–39 years and 40–59 years, whereas no increase was observed among those aged ≥ 60 years. A dose-related pattern was observed, with the 1.0 mg/week dose showing a positive association, while lower doses did not. Higher body weight (> 80 kg) was also associated with increased reporting, whereas no clear differences were observed by sex or indication.

AEMS showed broadly similar but stronger patterns, including higher reporting in younger adults, those weighing > 80 kg, and males. These subgroup findings should be interpreted as exploratory because of potential reporting bias, missing covariate data, and small numbers in some strata.

Comparison analyses

Comparator analyses were performed to evaluate whether the ventricular extrasystoles signal could be explained by diabetes, obesity, cardiometabolic risk, injectable therapy, or GLP-1RA class effects. As shown in Supplementary Table S12, semaglutide showed higher disproportionality for ventricular extrasystoles than metformin (ROR 2.51, 95% CI 1.63–3.89; $P < 0.001$), dulaglutide (ROR 4.69, 95% CI 2.22–9.92; $P < 0.001$), and insulin glargine (ROR 8.35, 95% CI 4.10–17.02; $P < 0.001$). These comparisons were considered the most clinically relevant because they address diabetes-related confounding, potential GLP-1RA class effects, and injectable glucose-lowering therapy in patients with more advanced diabetes.

Semaglutide also showed higher disproportionality than atorvastatin (ROR 1.63, 95% CI 1.11–2.40; $P < 0.05$). However, because atorvastatin is not an indication-matched comparator, this finding was considered exploratory and was not used as primary evidence for a semaglutide-specific association. Overall, these comparator analyses suggest that the ventricular extrasystoles signal is unlikely to be explained solely by diabetes, obesity, or GLP-1RA class effects, although residual confounding and reporting bias cannot be excluded.

Discussion

In this global pharmacovigilance analysis using two major safety-reporting systems, semaglutide was associated with disproportionate reporting of ventricular extrasystoles. Because AEMS reports may also be included in VigiBase, particularly for cases originating from the United States, the two datasets should be interpreted as partially overlapping rather than fully independent. Thus, our findings indicate cross-database consistency across distinct pharmacovigilance systems, but not independent epidemiological replication. The principal finding of this study is therefore a pharmacovigilance signal for ventricular extrasystoles that requires further evaluation, rather than evidence of a causal or prognostically significant association.

Because the primary objective was to evaluate rhythm-related safety signals, broader cardiovascular outcomes were used only for exploratory contextual screening. This distinction is important because cardiovascular endpoints such as myocardial infarction, palpitations, tachycardia, atrial arrhythmias, and ventricular ectopy represent heterogeneous clinical conditions with different substrates and risk factors. Accordingly, the broader cardiovascular findings should be interpreted cautiously and should not distract from the main hypothesis-generating signal for ventricular extrasystoles.

Across both databases, ventricular extrasystoles was the most consistent arrhythmia-related finding among semaglutide-associated cardiovascular adverse event reports. The signal persisted across sensitivity analyses and remained stronger than that observed with several cardiometabolic comparators. Although residual confounding related to diabetes, obesity, comorbidity, or treatment indication cannot be excluded, these findings suggest that the observed reporting pattern is unlikely to be explained solely by background disease risk. Among the comparator analyses, the comparisons with metformin and dulaglutide are the most conceptually relevant because they address diabetes-related confounding and potential GLP-1RA class effects, respectively. The insulin glargine comparison provides additional context in patients likely to have more advanced diabetes and higher baseline cardiovascular risk. By contrast, the atorvastatin comparison should be considered exploratory because statins are prescribed for cardiovascular risk reduction rather than glycaemic control or weight management. Subgroup analyses suggested that reporting clustered in younger and middle-aged adults, individuals with higher body weight, and those receiving the 1.0-mg weekly dose; however, these patterns should be interpreted as exploratory because of missing data, small numbers in some strata, and potential reporting bias.

These findings complement evidence from randomized trials, in which GLP-1RAs have been associated with modest increases in heart rate and occasional palpitations, but ventricular ectopy has not usually been evaluated as a prespecified or systematically monitored safety outcome (Grosicki et al. 2025). Trial populations are typically selected and may exclude patients with significant cardiac disease, while rhythm assessment is often limited to intermittent electrocardiography rather than continuous monitoring. Pharmacovigilance databases therefore provide a complementary

real-world approach for detecting uncommon or context-dependent arrhythmic events that may not be captured in randomized trials.

We explored whether GI toxicity and secondary electrolyte disturbance might account for the observed signal. Although semaglutide showed a notable disproportionality for gastrointestinal adverse events (Sodhi et al. 2023), GI events were not positively associated with arrhythmia reporting in either database, and ventricular extrasystoles was not enriched among reports that also included gastrointestinal events. These findings do not support a predominant gastrointestinal-electrolyte-arrhythmia pathway in the present analysis. Although GLP-1RA-related gastrointestinal effects may theoretically influence gut microbiota, barrier integrity, and circulating metabolites with potential electrophysiological relevance (Gao et al. 2024; Snelson et al. 2025; Guasti et al. 2021; Uddman et al. 1978), such mechanisms are unlikely to be the principal explanation for the observed disproportionality finding.

Alternative mechanisms may therefore warrant consideration. GLP-1 receptors are expressed in autonomic regulatory pathways and cardiac tissue, and GLP-1RAs may influence heart rate, autonomic balance, and myocardial excitability (Lubberding et al. 2024; Smits et al. 2016). Experimental evidence also suggests that these agents can modulate intracellular calcium handling and cyclic AMP signalling, which are central determinants of cardiac electrophysiology (Xiao et al. 2011). In susceptible individuals, including those with subclinical myocardial disease or autonomic dysfunction, these effects could theoretically lower the threshold for ventricular ectopy. The observed dose-related pattern, with a stronger signal at the 1.0-mg weekly dose, is consistent with biological plausibility, but it should be interpreted cautiously given the limitations of spontaneous reporting data.

From a clinical perspective, ventricular extrasystoles, corresponding clinically to premature ventricular contractions, are heterogeneous. Idiopathic premature ventricular contractions in individuals without structural heart disease are often benign, whereas those occurring in the setting of prior myocardial infarction, cardiomyopathy, reduced left ventricular ejection fraction, high premature ventricular contraction burden, complex ventricular ectopy, or non-sustained ventricular tachycardia may have greater prognostic relevance. The present pharmacovigilance analysis could not distinguish between these clinical contexts because AEMS and VigiBase do not systematically provide electrocardiographic findings, premature ventricular contraction burden, arrhythmia complexity, non-sustained ventricular tachycardia frequency, cardiac imaging data, or left ventricular ejection fraction. Therefore, the clinical severity and prognostic significance of the reported ventricular extrasystoles cannot be determined from these data.

Importantly, these findings should be interpreted in the context of the well-established cardiovascular benefits of semaglutide and do not diminish its proven efficacy in reducing major cardiovascular events. Rather than suggesting treatment avoidance or implying adverse prognosis, the present results support clinical awareness and further prospective evaluation. Individualized rhythm assessment may be considered in selected patients with symptomatic palpitations, known ventricular ectopy, structural heart disease, autonomic dysfunction, or other established arrhythmic risk factors, particularly during dose escalation. Such monitoring should remain proportionate and balanced against the substantial therapeutic benefits of semaglutide within a shared decision-making framework.

Strengths and limitations

The major strengths of this study include the use of two large pharmacovigilance databases, standardized MedDRA mapping, and multiple sensitivity, subgroup, and comparator analyses. Nevertheless, several important limitations should be acknowledged. Spontaneous reporting systems are inherently subject to under-reporting, selective reporting, stimulated reporting, and notoriety bias, particularly for recently introduced and widely discussed therapies. The absence of exposure denominators precludes estimation of incidence, and residual confounding by indication, comorbidity, concomitant medication, or healthcare-seeking behavior cannot be fully excluded. Accordingly, disproportionality analyses identify signals of disproportionate reporting rather than causal associations and should be considered hypothesis-generating.

A key limitation is the lack of detailed clinical information. Many reports lacked electrocardiographic data, electrolyte measurements, temporal information, and cardiac imaging findings. In particular, the arrhythmic substrate could not be characterized. The databases did not allow reliable differentiation between idiopathic ventricular extrasystoles and events occurring in patients with structural heart disease, prior myocardial infarction, cardiomyopathy, or heart failure. Information on premature ventricular contraction burden, morphology, coupling interval, complexity such as couplets or runs, non-sustained ventricular tachycardia, and left ventricular ejection fraction was generally unavailable. Therefore, risk stratification and assessment of prognostic significance were not possible.

Several analyses, including subgroup, dose-stratified, GI co-reporting, and comparator analyses, were exploratory. These analyses may be affected by small case numbers, missing data, multiple testing, and differential reporting patterns. They should therefore be interpreted as

hypothesis-generating and not as definitive evidence of risk modifiers, mechanisms, or causality.

Another important limitation is the potential overlap between AEMS and VigiBase. VigiBase aggregates individual case safety reports from multiple national pharmacovigilance systems, including the United States; therefore, some AEMS reports may also be represented in VigiBase. Because individual report identifiers cannot be linked across the two systems, the extent of overlap could not be quantified. Consequently, concordant findings across AEMS and VigiBase should be interpreted as evidence of cross-database consistency rather than independent replication.

Conclusions

Using contemporary data from WHO VigiBase and AEMS, we identified a consistent disproportionality signal for ventricular extrasystoles among reports involving semaglutide. Because spontaneous reporting systems do not provide exposure denominators, systematic electrocardiographic data, premature ventricular contraction burden, non-sustained ventricular tachycardia frequency, structural heart disease status, or left ventricular ejection fraction, these findings cannot establish incidence, causality, clinical severity, or prognostic significance. The signal should therefore be interpreted as hypothesis-generating and should not be viewed as evidence that semaglutide causes clinically important ventricular arrhythmias. Prospective studies incorporating systematic rhythm monitoring, assessment of ventricular ectopy burden and complexity, non-sustained ventricular tachycardia detection, cardiac imaging, and left ventricular ejection fraction evaluation are needed to clarify the incidence, mechanisms, and clinical relevance of ventricular ectopy during semaglutide therapy.

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Author contributions Dr Yan Wei had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Wu and Dr Yang are co–first authors. Concept and design: Yan Wei, Kenji Hashimoto, Lijia Chang, Daobin Wu, Rongying Yang. Acquisition, analysis, or interpretation of data: Daobin Wu, Rongying Yang, Jun Zeng, Zhou Bai, Chunda Zhang, Xinrong Fan, Xiangyu Zhou, Sui Zhu. Drafting of the manuscript: Daobin Wu, Rongying Yang, Yan Wei. Critical review of the manuscript for important intellectual content: Yan Wei, Kenji Hashimoto, Lijia Chang. Statistical analysis: Zhou Bai, Chunda Zhang, Daobin Wu, Sui Zhu. Administrative, technical, or material support: Xinrong Fan, Jun Zeng, Xiangyu Zhou, Lin Wu, Ibrahim Akin, Xiaobo Zhou. Supervision: Yan Wei, Kenji Hashimoto, Lijia Chang. All authors reviewed the manuscript. The authors declare that the study-specific analyses were performed and the derived results were generated by the research team using data obtained from VigiBase and AEMS, and that no paper mill was used.

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Data availability The data underlying this article were obtained from WHO VigiBase and the US Food and Drug Administration Adverse Event Monitoring System (AEMS). AEMS data are publicly available. Access to VigiBase data is subject to permission from the Uppsala Monitoring Centre. Derived data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests Dr. Hashimoto reports receiving research funding from Otsuka (Japan) outside the submitted work. All other authors declare no conflicts of interest.

Disclaimer The information presented in this article is based on data obtained from the WHO global individual case safety reports database (VigiBase®) maintained by the Uppsala Monitoring Centre (UMC). The authors alone are responsible for the interpretation and conclusions drawn from these data. The views expressed in this publication do not necessarily reflect the views of the UMC, the World Health Organization, or its member states.

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