The Journal of Clinical Pharmacology
2023, 0(0) 1–5

DOI: 10.1002/jcph.2193

Prevalence of Baseline Cardiac Arrhythmias in Participants with Overweight or Obesity in Phase 1 Clinical Trials: Analysis of 24-Hour Holter Electrocardiogram Recordings

Dorthe Skovgaard, MD, PhD[1], Poul-Martin Haahr, MD[1], Robert Lester, MD, FACC[2], Katherine Clark, [2], Sabina Paglialunga, PhD[2], Nick Finer, MBBS, FRCP[1], Martin H. Friedrichsen, PhD[1], Julie B. Hjerpsted, PhD[3], and Mads D.M. Engelmann, MD, PhD[1]

Abstract

Although estimates of the prevalence of cardiac arrhythmias in healthy volunteers exist, there is a lack of baseline data in other specific populations, such as people living with overweight and obesity, who are increasingly involved in clinical trials. This study investigated the baseline prevalence of arrhythmias in participants with overweight or obesity in 2 phase 1 trials of weight management medications (NCT03661879, NCT03308721). Participants aged 18–55 years, without a history of cardiovascular disease, and with body mass index (BMI) of 25.0–39.9 kg/m^2, were screened for abnormalities in vital signs, electrocardiogram (ECG) recordings, and electrolytes. Baseline 24-hour ECG (Holter) data were collected and manually reviewed by a cardiologist. The primary endpoint was the proportion of participants with $\geq$1 episode of the predefined cardiac arrhythmias. Continuous 12-lead ECG data were obtained from 207 participants. Most arrhythmias occurred in <3% of participants. Atrioventricular blocks and other potentially malignant arrhythmias were uncommon. There were no associations with age, sex, or BMI. Prevalence of atrioventricular blocks, nonsustained ventricular tachycardia, and other potentially malignant arrhythmias mirrored those reported in healthy participants with normal weight. In clinical trials of weight management medication, knowledge of the baseline prevalence of arrhythmias in people with overweight and obesity may inform trial eligibility criteria, improve on-trial decisions, and could be useful in discussions with health authorities. Baseline Holter readings and real-time ECG telemetry monitoring should be considered in such trials if arrhythmia risk is intrinsic to the molecule, or when signals have been observed in preclinical studies.

Keywords

cardiac arrhythmia, clinical trials, electrocardiogram, obesity, overweight

In early-phase clinical trials, it is important to determine whether any cardiac arrhythmias detected among study participants are: (1) present at baseline, (2) the result of drug exposure, or (3) the result of an increased susceptibility owing to disease rather than the drug. Regulatory agencies have historically focused on ventricular repolarization and the proarrhythmic potential of agents, using the QT interval as a surrogate marker for arrhythmia risk.[1] However, with an increased focus on cardiac safety in drug development in recent years, regulators have encouraged sponsors, in select situations, to collect continuous 24-hour (usually postdose) digital Holter electrocardiogram (ECG) recordings as an adjunct to the assessment of cardiac safety in clinical trials of new drugs.[2,3]

Reports addressing the prevalence of baseline arrhythmias in healthy volunteers enrolled in early-phase pharmaceutical trials have been published.[4–7] These studies provide useful baseline data in heterogeneous groups of otherwise healthy people, but there remains a need to describe arrhythmias in other specific populations, such as people living with overweight or obesity. Pharmacological interventions that assist with weight loss and weight management are an increasing focus of research. Given some cardiovascular concerns (including but not limited to arrhythmia) associated with early weight management medications (eg, sibutramine,[8,9] tesofensine,[10] fenfluramine,[11] lorcaserin[12]) and the potential for an arrhythmogenic impact of rapid weight loss,[13] it is pertinent to study the effect of new weight management medications on cardiac rhythm if risk

[1]Novo Nordisk A/S, Søborg, Denmark
[2]Celerion, Tempe, Arizona, USA
[3]Novo Nordisk A/S, Målev, Denmark

Submitted for publication 6 October 2022; accepted 7 December 2022.

Corresponding Author:
Dorthe Skovgaard, MD, PhD, Novo Nordisk A/S, Vandtårnsvej 110, 2860 Søborg, Denmark
Email: dcsk@novonordisk.com

of arrhythmia is intrinsic to the molecule or mechanism of action, or when signals have been observed in preclinical studies. To do this accurately, improved characterization of baseline arrhythmias among people with overweight and obesity is required.

This analysis investigated the baseline prevalence of cardiac arrhythmias in otherwise healthy participants with overweight or obesity in 2 phase 1 clinical trials.

Methods

Participants

This analysis included participants with overweight or obesity in 2 phase 1 trials of weight management medications (NCT03661879, NCT03308721). These trials were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines, and the protocols were approved by the Midlands Independent Review Board (for study NN9277-4328) and Midlands-A WIRB Copernicus Group (for study NN9423-4393), both at Overland Park, Kansas. All patients provided written informed consent. Participants were men or women, aged 18–55 years at the time of signing informed consent, with a body mass index (BMI) of 25.0–39.9 kg/m^2 at screening. All participants were screened for abnormalities in vital signs, 10-second 12-lead ECGs, and electrolytes. Participants with a history of cardiovascular disease (CVD) or long QT syndrome were excluded. Concomitant medications were not permitted. Participants were excluded on the basis of 12-lead ECGs if they had baseline conduction abnormalities or abnormal interval measurements (PR, QRS, heart rate, and Fridericia corrected QT interval), as well as ambient arrhythmias, deemed by the investigator to be clinically relevant. Nicotine or alcohol use and pregnancy were also exclusion criteria.

Data Collection

One baseline 24-hour, 12-lead continuous ECG recording (Welch Allyn H12+^{TM} Digital Holter Recorder, Hill-Rom, Chicago, Illinois) was collected before randomization and used for predosing calculation of corrected QT interval. The recordings were not part of the eligibility assessments in the 2 trials. The recordings were, for the purpose of this report, imported into Celerion's Global Instrumentation M12A system, and analyzed retrospectively at the Celerion ECG Core Laboratory (Tempe, Arizona). The recordings were cleaned of artifacts and then manually reviewed by qualified Holter technicians for the presence of any arrhythmias. The Holter reports were then sent to a single experienced and appropriately qualified cardiologist for further review, analysis, and final adjudication.

Arrhythmias were predefined according to generally accepted criteria from the literature (Table S1) and based on clinical judgment (specific arrhythmias are listed in Table 1).

Table 1. Overview of All Arrhythmias

Parameter	Participants (n)	Proportion of Total Cohort (%)
Supraventricular rhythms		
Sinus bradycardia	70	34
Sinus tachycardia	200	97
Sinus pauses	3[a]	1
Sinus arrest	0	0
Ectopic atrial rhythm	2	1
Ectopic atrial tachycardia	4	2
Atrial tachycardia	0	0
Supraventricular tachycardia	7	3
Atrial fibrillation	0	0
Atrial flutter	0	0
Junctional rhythm	2	1
Junctional bradycardia	0	0
Junctional tachycardia	0	0
Ventricular rhythms		
Idioventricular rhythm	0	0
Accelerated idioventricular rhythm	2	1
Ventricular tachycardia —nonsustained	3	1
Ventricular tachycardia —sustained	0	0
Torsades de pointes	0	0
Ventricular flutter/fibrillation	0	0
Premature contractions		
Atrial premature contractions	130	63
PVCs	132	64
PVCs (>200/24 h)	6	3
Supraventricular premature contractions	140	68
Multifocal PVCs	48	23
Heart block		
First-degree AV block	2	1
Second-degree AV block type I	5	2
Second-degree AV block type II	0	0
Third-degree/complete AV block	0	0
Conduction abnormalities		
Nonspecific intraventricular conduction delay	0	0
Right bundle branch block	0	0
Left bundle branch block	0	0

AV, atrioventricular; PVC, premature ventricular contraction.
[a] Sinus pauses were seen in 3 (1.4%) participants, and all fell into a range that would be considered physiologic as none exceeded 3.0 seconds in duration.

The primary endpoint was the proportion of participants with at least 1 episode of the predefined cardiac arrhythmias in baseline 24-hour continuous Holter ECG recordings. The occurrence of at least 1 episode of the predefined cardiac arrhythmias stratified by sex, age, and BMI was an exploratory endpoint.

Table 2. Arrhythmias Considered Clinically Relevant/Potentially Malignant

Parameter	Proportion of Total Cohort (%)	Participants (n)	Expected Number With Observation in a Population of 200 Healthy Individuals[4] (n)
Supraventricular tachycardia	3	7	9
Accelerated idioventricular rhythm	1	2	2
Ventricular tachycardia—nonsustained	1	3	4
Multifocal premature ventricular contractions	23	48	17
Second-degree AV block type I	2	5	10
Premature ventricular complexes >200/24 h	3	6	10

AV, atrioventricular.

Statistical Analyses

The proportions of participants with each of the predefined arrhythmias were summarized using descriptive statistics. Mean age, BMI, and heart rate were analyzed by *t*-test or analysis of variance as appropriate. Chi-square tests were performed using Prism GraphPad (San Diego, California) to determine statistical significance.

Results

Of the 626 participants who were screened for inclusion in the 2 trials, a total of 326 participants were categorized as screen failures. Reasons for screen failure related to cardiovascular/arrhythmic risk were as follows: 37 participants due to abnormal 12-lead ECGs (as adjudicated by the investigator); 19 participants due to age ≥40 years, with an estimated 10-year atherosclerotic CVD risk ≥5%; 8 participants due to high blood pressure (>159/99 mmHg); and 4 participants due to elevated resting heart rate (>99 beats per minute). An additional 93 participants were withdrawn prior to ECG monitoring because of changes in medication between screening and Holter monitoring, voluntarily withdrawing, or being surplus to need. Thus, a total of 207 participants (133 women and 74 men) with 24-hour Holter ECG recordings were included in the present study. Participants' mean age was 36 (range, 18–55) years, BMI was 32.6 (25.4–40.3) kg/m^2, and heart rate was 75.5 (49–104) beats per minute (Table S2).

Most arrhythmias were uncommon and occurred in ≤3% of participants, except for sinus tachycardias/bradycardias and premature contractions (Table 1). Of the arrhythmias that occurred more frequently, sinus tachycardia was observed in 200 individuals (97%), and sinus bradycardia was recorded in 70 participants (34%). Atrial and ventricular premature contractions were seen in 130 (63%) and 132 (64%) participants, respectively. A total of 140 participants (68%) recorded supraventricular premature contractions (Table 1).

Occurrence of atrioventricular (AV) blocks of any kind, nonsustained ventricular tachycardia (NSVT), and other potentially malignant arrhythmias were uncommon (Table 2). However, 48 participants (23%) had multifocal premature ventricular contractions (PVCs). There were no associations between the occurrence of arrhythmias and age, sex, or BMI ≥25.0–≤39.9 kg/m^2 (Tables S3–S5). An increase in the prevalence of premature atrial and ventricular contractions was evident with advancing age (Table S6). Sinus bradycardia, junctional rhythm, first-degree AV block, and premature atrial contractions were more often observed in males than females.

Discussion

Overall, in the 2 trials included in this analysis, arrhythmias occurred infrequently, were benign, and would not warrant a further cardiac evaluation in otherwise asymptomatic individuals. The most frequent arrhythmias were premature contractions of the atria and ventricles. The prevalence of these arrhythmias, as well as episodes of sinus bradycardia and sinus tachycardia, were consistent with the prevalence in healthy normal-weight populations.[4,14] Although these results are generalizable to the current literature,[4,14] there is a novelty in the data obtained from these 2 phase 1 studies, as the focus is specifically in relation to participants with overweight or obesity as opposed to healthy, normal-weight individuals.

No association between heart rate and arrhythmias was found. Since patient diaries were not used (and therefore periods of physical activity were not recorded during this analysis), the investigators were unable to explore whether the episodes of sinus tachycardia reported may represent an increased heart rate, due to a physiological response to exercise, or other external factors such as stress, rather than pathological sinus tachycardia events. Future studies may benefit from the recording of data to explore this aspect.

The prevalence of AV blocks, NSVT, and other potentially malignant arrhythmias in the 2 trials appeared lower, or similar to, that observed in the most comprehensive data set published to date of healthy, normal-weight individuals who volunteered to participate in early clinical trials.[4] However, in the present study, more participants than expected from those data had multifocal PVCs (48 vs 17 based on Hingorani et al[4]). The predictive value of PVCs for further arrhythmias is not well established, and other older studies have found similar or higher incidences in healthy participants.[4,15,16] The current Cardiac Safety Research Consortium recommendations do not suggest exclusion of volunteers with PVCs from clinical studies (unless the total number exceeds 200 PVCs/24 h).[6] In our cohort, there are only 6 participants meeting this more clinically significant criterion.

As weight management medications are increasingly developed for people living with overweight or obesity, it is important to ascertain the proarrhythmic potential of such new compounds. Differentiating ambient arrhythmias from drug-induced proarrhythmias requires a better characterization of arrhythmias in otherwise healthy volunteers with normal weight, overweight, or obesity typically included in early clinical trials. Populations with overweight and obesity may exhibit a wide variety of ECG abnormalities, including arrhythmias (eg, an increased risk of both paroxysmal and permanent atrial fibrillation).[17–20] Many of these events are likely to be associated with alterations in cardiac morphology, epicardial fat, left ventricular hypertrophy, atrial dilatation, and fibrosis,[17,19,20] but people with uncomplicated obesity can also exhibit a prolonged corrected QT interval.[18] Furthermore, the metabolic consequences of obesity, including elevated plasma volume, insulin resistance, and altered release of adipokines and chemical mediators, promote a proinflammatory and prothrombotic state that may contribute to an increased frequency of arrhythmias.[19]

In clinical trials of weight management medication, a knowledge of the baseline prevalence of arrhythmias in people with overweight and obesity could inform eligibility criteria and improve on-trial decisions (eg, discontinuation of a participant, dose escalations, or determining what arrhythmias constitute an adverse event), and could be useful in discussions with health authorities. Baseline Holter recording, and real-time ECG telemetry monitoring should be considered in all early-phase trials involving people with overweight and obesity if nonclinical signals warrant more extensive cardiac monitoring. Published data can be used as guidance for the estimated maximum number of participants with specific arrhythmias in different sample sizes. In the 2 trials, Holter recordings were not part of eligibility assessments. However, if baseline Holter recordings had been used as an exclusion criterion, 10% of the participants recruited to the 2 studies would likely have been excluded, if Cardiac Safety Research Consortium recommendations were followed.[6]

One important limitation of the current analysis was the selection of a population of otherwise healthy US participants with normal 12-lead ECG readings at screening. Given the subject selection criteria and that a high number of screening failures were related to prior CVD, electrolytes, blood pressure, and concomitant medication, higher numbers of arrhythmias could be expected in trials with less stringent screening, and these data may not represent the frequency of abnormalities in an unselected population with obesity. Moreover, the limited sample size and the lack of adjustment for multiple comparisons jeopardizes the validity of the comparisons based on age groups and sex. As an example, a power calculation showed that a 4-fold increase in NSVT in participants with overweight or obesity compared with the reported prevalence of 0.7% in healthy, normal-weight participants[4] could be detected with a statistical power of only 60%. Although the observed prevalence of sinus tachycardia and bradycardia is likely to be physiologically normal, data on participants' activity levels, meals, and other exogenous factors were not available to correlate with these recorded episodes.

Conclusions

In participants with overweight or obesity volunteering to take part in a phase 1 clinical trial, arrhythmias were uncommon and benign and would not warrant further cardiac evaluation in otherwise asymptomatic individuals. Overall, prevalence of AV blocks, NSVT, and other potentially malignant arrhythmias appeared to be similar to healthy participants with normal weight. There was no clinically relevant association of arrhythmias with age, sex, or BMI. Based on these data, if baseline Holter recordings were used as an exclusion criterion, 10% of participants with overweight or obesity recruited to a clinical trial would likely be excluded. Although potentially operationally challenging, sponsors should consider Holter prescreening prior to randomization and its use as a criteria for inclusion and randomization, particularly in cases where the risk of arrhythmia is intrinsic to the molecule or mechanism of action, or when signals have been observed in preclinical studies.

Acknowledgments

The authors thank Stephen Purver and Andy Bond of Axis, a division of Spirit Medical Communications Group Limited, for assistance with medical writing and editorial support (funded by Novo Nordisk A/S). The authors also gratefully

acknowledge the study participants and all personnel involved.

Conflicts of Interest

D.S. is an employee of Novo Nordisk. P.M.H., N.F., M.H.F., J.B.H., and M.D.M.E. are employees of and own shares in Novo Nordisk. R.L., K.C., and S.P. are employees of Celerion.

Funding Statement

Financial assistance to support the development of this article was provided by Novo Nordisk A/S, Søborg, Denmark.

Author Contributions

R.L. and K.C. designed and performed research. All other authors were involved in writing the manuscript and analyzing data.

Data Availability Statement

Data will be shared with bona fide researchers who submit a research proposal approved by the independent review board. Individual patient data will be shared in data sets in a deidentified and anonymized format. Data will be made available after research completion and approval of the product and product use in the European Union and the United States. Information about data access request proposals can be found at novonordisk-trials.com.

References

1. U.S. Food and Drug Administration. Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. https://www.fda.gov/media/71372/download. Published October 2005. Accessed December 20, 2021.
2. Kothari S, Karnad DR, Panicker GK, Turner JR. Cardiac safety investigations 10 years after ICH guidance E14: evolving industry and regulatory viewpoints on evaluation of proarrhythmic risk during new drug development. *J Clin Stud*. 2015;7:22-30.
3. European Medicines Agency. ICH guideline E14: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (R3) - questions and answers. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e14-clinical-evaluation-qt/qtc-interval-prolongation-proarrhythmic-potential-non-antiarrhythmic-drugs-r3-questions-answers-step_en.pdf. Published January 25, 2016. Accessed December 20, 2021.
4. Hingorani P, Karnad DR, Rohekar P, Kerkar V, Lokhandwala YY, Kothari S. Arrhythmias seen in baseline 24-hour Holter ECG recordings in healthy normal volunteers during phase 1 clinical trials. *J Clin Pharmacol*. 2016;56(7):885-893.
5. Hingorani P, Karnad DR, Natekar M, Kothari S, Narula D. Baseline and new-onset morphologic ECG abnormalities in healthy volunteers in phase I studies receiving placebo: changes over a 6-week follow-up period. *J Clin Pharmacol*. 2014;54(7):776-784.
6. Min SS, Turner JR, Nada A, et al. Evaluation of ventricular arrhythmias in early clinical pharmacology trials and potential consequences for later development. *Am Heart J*. 2010;159(5):716-729.
7. Stinson JC, Pears JS, Williams AJ, Campbell RW. Use of 24 h ambulatory ECG recordings in the assessment of new chemical entities in healthy volunteers. *Br J Clin Pharmacol*. 1995;39(6):651-656.
8. Scheen AJ. Cardiovascular risk-benefit profile of sibutramine. *Am J Cardiovasc Drugs*. 2010;10(5):321-334.
9. Harrison-Woolrych M, Ashton J, Herbison P. Fatal and non-fatal cardiovascular events in a general population prescribed sibutramine in New Zealand: a prospective cohort study. *Drug Saf*. 2010;33(7):605-613.
10. Astrup A, Madsbad S, Breum L, Jensen TJ, Kroustrup JP, Larsen TM. Under-reporting of adverse effects of tesofensine. *Lancet*. 2013;382(9887):127.
11. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med*. 1997;337(9):581-588.
12. Bohula EA, Wiviott SD, McGuire DK, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. *N Engl J Med*. 2018;379(12):1107-1117.
13. Vedel-Larsen E, Iepsen EW, Lundgren J, et al. Major rapid weight loss induces changes in cardiac repolarization. *J Electrocardiol*. 2016;49(3):467-472.
14. Ilson BE. Cardiovascular monitoring in normal healthy adults: a literature review and recommendations for the reporting of disturbances of cardiac rhythm. *Am J Ther*. 1995;2(11):893-899.
15. Bjerregaard P. Premature beats in healthy subjects 40–79 years of age. *Eur Heart J*. 1982;3(6):493-503.
16. von Rotz M, Aeschbacher S, Bossard M, et al. Risk factors for premature ventricular contractions in young and healthy adults. *Heart*. 2017;103(9):702-707.
17. Fraley MA, Birchem JA, Senkottaiyan N, Alpert MA. Obesity and the electrocardiogram. *Obes Rev*. 2005;6(4):275-281.
18. Arslan E, Yiğiner O, Yavaşoğlu I, Ozçelik F, Kardeşoğlu E, Nalbant S. Effect of uncomplicated obesity on QT interval in young men. *Pol Arch Med Wewn*. 2010;120(6):209-213.
19. Pathak RK, Mahajan R, Lau DH, Sanders P. The implications of obesity for cardiac arrhythmia mechanisms and management. *Can J Cardiol*. 2015;31(2):203-210.
20. Goudis CA, Korantzopoulos P, Ntalas IV, Kallergis EM, Ketikoglou DG. Obesity and atrial fibrillation: a comprehensive review of the pathophysiological mechanisms and links. *J Cardiol*. 2015;66(5):361-369.

Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.