Sex differences in the prognosis of nonsustained ventricular tachycardia detected on Holter recording

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BACKGROUND Nonsustained ventricular tachycardia (NSVT) is a common finding during cardiac evaluation and has been linked to increased mortality. While some studies report a sex difference, most data stem from research cohorts.

OBJECTIVE This study aimed to assess the prognostic significance of NSVT in a real-life outpatient clinic, focusing on sex differences in mortality.

METHODS Analysis was performed on a cohort of consecutive patients referred to 48-hour Holter monitoring between 2009 and 2011 at Copenhagen University Hospital – Bispebjerg. Indications for Holter monitoring included palpitations, dizziness, syncope, or arrhythmia testing. Baseline characteristics, blood tests, echocardiography results, and mortality data were obtained from electronic patient records.

RESULTS A total of 762 females (mean age 59 ± 18 years) and 693 males (mean age 59 ± 17 years) were enrolled. At least 1 episode of NSVT was detected in 9.7% of females and 20.6% of males. The median follow-up was 8.3 years. A total of 20% of females and 24% of males died during follow-up. In multivariable models, NSVT was linked to mortality in males (hazard ratio [HR] 1.6, 95% confidence interval [CI] 1.1–2.3) but not in females (HR 1.2, 95% CI 0.7–2.1). In case-control pairs matched on the propensity of being male conditional on relevant risk factors, NSVT was again linked to mortality in males (HR 3.1, 95% CI 2.0–4.8) but not in females (HR 1.4, 95% CI 0.8–2.4).

CONCLUSION In consecutive patients referred to symptom driven Holter monitoring, NSVT was associated with elevated all-cause mortality in males but not in females. These results can contribute to the risk assessment of patients presenting with NSVT.

KEYWORDS Nonsustained ventricular tachycardia; Prognosis; Sex differences; Mortality; Holter ECG; Premature ventricular complexes; Ventricular arrythmia

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Introduction

Nonsustained ventricular tachycardia (NSVT) is frequently observed during Holter monitoring for various diagnostic purposes. The prevalence of NSVT varies among different populations, ranging from 0.7% in a healthy army population[1] to 10% in middle-aged and elderly individuals without known heart disease[2] and even higher in patients with ischemic heart disease undergoing long-term electrocardiogram (ECG) monitoring.[3]

Consequently, the evaluation of associated mortality risk is an essential aspect, as emphasized by the recent guidelines on ventricular arrhythmias from the European Society of Cardiology,[4] and a recent review used NSVT as part of the risk stratification for sudden cardiac death in conditions such as arrhythmogenic cardiomyopathy.[5]

Much of the evidence regarding the prognosis of NSVT primarily stems from epidemiological studies involving healthy or unselected populations, rather than representative clinical cohorts. While many studies have reported an association between ventricular arrhythmias and mortality,[6–8] some

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KEY FINDINGS

- This study, with data from a real-life outpatient clinical setting, shows increased all-cause mortality in men especially with ≥5 complexes.
- Women with nonsustained ventricular tachycardia do not have increased mortality when compared with women without nonsustained ventricular tachycardia after 8 years of follow-up.
- The increased risk develops slowly over the years, rather than being a marker for imminent sudden cardiac death.

studies focusing on specific patient populations have yielded conflicting results.[9,10]

There is evidence suggesting that this association may be influenced by sex. In the Framingham Study, incidental ventricular arrhythmias (defined as more than 30 premature ventricular complexes [PVCs] per hour or multiform premature complexes, ventricular couplets, ventricular tachycardia, or R-on-T PVCs) detected during 1-hour ambulatory ECG recordings were associated with an increased risk of all-cause mortality and myocardial infarction in males, but not in females, independent of coronary heart disease.[11] Similarly, in the Copenhagen Holter Study, excessive PVCs and NSVT were associated with mortality in males but not in females.[12] However, both studies were epidemiological cohort studies.

In the present study, we aim to evaluate the prognostic value of NSVT in males and females referred to Holter ECG recording as part of diagnostic investigation for various symptoms or diseases.

Methods

Data collection

This study included 1455 consecutive patients. These patients were referred to the Department of Cardiology, Bispebjerg Hospital (Copenhagen, Denmark), and underwent 48-hour Holter recordings (Rozinn RZ 153+12; Rozinn Electronics) between December 2009 and October 2011.

All recordings were performed with 7 leads to create a 3-channel electrocardiogram output. The sampling rate for the electrocardiogram recordings was 180/s. An experienced technician from the Holter laboratory of the Copenhagen University Hospital of Bispebjerg performed all editing and analyses of the recordings.

General practitioners from 3 major areas of Copenhagen and the department's outpatient clinic made the referrals. The Holter recordings were performed as part of the clinical workup for various indications.

Patient data, including medical history, prescribed medications, echocardiography results, and blood test results, were extracted from the patient's medical charts and the echocardiography laboratory archives at the time of the Holter recording. Follow-up data, including information on mortality, were collected from electronic medical charts. The most recent follow-up was conducted in March 2019. In Denmark, all deaths are registered within 14 days in the Central Person Register (CPR). All electronic medical records are then automatically updated with this information.

Definitions

Three standard criteria defined PVC: (1) prematurity (the coupling interval to the preceding QRS complex had to be 70% or less of the mean RR interval of the basic rhythm prior), (2) postcontraction pause (undisturbed sinus node and atrial ectopic impulse formation demonstrated by a full compensatory pause or, on rare occasions, the interposition of the premature complex between 2 normally conducted beats of the regular basic rhythm), and (3) morphology (QRS complexes widened above 0.10 seconds and were morphologically different from those of the basic rhythm).

NSVT was defined as a run of at least 3 consecutive complexes compliant with the previous definition of PVCs with a rate of >100/min.

Significant valvular disease was defined as moderate-to-severe valvular stenosis or regurgitation, as evaluated by the attending cardiologist.

Definition of sex

The biological sex of the patients was taken from their Danish CPR number, which is their legal gender and is assigned at birth in accordance with apparent biological sex.

Statistical analysis

Non-normally distributed data are shown as median with interquartile range (IQR). Categorical variables are presented as frequency and percentage. Student's *t* test, Fisher's exact test, and the Wilcoxon rank sum test compared baseline factors as appropriate. We applied the Kaplan-Meier survival models to examine event-free survival relating to all-cause mortality and Cox proportional hazards models for estimating hazard ratio (HR) and confidence intervals (CIs) for the association between NSVT and all-cause mortality. The Cox models were adjusted for age, left ventricular ejection fraction (LVEF), known history of diabetes, ischemic heart disease, arterial hypertension, severe valvular disease, and the use of diuretics, beta-blockers, and aspirin. These potentially confounding covariates were selected, as their association with mortality and cardiovascular events is well established.

A propensity score–matched analysis was performed. From the total cohort, the propensity score for being male was calculated on baseline characteristics, quantified by logistic regression using the greedy match algorithm (Gmatch macro for SAS from the Mayo Clinic College of Medicine [http://bioinformaticstools.mayo.edu/research/gmatch/]). The baseline characteristics used were age, indication for Holter, NSVT on Holter, >30 PVCs on Holter, LVEF, and medical history of cancer, diabetes mellitus, ischemic heart disease,

Table 1 Baseline variables: differences between females and males

Baseline variable	All subjects (N = 1455)	Females (n = 762)	Males (n = 693)	*P* value
Participant characteristics				
Age, y	59 ± 18	59 ± 19	59 ± 17	.76
Indication for Holter				<.01
Palpitation	389 (27)	230 (30)	159 (23)	
Syncope	561 (39)	304 (40)	257 (37)	
Known rhythm disturbance	250 (17)	114 (15)	136 (20)	
Unknown	255 (18)	114 (15)	141 (20)	
Holter				
NSVT	217 (15)	74 (10)	143 (21)	<.01
PVCs/h	30 ± 136	25 ± 131	37 ± 141	<.01
PVCs (>30/h)	168 (12)	66 (9)	102 (15)	<.01
Medical history				
Ischemic heart disease	178 (12)	66 (9)	113 (16)	<.01
Atrial fibrillation	508 (35)	229 (30)	279 (40)	<.01
Stroke	102 (7)	48 (6)	54 (8)	.27
Diabetes mellitus	182 (13)	73 (10)	109 (16)	.03
Cancer	173 (12)	101 (13)	72 (10)	.09
Hypertension	700 (48)	357 (49)	343 (49)	.31
Blood tests				
Hemoglobin, mmol/L	9 ± 3	8 ± 1	9 ± 4	<.01
Leucocytes (10^9/L)	8 ± 5	8 ± 3	8 ± 7	.87
C-reactive protein, mg/L	8 ± 23	8 ± 24	8 ± 22	.67
Glucose, mmol/L	6 ± 5	6 ± 7	6 ± 2	<.01
eGFR, mL/min/1.73 m^2	69 ± 32	68 ± 17	72 ± 46	.21
Medication				
Diuretics	399 (27)	212 (28)	187 (27)	.72
Acetylsalicylic acid	401 (28)	191 (25)	210 (30)	.03
Beta-blockers	465 (32)	233 (31)	232 (33)	.24
Inhalation medication	124 (9)	78 (10)	46 (7)	.01
Echocardiography (n = 1163)				
Severe valvular disease	28 (2)	11 (1)	17 (2)	.21
LVEF, %	57 ± 9	58 ± 8	55 ± 9	<.01
LVEF (<40%)	87 (7)	31 (5)	56 (10)	<.01

Values are mean ± SD or n (%).

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction.

and atrial fibrillation. Male and female patients were matched 1:1 using greedy matching, thus successfully constructing a cohort of 466 pairs. Subsequent analysis showed equal distribution of risk factors and prognosis between the matched groups of females and males. Afterward, Cox proportional hazards models were performed similarly to the entire cohort.

The C-statistic was 0.63, indicating adequate discriminative power.

Results

A total of 1455 consecutive patients were included in the study, with 52.4% being female.

Table 1 displays baseline characteristics of included females and males. Females had a lower prevalence of ischemic heart disease, diabetes mellitus, atrial fibrillation, and systolic heart failure compared with males. Additionally, females had a higher LVEF and were more often referred for Holter monitoring due to palpitations.

A total of 215 (14.9%) patients experienced at least 1 episode of NSVT. Table 2 displays the baseline characteristics of patients with and without NSVT. Patients with NSVT tended to be older, primarily male, and had a higher burden of comorbidities, including a history of ischemic heart disease, diabetes mellitus, prior cancer, severe valvular disease, and reduced LVEF.

When looking at patients 60 years of age or older and those under 60 years of age as separate groups, the relationship between NSVT and comorbidities was overall consistent, except that the younger group was not more likely to have a history of diabetes, while the older was not more likely to have hypertension. Additionally, in the younger group, people with NSVT were more likely to be referred to Holter for a known rhythm disturbance and less likely to be referred because of syncope (Supplemental Tables 1 and 2).

The prevalence of NSVT and PVCs differed between females and males, with NSVT detected in 9.7% of females and 20.6% of males ($P < .001$). Similarly, PVCs were less frequent in females (median 0.15/h [IQR 0.0–3.0/h]) than in males (median 0.79/h [IQR 0–10.5/h]) ($P < .0001$).

The median length of NSVT was 4 beats (range 3–128 beats) for the entire group. In females, it was 4 beats (range 3–28 beats); in males, it was also 4 beats (range 3–128 beats).

Table 2 Characteristics of people with NSVT compared with people without NSVT

Baseline variable	All subjects (N = 1455)	Subjects with NSVT (n = 217)	Subjects without NSVT (n = 1238)	*P* value
Participant characteristics				
Male	693 (48)	143 (66)	550 (44)	<.01
Age, y	59 (18)	66 (14)	57 (19)	<.01
Indication for Holter				<.01
Palpitation	389 (27)	49 (23)	340 (27)	
Syncope	561 (39)	70 (32)	491 (40)	
Known rhythm disturbance	250 (17)	48 (22)	202 (16)	
Unknown	255 (18)	50 (23)	205 (17)	
Medical history				
Ischemic heart disease	178 (12)	62 (29)	116 (9)	<.01
Atrial fibrillation	508 (35)	118 (54)	390 (32)	<.01
Stroke	102 (7)	13 (6)	89 (7)	.52
Diabetes mellitus	182 (13)	43 (20)	139 (11)	<.01
Cancer	173 (12)	35 (16)	138 (11)	.04
Hypertension	700 (48)	140 (65)	560 (45)	<.01
Blood tests				
Hemoglobin, mmol/L	9 ± 3	9 ± 1	9 ± 3	.31
Leukocytes (10^9/L)	8 ± 5	8 ± 3	8 ± 5	.01
C-reactive protein, mg/L	8 ± 23	12 ± 30	8 ± 22	.15
Cholesterol, mmol/L	6 ± 5	5 ± 1	5 ± 1	.07
Glucose, mmol/L	69 ± 32	6 ± 2	6 ± 5	.03
eGFR, mL/min/1.73 m^2	9 ± 3	66 ± 17	70 ± 35	.07
Medication				
Diuretics	399 (27)	94 (43)	305 (25)	<.01
Acetylsalicylic acid	401 (28)	71 (33)	330 (27)	.07
Beta-blockers	465 (32)	90 (42)	375 (30)	<.01
Inhalation medication	124 (9)	19 (9)	105 (9)	.90
Echocardiography (n = 1163)				
Severe valvular disease	28 (2)	9 (4)	19 (2)	<.01
LVEF, %	57 ± 9	53 ± 11	57 ± 8	<.01
LVEF (<40%)	348 (5)	25 (13)	31 (3)	<.01

Values are n (%) or mean ± SD.

eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia.

When studied in groups of short vs long NSVT (≥ 5 vs <5), it was found that 24 (3%) females had runs of long NSVT and 50 (7%) had short runs. Among males, 61 (9%) had long runs, while 82 (12%) had short runs.

Follow-up and event rates

Over a median follow-up period of 8.3 years (range 7.9–8.7 years), 322 (22%) patients died, corresponding to a mortality rate of 30 per 1000 patient-years. Mortality was higher in patients with NSVT (n = 83 of 217; 58 per 1000 patient-years) compared with those without NSVT (n = 239 of 1238; 26 per 1000 patient-years) ($P < .001$).

In the subgroup analysis based on sex, 20% (n = 153 of 762) of females died during follow-up, with a mortality rate of 27 per 1000 patient-years. Among females with NSVT, the mortality rate was 24%, against 17% in females without NSVT (34 vs 26 per 1000 patient-years; HR 1.3, 95% CI 0.8–2.2, $P = .6$) (Table 3).

In contrast, total mortality for males was 24% (n = 169 of 693), corresponding to 33 per 1000 patient-years. The mortality rate in males with NSVT was 45% (71 per 1000

Table 3 Cox proportional hazards models of the associations between NSVT and frequent PVCs (>30/h) in relation to all-cause mortality in females and males

	NSVT		>30 PVCs/h	
	Univariable	Multivariable*	Univariable	Multivariable*
Females	1.3 (0.8–2.2), .3	1.2 (0.7–2.1), .4	1.2 (0.7–2.0), .6	1.3 (0.7–2.3), .4
Males	2.8 (2.1–3.9), <.001	1.6 (1.1–2.3), .01	2.5 (1.8–3.5), <.001	1.6 (1.1–2.3), .02
Interaction analysis (*P*)	.01	.26	.02	.4

Values are hazard ratio (95% confidence interval), *P*.

NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction.

*Adjusted for age, known diabetes, ischemic heart disease, arterial hypertension, atrial fibrillation, left ventricular ejection fraction, severe valvular disease, and usage of beta-blockers, acetylsalicylic acid, and diuretics.

Table 4 Cox proportional hazards models of the associations between NSVT, frequent PVCs (>30/h), and all-cause mortality in a propensity score matched cohort of females and males*

	NSVT	>30 PVCs/h
Females	1.4 (0.8–2.4), .2	1.1 (0.6–2.1), .9
Males	3.1 (2.0–4.8), .01	2.4 (1.5–4.0), <.01
Interaction (*P*)	.02	.05

Values are hazard ratio (95% confidence interval), *P*.

NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction.

*The case-control pairs of the cohort were matched on the propensity for being male conditional of the following baseline characteristics: age, indication for Holter, NSVT on Holter and >30 PVCs/h on Holter, left ventricular ejection fraction, a medical history of cancer, diabetes mellitus, ischemic heart disease, and atrial fibrillation as well as usage of diuretics, acetylsalicylic acid, and lung medication.

patient-years), significantly higher than in males without NSVT 19% (25 per 1000 patient-years) (HR 2.8, 95% CI 2.1–3.9, $P < .001$). After adjusting for relevant factors, NSVT remained associated with all-cause mortality in males (HR 1.64, 95% CI 1.14–2.35, $P = .01$) (Table 3).

There was a significant interaction between sex and NSVT in the unadjusted model ($P = .01$) but not in the adjusted model (Table 3).

Supplemental Figures 1 and 2 show cumulative incidence curves for mortality in males and females with and without NSVT.

Frequent PVCs (>30 PVCs/h) and all-cause mortality

As shown in Table 3, the findings regarding frequent PVCs (>30/h) followed a similar pattern to NSVT, with an increased risk of all-cause mortality in males but not in females.

Supplemental Figures 3 and 4 show cumulative incidence curves for mortality in males and females with and without more than 30 PVCs/h.

When examining PVC burden in 3 groups, A (<10 PVCs/h), B (10–29 PVCs/h), and C (≥30 PVCs/h), group B is not associated with increased mortality in either sex. In contrast, group C is associated with increased mortality only in males, consistent with our other findings (Supplemental Table 3).

Supplemental Table 4 shows the characteristics of people with over 30 PVCs/h compared with people with under 30 PVCs/h.

Propensity score analysis

Supplemental Table 5 shows an even distribution of the baseline variables for males and females in the propensity score–matched cohorts. Supplemental Figure 5 compares the mortality rates of males and females in the propensity score–matched groups.

Cox analysis in the propensity score–matched group confirmed the association between NSVT and mortality in males (HR 3.1, 95% CI 2.0–4.8, $P < .01$), but no significant association was observed in females (HR 1.4, 95% CI 0.8–2.4, $P = .2$) (Table 4).

Interaction between sex and NSVT was significant in the propensity score–matched cohort (Table 4).

NSVT and mortality in other subgroups of interest

Figure 1 compares the prognosis of NSVT in different subgroups of patients regarding all-cause mortality. The increased mortality risk was consistent in all patient subgroups except females and treatment with calcium-channel blockers (CCBs) (Figure 1).

Sensitivity analyses

In sensitivity analyses, the value of different comorbid conditions in different age groups (≥60 years vs <60 years) was evaluated (Supplemental Figures 6 and 7). The results were consistent except for an interaction in the elderly group with beta-blockers (BBs).

BB use in patients with NSVT was associated with higher mortality in this group. Selection bias or aggravation of NSVT due to heart rate reduction may be postulated.

Length of NSVT and all-cause mortality

In females, neither long nor short NSVT was associated with all-cause mortality in univariable or multivariable models (Supplemental Table 6). In males, shorter runs of NSVT were associated with increased all-cause mortality in univariate but not multivariate analyses. Longer runs of NSVT were associated with increased all-cause mortality in univariable and multivariable analyses (Supplemental Table 6).

The cutoff between short and long NSVT was chosen at the length of ≥5 complexes, which was done pragmatically based on the median value to retain power.

Cardiovascular endpoints

The incidence of cardiovascular endpoints (cardiovascular death, acute myocardial infarction, or coronary revascularization) was low in this population (Supplemental Table 6). Still, the pattern observed mirrored that of all-cause mortality (Supplemental Table 7).

Discussion

In this cohort of consecutive patients referred for clinically indicated Holter assessment, increased ventricular ectopy and short runs of NSVT were associated with increased all-cause mortality risk in males but not in females. The increased risk was consistent in other clinically defined subgroups, including different indications for the Holter recordings.

These findings align with previous studies indicating elevated mortality risk in NSVT subjects in diverse populations.[6–8]

Only a few other studies have reported the difference in outcomes in males and females. For instance, the Framingham Heart Study found that complex or frequent ventricular arrhythmias detected on a 1-hour ECG recording were not

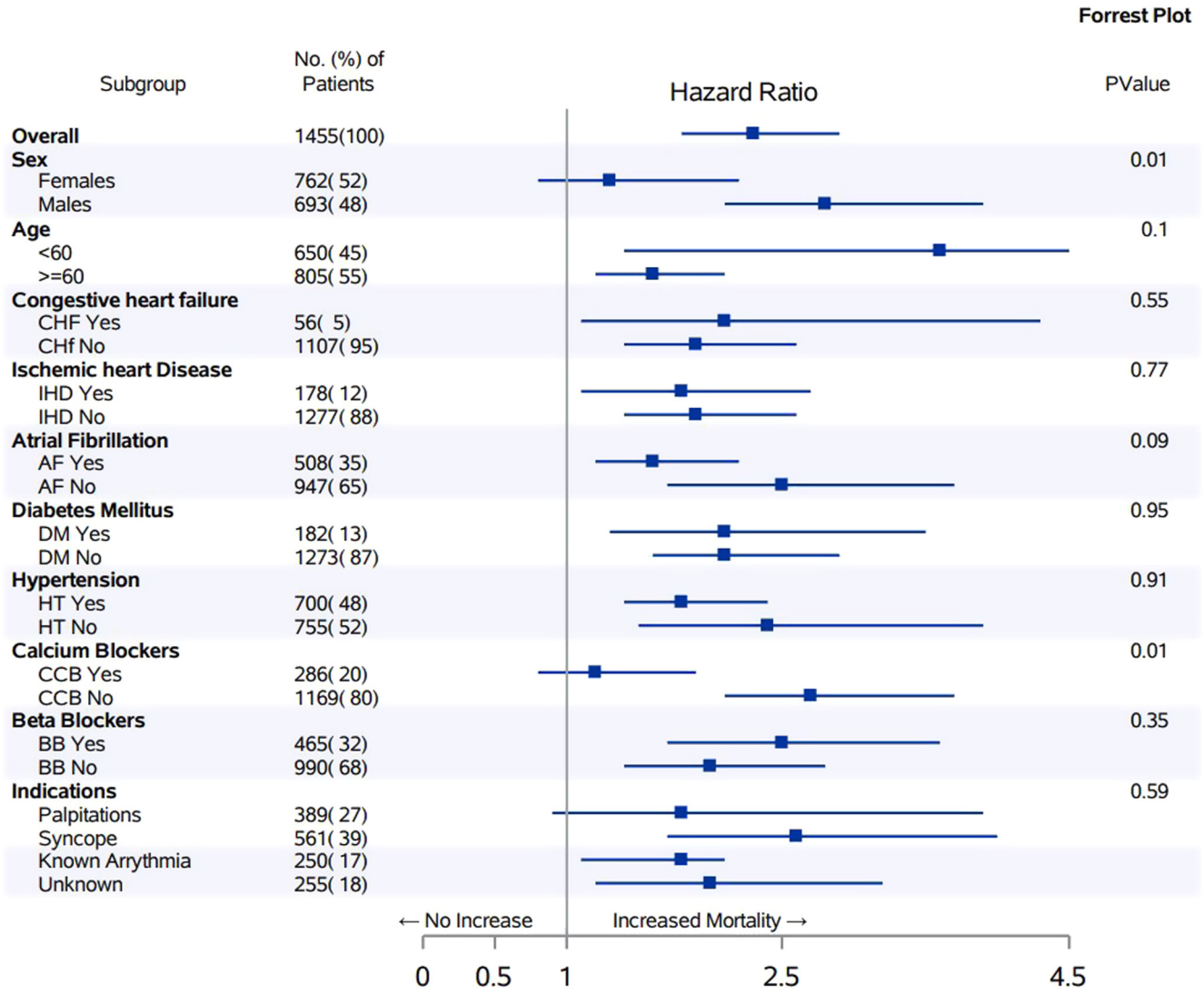

Figure 1 Forest plot showing hazard ratios with 95% confidence intervals and the *P*-value for interaction for all-cause mortality in patients with non-sustained ventricular tachycardia on 48-hour Holter recording.

associated with increased risk of all-cause mortality and cardiovascular events in females, regardless of coronary heart disease status, while males had an increased risk.[11] In a smaller population with a shorter follow-up time of middle-aged to elderly, apparently healthy females and males, the Copenhagen Holter study demonstrated a similar favorable prognosis in females with increased ventricular ectopy or NSVT.[12]

Although our study yields similar findings, there are some essential differences. It reflects a real-life clinical setting involving patients referred for ambulatory ECG monitoring due to suspected arrhythmias, rather than observations in a general population. Consequently, our findings are more likely to be clinically applicable.

Another study, using interrogation data from pacemakers, found no prognostic value of NSVT regarding mortality when adjusted for relevant risk factors.[9] However, studies based on arrhythmias detected on pacemaker data cannot readily be compared with arrhythmia detected on Holter. The difference in recording length is crucial because findings in a very long recording may not have the same significance as short-term recordings. Equivalently, short runs of atrial fibrillation on pacemakers or internal loop recorders do not have the impact that the same arrhythmias have when found on 24- to 48-h recording.[13] Furthermore, patients with pacemakers may not readily be comparable with those without.

Our data indicate that the length of NSVT could be of importance. Especially in males, the length of NSVT was associated with all-cause mortality, and males with runs $\geq$5 complexes had an inferior prognosis. In contrast, the poor prognosis in those with shorter NSVT was related to their comorbidities.

The observed sex difference in the prognosis of NSVT and excessive ectopy may be related to the origin site of the ectopy.[14] Studies show that ventricular tachycardia originating from the right ventricular outflow tract (RVOT) is twice as frequent in females.[15,16] Asymptomatic PVCs and NSVT

originating from the RVOT are usually not associated with increased risk.[17] This could be a plausible biological explanation for the observed difference in prognosis.

A recent study of young athletes and sedentary control subjects showed that the burden of NSVT and PVCs was only associated with age and not with sex or level of training,[18] suggesting age and cardiovascular risk factors as the main factors.

Both this study and previous studies[2] show that the increased risk in outpatients with NSVT is manifested by a mild increase in hazard and a slow pace of events over the years, as seen by cumulative incidence curves (Supplemental Figures 1–4). Thus, NSVT detected on a general Holter monitor likely signals a higher cardiovascular risk burden, rather than an immediate risk of sudden cardiac death.

Although increased ventricular ectopy is associated with an increased risk of adverse outcomes, many patients with frequent PVCs never develop systolic dysfunction or heart failure.[19] Interestingly, in patients with nonischemic heart failure, NSVT was correlated with a worse prognosis but not with sudden cardiac death, and the patients had no benefit from an implantable cardioverter-defibrillator.[20]

The new European Society of Cardiology guidelines[4] have extensive recommendations for managing NSVT. Upon an incidental finding of NSVT, comprehensive personal and family history should be conducted, followed by 12-lead ECG, echocardiography, and Holter, which should be considered to investigate for structural heart disease or primary electrical disease, which are then treated accordingly. If assessment favors idiopathic NSVT, symptoms are treated with ablation if they are of RVOT or fascicular origin or medically if not, with BBs and CCBs being first-line choices. If asymptomatic with under 10% PVCs, the patient can be discharged without follow-up.

While specific antiarrhythmic therapy is not indicated except in the management of symptoms, more intensive risk modification of the background risk factors is indicated because the presence of NSVT puts the patient in a higher-risk category.

The increased risk in NSVT may be due to subclinical organic heart disease. The evidence that supports this idea comes from studies showing that increased ectopy and NSVT are significantly greater in subjects with structural heart disease than in those without. Alternatively, increased ventricular ectopy and NSVT could be a primary electrophysiologic condition or abnormality that can predispose to malignant arrhythmias in certain circumstances. NSVT and increased ectopy can be detected without echocardiographic, angiographic, and clinical evidence of organic heart disease, supporting this hypothesis.[21] In females, the burden of risk factors is lower, and NSVT and ventricular ectopy more frequently arises from the RVOT, which may explain the better prognosis. However, unknown factors may play a role.[16]

Subgroup analyses suggest that CCBs may have a protective effect on the prognosis of NSVT, consistent with previous studies showing that CCBs can reduce the burden of ventricular ectopy and NSVT.[22] This suggests a potential advantage of CCBs over BBs as a first-line choice, though prospective randomized studies are needed to confirm the protective effect.

Limitations

Although Holter data were registered and gathered prospectively, some baseline variables were recorded retrospectively from patient files. Social data, smoking status, and level of physical activity of the patients that could impact the results were not recorded.

Additionally, in females, the use of hormone replacement therapy, which may affect conduction and, thus, probably ventricular ectopy, was not reported in this cohort. This study could not ascertain the origin points of the ventricular arrhythmia, as this is usually not possible in long-term ECG recordings with only 2 to 3 leads. Likewise, circadian variation of VPC and NSVT, which could have prognostic importance, was not recorded.

Selection bias is another limitation. These patients are similar to typical referral patients with specific symptoms and problems like palpitations and syncope or presyncope. Thus, they may not represent incidental findings in the general population or groups of patients with specific diagnoses like hypertrophic cardiomyopathy or congenital heart disease. On the other hand, the majority of previous studies are from epidemiological studies and are interestingly in line with the results of the current study. Referrals to smaller community centers and private clinics may also differ.

This study examines prognostic differences in biological sex. We have chosen to use legal gender from the Danish CPR registry as equivalent to biological sex. However, a person can apply to have their legal gender changed to be in accordance with one's gender identity. We do not have data on whether anyone in the cohort has made this change. As of August 2023, a total of 2301 people, or 0.04% of the Danish population, have had this change approved, and as such, we do not expect this to influence the overall results.

As most patients enrolled were Caucasian, the results cannot be directly applied to other ethnic populations.

Conclusion

In a cohort of consecutive patients referred for symptom-driven Holter monitoring at a cardiology outpatient clinic, short runs of NSVT were associated with increased all-cause mortality in males but not in females. These results could be helpful to clinicians in the risk evaluation of patients with NSVT.

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Ethics Statement: The database was approved by the local institutional review board at the Department of Cardiology at Bispebjerg Hospital as part of internal quality assurance, and the institutional review board thus waived written informed consent. The research in this study was conducted according to the Helsinki Declaration guidelines on human research

Data Availability: The data underlying this article were accessed from the "Registry on Holter Recordings" at Bispebjerg-Frederiksberg Hospital and from the patient's electronic records. Anonymized data will be shared on reasonable request to the corresponding author.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2024.05.007.

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