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Electrocardiographic deep terminal negativity of the P wave in V1 and risk of mortality: The National Health and Nutrition Examination Survey III

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Abstract

Introduction—Deep terminal negativity of P wave in V1 (DTNPV1), defined as negative P prime larger than one small box (1mm, or 0.1mV), could be easily detected by simple visual inspection of the resting 12-lead ECG. The objective of this study was to determine the relationship between DTNPV1 and all-cause-, cardiovascular disease (CVD)-, and ischemic heart disease (IHD) mortality in the National Health and Nutrition Examination Survey III (NHANES III).

Methods and Results—After exclusion of participants with atrial fibrillation and missing data, DTNPV1 was automatically measured from standard 12-lead ECG in 8,146 participants. Minnesota and Novacode algorithms were used for the determination of major and minor ECG abnormalities. National Death Index was used to identify the date and cause of death. During a median follow-up of 13.8 years, a total of 2,975 deaths (1303 CVD and 742 IHD deaths) occurred. After adjustment for age, gender, race/ethnicity, IHD, heart failure, chronic obstructive pulmonary disease, cancer, diabetes, body mass index, smoking, dyslipidemia, hypertension, use of antihypertensive and lipid-lowering medications, and ECG abnormalities, DTNPV1 was associated with significantly increased risk of all-cause death (HR [95% CI]: 1.30 [1.10, 1.53]; $p=0.002$), CVD death (HR [95% CI]: 1.36 [1.08, 1.72]; $p=0.010$), and IHD death (HR [95% CI]: 1.36 [1.00, 1.85]; $p=0.047$).

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Conclusion—In a large sample of the adult United States population DTNPV1 is independently associated with increased risk of death due to all-cause, CVD, and IHD, findings suggesting its potential usefulness as a simple marker to identify individuals at risk of poor outcomes.

Keywords

cardiovascular mortality; all-cause mortality; P-wave indices; NHANES III

Introduction

Cardiovascular mortality remains the most frequent mode of death in the United States(1), and across the globe. About half of death victims are not aware of preexisting cardiovascular disease (CVD). Accurate stratification of CVD death risk in the general population of asymptomatic or mildly symptomatic adults is an important step towards improvement of outcomes. Resting 12-lead electrocardiogram (ECG) is an inexpensive and widely available tool, which could be used for the screening. Thus, development of novel ECG risk markers is needed.

Recently, prolonged PR interval has been gaining wide interest due to its associations with adverse outcomes(2–4). However, there have been emerging concerns about using PR interval in risk prediction models. These concerns stem from the notion that PR interval association with outcomes seem to depend on the level of contribution of P-wave duration to its length(5). This suggests that using P wave duration may be more appropriate. However, wide use of P-wave duration(6) is limited by the fact that P duration is not always automatically reported by the automated ECG analysis algorithms, and it is not easy to manually measure with precision.

Other P-wave indices (P axis (7) and P-terminal force in V1(8)) have shown associations with outcomes and, therefore, may be considered as alternatives to P wave duration. In particular, impaired interatrial conduction (9;10), assessed by abnormal P-terminal force in V1(11) defined as the product of the duration and amplitude of the terminal portion of P-wave at V1 that is $-0.04\text{mm}\cdot\text{s}$, or $-4\text{mV}\cdot\text{ms}$. P-terminal force in V1 was shown to be associated with atrial fibrillation (AF)(12), stroke(13), left ventricular hypertrophy (LVH) (14), and composite endpoint of heart failure (HF) hospitalizations or death(8).

The main challenge for a wide use of P terminal force is the need to measure both the amplitude and duration of the terminal P wave portion in V1. Generally, however, the amplitude of the terminal P_{V1} portion that is -1 mm , or -0.1mV (one small ECG grid box) is accompanied by a duration 0.04 sec , or 40ms in most of the times, which subsequently yields a P terminal force $-0.04\text{mm}\cdot\text{s}$, or $-4\text{mV}\cdot\text{ms}$. Therefore, we hypothesize that the presence of a negative P wave in V1 that is deeper than one small ECG grid square, which could be easily visualized without calculation, should be a good surrogate for P terminal force and subsequently would be a good predictor of outcomes. This simple approach would enhance utilization of a useful ECG marker such as P-terminal force in V1 without the need to make any calculations.

The objective of this study was to determine the relationship between a negative P-prime wave in V1 that is deeper than one small ECG grid square, referred to in this report as deep terminal negativity in V1 (DTNPV1) and risk of mortality in the National Health and Nutrition Examination Survey III (NHANES III).

Methods

Study population

NHANES is an episodic survey of the noninstitutionalized civilian population in the United States. The survey design, methods, and collected data are available online at <http://www.cdc.gov/nchs/nhanes/nh3data.htm>. The survey is conducted by the National Center for Health Statistics (NCHS) of the Center for Disease Control and Prevention. The NCHS institutional review board approved the protocol for NHANES III. All participants gave written informed consent. The NHANES design was previously described elsewhere(5;6;15). NHANES III was conducted from 1988 to 1994 and screened 39,695 adults and children. In this study, we included 11,448 adults of age 40 years or older. Out of them 8,561 underwent an ECG, standardized physical examination, and laboratory testing. We excluded participants with AF and missing data from the ECG analysis. Data of the remaining 8,146 individuals were included in this ECG study.

Hypertension was defined as self-reported history or use of antihypertensive medications or blood pressure above 140/90 mmHg on physical examination. Blood pressure was measured 3 times during the in-home interview and 3 additional times during a visit to the mobile examination center. Hypercholesterolemia was defined as self-reported history or use of lipid-lowering medication or low-density lipoprotein cholesterol values above the normal cutoff as per the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines(16). CAD was defined as a participant's self-reported history of MI/heart attack, patient history of typical angina pectoris, or ECG changes suggestive of probable or possible MI by the Minnesota Code. HF was defined as a participant's self-reported history of HF or receiving HF treatment. Diabetes mellitus was defined as self-reported history of diabetes, use of diabetes medication, or glycosylated hemoglobin $\geq 6.5\%$. The total serum cholesterol and high-density lipoprotein cholesterol were measured enzymatically. Serum creatinine was measured using the Jaffe modified kinetic method. Self-reported history of thyroid disease (other than goiter) was recorded. Self-reported use of antiarrhythmic medications (including beta-blockers and Ca antagonists) was documented.

Electrocardiogram analysis

Standard 12-lead ECG was recorded on a Marquette MAC 12 system (Marquette Medical Systems, Milwaukee, WI) by trained technicians during the participant's visit to a mobile examination center. Automated ECG analysis was performed at the EPICARE Center at the Wake Forest School of Medicine, Winston Salem, NC. Minnesota and Novacode algorithms were used for the determination of major and minor ECG abnormalities(17–19). Amplitude of the terminal negative phase of P wave in lead V1 was measured automatically. We defined presence of DTNPV1 if the amplitude of the terminal negative phase of P wave in

lead V1 exceeded 100 μ V. For the reference, 100 μ V = 0.1mV = 1mm (one small box). Figure 1 illustrates the DTNPV1 metric.

Study outcomes

Mortality data were constructed by the NCHS using National Death Index records' publically available dataset. All-cause mortality, cardiovascular mortality, and IHD death served as outcomes in this study. As described by the NCHS, the "International Classification of Disease" (ICD), ICD-9 (for deaths occurred in 1988 – 1998) and the ICD-10 (for deaths occurred in 1999–2006) codes were used to adjudicate mode of death. Cardiovascular mortality was defined by the ICD-9 codes 390–434 and 436–459, and ICD-10 codes I00-I99. The follow-up period was calculated as the interval between NHANES III examination and the date of death or December 31, 2006, whichever occurred first.

Statistical analysis

Statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, North Carolina), and STATA 13.1 (StataCorp, College Station, Texas). All analyses adhered to the analytic guidelines articulated by the NCHS. Continuous variables are presented as mean and standard deviation (SD). Clinical and demographic characteristics of individuals with and without DTNPV1 were compared using a 2-sided *t*-test (continuous variables), or chi-squared test (categorical variables). The descriptive analyses were not weighted because our study focused on the association between DTNPV1 and outcomes rather than on the evaluation of the prevalence or distribution of DTNPV1 in the US.

Unadjusted Kaplan-Meier plots were constructed for DTNPV1 groups, and the log-rank test was used to test equality of survival functions. The association between DTNPV1 and outcomes was examined using Cox proportional hazards regression analysis. Two incremental models were constructed: model 1 was adjusted for demographics [age, gender, and race/ethnicity], prevalent CVD [IHD and HF], CVD risk factors [diabetes, body mass index (BMI), smoking, hyperlipidemia, hypertension, use of antihypertensive and lipid-lowering medications], and major non-CVD comorbidities [chronic obstructive pulmonary disease (COPD), and cancer]. Model 2 was further adjusted for major and minor ECG abnormalities.

Using a fully adjusted model, we conducted a subgroup analysis stratified by age (using 65 years as a cut-point), sex, race (whites vs. non-whites), diabetes, thyroid disease, cancer, COPD, CHF, IHD, and use of antiarrhythmic drugs. Test for interaction was performed with all mortality outcomes. Generalized linear regression models of the scaled Schoenfeld residuals on functions of time were plotted and quantified to test proportionality assumption of the Cox models.

Results

The ECG study population included 8,146 participants. DTNPV1 was observed in 243 (2.98%) individuals. Demographic, clinical, and ECG characteristics of participants with and without DTNPV1 are compared in Table 1. Individuals with DTNPV1 were likely to be

older, smokers, with past history of IHD, HF, hypertension, COPD, cancer, and other-than-goiter thyroid disease, and with higher prevalence of major and minor ECG abnormalities. On the other hand, BMI was smaller, and HDL was higher in DTNPV1 group (Table 1).

During a median follow-up of 13.8 years, a total of 2,975 deaths occurred, of which 1303 were due to CVD and 742 deaths were due to IHD. Compared to no DTNPV1, DTNPV1 was associated with more than twice the risk of all-cause mortality (incidence 63.2 vs. 28.4 per 1,000 person-years; $P<0.0001$), CVD mortality (31.2 vs. 12.3 per 1,000 person-years, $P<0.0001$) and IHD mortality (18.4 vs. 7.0 per 1,000 person-years, $P<0.0001$). Figure 2 shows unadjusted Kaplan-Meier survival curves for all 3 outcomes.

In unadjusted Cox proportional hazard analysis, DTNPV1 was associated with more than twice higher all-cause mortality, 2.6 times higher CVD mortality, and 2.7 times higher mortality due to IHD (Table 2). These associations remained significant after further adjustment for demographics, CVD risk factors and potential confounders (Table 2).

In general, the association between DTNPV1 and mortality was consistent across several subgroups of the NHANES III (Table 3). However, DTNPV1 showed a stronger association with all-cause mortality and CVD mortality in non-whites compared to whites (interaction $P=0.008$ and 0.0270 , respectively) and a stronger association with all-cause mortality in individual aged <65 years compared to older participants (interaction $p=0.017$). No other significant interactions were observed.

Discussion

In this analysis from the NHANES III survey, we showed that DTNPV1, an easily detected ECG marker, is associated with an increased risk of all-cause-, CVD-, and IHD- mortality in a community-based sample of the United States adult population. Such associations persisted after comprehensive adjustment for demographics, prevalent CVD and non-CVD comorbidities, traditional CVD risk factors and both major and minor ECG abnormalities, suggesting independent association of DTNPV1 with mortality. DTNPV1 is an easily recognizable ECG finding, which could be detected with the naked eye.

Independent predictive value of several ECG parameters has been previously demonstrated in the NHANES III. This includes positive or near isoelectric T wave in lead aVR (20), prolongation of QRS duration, (21) left and right bundle branch blocks, nonspecific ST-segment and T-wave abnormalities(22), abnormal spatial QRS-T angle(23), ECG-left ventricular hypertrophy (LVH) (24), abnormal P-axis(7), and prolonged P-wave duration (6). These findings provide evidence for the utility of ECG as a simple, inexpensive tool that has the potential to identify individuals at risk of poor outcomes. Our results further emphasize this fact by providing another simple ECG marker, DTNPV, predictive of increased risk of mortality. The magnitude of risk associated with DTNPV1 in our study is seemingly greater than or at least similar to the magnitude of risk observed with the above mentioned ECG markers.

Morris et al(11) in 1964 compared P terminal force metric in healthy subjects and patients with valvular heart disease, and reported a positive correlation between P-terminal force and

mean aortic systolic gradient, as well as negative correlation between P-terminal force and mitral valve area. Authors defined abnormal P-terminal force as “a terminal portion of the P wave at V1 one box in depth (– 1.0 mm.) and one box in duration (0.04 sec.)”, yielding a P terminal force of – 0.04. Morris et al(11) reported 92% sensitivity of abnormal P-terminal force in the diagnosis of valvular heart disease, regardless of specific valvular lesion. We simplified P-terminal force metric, and suggested that it is enough to know only amplitude of terminal negative P_{V1} deflection. Based on observation, a terminal negative portion of P_{V1} amplitude – 1.00 mm in depth is usually accompanied by a duration of terminal negative P_{V1} portion that exceeds one small ECG grid box (0.04sec). Therefore, one can ignore duration and look only at the amplitude (i.e., DTNPV1) in order to get an impression on the presence or absence of abnormal P terminal force in V1. Significant associations of DTNPV1 with mortality, observed in this study, support this proposition. Notably, DTNPV1 was measured in NHANES by automated software (12SL algorithm, General Electric), and hence, future studies are needed to verify the assumption that visual ECG inspection is as good as automated amplitude measurement for DTNPV1 diagnosis.

Several underlying mechanisms could result in appearance of DTNPV1. Romhilt et al(14) regarded DTNPV1 as a “sign of left atria involvement” and included it into LVH criteria. At least for a decade DTNPV1 was considered as a sign of left atrial enlargement, until Josephson et al demonstrated that P-terminal force represents an interatrial conduction defect that can be produced by a variety of factors(25). It is suggested(26) that a localization of left atrial breakthrough defines left atrial depolarization vector and is primarily responsible for the appearance of P-wave terminal negative deflection in V1. In concordance with this assumption, Janin et al(27) showed that pulmonary vein isolation in patients with paroxysmal AF could modify P-wave morphology in V1, leading to the disappearance of previously observed DTNPV1 in 96% of cases. Such procedure-related modification of P-wave appearance suggests that isolation of pulmonary veins is associated with further modification of interatrial conduction pattern.

Previous studies showed that abnormal P-terminal force is associated with AF(12), stroke(13), LVH(14), and HF(8). All these conditions are well-known risk factors of mortality, and therefore, DTNPV1 could be a sign of subclinical and/or manifested structural heart disease. While the nature of our investigation did not allow us to examine whether the association between DTNPV1 and mortality is explained by incident AF, stroke, and HF, data of previous studies suggest that AF, in particular, could be a mediator between DTNPV1 and mortality. Soliman et al(12) showed that individuals with P-terminal force in V1 in an upper 5th percentile have 2-fold increased risk of incident AF (Hazard Ratio 1.9 [95%CI 1.02–3.55] after adjustment for hypertension, systolic blood pressure, diabetes, blood lipids, smoking status, and BMI).

The association of DTNPV1 with IHD death was consistent in all subgroups; no significant interaction was noted. However, the association of DTNPV1 with CVD death revealed significant interaction by race with DTNPV1 more predictive of CVD death in non-whites than in whites. Similar interaction with race was observed with all-cause mortality. A previous report from a large multiracial population of adults without evidence of CVD suggests similar interactions as those observed in our study. Soliman et al showed that P-

wave terminal force in V1 is smaller in middle-age participants (< 65 y), as compared to seniors (≥ 65y), and it is larger in African Americans, as compared to whites(28). Interestingly, while larger P-wave terminal force was more prevalent in elderly, DTNPV1 was more predictive of mortality in our study participants aged less than 65 years. This could be because African Americans' longevity is shorter, as compared to whites, and therefore, the observed interaction with age could be a simple reflection of the observed interaction with race. These findings possibly suggest that developing race- and age- specific threshold of abnormal P-wave terminal force might result in a better precision of prognostication.

Strong association of DTNPV1 with mortality suggests that this easily identifiable ECG marker could serve for screening and selection of a subgroup of individuals at high risk among overall low-risk general population of adults. Future studies are needed to determine the best intervention strategy to prevent the development of AF, stroke, HF, and death in such individuals. Furthermore, in some populations P-wave amplitude in V1 was associated with the pulmonary capillary wedge pressure, and thus potentially DTNPV1 could be reversible (29;30). Thus, DTNPV1 ECG sign could possibly serve as an endpoint-surrogate for the assessment of the effectiveness of preventive interventions. Further studies are needed to test this hypothesis.

Limitations and strength of the analysis

Although we have adjusted for several potential confounders, we recognize the possibility of residual confounding that is the case in all similar observational studies. NHANES III does not have serial ECGs that could have enabled us to examine the natural history of DTNPV1 over time. Incident AF was not a pre-defined outcome in NHANES III study and, therefore, in this study we were not able to evaluate if AF is a mediator between DTNPV1 and the mortality outcomes. Despite these limitations, this is the first large study from a racially diverse, community-based US population showing the predictive ability of DTNPV1, an ECG marker that could be easily detected visually by clinicians. Other strengths include well-ascertained outcomes and variables including standard ECG recording using a chest electrode locator and the ECG's were processed centrally at a central ECG core laboratory.

Conclusion

In this large sample of the US population, DTNPV1, an easy to visually detect ECG marker, is independently associated with increased risk of all-cause, CVD and IHD mortality. Further investigations are needed to study if DTNPV1 is associated with sudden cardiac death. Replication of these results in an independent population is warranted. After validation in another cohort, DTNPV1 could be recommended for risk stratification of individuals early in the continuum of structural heart disease, and for the monitoring of the response on preventive interventions.

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Figure 1.

Representative example of deep terminal negativity of P wave in V1 (DTNPV1). Onset of P-wave serves as a reference for the measurement of P-prime amplitude.

Figure 2.

Unadjusted Kaplan-Meier survival curves for participants with and without deep terminal negativity of P-wave in V1: A. all-cause mortality; B. cardiovascular mortality; C. ischemic heart disease mortality.

Table 1

Comparison of clinical, demographic, and ECG characteristics of participants with and without Deep Terminal Negativity of P-wave in V1 (negative amplitude > 0.1 mV)

	No DTNPV1 (n=7,903)	Yes DTNPV1 (n=243)	P
Men, n(%)	3,905(49.1)	126(51.9)	0.454
Whites, n(%)	3,798(48.1)	111(45.7)	0.465
Age(SD), y	59.9(13.5)	66.4(11.2)	<0.0001
Systolic Blood Pressure (SD), mmHg	133.4(27.4)	141.8(20.1)	<0.0001
Diastolic blood pressure (SD), mmHg	76.8(24.6)	77.6(11.8)	0.346
Total cholesterol(SD), mg/dL	217.8(44.2)	222.1(43.0)	0.130
HDL(SD), mg/dL	50.6(16.1)	54.4(18.6)	0.003
Triglycerides(SD), mg/dL	163.4(131.8)	158.7(110.5)	0.518
Hypercholesterolemia, n(%)	1,928(24.4)	62(25.5)	0.689
BMI(SD),	27.7(5.5)	26.7(5.6)	0.007
Diabetes mellitus, n(%)	936(11.8)	38(15.6)	0.073
Previous IHD, n(%)	521(6.6)	42(17.3)	<0.0001
History of HF, n(%)	371(4.7)	36(14.8)	<0.0001
Hypertension, n(%)	2,837(35.9)	132(54.3)	<0.0001
Use of antihypertensive drugs, n(%)	1,883(23.8)	97(39.9)	<0.0001
Use of AV-nodal agents, n(%)	1,142(15.8)	53(24.9)	<0.0001
COPD, n(%)	531(6.72)	27(11.1)	0.008
Asthma, n(%)	390(4.9)	12(4.9)	0.998
Other-than-goiter-thyroid, n(%)	405(5.1)	25(10.3)	<0.0001
Cancer, n(%)	873(11.1)	38(15.6)	0.025
Current smoker, n(%)	1,752(22.2)	80(32.9)	<0.0001
Major ECG abnormalities, n(%)	1,352(17.1)	91(37.5)	<0.0001
Minor ECG abnormalities, n(%)	1,693(21.4)	77(31.7)	<0.0001

HDL=high density lipoprotein; BMI=body mass index; IHD=ischemic heart disease; HF=heart failure; COPD=chronic obstructive pulmonary disease; LVH=left ventricular hypertrophy; MI=myocardial infarction.

Deep terminal negativity of P-wave in V1 and risk of all-cause mortality, cardiovascular mortality, and ischemic heart disease death

Table 2

	All-cause mortality			CVD mortality			IHD mortality		
	HR (95%CI)	P		HR (95%CI)	P		HR (95%CI)	P	
Unadjusted	2.32(1.97–2.73)	<0.0001		2.62(2.08–3.30)	<0.0001		2.71(2.00–3.67)	<0.0001	
Model 1, Adjusted for demographics and clinical characteristics	1.38(1.17–1.63)	<0.0001		1.49(1.18–1.88)	0.001		1.50(1.10–2.03)	0.010	
Model 2, Adjusted for demographics, clinical and ECG characteristics	1.30(1.10–1.53)	0.002		1.36(1.08–1.72)	0.010		1.36(1.00–1.85)	0.047	

Demographics included age, gender, and race/ethnicity. Clinical characteristics included prevalent CVD [IHD, HF], IHD risk factors [diabetes, body mass index, smoking, hyperlipidemia, hypertension, use of antihypertensive and lipid-lowering medications], and major non-CVD comorbidities [chronic obstructive pulmonary disease (COPD), thyroid disease, and cancer]. ECG characteristics included major and minor ECG abnormalities as detected by Minnesota code.

Table 3

Deep terminal negativity of P-wave in V1 and risk of all-cause, cardiovascular, and IHD mortality across subgroups

	All-cause mortality			CVD mortality			IHD mortality		
	HR (95%CI)	P		HR (95%CI)	P		HR (95%CI)	P	
Male	1.38(1.09–1.73)	0.007		1.63(1.19–2.22)	0.002		1.59(1.07–2.34)	0.020	
Female	1.20(0.95–1.53)	0.126		1.11(0.76–1.60)	0.592		1.06(0.64–1.78)	0.811	
Interaction		0.466			0.069			0.160	
Age 65 y	1.20(0.99–1.27)	0.065		1.31(1.00–1.72)	0.048		1.19(0.82–1.71)	0.362	
Age < 65 y	1.61(1.18–2.20)	0.002		1.56(0.96–2.56)	0.075		1.72(0.95–3.10)	0.074	
Interaction		0.017			0.209			0.080	
White	1.09(0.87–1.36)	0.462		1.14(0.83–1.57)	0.414		1.21(0.81–1.80)	0.342	
Non-White	1.66(1.30–2.13)	<0.0001		1.84(1.28–2.67)	0.001		1.75(1.07–2.87)	0.025	
Interaction		0.008			0.027			0.174	
Diabetes Yes	1.05(0.71–1.57)	0.792		1.02(0.57–1.82)	0.958		0.89(0.41–1.96)	0.775	
Diabetes No	1.38(1.15–1.65)	0.001		1.49(1.15–1.93)	0.003		1.51(1.08–2.11)	0.015	
Interaction		0.150			0.198			0.198	
Thyroid Yes	1.60(0.94–2.73)	0.083		2.84(1.37–5.90)	0.005		4.09(1.52–10.98)	0.005	
Thyroid No	1.26(1.05–1.50)	0.011		1.27(0.99–1.64)	0.060		1.25(0.90–1.74)	0.178	
Interaction		0.300			0.131			0.117	
Cancer Yes	1.03(0.70–1.54)	0.862		1.10(0.63–1.92)	0.747		1.13(0.56–2.28)	0.738	
Cancer No	1.39(1.16–1.67)	<0.0001		1.45(1.11–1.88)	0.005		1.42(1.01–2.00)	0.046	
Interaction		0.058			0.232			0.398	
COPD Yes	1.23(0.74–2.06)	0.427		1.13(0.50–2.55)	0.762		1.22(0.44–3.37)	0.706	
COPD No	1.31(1.10–1.55)	0.003		1.38(1.07–1.77)	0.011		1.37(0.99–1.90)	0.056	
Interaction		0.823			0.676			0.732	
HF Yes	1.39(0.92–2.09)	0.119		1.37(0.81–2.32)	0.242		1.83(1.00–3.34)	0.051	
HF No	1.25(1.04–1.50)	0.016		1.29(1.16–1.48)	0.064		1.17(0.81–1.69)	0.398	

	All-cause mortality			CVD mortality			IHD mortality		
	HR (95%CI)	P		HR (95%CI)	P		HR (95%CI)	P	
Interaction		0.322			0.331			0.102	
IHD Yes	1.26(0.88–1.81)	0.215		1.39(0.89–2.17)	0.143		1.75(1.09–2.80)	0.020	
IHD No	1.30(1.08–1.56)	0.006		1.31(0.99–1.74)	0.059		1.08(0.72–1.64)	0.706	
Interaction		0.827			0.739			0.120	
AA drugs Yes	1.30(0.92–1.84)	0.133		1.53(0.99–2.38)	0.056		1.21(0.66–2.21)	0.525	
AA drugs No	1.31(1.06–1.62)	0.014		1.30(0.93–1.81)	0.123		1.38(0.90–2.13)	0.140	
Interaction		0.865			0.418			0.899	

Thyroid = self-reported history of non-goiter-thyroid condition; COPD= chronic obstructive pulmonary disease; CHF=heart failure; IHD=ischemic heart disease; AA drugs=use of antiarrhythmic drugs, including beta-blockers and calcium antagonists. Models were adjusted for age, gender, race/ethnicity, IHD, HF, diabetes, body mass index, smoking, hyperlipidemia, hypertension, use of antihypertensive and lipid-lowering medications, COPD, cancer, major and minor ECG abnormalities.