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Frontal Plane T-Wave Axis Orientation Predicts Coronary Events: Findings from the Moli-sani Study

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Abstract

Background and aims The orientation of the frontal plane T-wave axis (T axis) is a reliable measure of ventricular repolarisation. We investigated the association between T-axis and the risk of coronary heart disease (CHD), heart failure (HF), atrial fibrillation (AF), stroke and cardiovascular (CVD) mortality.

Methods A sample of 21,287 Moli-sani participants randomly recruited from the general adult (≥35 y) Italian population, free of CVD disease, was followed for a median of 4.4 years. T-axis was measured from a standard 12-lead resting ECG.

Results After adjusting for CVD risk factors, subjects with abnormal T-axis showed an increase in the risk of both CHD (Hazard Ratio (HR)=2.65; 95 %CI= 1.67-4.21), HF (HR=2.56; 1.80-3.63), AF (HR=2.48;1.56-3.94) and CVD mortality (HR=2.83; 1.50-5.32). The association with CHD and HF, but not with AF or CVD death, remained significant after further adjustment for ECG abnormalities. Subjects with abnormal T-axis showed higher levels of subclinical inflammation, hs-troponin I and hs-NT-proBNP ($p<0.001$ for all). However, further adjustment for troponin I and/or NT-proBNP determined a reduction of HRs ranging from 12.1 to 24.0% for CHD, while additional adjustment for inflammation markers did not change any association.

Conclusion An abnormal T-axis orientation is associated with an increased risk of both CHD and HF, independently of common CVD risk factors and other ECG abnormalities. This association was partially explained by increased hs-troponin I and hs-NT-proBNP levels.

Introduction

Electrocardiographic signs of ventricular repolarisation may reflect subclinical myocardial damage. Changes in the ST-T segment (1,2) and increased QT dispersion (3) have been associated with the risk of coronary heart disease (CHD) and mortality. Thereafter, the orientation of frontal plane T-wave axis (T-axis) has been proposed as a more efficient and reliable measure of ventricular repolarisation abnormality that can be easily and repeatedly evaluated from a standard electrocardiogram (4) in epidemiological settings.

Results on the predictive value of T-axis on cardiovascular disease are sparse and controversial and mainly confined to CHD and mortality. Two studies reported that abnormal frontal or spatial T-axis measured from standard 12-lead electrocardiograms was independently associated with an increased risk of CHD and total mortality in older persons (5-6). The Multiple Risk Factor Intervention Trial found that the change over time in the spatial T-axis was associated with incident CHD (7). In contrast, the ARIC study failed to show any association between spatial T-axis and incident coronary events (8). However, no studies have investigated the association between T-axis and other cardiovascular features such as heart failure, atrial fibrillation or stroke.

T-axis is associated with several risk factors (9-11) and with some cardiac abnormalities, such as left ventricular hypertrophy, predictive of such cardiovascular conditions (12). It has been recently speculated that obesity and hypertension could have a relevant role in the pathogenesis of abnormal T-axis (13). In addition, later studies showed that abnormal T-wave axis shift is independently associated with the metabolic syndrome (14), suggesting that a careful electrocardiogram (ECG) recording should be made in persons with metabolic syndrome in order to make an early detection of abnormal T-axis in clinical practice.

Recently, an ECG risk equation based on the First National Health and Nutrition Examination Survey (NHANES) cohort was able to correctly assess the risk for CVD death in the Third NHANES cohort (15). The risk score based on frontal T axis deviation together with age, sex, heart rate and QT interval and compares favourably with the Framingham risk score alone (15).

We conducted a prospective analysis among 24,325 persons recruited within the Moli-sani study to investigate the following novel hypotheses: 1) deviation from normality of frontal T-axis is associated with risk of heart failure (HF), atrial fibrillation (AF) and stroke in a general population, independently of common risk factors for cardiovascular disease and other ECG abnormalities; 2) markers of sub-clinical inflammation, hs-troponin I and hs-NT-proBNP are biological mediators of the possible associations of frontal T-axis with vascular outcomes. As a secondary aim, we wished to confirm the association of T-axis deviation with CHD or cardiovascular mortality.

Methods

Study Population

The Moli-sani Study is an ongoing, prospective, population based, cohort of 24,325 men and women (aged ≥35 years) living in the Molise region, a southern-central area of Italy. Participants were randomly enrolled from city hall registries between March 2005 and April 2010 by a multistage sampling (16).

Exclusion criteria were pregnancy at the time of recruitment, lack of understanding or willingness, current poly-traumas or coma, or refusal to sign the informed consent. Thirty percent of subjects refused to participate; these individuals were generally older and had a higher prevalence of cardiovascular disease and cancer.

The Moli-sani study complies with the Declaration of Helsinki and was approved by the Catholic University of Rome ethical committee. All participants provided written informed consent.

Individuals with an incomplete anamnestic questionnaire (n=235), history of CHD or stroke or unascertained illness (n=1,729), history of HF (n= 143), inferior or anterior myocardial infarction by electrocardiogram (n= 1,033 and n=38 respectively), T-wave axis value missing (n=195), lost to follow-up (n=44), or missing information on incident outcomes (n=10) were also excluded. The final study sample included 21,287 subjects. Participants were asymptomatic for vascular diseases at baseline.

ECG measurements

ECG measures were obtained from the standard 12-lead resting electrocardiogram recorded by Cardiette®ar2100-view electrocardiograph, which stored electrocardiograms in SCP format. ECGs were then automatically processed by the "University of Glasgow 12-Lead ECG Analysis Algorithm" (17). Among many features, the Glasgow algorithm provides T-wave frontal axis and MINNESOTA coding -the internationally agreed standard for epidemiological studies and clinical trials (18). This algorithm has been involved in numerous clinical studies, and is generally regarded as one of the premiere ECG interpretation algorithms within the cardiology community worldwide. T-wave frontal axis was classified as: normal (15° to 75°), borderline (-15° to 15° or 75° to 105°) or abnormal (-180° to -15° or 105° to 180°). These values were chosen to facilitate comparisons with other studies in which a frontal axis between 15° and 75° was defined as normal (5, 9, 11, 14). Other ECG abnormalities were defined according to MINNESOTA codes (MNC): Q-QS waves (MNC=1.1-1.3.6), QRS axis deviation (MNC=2.1-2.5), high amplitude R waves (MNC=3.1-3.3), ST junction and segment depression (MNC=4.1-4.4), T wave changes (MNC=5.1-5.2 (anterior), 5.3-5.4), A-V conduction defects (MNC=6.1-6.8), ventricular conduction defects (MNC=7.1-7.8), arrhythmias (MNC=8.1-8.9), and miscellaneous findings including ST segment elevation (MNC=9.1-9.8.2) (18). Major T wave changes (MNC=5.1-5.2 (anterolateral and inferior)) are linked with abnormal T-axis orientation and were not included in the list of ECG abnormalities.

Definition of common risk factors

Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90mmHg, or the use of pharmacological treatment for hypertension. Values of systolic blood pressure ≥130 and <140 or diastolic blood pressure ≥85 and <90 were used to define prehypertension.

Diabetes was defined as glucose level ≥126 mg/dl or current antidiabetic treatment, while prediabetes was defined as glucose level ≥110 and <126 mg/dl.

Subjects were also classified as never-*smokers*, current smokers or ex-smokers (having stopped for at least 1 year). *Education* was used as proxy of socioeconomic status and was based on the highest qualification attained and was categorized as low (up to lower secondary school; approximately ≤8 years of study) or high (upper secondary education or higher; approximately >8 years of study). *Physical activity* was assessed by using the MOSPA-Q structured, validated questionnaire (24 questions on working time, leisure time and sport participation (19) and expressed as daily energy expenditure in metabolic equivalent task-hours (MET-h/day) (20). *Body mass index* (BMI) was calculated as kg/m^2 and then classified as normal (BMI≤25), overweight (25<BMI<30) or obese (BMI≥30).

Blood measurements

Blood samples were obtained between 07:00 and 09:00 from participants who had fasted overnight and had refrained from smoking for at least 6 h. Hemocromocytometric, high sensitivity C reactive protein (CRP), lipids and glucose analyses were performed in the centralized Moli-sani laboratory on fresh samples within three hours from venipuncture (10). All hemocromocytometric analyses were performed by the same cell counter (Coulter HMX, Beckman-Coulter, IL-Milan, Italy). CRP was measured, by a latex particle-enhanced immunoturbidimetric assay (IL-Coagulation Systems on ACL9000). Inter- and intra-day CV were 5.5% and 4.2%, respectively.

For INFLA-score, the 10-tiles of four biomarker levels (i.e. CRP, white blood cell and platelet counts, granulocyte to lymphocyte ratio) were generated (21). For all components, higher levels (i.e. >Q6) scored increasing positively while lower levels got negative scoring. The INFLA-score ranged between -16 and 16.

Serum lipids and glucose were assayed by enzymatic reaction methods using an automatic analyser (ILa350, Instrumentation Laboratory, Milan, Italy). LDL-cholesterol was calculated according to Friedewald.

Highly sensitive Troponin I (hsTnI) and NT-proBNP levels were determined in the frame of the BiomarCaRE project (22) on serum samples frozen in liquid nitrogen at baseline. hsTnI concentrations were determined by the ARCHITECT-STAT highly sensitive Troponin I immunoassay (Abbott Diagnostics, USA; ARCHITECT-i2000SR)

The limit of detection is 1.9 ng/L with 10% coefficient of variation at a concentration of 5.2 ng/L. NT-proBNP levels were measured on the ELECSYS-2010 using an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics). The analytical reporting range is 5–35,000 ng/L. The functional assay sensitivity (defined as the lowest concentration detectable with an inter assay CV of 20%) is <50 ng/L.

Ascertainment of cases

The whole Moli-sani cohort (n=24,325) was followed-up for HF, AF, CHD, stroke and death for a median of 4.3 years (maximum 6.8 years).

The ascertainment of vital status was carried out through linkage with demographic registers, to identify the date of death. Moreover, death certificates were retrieved; these reported the initial and underlying causes of death and were coded according to the International Classification of Diseases, ninth revision (ICD-9). In-hospital deaths were also checked through regional hospital discharge databases by record linkage to the Moli-sani database.

On 31/12/2011, a total of 575 deaths had occurred among the whole Moli-sani cohort, 102 CVD deaths have been included in the present analysis.

CHD was defined as primary incident cases of fatal and nonfatal events of unstable angina, myocardial infarction, coronary revascularization, or both as well as sudden death for an unspecified cardiac event.

Suspected CHD deaths were identified when death certificates stated (i) ischemic heart disease (ICD-9 included in the range 410-414) as the underlying cause of death; (ii) sudden death (ICD-9 798 and 799) as the underlying cause of death; (iii) diabetes (ICD-9 250) or arterial hypertension

(ICD-9 401-405) or other form of heart disease (ICD-9 420-429), as the underlying cause of death, associated with ischemic heart disease (ICD-9 410-414) as a secondary cause of death. After linkage with the hospital discharge files, all records reporting ICD-9 410–414 and/or reperfusion procedure (ICD-9 36.0-36.9) were considered. The disease was verified when CHD was noted on the clinical records, backed up by information on symptoms at onset and concentrations of cardiac enzymes (troponins). When troponin was not available, ECG data coded according to the Minnesota Code were used (23). CHD events were validated using procedures of the AHA, WHF, ESC, CDC and NHLBI for epidemiology and clinical research studies (24).

Suspected stroke deaths were identified when ICD-9 430-438 were reported as the underlying, antecedent, or direct cause of death. Fatal stroke was assigned after verification against hospital discharge and clinical records, when possible.

Persons with suspected stroke were identified on hospital discharge forms by ICD-9 430-432, 434, 436–438 or by procedure codes for carotid revascularization (ICD-9 38.12). If clinical documentation was found, the event was validated using the MONICA procedure. However, if during the validation of a stroke, computed tomography or nuclear magnetic resonance revealed a cerebral infarction or haemorrhage, the stroke event was confirmed even if the MONICA criteria were not fulfilled.

Incident HF and AF at follow-up were defined by HF or AF hospitalization or HF or AF death, according to the ICD-9 428 and 427.3, respectively. Classification obtained from administrative registers has high specificity and can be used in follow-up studies with HF as an end point (27). Hospital discharge diagnosis have a positive predictive value of 98.6% for AF (26) and only 0.1% of persistent or intermittent AF are not identified (27).

Statistical analysis

Main characteristics of the study population were presented as numbers and percentages for categorical variables, or means ± standard deviation (SD) for continuous variables. Analysis of

variance was used to identify potential predictors tested for association with abnormalities of T-axis. Several models of adjustment were used (see the footnote of Table 2). Percentage change in hazard ratios was calculated by the formula: [(HR models 3 or 4 or 5 or 6) - (HR model 2)]/ [(HR model 2) – 1]. Tests for violation of the proportional hazards assumption were conducted through the introduction of linear interaction between categories of frontal T wave axis and the time variable. Terms of interaction between frontal T wave axis with sex and age (≤65 or >65 years) were included in the multivariable models to test for modification of effects. A two-sided P-value<0.05 was considered as statistically significant. Dummy variables for missing values of each variable of interest were created. The data analysis was generated using SAS/STAT software, Version 9.1.3 of the SAS System for Windows©2009 (SAS Institute Inc. Cary, NC, USA).

RESULTS

Characteristics of the study population according to frontal T wave axis are illustrated in Table 1. Borderline or abnormal T-axis was observed in 19.5% and 1.5% of subjects, respectively. Compared to persons with normal frontal T wave axis, those in the borderline or abnormal group were older, had lower education and higher BMI, higher prevalence of hypertension and diabetes. The prevalence of other electrocardiographic abnormalities was also higher in the abnormal T-axis group. The number of participants with borderline (abnormal) frontal T wave axis who did not have other ECG abnormalities at baseline was n=859 (n=10).

A total of 21,287 Moli-sani participants (mean age 55±11 years, 46% men) were followed for heart disease and mortality for a median of 4.4 years (range Q1-Q3: 3.5-5.3 years; 93,016 person-years). During this time 270 CHD (1.3%), 400 HF (1.9%), 252 AF (1.2%), 64 stroke (0.3%) and 102 (0.5%) cardiovascular deaths occurred (Table 2).

T-axis and cardiovascular disease

Participants with borderline (HR=1.56;1.19-2.04) or abnormal (HR=2.87;1.82-4.53) T-axis had an increased age and sex adjusted relative risk of CHD compared with individuals with normal frontal T wave axis (Table 2). After further adjustment for smoking habit, physical activity, education, BMI, hypertension, diabetes and personal history of cancer at baseline, the associations were not modified. The inclusion in the model of ECG abnormalities slightly reduced the associations (HR=1.42;1.07-1.89 and HR=2.04;1.20-3.46 for borderline and abnormal, respectively). No associations were found with stroke (Table 2). All results did not differ for men and women (p for difference of effect >0.05; data not shown).

T-axis and hospitalized Heart Failure

Subjects with abnormal T-axis showed a significant increase in the relative risk of heart failure (HR=2.89; 95% CI= 2.04-4.10, table 2) that was slightly modified by further adjustment for possible confounders (HR=2.56; 1.80-3.63, Table 2, model 1) or for concomitant ECG abnormalities (HR=1.81; 95% CI=1.21-2.70, Table 2, model 2).

T-axis and hospitalized Atrial Fibrillation

Abnormal T-axis was associated with an increase in the relative risk of atrial fibrillation (Table 2). However, the association was strongly reduced and it was no longer statistically significant when adjusted for concomitant ECG abnormalities (Table 2, model 2).

T-axis and CVD mortality

Abnormal T-axis was associated with an increased risk of CVD mortality (Table 2). The association was strongly reduced and it was no more statistically significant when adjusted for concomitant ECG abnormalities (Table 2, model 2).

T-axis and circulating markers of subclinical inflammation and cardiac ischemia

Frontal T wave axis was positively associated with an inflammatory score (including hs-CRP levels, platelet count, with blood cell count and granulocyte/lymphocyte ratio), with troponin I and NT-proBNP levels (Table 1). Individuals with abnormal T-axis clearly showed higher levels of all these biomarkers ($p<0.001$ for all). However, while the inclusion of the inflammation score in the multivariable models did not change the association between T-axis and outcomes (Table 2, model 3), further adjustment for troponin I (model 4) or NT-proBNP (model 5) determined a reduction of 12.1% or 14.0% and 1.2% or 16.0% of the hazard ratio for CHD and HF, respectively (Table 2). When the two biomarkers were added simultaneously in the multivariable model 6, the reduction was 24.0 for CHD and 14.8% for HF (Table 2, model 6). However, all the associations remained statistically significant.

Sensitivity analyses

Subgroups analyses were undertaken for each outcome under study. No significant interaction was found either for age groups (≤65 or >65 years, $p>0.26$ in models 2 for all outcomes) or for sex ($p>0.18$ in models 2 for all outcomes).

DISCUSSION

This study demonstrates that abnormalities of frontal T-axis are associated with an increased risk of coronary heart disease, heart failure, atrial fibrillation and cardiovascular mortality, but not with stroke in a large sample of Italian adult population. The associations were independent of age, sex and common risk factors for cardiovascular disease, including hypertension and obesity. The associations of T-axis orientation with coronary heart disease and heart failure were still significant after further adjustment for other ECG abnormalities, while those for atrial fibrillation and cardiovascular mortality disappeared.

Data from epidemiological settings showing that T-axis is a predictor of cardiovascular morbidity and mortality are confined to elderly or middle age subjects (6,7), or to patients with previous

cardiac events (28, 29) or with chronic Chagas' disease (30). To the best our knowledge, this is the first time that such studies have been extended to a wide age range of the general adult population and also include associations with HF.

T-axis has long been known to provide a global measure of repolarisation abnormalities that have been attributed to ischemic changes in the heart, but the mechanisms underlying ventricular repolarisation are far from being clear (10-12). We have previously showed that T-axis was strongly associated with inflammation indexes (10), speculating that T-wave axis abnormalities may allow early identification of subclinical cardiac damage likely to be attributable to a chronic inflammation status. We have now analysed this possible mediation effect by using an inflammatory score of low-grade inflammation (21) that accounts for the possible synergistic effects of plasmatic and cellular biomarkers of inflammation. Again T-axis abnormality was significantly associated with an increased inflammation score. However, the latter did not account even partially for the association between T-axis and the outcomes.

We also observed that T-axis is associated with circulating levels of troponin I and NT-proBNP. These cardiac markers have been recently associated with the risk of cardiovascular disease in the healthy population (31). Troponin is a cardiac specific structural protein whose determination in blood is useful for the diagnosis and management of acute coronary syndromes and that may directly reflect various pathophysiological processes including cardiac myocyte necrosis and apoptosis.

The biological mechanism of the relation between natriuretic peptides and cardiovascular risk is not well understood. Natriuretic peptide levels have been reported to increase progressively with increasing numbers of diseased coronary arteries (32) possibly reflecting increased cardiac expression and release of natriuretic peptides during myocardial ischemia (32) due to elevated ventricular wall stress.

These biomarkers attenuated the association between T-axis abnormalities and risk of cardiovascular outcomes both when considered individually in the multivariable model and when added

simultaneously. However, the association was still significant, indicating that measuring T-axis can capture more than the risk associated with the two biomarkers.

Strengths and limitations of this study

Major strengths of this study include a large community-based cohort and a prospective design. In addition, further control of all analyses by a wide panel of possible confounding factors, also including other electrocardiographic abnormalities, assures consistency among the observed associations.

The observational nature of our study does not allow for inference of causality. The presence of unknown or residual confounders could not be completely ruled out, although adjustment for a large panel of potential key confounders was performed. One more limitation of the present study is the short duration of the follow-up and consequently the relatively low number of events. However, the dose response and the consistency of the association through the different outcomes evaluated offers reassurance on the reliability of our findings. A further limitation of our approach is the one-time measures of ECG, behavioural and biomedical factors that are unlikely to fully capture exposure over the life course, although this is common in large population based studies.

Conclusions and perspectives

This study has explored the association of frontal T-wave axis with several cardiac clinical phenotypes, including HF and AF in an adult population free from CVD disease. The value of T-wave axis deviation is already incorporated in the electrocardiogram and it is easy to understand by clinicians. Electrocardiography still represents the most widely used cardiovascular test in clinical practice. Despite this, physicians rarely take full advantage of the amount of information provided by this simple and almost inexpensive tool. The introduction of digital electrocardiography, currently standard in most Countries, has further widened the diagnostic capabilities of this technique for pharmacological and epidemiological studies as well as for a preclinical diagnosis of cardiac disease

(33). T wave axis seems to be an ECG measure which is useful for better stratifying individual risk, as compared and in addition with the traditional use of cardiovascular risk factors (14). A better stratification with an inexpensive tool could allow, in the next future, a more focused and effective preventive intervention in individuals.

In conclusion, our findings suggest the opportunity of using T-wave monitoring, which is an easy to measure and inexpensive test, as a useful tool for early detection of future adverse health-outcomes especially in large population settings.

Conflict of interest

None of the Authors has a personal or financial conflict of interest. The funders had no role in study design, collection, analysis, and interpretation of data, in the writing of the report and in the decision to submit the article for publication. All Authors were and are independent from funders.

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Table 1 Main characteristics of the study population at baseline

Sample =21,287	**Frontal T-wave axis**			
	Normal *15° to 75°*	**Borderline** *-15° to 15° or 75° to 105°*	**Abnormal** *-180° to -15° or 105° to 180°*	
N of subjects (%)	16,481(77.5)	4,352 (20.4)	454 (2.1)	**P value***
Men	7344 (44.6)	2323 (53.4)	201 (44.3)	<.0001
Age	54.2 (11.2)	55.3 (10.9)	61.1 (12.3)	<.0001
Education (high)	8318 (50.5)	1757 (40.4)	168 (37.0)	<.0001
Smokers	4218 (25.6)	775 (17.8)	85 (18.7)	0.0045
Total physical activity (MET-h/day)	43.1 (8.6)	43.9 (9.6)	43.1 (6.9)	<.0001
BMI (kg/m^2)	27.4 (4.6)	29.7 (4.6)	28.9 (5.2)	<.0001
Hypertension	8382 (50.9)	2689 (61.8)	332 (73.1)	<.0001
Diabetes	1231 (7.5)	447 (10.3)	66 (14.5)	<.0001
Low-grade inflammation (score)	-0.36 (6.1)	0.34 (5.8)	0.96 (5.8)	<.0001
Troponin I (ng/L)	2.9 (5.8)	3.3 (5.2)	7.4 (8.0)	<.0001
NT-proBNP (ng/L)	72 (93)	85 (173)	240 (370)	<.0001
Heart rate (bpm)	67.1 (10.0)	66.9 (10.2)	67.9 (12.6)	0.10
QT dispersion (ms)	47.6 (23.2)	47.7 (23.2)	67.3 (31.7)	<.0001
QRS duration (ms)	89.0 (9.8)	92.2 (12.9)	100.5 (21.9)	<.0001
Q-QS waves	2893 (18.1)	1039 (23.9)	119 (26.2)	<.0001
QRS axis deviation	702 (4.3)	243 (5.6)	34 (7.5)	0.013
High amplitude R waves	133 (0.8)	109 (2.5)	9 (2.0)	<.0001
ST junction and segment depression	221 (1.3)	157 (3.6)	142 (31.3)	<.0001
T waves changes	1076 (6.8)	504 (11.6)	259 (57.1)	<.0001
A-V conduction defects	1496 (9.1)	350 (8.0)	63 (13.9)	0.0002
Ventricular conduction defects	8302 (50.4)	2316 (53.2)	282 (62.1)	<.0001
Arrhythmias	918 (5.6)	327 (7.5)	90 (19.8)	<.0001
Miscellaneous including ST segment elevation	505 (3.1)	121 (2.8)	15 (3.3)	0.030

*Comparison among normal, borderline and abnormal individuals.

Categorical variables are presented as numbers and percentages; continuous variables (total physical activity, BMI, heart rate, QT dispersion, QRS duration, low-grade inflammation score, troponin I, NT-proBNP) as means ± SD. Means and p values are adjusted for age and sex.

Table 2. Hazard Ratio (95% Confidence intervals) for heart disease and stroke according to T-wave axis orientation

	Frontal T-wave axis orientation			
	Normal	**Borderline**	**Abnormal**	**% change (Abn vs Nor)**
	Coronary heart disease (n=270; 92,509 person-years)			
N of events (%)	173 (1.1)	76 (1.8)	21 (4.6)	
Age/sex adjusted	-1-	1.56 (1.19-2.04)	2.87 (1.82-4.53)	
Model 1	-1-	1.51 (1.14-1.98)	2.65 (1.67-4.21)	
Model 2	-1-	1.42 (1.07-1.89)	2.07 (1.21-3.53)	-reference-
Model 3	-1-	1.42 (1.07-1.89)	2.04 (1.20-3.46)	-2.8
Model 4	-1-	1.40 (1.05-1.85)	1.94 (1.14-3.28)	-12.1
Model 5	-1-	1.41 (1.07-1.87)	1.92 (1.13-3.26)	-14.0
Model 6	-1-	1.40 (1.05-1.85)	1.81 (1.07-3.07)	-24.0
	Heart failure (n=400; 92,246 person-years)			
N of events (%)	264 (1.6)	99 (2.3)	37 (8.2)	
Age/sex adjusted	-1-	1.38 (1.10-1.74)	2.89 (2.04-4.10)	
Model 1	-1-	1.24 (0.98-1.56)	2.56 (1.80-3.63)	
Model 2	-1-	1.12 (0.88-1.43)	1.81 (1.21-2.70)	-reference-
Model 3	-1-	1.12 (0.88-1.43)	1.79 (1.20-2.67)	-2.5
Model 4	-1-	1.12 (0.88-1.43)	1.80 (1.21-2.69)	-1.2
Model 5	-1-	1.11 (0.87-1.41)	1.68 (1.12-2.50)	-16.0
Model 6	-1-	1.12 (0.89-1.43)	1.69 (1.13-2.52)	-14.8
	Atrial fibrillation (n=252; 92,253 person-years)			
N of events (%)	168 (1.0)	63 (1.5)	21 (4.9)	
Age/sex adjusted	-1-	1.39 (1.04-1.86)	2.76 (1.75-4.36)	
Model 1	-1-	1.29 (0.96-1.73)	2.48 (1.56-3.94)	
Model 2	-1-	1.16 (0.86-1.57)	1.56 (0.92-2.63)	-reference-
Model 3	-1-	1.16 (0.86-1.57)	1.57 (0.93-2.64)	1.8
Model 4	-1-	1.16 (0.86-1.57)	1.62 (0.96-2.73)	10.7

Model 5	-1-	1.13 (0.83-1.53)	1.43 (0.85-2.40)	-23.2
Model 6	-1-	1.14 (0.84-1.55)	1.46 (0.87-2.44)	-17.9
Stroke (n=64; 92,932 person-years)				
N of events (%)	46 (0.3)	12 (0.3)	6 (1.3)	
Age/sex adjusted	-1-	0.95 (0.50-1.79)	2.31 (0.98-5.45)	
Model 1	-1-	0.98 (0.52-1.87)	2.28 (0.96-5.43)	
Model 2	-1-	0.76 (0.39-1.47)	0.87 (0.33-2.30)	-reference-
Model 3	-1-	0.75 (0.38-1.45)	0.84 (0.32-2.22)	23.1
Model 4	-1-	0.75 (0.39-1.46)	0.82 (0.31-2.17)	38.5
Model 5	-1-	0.75 (0.39-1.46)	0.80 (0.30-2.09)	53.8
Model 6	-1-	0.75 (0.39-1.47)	0.78 (0.30-2.07)	69.2
CVD deaths (n=102; 93,016 person-years)				
N of events (%)	65 (0.4)	25 (0.6)	12 (2.6)	
Age/sex adjusted	-1-	1.39 (0.88-2.21)	3.12 (1.67-5.81)	
Model 1	-1-	1.39 (0.87-2.23)	2.83 (1.50-5.32)	
Model 2	-1-	1.27 (0.78-2.07)	1.70 (0.78-3.68)	-reference-
Model 3	-1-	1.28 (0.79-2.09)	1.78 (0.83-3.82)	11.4
Model 4	-1-	1.25 (0.77-2.03)	1.66 (0.78-3.53)	-5.7
Model 5	-1-	1.25 (0.76-2.03)	1.68 (0.79-3.58)	-2.9
Model 6	-1-	1.24 (0.76-2.02)	1.60 (0.75-3.40)	-14.3

*CHD: fatal and non-fatal UA, IMA, revascularizations.

Model 1 adjusted for age, sex, smoking habit, total physical activity, education, BMI, hypertension, diabetes and personal history of cancer at baseline

Model 2: as model 1 further adjusted for heart rate, QT dispersion, QRS duration, Q-QS waves, QRS axis deviation, High amplitude R waves, ST junction and segment depression, T waves changes, A-V conduction defects, Ventricular conduction defects, Arrhythmias, Miscellaneous including ST segment elevation

Model 3: as model 1 further adjusted for a low-grade inflammation score

Model 4: as model 1 further adjusted for troponin levels

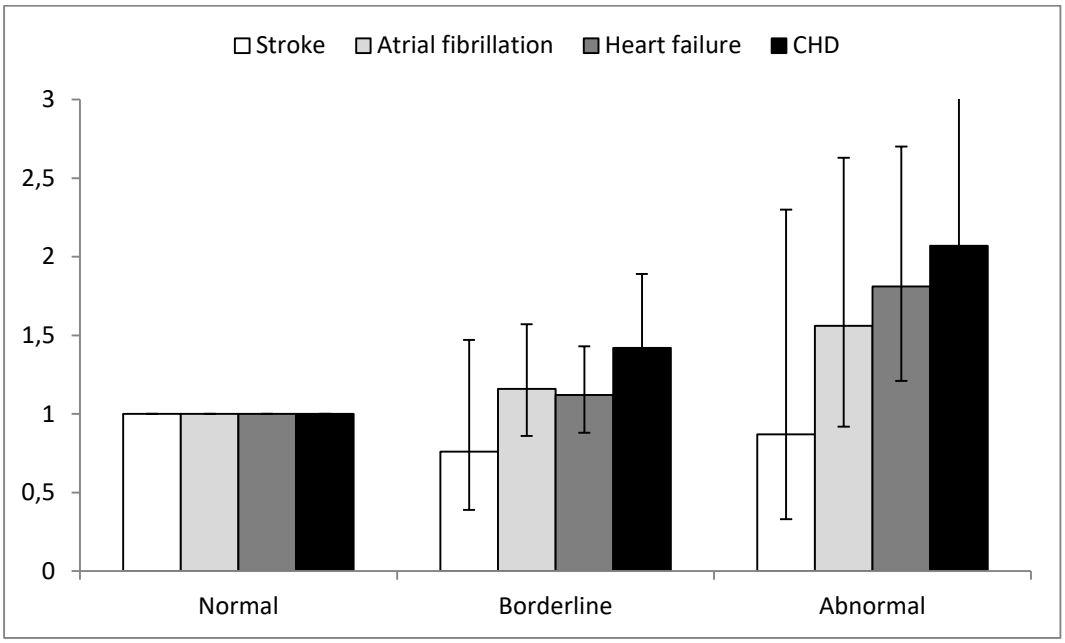
Model 5: as model 1 further adjusted for probNTP levels

Model 6: as model 1 further adjusted for troponin levels and probNTP levels simultaneously.

Percentage change in hazard ratios calculated by [(HR models 3 or 4 or 5 or 6) - (HR model 2)]/ [(HR model 2) – 1].

Legend to the Figure

Figure 1. Association of T-wave axis orientation (normal, borderline, abnormal) with risk of heart failure, atrial fibrillation, CHD and stroke. Hazard ratios are from Model 2 in Table 2.



Appendix Moli-sani Study Investigators

The enrolment phase of the Moli-sani study was conducted at the Research Laboratories of the Catholic University in Campobasso (Italy), the follow up of the Moli-sani cohort is being conducted at the IRCCS Neuromed, Pozzilli, Italy.

Steering Committee: Licia Iacoviello (Neuromed, Pozzilli, Italy), Chairperson, Maria Benedetta Donati and Giovanni de Gaetano (Neuromed, Pozzilli, Italy).

Safety and data monitoring Committee: Jos Vermylen (Catholic University, Leuven, Belgio), Chairman, Ignacio De Paula Carrasco (Accademia Pontificia Pro Vita, Roma, Italy), Simona Giampaoli (Istituto Superiore di Sanità, Roma, Italy), Antonio Spagnuolo (Catholic University, Roma, Italy).

Event adjudicating Committee: Deodato Assanelli (Brescia, Italy), Vincenzo Centritto (Campobasso, Italy), Pasquale Spagnuolo and Dante Staniscia (Termoli, Italy).

Scientific and organizing secretariat: Francesco Zito (Coordinator)^, Americo Bonanni, Chiara Cerletti, Amalia De Curtis, Augusto Di Castelnuovo, Licia Iacoviello, Roberto Lorenzet*, Antonio Mascioli^, Marco Olivieri and Domenico Rotilio^.

Data management and analysis: Augusto Di Castelnuovo (Coordinator), Marialaura Bonaccio, Simona Costanzo and Francesco Gianfagna.

Informatics: Marco Olivieri (Coordinator), Maurizio Giacci^, Antonella Padulo^ and Dario Petraroia^.

Biobank and biomedical analyses: Amalia De Curtis (Coordinator), Federico Marracino^, Maria Spinelli^, Christian Silvestri^.

Communication and Press Office: Americo Bonanni (Coordinator), Marialaura Bonaccio and Francesca De Lucia.

Moli-family Project: Francesco Gianfagna, Branislav Vohnout^.

Recruitment staff: Franco Zito ^(General Coordinator), *Secretariat*: Mariarosaria Persichillo (Coordinator), Angelita Verna^, Maura Di Lillo^, Irene Di Stefano^, *Blood sample:* Agostino Pannichella^, Antonio Rinaldo Vizzarri^, Branislav Vohnout^, Agnieszka Pampuch^; *Spirometry:* Antonella Arcari^ (Coordinator), Daniela Barbato^, Francesca Bracone, Simona Costanzo, Carmine Di Giorgio^, Sara Magnacca^, Simona Panebianco^, Antonello Chiovitti^, Federico Marracino^, Sergio Caccamo^, Vanesa Caruso^; *Electrocardiograms* : Livia Rago (Coordinator), Daniela Cugino^, Francesco Zito^, Francesco Gianfagna, Alessandra Ferri^, Concetta Castaldi^, Marcella Mignogna^; Tomasz Guszcz^ , *Questionnaires*: Romina di Giuseppe^ (Coordinator), Paola Barisciano^, Lorena Buonaccorsi^, Floriana Centritto^, Antonella Cutrone^, Francesca De Lucia, Francesca Fanelli^, Iolanda Santimone^, Anna Sciarretta^, Maura Di Lillo^, Isabella Sorella^, Irene Di Stefano^, Emanuela Plescia^, Alessandra Molinaro^ and Christiana Cavone^.

Call Center: Giovanna Galuppo, Maura Di Lillo^, Concetta Castaldi^, Dolores D'Angelo^ and Rosanna Ramacciato^.

Follow-up: Simona Costanzo (Coordinator); Data management: Simona Costanzo, Marco Olivieri; Event adjudication: Livia Rago (Coordinator), Simona Costanzo, Amalia de Curtis, Licia Iacoviello, Mariarosaria Persichillo.

Regional Health Institutions: Azienda Sanitaria Regionale del Molise (ASReM, Campobasso, Italy), UOC Servizio Igiene e Sanità Pubblica - Dipartimento di Prevenzione; Offices of vital statistics of the Molise region and Molise Dati Spa (Campobasso, Italy).

Hospitals: Presidi Ospedalieri ASReM (Presidio Ospedaliero A. Cardarelli - Campobasso, Ospedale F. Veneziale - Isernia, Ospedale San Timoteo - Termoli (CB), Ospedale Ss. Rosario. Venafro (IS), Ospedale Vietri – Larino (CB), Ospedale San Francesco Caracciolo - Agnone (IS)), Istituto di cura Villa Maria - Campobasso; Fondazione di Ricerca e Cura Giovanni Paolo II - Campobasso; IRRCS Neuromed - Pozzilli (IS).

*Deceased, ^ Contributed to the enrolment phase