

# Counterclockwise and Clockwise Rotation of QRS Transitional Zone: Prospective Correlates of Change and Time-Varying Associations With Cardiovascular Outcomes

Siddharth Patel, MD, MPH; Lucia Kwak, MS; Sunil K. Agarwal, MD, PhD; Larisa G. Tereshchenko, MD, PhD; Josef Coresh, MD, PhD; Elsayed Z. Soliman, MD; Kunihiro Matsushita, MD, PhD

**Background**—A few studies have recently reported clockwise and counterclockwise rotations of QRS transition zone as predictors of mortality. However, their prospective correlates and associations with individual cardiovascular disease (CVD) outcomes are yet to be investigated.

**Methods and Results**—Among 13 567 ARIC (Atherosclerosis Risk in Communities) study participants aged 45 to 64 years, we studied key correlates of changes in the status of clockwise and counterclockwise rotation over time as well as the association of rotation status with incidence of coronary heart disease (2408 events), heart failure (2196 events), stroke (991 events), composite CVD (4124 events), 898 CVD deaths, and 3469 non-CVD deaths over 23 years of follow-up. At baseline, counterclockwise rotation was most prevalent (52.9%), followed by no (40.5%) and clockwise (6.6%) rotation. Of patients with no rotation, 57.9% experienced counterclockwise or clockwise rotation during follow-up, with diabetes mellitus and black race significantly predicting clockwise and counterclockwise conversion, respectively. Clockwise rotation was significantly associated with higher risk of heart failure (hazard ratio, 1.20; 95% confidence interval [CI], 1.02–1.41) and non-CVD death (hazard ratio, 1.28; 95% CI, 1.12–1.46) after adjusting for potential confounders including other ECG parameters. On the contrary, counterclockwise rotation was significantly related to lower risk of composite CVD (hazard ratio, 0.93; 95% CI, 0.87–0.99), CVD mortality (hazard ratio, 0.76; 95% CI, 0.65–0.88), and non-CVD deaths (hazard ratio, 0.92; 95% CI, 0.85–0.99 [borderline significance with heart failure]).

**Conclusions**—Counterclockwise rotation, the most prevalent QRS transition zone pattern, demonstrated the lowest risk of CVD and mortality, whereas clockwise rotation was associated with the highest risk of heart failure and non-CVD mortality. These results have implications on how to interpret QRS transition zone rotation when ECG was recorded. (*J Am Heart Assoc.* 2017;6:e006281. DOI: 10.1161/JAHA.117.006281.)

**Key Words:** cardiovascular outcomes • electrocardiography • epidemiology • mortality • QRS transition zone

ECG has been useful for diagnosing several heart conditions including cardiac arrhythmia, cardiac ischemia, and structural changes such as left ventricular hypertrophy. In addition, several ECG parameters (eg, bundle branch block, frontal QRS-T angle, QT interval, left ventricular hypertrophy)

predict future cardiovascular events.<sup>1–4</sup> In this context, clockwise and counterclockwise rotations of QRS transition zone in horizontal plane are long-recognized ECG findings, but their prognostic value is not fully understood. A study from Japan was the first to report that clockwise and

From the Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (S.P., L.K., J.C., K.M.); Division of Cardiology, Mount Sinai Health System, New York, NY (S.K.A.); Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR (L.T.); Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston-Salem, NC (E.Z.S.).

Accompanying Tables S1, S2 and Figures S1, S2 are available at <http://jaha.ahajournals.org/content/6/11/e006281/DC1/embed/inline-supplementary-material-1.pdf>

**Correspondence to:** Kunihiro Matsushita, MD, PhD, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2024 East Monument Street, Baltimore, MD 21287. E-mail: [kuni.matsushita@jhu.edu](mailto:kuni.matsushita@jhu.edu)

Received April 3, 2017; accepted September 1, 2017.

© 2017 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

## Clinical Perspective

### What is New?

- This study uniquely investigated rotations of QRS transition zone over time, their correlates, and their associations with subsequent cardiovascular outcomes including nonfatal cases.
- Diabetes mellitus and black race were significantly related to clockwise and counterclockwise conversion, respectively.
- Counterclockwise rotation was the most prevalent QRS transition zone pattern and demonstrated the lowest risk of cardiovascular outcomes and total mortality.
- Clockwise rotation was associated with the highest risk of heart failure and noncardiovascular mortality.

### What Are the Clinical Implications?

- Our results support a proposal from some experts to rethink the definition of “normal” QRS transitional zone.
- Overall modest associations may question the prognostic value of QRS transitional zone. However, QRS transitional zone information is automatically obtained when ECG is assessed, and, thus, in such a case, clinical attention should be paid to persons with clockwise rotation, particularly for the risk of heart failure.

counterclockwise rotation of QRS transition zone in 12-lead ECGs were associated with significantly higher and lower risk of mortality caused by composite cardiovascular disease (CVD) and all causes, respectively, as compared with no rotation.<sup>5</sup> Similar patterns for mortality were confirmed in 2 recent studies from the United States (based on the third NHANES [National Health and Nutrition Examination Survey])<sup>6</sup> and Finland (based on the Finnish Social Insurance Institution's Coronary Heart Study).<sup>7</sup> Mortality is an important outcome but, from an etiological perspective, it is important to investigate individual CVD outcomes including nonfatal cases. In this context, it is of note that the Finnish study did not observe significant associations of QRS transition zone with hospitalizations caused by coronary heart disease (CHD) and heart failure (HF),<sup>7</sup> warranting further investigations. Also, those 3 previous studies looked at rotation at baseline only, and, therefore, it is unclear to what extent the rotation changes within an individual over time, what factors correlated with those changes, and whether time-varying data on rotation has prognostic information. Thus, we aimed to investigate the association of clockwise and counterclockwise rotation of QRS transition zone over 9 years, as a time-varying exposure, with subsequent risk of CVD during a median follow-up of 23 years in whites and blacks from the ARIC (Atherosclerosis Risk in Communities) study. In addition, we explored baseline factors

associated with subsequent changes in QRS transition zone over 9 years.

## Methods

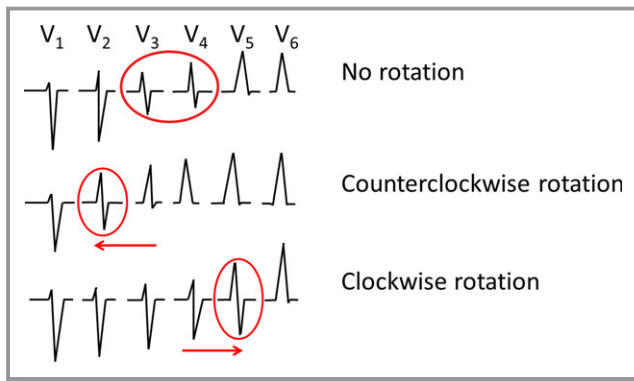
### Study Participants

The ARIC study is a community-based prospective cohort with a main focus on the cause and natural history of atherosclerosis and its clinical manifestations and community burden. Between 1987 and 1989, 15 792 adults aged 45 to 64 years were enrolled from 4 US communities—northwest suburbs of Minneapolis, MN; Washington County, MD; Jackson, MS; Forsyth County, NC—and underwent a comprehensive baseline assessment. Subsequent contact included annual phone interviews, 3 short-term repeat examinations spaced  $\approx$ 3 years apart (1990–1992, 1993–1995, and 1996–1998), and the latest visit, which was completed between 2011 and 2013.<sup>8</sup> The ARIC study was approved by the institutional review board at each site. All participants also provided written informed consent.

The study sample of 13 567 men and women was derived from 15 792 ARIC participants at visit 1, excluding those with race other than blacks or whites ( $n=48$ ), with a history of CVD including CHD, HF, and stroke ( $n=1551$ ) (Figure S1). History of CHD at baseline was defined by self-reported episode of myocardial infarction, major Q waves at the baseline ECG (Minnesota Code [MC] 1.1),<sup>9</sup> and previous coronary revascularization. History of HF was determined on the basis of evidence of the use of HF-related medications and the Gothenburg criteria.<sup>10</sup> History of stroke was defined as self-reported physician diagnosis of stroke. We further excluded individuals with missing ECG data on QRS transition zone rotation or those with concomitant cardiac conditions precluding the assessment of QRS transitional rotation (ie, Wolff-Parkinson-White pattern, complete left or right bundle branch block, and intraventricular block,  $n=626$ ).

### Visit Examinations

Information regarding age, race, smoking status, drinking status, and education level was obtained through interviews. Body mass index (BMI) in  $\text{kg}/\text{m}^2$  was calculated based on measured body weight and height. Diabetes mellitus was defined as a fasting glucose level of  $\geq 126$  mg/dL, a nonfasting glucose level of  $\geq 200$  mg/dL, self-reported physician diagnosis of diabetes mellitus, or on pharmacological treatment for diabetes mellitus. Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or taking antihypertensive medicines. Total cholesterol level and high-density lipoprotein cholesterol level were determined by enzymatic methods.<sup>8,11</sup>



**Figure 1.** Scheme for no rotation, counterclockwise rotation, and clockwise rotation of QRS transition zone.

## ECG Assessment

Participants underwent standard supine 12-lead ECG based on standardized protocol, with each tracing consisting of 10 seconds of each of the 12 leads simultaneously at least 1 hour after smoking or caffeine ingestion if any. An electrode locator was used to determine and standardize the positioning of chest electrodes. Tracings were sent via a phone modem to be computer coded at the ARIC ECG Reading Center. All records with significant MC findings as determined by the computer, as well as a random sample of tracings, were sent to the ECG coding center to be visually coded. Discrepancies between the computer code and visual code were adjudicated by a senior coder.<sup>12</sup>

Counterclockwise rotation was defined as MC 9-4-1, namely a QRS transition zone at V3 or rightward of V3 on chest, and clockwise rotation as MC 9-4-2, a QRS transition zone at V4 or leftward of V4 on chest. Those with neither 9-4-1 nor 9-4-2, ie, dominant S wave in V3 lead and dominant R wave in V4 lead, were categorized as no rotation (Figure 1). Additional ECG findings of ventricular conduction defect (MC 7-1 to 7-8), ST depression (MC 4-1 to 4-4), first- or second-degree atrioventricular block (MC 6-2 or 6-3), and atrial fibrillation/atrial flutter (MC 8-3) were combined as major ECG abnormality. Similarly, mild Q-wave abnormality (MC 1-3), frontal plane QRS axis deviations (MC 2-1, 2-2, 2-3), high R wave (MC 3-1 to 3-3), T-wave abnormality (MC 5-1 to 5-4), ventricular premature beats (MC 8-1-2), sinus tachycardia (MC 8-7), sinus bradycardia (MC 8-8), low QRS voltage (MC 9-1), ST elevation (MC 9-2), tall P wave (MC 9-3), and combination of high R wave and either ST depression or T-wave abnormality were combined as minor ECG abnormality.

## Outcomes

The ARIC study conducts active surveillance to identify CVD outcomes, including annual telephone interviews of

participants and/or their proxy, hospitalization surveillance of the ARIC community hospitals, and the review of death certificates, physician questionnaires, and coroner/medical examiner reports.<sup>11</sup> A group of ARIC physician investigators adjudicated CHD and stroke outcomes using validated protocols. For the present analysis, incident CHD was defined as definite or probable myocardial infarction, fatal CHD, or coronary revascularization.<sup>13</sup> Stroke was defined as sudden neurologic insult of  $\geq 24$ -hour duration or a neurologic insult associated with death without evidence of a nonstroke cause of death. For the present analysis, we included definite, probable, or possible stroke.<sup>13</sup> HF was defined as hospitalization or death with an *International Classification of Diseases, Ninth Revision*, code of 428 and/or *International Classification of Diseases, Tenth Revision*, code I50.<sup>14,15</sup> To increase the statistical power, particularly for subgroup analysis, we also investigated a composite CVD event including CHD, HF, and stroke. We also analyzed total mortality, CVD mortality (mortality caused by those 3 CVD events), and non-CVD mortality (deaths other than that caused by CVD mortality).

## Statistical Analysis

STATA version 13 for Windows (StataCorp) was used throughout the analyses. Variables were compared among the 3 groups according to QRS transition zone rotation (counterclockwise rotation, no rotation, and clockwise rotation) at baseline. Chi-square test and 1-way ANOVA were used to compare differences in categorical or continuous variables across 3 groups, as appropriate. We then assessed the patterns of changes in QRS transition zone rotation from baseline (visit 1) during subsequent visits (visit 2 to visit 4). We explored baseline demographic and clinical predictors of conversions to counterclockwise or clockwise rotation from no rotation using multinomial logistic regression models (Figure S2).

Subsequently, Cox proportional hazards models were used to quantify the association of counterclockwise/clockwise rotation (no rotation as a reference) with outcomes of interest. We modeled QRS transition zone rotation as well as all covariates updated at every visit whenever available as time-varying variables. Figure S2 demonstrates the study scheme for changes in QRS transitional zone over time and the allocation of follow-up time corresponding to them. When updated information was not available, data from the prior visit were carried over. We implemented 4 models for the adjustment of covariates. Model 1 was unadjusted. Model 2 included demographic variables, ie, age, sex, race, and education level. Model 3 further adjusted for other established risk factors, ie, current smoking, current drinking, hypertension, diabetes mellitus, total and high-density lipoprotein cholesterol levels, and BMI. Model 4 additionally adjusted for major and minor ECG abnormalities.

Finally, to evaluate potential effect modifications in QRS transition zone rotation and the incident CVD relationship, we performed subgroup analysis by age ( $\leq 55$  and  $> 55$  years), sex, race, BMI ( $<$  and  $\geq 30$  kg/m<sup>2</sup>), education level, smoking status, drinking status, diabetes mellitus, hypertension, and total cholesterol ( $< 6$  and  $\geq 6$  mmol/L) level at baseline using model 4.

## Results

### Participant Characteristics

Demographic and clinical characteristics according QRS transition zone at baseline are presented in Table 1. At baseline, counterclockwise rotation was most prevalent (52.9%), followed by no rotation (40.5%) and clockwise rotation (6.6%). As compared with the no rotation group, individuals with counterclockwise rotation tended to be slightly older and black and to have higher BMI but a lower prevalence of current smoking, diabetes mellitus, and hypertension. In contrast, the prevalence of diabetes mellitus and hypertension was higher in the clockwise rotation group than in the no rotation group despite its younger average age and

lower BMI. Also, the clockwise rotation group had a higher smoking prevalence.

Baseline ECG characteristics according to QRS transition zone rotation groups are shown in Table 2. The counterclockwise rotation group had a lower proportion of major and minor ECG abnormalities as compared with the no rotation group, except high R wave. In contrast, the clockwise rotation group showed a higher prevalence of major and minor ECG abnormalities than the no rotation group. The difference across the 3 rotation groups was particularly evident for Q wave abnormalities, ST-T abnormalities, intraventricular conduction disturbances, low QRS voltage, and tall P wave.

### Pattern of QRS Transition Zone Rotation Over $\approx 9$ Years

Patterns of changes in QRS transition zone rotation of all the participants who had ECG recorded at every visit from visit 1 through visit 4 are shown in Table 3. Of those with no rotation at baseline, 42.1% remained in the no rotation group over  $\approx 9$  years, and 57.2% experienced either counterclockwise rotation (46.2%) or clockwise rotation (11.1%) during follow-up

**Table 1.** Baseline Characteristics According to QRS Transition Zone Rotation

	ECG Rotation Status			P Value
	Counterclockwise	No Rotation	Clockwise	
No. (%)	7171	5500	896	
Age, (SD), y	54.5 (5.8)	54.3 (5.7)	53.9 (5.7)	0.006
Race, No. (%)				
Black	1939 (27)	1390 (25)	227 (25)	0.067
White	5232 (73)	4110 (75)	669 (75)	
Sex, No. (%)				
Female	4290 (60)	2854 (52)	511 (57)	<0.001
Male	2881 (40)	2646 (48)	385 (43)	
Education, No. (%)				
Basic	1576 (22)	1203 (22)	234 (26)	0.012
Intermediate	2943 (41)	2252 (41)	377 (42)	
High	2638 (37)	2037 (37)	285 (32)	
BMI, kg/m <sup>2</sup>	27.8 (5.2)	27.2 (5.2)	27.1 (6.2)	<0.001
Current smoker, No. (%)	1576 (22)	1591 (29)	317 (35)	<0.001
Current drinker, No. (%)	4031 (56)	3189 (58)	499 (56)	0.103
Diabetes mellitus, No. (%)	659 (9)	625 (11)	120 (13)	<0.001
Hypertension, No. (%)	2209 (31)	1748 (32)	315 (35)	0.023
Total cholesterol, mmol/L	5.56 (1.08)	5.52 (1.08)	5.52 (1.06)	0.121
HDL cholesterol, mmol/L	1.36 (0.43)	1.34 (0.45)	1.37 (0.45)	0.086

Values are expressed as mean (SD) or number (percentage). Baseline characteristics were compared across counterclockwise, no, and clockwise rotation of QRS transition zone. BMI indicates body mass index; HDL, high-density lipoprotein.

**Table 2.** Baseline ECG Characteristics According to QRS Transition Zone Rotation

	Counterclockwise, %	No Rotation, %	Clockwise, %	P Value
Major ECG abnormality	6.2	7.7	10.7	<0.001
Major Q wave abnormalities (old MI)	1.4	1.8	2.8	0.009
Minor Q, QS waves with ST, T abnormalities (possible old MI)	0.28	0.58	0.45	0.031
Major isolated ST/T abnormalities	4.0	5.3	7.3	<0.001
Left ventricular hypertrophy+major STT change	1.1	1.3	1.5	0.646
Atrial fibrillation	0.08	0.15	0.22	0.385
Mobitz type II, second-degree atrioventricular block, Wenckebach phenomenon	0	0.02	0	0.480
Major QT prolongation $\geq 116\%$	1.1	1.1	1.6	0.402
Atrial flutter, intermittent atrial fibrillation, intermittent atrial flutter	0	0.04	0	0.231
Minor ECG abnormality	41.4	51.8	61.1	<0.001
Minor isolated Q, QS waves	4.3	6.8	9.6	<0.001
Minor isolated ST, T abnormalities	10.1	11.2	14.5	<0.001
High R waves	9.8	8.2	4.1	<0.001
ST-segment elevation, anterolateral site	0.25	0.18	0	0.258
ST-segment elevation, posterior site	0.25	0.22	0	0.320
ST-segment elevation, anterior site	1.6	1.5	1.0	0.323
Incomplete RBBB	11.3	20.2	25.6	<0.001
Incomplete LBBB	1.9	2.7	3.9	<0.001
Minor QT prolongation $\geq 112\%$	3.3	3.4	4.0	0.538
Short PR interval	1.5	1.6	2.0	0.455
Left axis deviation	2.2	4.3	9.8	<0.001
Right axis deviation	0	0.05	0.11	0.069
Frequent ventricular premature beats	1.3	1.6	1.3	0.245
PR interval >0.22 s	1.9	2.4	2.5	0.170
Frequent atrial or premature beats	1.4	1.8	1.5	0.554
Supraventricular rhythm	0.11	0.25	0.22	0.156
Sinus tachycardia	0.32	0.45	0.56	0.346
Sinus bradycardia	3.3	3.9	4.6	0.057
Low QRS amplitude	0.79	1.49	4.13	<0.001
P-wave amplitude high	1.3	1.6	3.0	<0.001

LBBB indicates left bundle branch block; MI, myocardial infarction; RBBB, right bundle branch block.

visits. Only 0.6% experienced both counterclockwise and clockwise rotations. Among participants with counterclockwise rotation at baseline, 72.5% stayed in the same rotation category over  $\approx 9$  years, and 26.7% showed no rotation at some visits. Only 0.8% of those with a counterclockwise rotation at baseline experienced clockwise rotation over  $\approx 9$  years. Among individuals with clockwise rotation at baseline, 33.2% stayed in the same rotation category over  $\approx 9$  years, but 58.4% experienced normal rotation and 8.4% had counterclockwise rotation during follow-up.

As shown in Table 4, among the predictors tested, only black race was significantly associated with higher relative

odds of experiencing counterclockwise rotation compared with white race during follow-up. For conversion to clockwise rotation, diabetes mellitus was the sole significant predictor. Diabetes mellitus was also significantly associated with conversion to no rotation and clockwise rotation from counterclockwise rotation (Table S1).

### QRS Transition Zone Rotation and Cardiovascular Outcomes

During a median follow-up time over 23 years, there were 2408 CHD events, 2196 HF events, 991 stroke events, 4124 CVD

**Table 3.** Pattern of Changes in QRS Transition Zone Rotation Among Participants Who Had ECGs Recorded at all Visits From Visit 1 Through Visit 4

ECG Rotation Status at Visit 1	Followed ECG Rotation Status From Visit 2 to Visit 4	No. (%)
No rotation (n=3605)	Only no rotation	1516 (42.1)
	Experienced both counterclockwise and clockwise	22 (0.6)
	Experienced counterclockwise	1666 (46.2)
	Experienced clockwise	401 (11.1)
Counterclockwise (n=4936)	Only counterclockwise	3581 (72.5)
	Experienced clockwise (some experienced no rotation as well)	37 (0.8)
	Experienced no rotation but not clockwise	1318 (26.7)
Clockwise (n=527)	Only clockwise	175 (33.2)
	Experienced counterclockwise (some experienced no rotation as well)	44 (8.4)
	Experienced no rotation but not counterclockwise	308 (58.4)

events, and 4367 total deaths (898 CVD deaths and 3469 non-CVD deaths). The incidence rate of all CVD outcomes was slightly but consistently lower in the counterclockwise group (based on time-varying information) as compared with the no rotation group (Figure 2). Noticeably, individuals with clockwise rotation demonstrated considerably higher incidence rates of all CVD outcomes than in the other 2 groups.

These patterns remained similar even after adjusting for potential confounders (Table 5). Specifically, counterclockwise rotation was associated with lower risk of all outcomes in demographically adjusted models (model 2). Once we additionally adjusted for traditional CVD risk factors, the association was attenuated for CHD and stroke but remained significant for HF, composite CVD, total mortality, CVD mortality, and non-CVD mortality (model 3). For those significant outcomes, the further adjustment for major and minor ECG abnormality did not substantially attenuate the associations, although the relationship to HF became borderline significant (model 4). In terms of cause of death, counterclockwise rotation was more evidently associated with lower risk of CVD mortality than non-CVD mortality (adjusted hazard ratio, 0.76 [95% confidence interval, 0.65–0.88] versus adjusted hazard ratio, 0.92 [95% confidence interval, 0.85–0.99]).

For clockwise rotation, the association was not significant even in model 1 for CHD and in model 2 for stroke. Once we adjusted for traditional risk factors (model 3), clockwise rotation remained significant for HF, total mortality, CVD mortality, and non-CVD mortality. Of note, when we accounted for major and minor ECG abnormalities, clockwise rotation was associated with non-CVD mortality (adjusted hazard ratio, 1.28; 95% confidence interval, 1.12–1.46) but not with CVD mortality (adjusted hazard ratio, 1.14; 95% confidence interval, 0.90–1.45 [model 4]).

We confirmed the largely consistent association between counterclockwise rotation and lower risk of composite CVD

events across various subgroups after adjusting for potential confounders (Table S2). For clockwise rotation, the association with high risk of CVD was neutral or modest across subgroups, with statistical significance only in a few subgroups.

## Discussion

In our study, the counterclockwise rotation was the most prevalent ECG rotation at baseline as well as the most stable rotation during subsequent follow-up visits. Blacks were more likely to present with counterclockwise rotation compared with whites, and diabetes mellitus was associated with clockwise conversion. Modeling QRS rotation and potential confounders as time-varying variables, counterclockwise rotation showed the lowest risk of composite CVD events and mortality among the 3 rotation types. This relationship was consistent across demographic and clinical subgroups. After accounting for traditional CVD risk factors and other ECG abnormalities, HF was the only CVD outcome independently associated with clockwise rotation. Of note, in the same model, clockwise rotation was significantly associated with non-CVD mortality but not with CVD mortality.

To our knowledge, only 3 studies have specifically explored the prognostic significance of QRS transition zone rotation.<sup>5–7</sup> When those 3 studies and ours are compared in detail, we recognize some discrepancy. Specifically, counterclockwise rotation was significantly associated with lower CVD mortality risk in our and Nakamura et al's studies<sup>5</sup> but not in Bradford et al's study<sup>6</sup> and Aro et al's study<sup>7</sup> (for CHD mortality or sudden cardiac death). Of interest, Bradford et al's study demonstrated a stronger association of counterclockwise rotation with all-cause mortality than CVD mortality, but the opposite was seen in our and Nakamura et al's studies. Of interest, Aro et al's study reported a significantly lower risk of

**Table 4.** RRR of Changes From no Rotation According to Each Predictor Tested

	Counterclockwise		Clockwise	
	RRR* (95% CI)	P Value	RRR (95% CI)	P Value
Age	1.01 (1.00–1.02)	0.185	1.02 (1.00–1.04)	0.095
Male	0.98 (0.84–1.15)	0.821	0.98 (0.77–1.27)	0.904
Black	1.34 (1.09–1.65)	0.005	1.07 (0.78–1.48)	0.672
Education				
Intermediate	0.98 (0.79–1.22)	0.866	1.00 (0.71–1.40)	0.989
High	0.86 (0.69–1.07)	0.178	1.02 (0.72–1.43)	0.932
Current smoker	0.94 (0.79–1.11)	0.466	1.08 (0.83–1.42)	0.563
Current drinker	0.98 (0.83–1.15)	0.775	1.00 (0.77–1.29)	0.985
Hypertension	1.05 (0.89–1.25)	0.540	1.25 (0.96–1.62)	0.097
Diabetes mellitus	0.86 (0.66–1.12)	0.254	1.58 (1.10–2.26)	0.013
Body mass index	1.00 (0.99–1.02)	0.880	1.02 (0.99–1.04)	0.168
Total cholesterol	1.07 (1.00–1.15)	0.067	0.99 (0.88–1.11)	0.841
HDL cholesterol	0.92 (0.76–1.11)	0.382	1.23 (0.93–1.64)	0.152

CI indicates confidence interval; HDL, high-density lipoprotein.

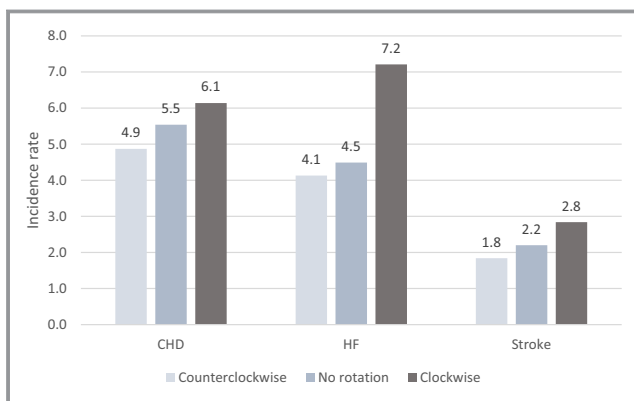
\*Relative risk ratio (RRR): the reference group included those who had no rotation across all 4 visits.

atrial fibrillation hospitalizations in patients with counterclockwise rotation versus the rest of the study population. For clockwise rotation, the association was stronger for non-CVD mortality than for CVD mortality in our study, which was contrary to Nakamura et al's and Bradford et al's studies.<sup>5,6</sup> Although Aro et al's study did not investigate non-CVD mortality, clockwise rotation demonstrated a stronger association with all-cause mortality than CHD mortality.<sup>7</sup> We are not sure about the reasons behind this discrepancy and thus future studies are warranted in different settings. Nonetheless, it is of importance that the general pattern of counterclockwise conferring lower mortality risk and clockwise

contributing to higher risk compared with no rotation is consistent among the previous 3 studies and ours.

The investigation of individual CVD events including stroke as well as repeated assessments of ECG (allowing us to model QRS transitional zone as a time-varying exposure and explore baseline factors related to changes in QRS transitional zone over time) are unique to our study, which adds a few new insights to the literature. In terms of the individual CVD outcomes tested, HF appeared to be most robustly associated with both counterclockwise rotation (lower risk) and clockwise rotation (higher risk). Clockwise rotation may reflect subclinical cardiac abnormality increasing the risk of HF. Indeed, Tahara et al<sup>16</sup> reported dilated cardiomyopathy as a cause behind clockwise rotation. Based on repeated ECG assessments over 9 years, we confirmed counterclockwise rotation as the most prevalent and stable QRS transitional pattern and observed black race and diabetes mellitus as key correlates of conversion to counterclockwise and clockwise rotation, respectively.

There are a few clinical and research implications derived from our study. Although some clinical conditions can lead to counterclockwise rotation (eg, right ventricular hypertrophy, posterior myocardial infarction, and left septal fascicular block), our results support the proposal from Bradford et al to rethink the definition of "normal" QRS transitional zone. In both Bradford's and our studies from the United States, counterclockwise rotation was most common and was associated with the lowest risk among the 3 rotation types—2 core elements to consider normality. Of interest,



**Figure 2.** Incident rate (per 1000 person-years) of cardiovascular events according to ECG QRS transition rotation. CHD indicates coronary heart disease; HF, heart failure.

**Table 5.** Association of Counterclockwise and Clockwise Rotation of QRS Transition Zone With Incident Cardiovascular Outcomes

	Counterclockwise			Clockwise		
	HR	95% CI	P Value	HR	95% CI	P Value
<b>CHD</b>						
Model 1	0.88	(0.81–0.96)	0.003	1.12	(0.94–1.33)	0.192
Model 2	0.91	(0.83–0.99)	0.024	1.10	(0.93–1.31)	0.269
Model 3	0.95	(0.87–1.04)	0.265	1.04	(0.88–1.24)	0.642
Model 4	1.00	(0.91–1.09)	0.923	0.95	(0.79–1.13)	0.543
<b>HF</b>						
Model 1	0.83	(0.76–0.91)	<0.001	1.53	(1.30–1.79)	<0.001
Model 2	0.79	(0.72–0.86)	<0.001	1.42	(1.21–1.67)	<0.001
Model 3	0.86	(0.79–0.95)	0.002	1.35	(1.15–1.59)	<0.001
Model 4	0.92	(0.84–1.01)	0.077	1.20	(1.02–1.41)	0.031
<b>Stroke</b>						
Model 1	0.85	(0.75–0.98)	0.020	1.32	(1.03–1.69)	0.030
Model 2	0.82	(0.71–0.93)	0.003	1.24	(0.96–1.59)	0.093
Model 3	0.87	(0.76–1.00)	0.057	1.15	(0.89–1.48)	0.298
Model 4	0.92	(0.80–1.06)	0.232	1.05	(0.81–1.35)	0.737
<b>CVD</b>						
Model 1	0.85	(0.80–0.91)	<0.001	1.25	(1.10–1.41)	0.001
Model 2	0.85	(0.79–0.90)	<0.001	1.20	(1.06–1.36)	0.005
Model 3	0.89	(0.83–0.95)	0.001	1.12	(0.98–1.27)	0.095
Model 4	0.93	(0.87–1.00)	0.037	1.02	(0.90–1.16)	0.749
<b>Death</b>						
Model 1	0.80	(0.75–0.86)	<0.001	1.49	(1.33–1.67)	<0.001
Model 2	0.78	(0.73–0.83)	<0.001	1.40	(1.25–1.57)	<0.001
Model 3	0.85	(0.80–0.91)	<0.001	1.34	(1.20–1.51)	<0.001
Model 4	0.88	(0.83–0.94)	<0.001	1.25	(1.12–1.41)	<0.001
<b>CVD mortality</b>						
Model 1	0.65	(0.56–0.75)	<0.001	1.61	(1.27–2.03)	<0.001
Model 2	0.62	(0.54–0.72)	<0.001	1.46	(1.16–1.85)	0.001
Model 3	0.70	(0.60–0.81)	<0.001	1.37	(1.08–1.74)	0.010
Model 4	0.76	(0.65–0.88)	<0.001	1.14	(0.90–1.45)	0.284
<b>Non-CVD mortality</b>						
Model 1	0.85	(0.79–0.91)	<0.001	1.46	(1.28–1.66)	<0.001
Model 2	0.83	(0.77–0.89)	<0.001	1.38	(1.22–1.57)	<0.001
Model 3	0.90	(0.84–0.97)	0.006	1.33	(1.17–1.52)	<0.001
Model 4	0.92	(0.85–0.99)	0.024	1.28	(1.12–1.46)	<0.001

Model 1: crude model. Model 2: adjusted for age, sex, race, and education level. Model 3: further adjusted for current smoking status, current drinking status, hypertension, diabetes mellitus, total and high-density lipoprotein cholesterol levels, and body mass index. Model 4: additionally adjusted for major and minor ECG abnormalities. CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; OR, odds ratio.

no rotation was most prevalent in Nakamura et al's study from Japan. In terms of prognostic value of QRS transitional zone, overall modest associations (particularly after accounting for potential confounders and other ECG parameters) may

question its value. Nonetheless, QRS transitional zone information is automatically obtained when ECG is assessed, and, in such a case, clinical attention should be paid to persons with clockwise rotation, particularly for HF risk. With



respect to research implications, future studies are needed to investigate mechanisms linking clockwise rotation to HF risk as well as black race and diabetes mellitus correlating to counterclockwise transition and clockwise conversion, respectively.

### Study Limitations

There are some limitations that should be considered when interpreting our results. Our study included black and white participants in the United States, and thus care should be taken when generalizing its findings to other racial/ethnic groups. ECG assessments were not evenly distributed over follow-up, and thus the weight of information at visit 4 (linked to up to 14 years of follow-up) is higher than that at the other visits (on average linked to 3 years of follow-up). Nonetheless, follow-up ECGs allowed us to evaluate changes in rotation pattern over time and their correlates. Also, as in any observational study, we cannot deny the possibility of residual confounding.

### Conclusions

Counterclockwise rotation was the most prevalent QRS transition zone pattern and consistently demonstrated the lowest risk of CVD and mortality. Clockwise rotation was modestly associated with higher risk of HF as well as mortality compared with no rotation. These results have implications on how to interpret QRS transition zone rotation when ECG was recorded.

### Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions.

### Sources of Funding

The ARIC study is performed as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN2682-01100009C, HHSN268201100010C, HHSN2682011000-11C, and HHSN268201100012C).

### Disclosures

None.

### References

- Gotsman I, Keren A, Hellman Y, Banker J, Lotan C, Zwas DR. Usefulness of electrocardiographic frontal QRS-T angle to predict increased morbidity and mortality in patients with chronic heart failure. *Am J Cardiol*. 2013;111:1452–1459.
- Mandyam MC, Soliman EZ, Alonso A, Dewland TA, Heckbert SR, Vittinghoff E, Cummings SR, Ellinor PT, Chaitman BR, Stocke K, Applegate WB, Arking DE, Butler J, Loehr LR, Magnani JW, Murphy RA, Satterfield S, Newman AB, Marcus GM. The QT interval and risk of incident atrial fibrillation. *Heart Rhythm*. 2013;10:1562–1568.
- Soliman EZ, Shah AJ, Boerckircher A, Li Y, Rautaharju PM. Inter-relationship between electrocardiographic left ventricular hypertrophy and QT prolongation as predictors of increased risk of mortality in the general population. *Circ Arrhythm Electrophysiol*. 2014;7:400–406.
- Zhang ZM, Rautaharju PM, Soliman EZ, Manson JE, Cain ME, Martin LW, Bavy AA, Mehta L, Vitolsins M, Prineas RJ. Mortality risk associated with bundle branch blocks and related repolarization abnormalities (from the Women's Health Initiative [WHI]). *Am J Cardiol*. 2012;110:1489–1495.
- Nakamura Y, Okamura T, Higashiyama A, Watanabe M, Kadota A, Ohkubo T, Miura K, Kasagi F, Kodama K, Okayama A, Ueshima H. Prognostic values of clockwise and counterclockwise rotation for cardiovascular mortality in Japanese subjects: a 24-year follow-up of the National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged, 1980–2004 (NIPPON DATA80). *Circulation*. 2012;125:1226–1233.
- Bradford N, Shah AJ, Usoro A, Haisty WK Jr, Soliman EZ. Abnormal electrocardiographic QRS transition zone and risk of mortality in individuals free of cardiovascular disease. *Europace*. 2015;17:131–136.
- Aro AL, Eranti A, Anttonen O, Kerola T, Rissanen HA, Knekt P, Porthan K, Tikkanen JT, Junttila MJ, Huikuri HV. Delayed QRS transition in the precordial leads of an electrocardiogram as a predictor of sudden cardiac death in the general population. *Heart Rhythm*. 2014;11:2254–2260.
- The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. The ARIC investigators. *Am J Epidemiol*. 1989;129:687–702.
- Prineas R, Crow R, Zhang Z. The Minnesota code manual of electrocardiographic findings. 2010. Springer-Verlag London.
- Eriksson H, Caidahl K, Larsson B, Ohlson LO, Welin L, Wilhelmsen L, Svardsudd K. Cardiac and pulmonary causes of dyspnoea—validation of a scoring test for clinical-epidemiological use: the Study of Men Born in 1913. *Eur Heart J*. 1987;8:1007–1014.
- ARIC investigators. ARIC study protocols and manuals of operation. 1987.
- Olson KA, Viera AJ, Soliman EZ, Crow RS, Rosamond WD. Long-term prognosis associated with J-point elevation in a large middle-aged biracial cohort: the ARIC study. *Eur Heart J*. 2011;32:3098–3106.
- Atherosclerosis risk in communities study. Available at: <https://www2.csc.unc.edu/aric/>. Accessed August 1, 2017.
- Estes EH, Zhang ZM, Li Y, Tereshchenko LG, Soliman EZ. Individual components of the Romhilt-Estes left ventricular hypertrophy score differ in their prediction of cardiovascular events: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2015;170:1220–1226.
- Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol*. 2008;101:1016–1022.
- Tahara Y, Mizuno H, Ono A, Ishikawa K. Evaluation of the electrocardiographic transitional zone by cardiac computed tomography. *J Electrocardiol*. 1991;24:239–245.

# **SUPPLEMENTAL MATERIAL**

**Table S1. Relative risk ratio of changes from counterclockwise rotation for each predictor tested**

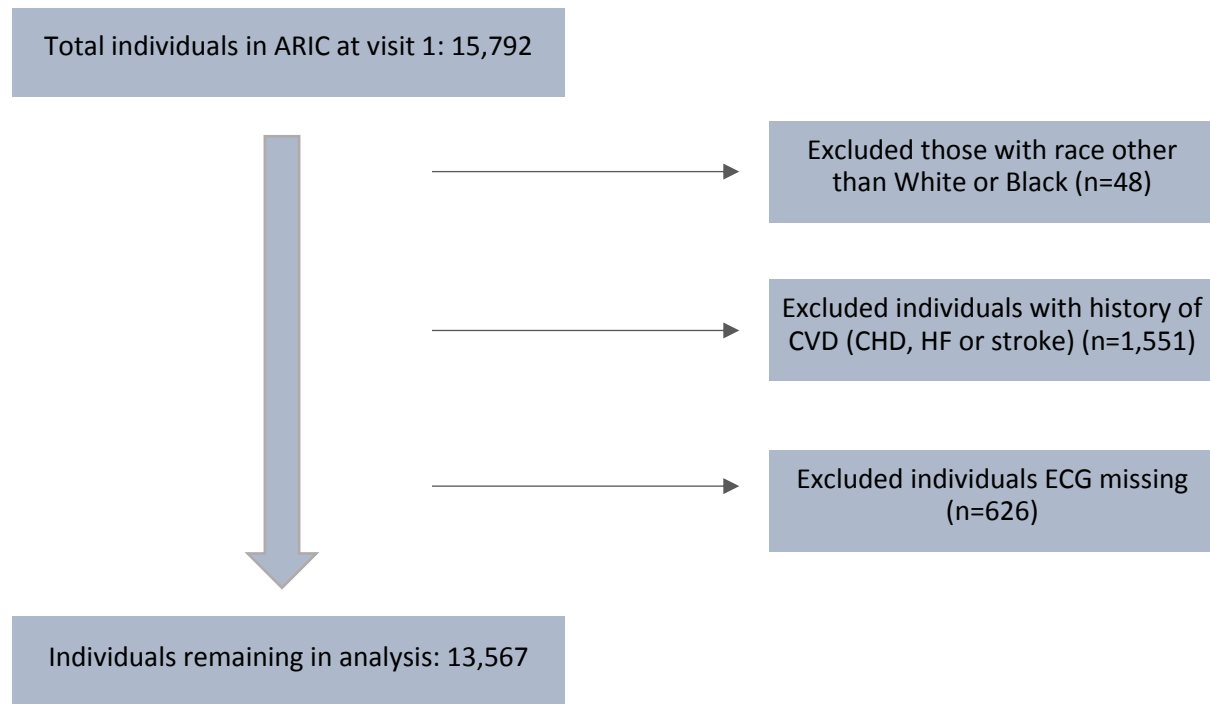
		Clockwise		No rotation	
		RRR (95% CI)	P-value	RRR (95% CI)	P-value
Age		1.01 (0.95-1.07)	0.815	1.00 (0.99-1.01)	0.644
Male		3.19 (1.44-7.05)	0.004	1.08 (0.93-1.25)	0.336
Black		1.19 (0.51-2.80)	0.683	0.99 (0.83-1.19)	0.926
Education	Intermediate	0.83 (0.36-1.95)	0.671	1.18 (0.97-1.43)	0.095
	High	0.65 (0.26-1.58)	0.340	1.16 (0.95-1.41)	0.147
current smoking		1.73 (0.81-3.73)	0.159	0.98 (0.83-1.17)	0.839
current drinking		0.75 (0.37-1.54)	0.437	0.90 (0.78-1.04)	0.140
Hypertension		0.98 (0.46-2.11)	0.965	1.15 (0.99-1.34)	0.069
Diabetes		2.75 (1.13-6.66)	0.025	1.36 (1.06-1.74)	0.015
BMI		1.03 (0.96-1.11)	0.386	0.98 (0.96-0.99)	0.003
Total cholesterol		0.76 (0.55-1.05)	0.100	0.99 (0.93-1.05)	0.742
HDL cholesterol		0.92 (0.33-2.56)	0.876	1.05 (0.88-1.25)	0.603

\* Relative risk ratio: Reference group is those who had no rotation across all four visits.

**Table S2. Associations of counterclockwise- and clockwise-rotation with CVD outcomes by subgroups**

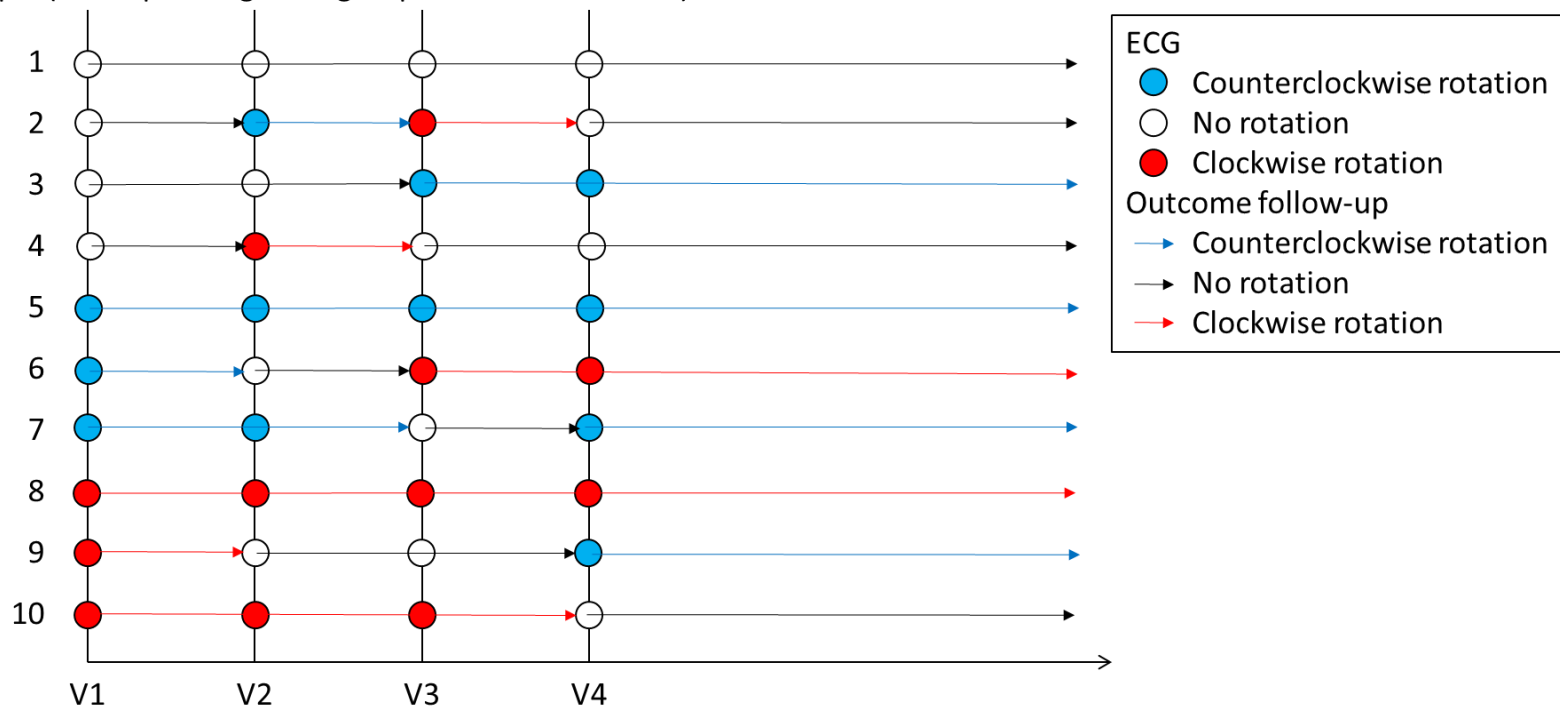
Subgroups		Counterclockwise				Clockwise			
		HR	95% CI	P	P for Interaction	HR	95% CI	P	P for Interaction
Age	≤ 55	0.99	(0.92-1.06)	0.744	0.101	1.19	(1.04-1.37)	0.012	0.015
	> 55	0.91	(0.88-0.96)	<0.001		1.01	(0.92-1.10)	0.904	
Sex	Female	0.96	(0.91-1.02)	0.165	0.441	1.07	(0.96-1.19)	0.199	0.442
	Male	0.91	(0.87-0.96)	0.001		1.06	(0.95-1.17)	0.282	
Race	White	0.95	(0.91-0.99)	0.014	0.432	1.03	(0.94-1.13)	0.491	0.161
	Black	0.91	(0.85-0.98)	0.018		1.13	(0.99-1.30)	0.073	
BMI	< 30	0.93	(0.89-0.98)	0.004	0.374	1.07	(0.97-1.18)	0.174	0.876
	≥ 30	0.96	(0.90-1.02)	0.220		1.05	(0.94-1.18)	0.405	
Diabetes	No	0.95	(0.91-0.99)	0.025	0.529	1.07	(0.98-1.17)	0.130	0.519
	Yes	0.90	(0.83-0.98)	0.011		1.03	(0.89-1.18)	0.697	
Hypertension	No	0.94	(0.89-0.99)	0.019	0.693	1.13	(1.02-1.26)	0.021	0.062
	Yes	0.94	(0.89-0.99)	0.017		1.00	(0.90-1.11)	0.986	
Total cholesterol	< 6	0.95	(0.91-0.99)	0.027	0.294	1.10	(1.01-1.19)	0.037	0.079
	≥ 6	0.92	(0.85-0.98)	0.014		0.96	(0.83-1.10)	0.554	
Current smoking status	No	0.90	(0.83-0.97)	0.004	0.233	1.11	(0.98-1.26)	0.109	0.231
	Yes	0.96	(0.92-1.00)	0.052		1.02	(0.93-1.11)	0.691	
Current drinking status	No	0.94	(0.89-0.99)	0.024	0.958	1.06	(0.96-1.18)	0.265	0.985
	Yes	0.94	(0.89-1.00)	0.040		1.06	(0.95-1.17)	0.308	
Education	Basic	0.87	(0.81-0.93)	<0.001	0.038	1.00	(0.87-1.14)	0.985	0.327
	Intermediate	0.96	(0.91-1.02)	0.195		1.05	(0.94-1.18)	0.389	
	High	0.98	(0.91-1.04)	0.480		1.14	(1.00-1.30)	0.051	

**Figure S1. Flow chart for the selection of study participants**



**Figure S2. Scheme demonstrating several examples of QRS transitional zone over nine years and allocation of follow-up time corresponding to time-varying QRS transitional zone**

Example (corresponding to 10 groups in Table 3 in order)



Baseline correlates  
assessed at V1