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Prognostic implications of QRS dispersion for major adverse cardiovascular events in asymptomatic women and men: the Multi-Ethnic Study of Atherosclerosis

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Abstract

Background QRS dispersion measured as the difference between maximal and minimal QRS duration in the standard 12-lead electrocardiogram has been shown to be associated with increased mortality in heart failure (HF) patients and increased arrhythmic events in patients with cardiomyopathy.

Aims This study sought to examine the prognostic association between baseline QRS dispersion and future cardiovascular events in individuals without known prior cardiovascular disease.

Methods The association of QRS dispersion with cardiovascular events was examined in 6510 MESA (Multi-Ethnic Study of Atherosclerosis) participants. Participants with bundle branch block were excluded. Study participants were divided into two groups based on the 95th percentile of QRS dispersion (QRS dispersion < 34 ms [group I] and QRS dispersion ≥ 34 ms [group II]). Cox proportional hazard models adjusting for demographic and clinical risk factors were used to examine the association of QRS dispersion with incident cardiovascular events (major adverse cardiovascular events [MACE]) and mortality. Analysis was repeated by forcing Framingham risk factors.

Results Mean age was 62 ± 10 years in group I and 63 ± 10 years in group II ($P = 0.02$). QRS dispersion ≥ 34 ms was associated significantly with MACE (HR 1.30; 95% CI 1.04–1.62) and mortality (HR 1.33; 95% CI 1.03–1.73) after adjustment for cardiovascular risk factors and potential cofounders. Similar results were seen for mortality after adjustment for Framingham risk factors.

Conclusion QRS dispersion ≥ 34 ms predicts cardiovascular events and mortality.

Keywords QRS dispersion · Mortality · Major adverse cardiovascular events · Multi-Ethnic Study of Atherosclerosis · Heart failure

1 Introduction

Current knowledge about predictors for cardiovascular events in healthy adults remains incomplete. Left ventricular ejection fraction (LVEF), a standard measurement of global systolic function, is commonly used to predict future cardiovascular events [1]. Current guidelines emphasize LVEF as the primary variable for identification of candidates for cardiovascular

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event including ventricular arrhythmias requiring implantable defibrillator insertion [2]. However, LVEF is an insensitive indicator of cardiovascular health, and other parameters have been proposed to better risk stratify asymptomatic individuals. [3–6] In the Multi-Ethnic Study of Atherosclerosis (MESA) population, higher left ventricular (LV) mass to volume ratio (LVMR), [7] the LV global function index, [8] and decreased myocardial circumferential strain [9] have been documented as risk predictors of adverse cardiac events.

QRS dispersion is an electrocardiographic (ECG) parameter that has been shown to be associated with increased mortality in patients with heart failure (HF) [10, 11]. QRS dispersion is measured as the difference between maximal and minimal QRS duration on the 12-lead electrocardiogram (ECG). Kountouris et al. [12] reported that QRS dispersion exhibits a stronger association with LV systolic function than QRS duration. Its significance in individuals without known cardiovascular disease has not been determined.

We sought to examine the prognostic implications of QRS dispersion for major adverse cardiovascular events (MACE) and all-cause mortality as a separate endpoint in asymptomatic men and women.

2 Methods

2.1 Study population

MESA is a prospective cohort study designed to examine the characteristics and underlying mechanisms of development and progression of subclinical cardiovascular disease in asymptomatic individuals. Inclusion criteria and methods of the MESA study were previously described. [13] Individuals with known cardiovascular disease or prior cardiac symptoms were excluded. On enrollment, study participants underwent extensive baseline evaluation including clinical questionnaires, physical examinations, and laboratory tests at 6 participating centers in the USA: Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan and the Bronx, NY; and St. Paul, MN. Standard questionnaires were used to obtain information about self-reported race/ethnicity, smoking history, medication use for high blood pressure, high cholesterol levels, and diabetes. Participant height and weight were measured, and body mass index (BMI, kg/m^2) was calculated. Resting blood pressure was measured two times with participants in the seated position with an automated oscillometric sphygmomanometer (Critikon, GE Healthcare, Waukesha, WI). Diabetes was defined as fasting glucose ≥ 126 mg/dl or use of hypoglycemic medications. The institutional review board at each participating site approved the MESA study protocol, and written informed consent was obtained from each participant.

Participants with QRS duration of ≥ 120 ms were excluded from this study (299 participants). Data from the remaining 6515 out of 6814 MESA participants (who had complete ECG data) aged 45–84 years from 4 different ethnic backgrounds (white, black, Hispanic, and Chinese) was analyzed. The study was approved by the institutional review boards of participating centers, and participants gave informed consent.

2.2 Electrocardiographic analysis

A resting 12-lead ECG was recorded at the baseline examination using a MAC 1200 ECG machine (Marquette Electronics, Milwaukee, WI) at all field centers at 10 mm/mV calibration and speed of 25 mm/s. All ECGs were read at a central laboratory (EPICARE, Wake Forest School of Medicine, Winston Salem, NC) and visually inspected for adequate quality and technical errors. Electrocardiographic abnormalities were classified using the Minnesota ECG code (MC). All the intervals of QRS duration (q wave, r, r', s, s') were measured separately in each lead. These measurements were automatically calculated using GE. Marquette 12-SL program version 2001. During analysis, these durations were summed up to give QRS duration in each lead for every participant. QRS dispersion was then calculated as the difference of maximum QRS duration and minimum QRS duration on a 12-lead electrocardiogram for each participant. Similarly, QT interval and PR interval were also measured.

2.3 Clinical follow-up and event monitoring

Participants included in this study had a follow-up of 4261 ± 794 days for mortality from their baseline examination. In addition to the scheduled MESA examination, a telephone interviewer contacted each participant or representative by telephone every 9 to 12 months to inquire about all cardiovascular outpatient diagnoses and procedures, interim hospital admissions, and deaths. To verify self-reported diagnoses, copies of all death certificates and medical records for all hospitalizations and outpatient cardiovascular diagnoses were requested. Next of kin interviews for out of hospital cardiovascular deaths were performed. Medical records were successfully acquired from 99% of hospitalized cardiovascular events and 97% of outpatient diagnostic visits. Two physicians from the MESA study events committee independently reviewed all medical records for endpoint classification using pre-specified criteria. MACE was defined as including myocardial infarction, definite heart failure, and stroke and all-cause death. A detailed description of events and the process of adjudication can be found in MESA publications [13, 14]. The following outcomes were used as dependent variables in this study: (1) mortality (all-cause mortality) and (2) MACE including myocardial infarction, definite heart failure, stroke, and all-cause death. Causes of death were atherosclerotic

coronary event, stroke, atherosclerotic disease, other cardiovascular cause, non-cardiovascular cause, and unknown cause. Data was not available for arrhythmic-related death or sudden cardiac death.

2.4 Statistical analysis

Baseline participant characteristics and demographics are presented as mean ± SD or percentage as appropriate. QRS dispersion by rank plot (Fig. 1) showed a marked change in rate of increase in QRS dispersion at the 95th percentile (34 ms). Thus, 34 ms was chosen as a cutoff point for QRS dispersion, and the QRS dispersion indicator variable was defined as "< 34 ms" and "≥ 34 ms." The 95th percentile is a commonly used cutoff point to define abnormality when there is no agreed-upon cutoff point. Participant's characteristics were compared between those with QRS dispersion less than 34 ms (group I) and ≥ 34 ms (group II). The Mann-Whitney-Wilcoxon tests were used for comparison of continuous variables and chi-square tests were used for the discrete variables. The Kaplan-Meier plots were constructed for mortality and MACE comparing the patients with QRS dispersion less than 34 ms to those with QRS dispersion ≥ 34 ms. Cox proportional hazard models were used to calculate the hazard ratios for mortality and MACE associated with QRS dispersion treated as a continuous variable. We considered univariate (unadjusted) and fully adjusted multivariable Cox models (age, gender, hypertension, cigarette smoking, C-reactive protein, diabetes mellitus, heart rate, race, QT duration, PR interval duration, and RR interval. The variables included in the fully adjusted model were selected by stepwise procedures for mortality and MACE respectively. Age, race, gender, hypertension, cigarette smoking status, diabetes mellitus, heart rate, LDL, HDL, BMI, education, QT duration, PR interval, RR interval, and C-reactive protein were used in the stepwise selection to select explanatory variables for mortality and MACE. In the model for mortality and MACE, the process selected age, gender, hypertension, cigarette smoking, C-reactive protein, diabetes mellitus, heart rate, race, QT duration, PR interval, and RR interval (11 variables). Similar models were also fitted for mortality and MACE with QRS dispersion treated as a binary indicator. During analysis, older age alone was significantly associated with both increased mortality and MACE. Age was used as a dichotomous variable using the median value as the cutoff between older and younger participants. This binary age variable was included in an interaction term with QRS dispersion in the statistical analysis to understand whether the influence of QRS dispersion on the outcome of mortality or MACE was modified by age.

None of the listed antihypertensive medications has specific effects on the depolarization phase. Further details on medications beyond those listed in MESA questionnaires were not available.

Besides the stepwise selection method based on univariate significance, further analysis was done by forcing traditional cardiovascular risk factors (Framingham risk factors (age, gender, total cholesterol, HDL cholesterol, smoking, systolic blood pressure, antihypertensive medications)). In the analysis using traditional Framingham risk factors, QT duration, PR interval duration, and RR interval were also included. The analysis was done with QRS dispersion as a categorical variable (< 34 ms and ≥ 34 ms) and as a continuous variable. All analyses were performed with Stata Statistical Software: Release 13. College Station, TX: StataCorp LP. In all analyses, a two-sided P value < 0.05 was considered statistically significant.

3 Results

3.1 Baseline demographics and participant characteristics

There were 6161 participants with QRS dispersion less than 34 ms (group I) and the remaining 354 (5.4%) had QRS dispersion ≥ 34 ms (group II). Fifty-three percent of group I participants and 55% of group II participants were female. Mean age was 62 ± 10 years and 63 ± 10 years in groups I and II,

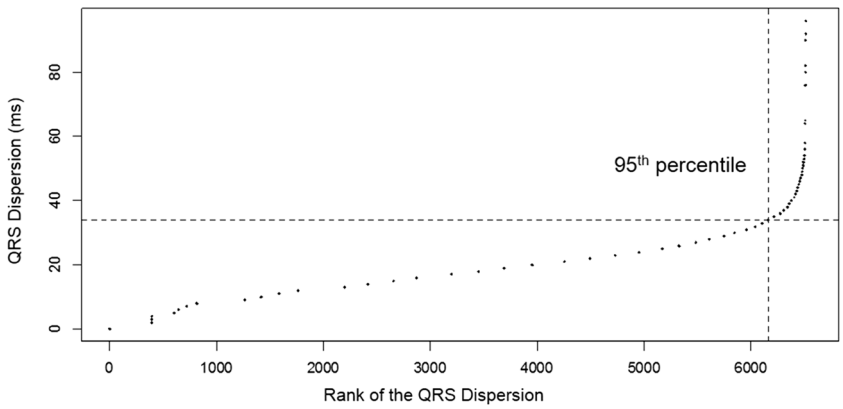

Fig. 1 QRS dispersion by rank plot. At the 95th percentile (34 ms), the rate of increase in QRS dispersion dramatically changed

respectively ($P = 0.02$). There were statistically significantly higher participants with hypertension in group II compared to group I. Detailed baseline demographics are summarized in Table 1. During a mean follow-up of 13.5 ± 2.2 years, 863 (14%) and 62 (17.5%) participants died, and 1199 (19.5%) and 83 (23.5%) participants had MACE in groups I and II, respectively.

3.2 Event rates and hazard ratios

3.2.1 QRS dispersion and hazard analysis for mortality

Mortality was statistically significantly higher among group II participants with a hazard ratio of 1.31 (95% CI 1.01–1.70, unadjusted model). Figure 2 shows the Kaplan-Meier analysis for mortality with stratification of participants using a QRS dispersion threshold of 34 ms. In the fully adjusted model where analysis was adjusted for age, gender, hypertension, cigarette smoking, C-reactive protein, diabetes mellitus, heart rate, race, QT duration, PR interval, and RR interval, mortality remained statistically significantly higher among group II participants (HR 1.33 with 95% CI 1.03–1.73), Table 2. The analysis was repeated with QRS dispersion as a continuous variable. In the unadjusted analysis, QRS dispersion was significantly associated with mortality (HR 1.01, 95% CI 1.00–1.04). After adjustment for age, gender, hypertension, cigarette smoking, C-reactive protein, diabetes mellitus, heart rate, race, QT duration, PR interval, and RR interval, QRS

Table 1 Participants' demographics and characteristics

Parameters	QRS dispersion < 34 ms ($n = 6161$)	QRS dispersion ≥34 ms ($n = 354$)	*P* value
Age, years	62 ± 10	63 ± 10	0.021
Gender, %			0.323
Females	52.67	55.37	
Males	47.33	44.63	
Race, %			0.026
White	38.66	32.20	
Chinese	11.69	15.82	
African-American	27.90	27.97	
Hispanics	21.75	24.01	
Diabetes mellitus, %			0.581
Normal	73.62	71.67	
Impaired fasting glucose	13.68	15.58	
Untreated	2.74	1.98	
Treated	9.97	10.76	
Hypertension, %			0.042
Yes	44.47	50.00	
No	55.53	50.00	
Smoking, %			0.899
Never	50.27	50.00	
Former	36.61	37.57	
Current	13.12	12.43	
Educational status, %			0.026
≤ 8th grade	10.95	12.15	
9th grade to bachelor's degree	70.58	75.14	
Graduate school	18.47	12.71	
Heart rate, beats/min	63.11 ± 9.64	63.48 ± 10.16	0.488
LDL cholesterol, mg/dl	117.50 ± 31.42	115.20 ± 31.95	0.183
HDL cholesterol, mg/dl	50.98 ± 14.84	50.26 ± 14.57	0.376
Body mass index, kg/m^2	28.34 ± 5.50	28.22 ± 5.10	0.689
C-reactive protein, mg/l	3.77 ± 5.84	3.75 ± 5.14	0.949
LV ejection fraction (%)	69.00 ± 7.40	69.70 ± 7.08	0.142
LVH, %	3.93	3.39	0.61

LDL low-density lipoprotein, *HDL* high-density lipoprotein, *LVH* left ventricular hypertrophy

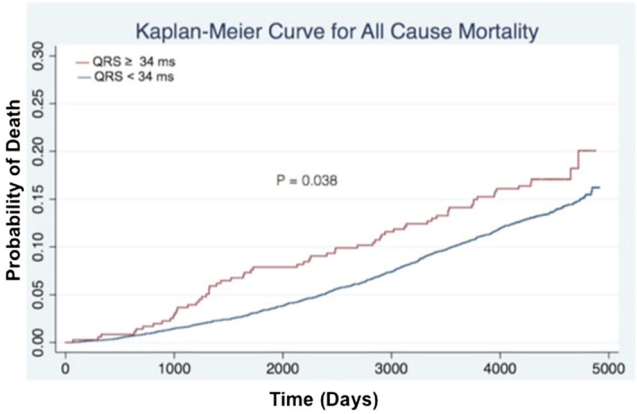

Fig. 2 The Kaplan-Meier curve for mortality. QRS < 95th percentile is the group with QRS dispersion < 34 ms and QRS ≥ 95th percentile is the group with QRS dispersion ≥ 34 ms

dispersion was statistically significantly associated with mortality (HR 1.01 with 95% CI 1.00–1.015) (Table 3).

In a model with traditional Framingham risk factors (age, gender, total cholesterol, HDL cholesterol, smoking, systolic blood pressure, antihypertensive medications, diabetes mellitus), QT duration, PR interval, and RR interval, QRS dispersion as a continuous variable was statistically significantly associated with mortality (HR 1.01 with 95% CI 1.00–1.01). On measuring QRS dispersion as a categorical variable, QRS dispersion ≥ 34 ms was not statistically associated with mortality ($P = 0.07$). However, when the analysis was repeated with addition of age (as a categorical variable with age as a dichotomous variable using the median value as the cutoff between older and younger participants) and QRS dispersion as an interaction term, QRS dispersion ≥ 34 ms was statistically associated with mortality in participants less or equal to 62 years (HR 1.97 with 95% CI 1.19–3.25, $P = 0.008$) (Tables 2 and 3).

3.2.2 QRS dispersion and hazard analysis for major adverse cardiovascular events

Among group I participants, 1199 participants (19.5%) experienced major adverse cardiovascular events (MACE), compared to 83 (23.5%) of group II participants ($P = 0.028$). Mean time to MACE was 3919 ± 1234 days. Figure 3 shows the Kaplan-Meier analysis for MACE based on a QRS dispersion threshold of 34 ms. The unadjusted hazard ratio was 1.28 with 95% confidence interval of 1.03–1.60 ($P = 0.028$). When adjusted for age, gender, hypertension, cigarette smoking, C-reactive protein, diabetes mellitus, heart rate, QT duration, PR interval, RR interval, and race, MACE was significantly higher in group II (HR = 1.30, CI 1.04–1.62, $P = 0.02$) (Table 4) (QRS dispersion analyzed as categorical variable).

QRS dispersion was then evaluated as a continuous variable for MACE as the outcome. In the unadjusted analysis, QRS dispersion was significantly associated with MACE (HR 1.01, 95% CI 1.00–1.01). After adjustment for age, gender, hypertension, cigarette smoking, C-reactive protein, diabetes mellitus, heart rate, race, QT duration, PR interval, and RR interval, QRS dispersion was still statistically significantly associated with MACE (HR 1.01, 95% CI 1.0–1.01, $P = 0.015$) (Table 5).

In a model with traditional risk factors (age, gender, total cholesterol, HDL cholesterol, smoking, systolic blood pressure, antihypertensive medications, diabetes mellitus), QT duration, PR interval, and RR interval and with age interaction variable (age used as a dichotomous variable), QRS dispersion

Table 2 Estimates of hazard ratios of mortality associated with QRS dispersion < 34 ms versus ≥ 34 ms

Mortality			
	Hazard ratio	95% hazard ratio confidence limits	*P* value
Unadjusted	1.31	1.02 1.70	0.038
Fully adjusted*	1.33	1.03 1.73	0.028
Framingham risk factors**	1.27	0.98 1.64	0.07
Framingham risk factors with age interaction*** (age ≤ 62 years)	1.97	1.19 3.25	0.008
Framingham risk factors with age interaction*** (age > 62 years)	1.12	0.83 1.52	0.44

*Adjusted for age, gender, hypertension, cigarette smoking, C-reactive protein, diabetes mellitus, heart rate, race, QT duration, PR interval duration, and RR interval

**Framingham risk factors: age, gender, total cholesterol, seated systolic blood pressure, HDL cholesterol, cigarette smoking, hypertension medications, diabetes mellitus, QT duration, PR interval duration, and RR interval

***Framingham risk factors with age interaction: age, age*QRS dispersion categorical, gender, total cholesterol, seated systolic blood pressure, HDL cholesterol, cigarette smoking, hypertension medications, diabetes mellitus, QT duration, PR interval duration, and RR interval

Table 3 Estimates of hazard ratios of mortality associated with QRS dispersion as a continuous variable

Mortality			
	Hazard ratio	95% hazard ratio confidence limits	*P* value
Unadjusted	1.01	1.00 1.04	0.015
Fully adjusted*	1.01	1.00 1.015	0.013
Framingham risk factors**	1.01	1.00 1.013	0.031
Framingham risk factors with age interaction****	1.013	0.998 1.028	0.082

*Adjusted for age, gender, hypertension, cigarette smoking, C-reactive protein, diabetes mellitus, heart rate, race, QT duration, PR interval duration, and RR interval

**Framingham risk factors: age, gender, total cholesterol, seated blood pressure, HDL cholesterol, cigarette smoking, hypertension medications, diabetes mellitus, QT duration, PR interval duration, and RR interval

****Framingham risk factors with age interaction: age, age*QRS dispersion, gender, total cholesterol, seated systolic blood pressure, HDL cholesterol, cigarette smoking, hypertension medications, diabetes mellitus, QT duration, PR interval duration, and RR interval

was statistically significantly associated with MACE as a continuous variable (HR 1.02 with 95% CI 1.00–1.03, $P = 0.01$). QRS dispersion as a categorical variable was also statistically significantly associated with MACE in ≤ 62 years with age interaction term (HR 1.8, with 95% CI 1.2–2.69, $P = 0.004$) (Tables 4 and 5).

When each MACE was looked separately, we found there was no statistically significant difference in incidence of myocardial infarction, stroke, or death based on QRS dispersion cutoff 34 ms. However, there was statistically significant higher congestive heart failure incidence with QRS dispersion ≥ 34 ms.

4 Discussion

Dispersion of surface ECG wave durations/intervals has been studied aggressively for non-invasive cardiac markers useful in predicting the risk of arrhythmias and sudden cardiac death.

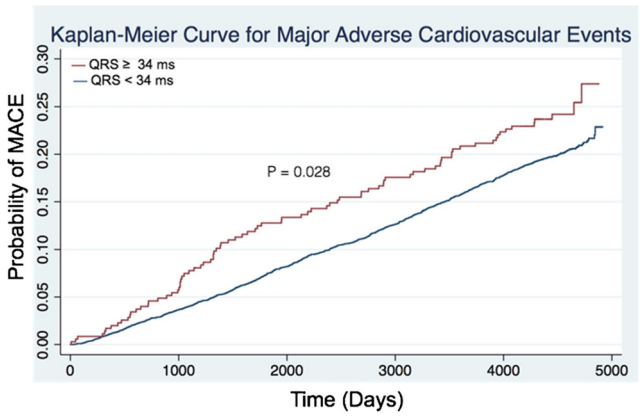

Fig. 3 The Kaplan-Meier curve for major adverse cardiovascular events. QRS < 95th percentile is the group with QRS dispersion < 34 ms and QRS ≥ 95th percentile is the group with QRS dispersion ≥ 34 ms. MACE indicates major adverse cardiovascular events

After initial positive results, QT dispersion (QT-d) slowly entered into obscurity. This was secondary to couple of reasons. It has been suggested that, at least in limb leads, QT-d is an "illusion." Other reasons being poor reproducibility, mostly due to the difficulty in identifying T wave offset.

Durrer et al. [15] and Cassidy et al. [16] have shown delayed activation of some parts of heart compared to other. They showed left ventricular (LV) endocardial activation began 0–15 ms after the QRS complex onset. Endocardial activation of LV was completed at 29–52 ms. The duration of LV endocardial activation was 28–50 ms. This comprised 41% of the total surface QRS complex. This heterogeneity and conduction delays are the basis of QRS dispersion (QRSd).

Perkiomako and colleagues [17] studied 100 patients: 30 healthy subjects, 40 patients with a history of myocardial infarction (MI), without arrhythmic events, or inducible ventricular tachycardia (VT) at electrophysiological study, and 30 patients with prior MI and history of cardiac arrest (12 patients) or VT (18 subjects) and inducible monomorphic VT at electrophysiological study. QRSd was 28 ± 11 ms in the normal group, 46 ± 13 ms in the group with MI and no VT, and 48 ± 16 ms in the group with MI and VT ($P < 0.001$ between patients without VT vs healthy subjects and between patients with VT vs healthy subjects). However, a more extensive study [18], which included 724 patients, showed that increased QRS duration or QRS dispersion was not correlated with arrhythmic events.

Anastasiou-Nana et al. studied 104 class II–IV NYHA heart failure patients with LVEF < 35% with cardiac death as endpoint [11]. QRS dispersion was increased in patients who died (54 ± 17 ms vs 46 ± 16 ms, $P < 0.02$). Also, patients with sudden death had significantly higher QRSd compared to survivors (56 ± 13 ms vs 46 ± 16 ms, $P < 0.02$). A cutoff value of 46 ms for QRSd identified a group with high risk of death in 3 years (mortality 13% vs 32%, relative risk 3.85, 95% confidence interval 1.6 to 9.5).

Table 4 Estimates of hazard ratios of MACE associated with QRS dispersion < 34 ms versus ≥ 34 ms

MACE			
	Hazard ratio	95% hazard ratio confidence limits	*P* value
Unadjusted	1.28	1.03 1.60	0.028
Fully adjusted*	1.30	1.04 1.62	0.023
Framingham risk factors**	1.22	0.98 1.53	0.073
Framingham risk factors with age interaction*** (age ≤ 62 years)	1.8	1.2 2.69	0.004
Framingham risk factors with age interaction*** (age > 62 years)	1.09	0.83 1.42	0.537

*Fully adjusted: age, gender, hypertension, cigarette smoking, C-reactive protein, diabetes mellitus, heart rate, race, QT duration, PR interval duration, and RR interval

**Framingham risk factors: age, gender, total cholesterol, seated blood pressure, HDL cholesterol, cigarette smoking, hypertension medications, diabetes mellitus, QT duration, PR interval duration, and RR interval

***Framingham risk factors with age interaction: age, age*QRS dispersion categorical, gender, total cholesterol, seated systolic blood pressure, HDL cholesterol, cigarette smoking, hypertension medications, diabetes mellitus, QT duration, PR interval duration, and RR interval

QRS dispersion was included in the prognostic index assessing the long-term mortality of 553 patients with class I–III NYHA heart failure from the UK-HEART study [19]. Mean QRSd was 44.6 ± 15.5 ms, median was 42.7 ms, and range was 12–125 ms. In survivors, QRSd was 40.6 ms compared with 45.1 ms in non-survivors ($P = 0.003$). The results showed that QRSd was an independent predictor of all-cause mortality with a hazard ratio of 1.06 (1.02–1.1) and *P* value of 0.004.

People of Chinese ethnicity had greater QT dispersion compared to Caucasians in the study by Fei et al. [20] Santhanakrishnan et al. [21] showed Asian men and women had a longer QRS duration than white men and women respectively. However, in our study, results on the relationship between QRS dispersion and mortality or MACE were unchanged after adjusting for race categories.

In the present study, we analyzed the association of QRS dispersion with all-cause mortality and MACE in the MESA population. In our study of MESA participants, a multi-ethnic group who did not have known cardiovascular disease on study entry, QRS dispersion ≥ 34 ms was associated with mortality and MACE after adjustment for risk factors selected based on selection model. This association with mortality was also seen with Framingham risk factors but after adjustment for age interaction with QRS dispersion. QRS dispersion as a continuous variable was associated with MACE after adjustment for age interaction for Framingham risk factors. To note, the analysis was done after adjusting for other electrical parameters like QT, PR, and RR interval.

Our data yields the following important findings about QRS dispersion:

Table 5 Estimates of hazard ratios of MACE associated with QRS dispersion as a continuous variable

MACE			
	Hazard ratio	95% hazard ratio confidence limits	*P* value
Unadjusted	1.01	1.00 1.01	0.026
Fully adjusted*	1.01	1.0 1.01	0.015
Framingham risk factors***	1.01	1.0 1.01	0.030
Framingham risk factors with age interaction****	1.02	1.00 1.03	0.010

*Adjusted for age, gender, hypertension, cigarette smoking, C-reactive protein, diabetes mellitus, heart rate, race, QT duration, PR interval duration, and RR interval

**Adjusted for age, age* QRS dispersion, gender, hypertension, cigarette smoking, C-reactive protein, diabetes mellitus, heart rate, race, QT duration, PR interval duration, and RR interval

***Framingham risk factors: age, gender, total cholesterol, seated blood pressure, HDL cholesterol, cigarette smoking, hypertension medications, diabetes mellitus, QT duration, PR interval duration, and RR interval

****Framingham risk factors with age interaction: age, age*QRS dispersion, gender, total cholesterol, seated systolic blood pressure, HDL cholesterol, cigarette smoking, hypertension medications, diabetes mellitus, QT duration, PR interval duration, and RR interval

1. Baseline QRS dispersion is associated with mortality and MACE.
2. Baseline QRS dispersion more than or equal to 34 ms is associated with mortality and MACE.
3. The association of QRS dispersion with MACE using Framingham risk factors is dependent upon effect modification by age, with significant association in the age group less than or equal to 62 years.

It has been shown experimentally that nonuniform ventricular activation as well as nonuniform recovery of excitability plays important roles in the mechanisms of ventricular arrhythmias. [22] Potential arrhythmogenic nonuniform recovery of excitability is the result of either dispersion of refractoriness or activation times depending on the underlying pathophysiologic substrate [23]. QT dispersion is thought to represent the global average of the regional inhomogeneity of repolarization times and QRS dispersion similarly represents the global inhomogeneity of regional depolarization as a consequence of regional ventricular conduction defects. Peter et al. [24] demonstrated that increased QRS dispersion in the precordial leads is associated with recurrent arrhythmic events in patients with arrhythmogenic right ventricular dysplasia (ARVD). Turrini et al. [25] also reported increased QRS dispersion among patients with ARVD who died suddenly. Other studies have shown an association between QRS dispersion and mortality in patients with heart failure. [10, 11]

Based on the above known facts, we can hypothesize that mortality was related to increased QRS dispersion in our study because of pathological depolarization inhomogeneity, which predisposes to arrhythmic events. Data as to cause of death, being sudden death, in our study is not available to prove this but this finding provides cause for future studies. Additionally, QRS dispersion secondary to depolarization inhomogeneity could lead to dyssynchrony of contraction patterns and predisposition to HF. We did find statistically significant heart failure with QRS dispersion ≥ 34 ms. It is possible that the predisposition to development of heart failure with increase QRS dispersion results in increased mortality. In previous published data, increased mortality was seen in patients with heart failure and increased QRS dispersion. To the best of our knowledge, this study is the first to examine the association of QRS dispersion with clinical cardiovascular outcomes and mortality in participants without prevalent cardiovascular disease.

4.1 Limitations

The number of MACE in the MESA cohort is relatively small. Consequently, reliable evaluation of individual types of cardiovascular event was not possible. Moreover, we do not have data on the sudden death as the cause of death. Since this was a relatively healthy population, generalizability of the study results may be limited. The 95th percentile cutoff is arbitrary but was employed since it is a commonly used discriminator to define abnormality in the absence of an agreed-upon cut point. Based on the association of the outcomes with QRS dispersion, we have suggested a cutoff (34 ms), which needs to be, evaluated in future studies. One of the major limitations of the study is the absence of data on sudden death or "arrhythmic events" as cause of death. In addition, although this study describes the significance of QRS dispersion in association with cardiovascular events, a detailed explanation of the underlying mechanism involving events is beyond the scope of this study.

5 Conclusion

Our study demonstrates that QRS dispersion, a reflection of ventricular activation inhomogeneity, is a prognostic marker of adverse cardiovascular events and mortality among an asymptomatic multiethnic population.

5.1 Clinical significance

This study provides a new parameter that might be useful for prediction of MACE and mortality in individuals without prevalent coronary disease.

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Compliance with ethical standards

The institutional review board at each participating site approved the MESA study protocol, and written informed consent was obtained from each participant. The study was approved by the institutional review boards of participating centers, and participants gave informed consent.

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