Predictive Value of Beat-to-Beat QT Variability Index across the Continuum of Left Ventricular Dysfunction: Competing Risks of Non-cardiac or Cardiovascular Death, and Sudden or Non-Sudden Cardiac Death

Running title: Tereshchenko et al.; QT variability in LVEF > 35%

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Abstract:

**Background** - The goal of this study was to determine the predictive value of beat-to-beat QT variability in heart failure (HF) patients across the continuum of left ventricular dysfunction.

**Methods and Results** - Beat-to-beat QT variability index (QTVI), heart rate variance (LogHRV), normalized QT variance (QTVN), and coherence between heart rate variability and QT variability have been measured at rest during sinus rhythm in 533 participants of the Muerte Subita en Insuficiencia Cardiaca (MUSIC) HF study (mean age 63.1±11.7; males 70.6%; LVEF >35% in 254 [48%]) and in 181 healthy participants from the Intercity Digital Electrocardiogram Alliance (IDEAL) database. During a median of 3.7 years of follow-up, 116 patients died, 52 from sudden cardiac death (SCD). In multivariate competing risk analyses, the highest QTVI quartile was associated with cardiovascular death [hazard ratio (HR) 1.67(95%CI 1.14-2.47), P=0.009] and in particular with non-sudden cardiac death [HR 2.91(1.69-5.01), P<0.001].

Elevated QTVI separated 97.5% of healthy individuals from subjects at risk for cardiovascular death [HR 1.57(1.04-2.35), P=0.031], and non-sudden cardiac death in multivariate competing risk model [HR 2.58(1.13-3.78), P=0.001]. No interaction between QTVI and LVEF was found.

QTVI predicted neither non-cardiac death (P=0.546) nor SCD (P=0.945). Decreased heart rate variability (HRV) rather than increased QT variability was the reason for increased QTVI in this study.

**Conclusions** - Increased QTVI due to depressed HRV predicts cardiovascular mortality and non-sudden cardiac death, but neither SCD nor excraccardiac mortality in HF across the continuum of left ventricular dysfunction. Abnormally augmented QTVI separates 97.5% of healthy individuals from HF patients at risk.

**Key words**: ECG; ejection fraction; heart failure; sudden death; QT variability
An aging population with a high prevalence of obesity, diabetes, and hypertension, along with advancements in the treatment of acute cardiovascular diseases has resulted in an increased incidence and prevalence of heart failure (HF) over the past decades. Studies estimate that about 2-3% of the population suffer from HF. Despite advances in therapy and management, HF carries substantial morbidity and mortality, as well as high rates of hospitalizations and hospital readmissions, which together represent a large burden to the health-care system.

Though mortality rates in HF with moderate and severe LV systolic dysfunction are slightly higher than those in mild HF with relatively preserved LVEF, the absolute number of deaths attributable to mild HF with LVEF >35% is large and continues to grow. While a certain amount of success has been achieved in the management of HF patients with LVEF ≤35%, resulting in improved survival over time, there are no effective therapies confirmed to improve the natural history of HF patients with LVEF >35%. Implantable cardioverter-defibrillators (ICDs) could potentially be game-changers. However, strategies for effective risk stratification in the population of patients with HF and LVEF >35% have not been developed.

It was previously shown that increased beat-to-beat QT variability predicts ventricular tachyarrhythmias, SCD, and cardiovascular and all-cause mortality in moderate and severe systolic heart failure. Still, data on the predictive value of QT variability in patients with LVEF >35% are limited. The threshold of abnormal QT variability is usually set up at its highest quartile in a studied population. However, it is unknown whether QT variability could separate healthy individuals from subjects at risk. SCD shares many of the same risks factors as non-sudden cardiac death. In addition, there are common risk factors of cardiovascular death and non-cardiac death (e.g. age). This creates a challenge in identifying those at risk of SCD while considering the competing risk of non-sudden cardiac death, and a challenge in identifying
subjects at risk of cardiovascular death while considering the competing risk of non-cardiac
death in an aging population.

**Methods**

We performed ad-hoc analysis using the prospectively collected data of 2 studies. The
multicenter prospective observational cohort study *Muerte Subita en Insuficiencia Cardiaca*
(MUSIC; Sudden Death in Heart Failure) was designed to assess risk predictors of cardiac
mortality and SCD in ambulatory patients with mild to moderate HF. To determine the
threshold of abnormal QT variability that would allow us to separate 97.5% of healthy
individuals from those at risk, we analyzed healthy subjects from the Intercity Digital
Electrocardiogram Alliance (IDEAL) database. The studies’ protocols were approved by
institutional investigational committees, and all participants gave written informed consent
before entering the study.

**MUSIC study population**

Design of this prospective multicenter observational cohort study has been previously described
Adult stable ambulatory symptomatic NYHA class II-III HF patients with either
depressed or preserved LVEF, either ischemic or non-ischemic cardiomyopathy, were enrolled in
8 Spanish University Hospitals between April 2003 and December 2004. Study subjects were
treated according to the guidelines of that time and did not have ICDs or cardiac
resynchronization therapy devices implanted. High resolution (1000 Hz) orthogonal ECG
recordings were performed using ELA Spiderview recorders (ELA Medical, Sorin Group, Paris,
France) during 10 minutes at rest at the time of enrollment. Patients were followed every 6
months in outpatient HF clinics. All death cases were adjudicated by the MUSIC study core
endpoints adjudication committee as previously described\textsuperscript{16}. Non-cardiac mortality, cardiovascular mortality, SCD, and non-sudden cardiac death served as end-points in this study.

**IDEAL healthy subjects database**

The Intercity Digital Electrocardiogram Alliance (IDEAL) database study \textsuperscript{17} was conducted by the University of Rochester (Rochester, NY, USA) and was provided for this analysis by the Telemetric and Holter ECG Warehouse (THEW)\textsuperscript{20}. Healthy individuals were eligible for enrollment if they had no history of cardiovascular disorders, no history of blood pressure above 150/90 mm Hg, no history of any chronic illness, did not take any medications, and fulfilled objective criteria of cardiovascular health: normal physical examination; no pregnancy; normal 12-lead ECG (specifically, without signs of ventricular hypertrophy, inverted T-waves, and conduction abnormalities). In the presence of borderline ECG changes, normal echocardiogram and normal ECG exercise testing were required for inclusion. High resolution (1000 Hz) orthogonal ECG recordings (SpaceLab-Burdick, Inc., Deerfield, WI) were performed at rest during 10 minutes.

**Beat-to-beat QT variability analysis**

QT variability analysis was performed at the Johns Hopkins Hospital by investigators (L.G.T., L.H., S.S) fully blinded to the study population’s clinical characteristics and outcomes. Software for this analysis was developed in Tereshchenko’s laboratory. Fiducial points [beginning of Q or R wave \textsuperscript{21} and end of T wave \textsuperscript{22}] were detected automatically by a customized software application written in Matlab (MathWorks, Inc, Natick, MA) on each beat during 3-minute ECG epochs. Accuracy of automated detection was verified for each beat, included in analysis, with the aid of a graphical display. Premature atrial and ventricular beats with one subsequent sinus beat were excluded from analysis. Mean heart rate (HRm), heart rate variance (HRv), mean
duration of QT interval (QTm), and QT variance (QTv) were measured on each of the XYZ leads and averaged. Normalized by the mean QT interval, QT variance (QTVN) was calculated according to equation: QTVN = QTv/QTm². The heart rate variance was log-transformed (LogHRV) to normalize distribution. The QT variability index (QTVI) was calculated as previously described¹² according to equation: QTVI = log₁₀ [(QTv/QTm²)/(HRv/HRm²)]. To assess coherence between the heart rate variability and QT variability, spectral analysis of the RR’ and QT intervals was performed, and a cross spectrum was generated using the Blackman-Tukey method ²³. Coherence was calculated as previously reported¹² according to the equation: 
\[ \gamma(f) = \frac{|P_{xy}(f)|^2}{[P_{xx}(f) \times P_{yy}(f)]} \].

**Statistical analysis**

Statistical analysis for this study was performed in the Statistical Core Laboratory of the Heart Research Follow-up Program at the University of Rochester. Results are presented as mean±standard deviation (SD) after confirmation of normal distribution. Continuous variables were compared using the independent samples t test. The Pearson chi-square test was used to compare categorical variables. To dissect which component of the QTVI formula contributes the most to the predictive power of QTVI, we pre-specified high-risk subgroups by identifying individuals in the highest quartile (≥75th percentile) of QTVI and of QTVN and in the lowest quartile (<25th percentile) of mean coherence and of LogHRV. To determine whether abnormal QTVI could robustly separate healthy individuals from HF patients at risk of death, an additional threshold of abnormal QTVI was determined at the 97.5th percentile of IDEAL healthy individuals’ QTVI values. Nelson-Aalen cumulative incidence function was used to test predictive value of QTVI in combination with LVEF for cardiovascular death, non-cardiac death, SCD and non-sudden cardiac death (Figure 2). Cox regression analyses were performed to
determine which demographic and clinical characteristics were associated with the risk of outcomes. The clinical and demographic variables that were significantly associated with endpoints in the MUSIC study as shown previously \(^{16,18,24}\) were included in the models. For each outcome, a backward stepwise algorithm determined the demographic and clinical characteristics significantly associated with outcome. From those, a set of covariates was selected for the use in competing risk models (Table 3). The univariate and multivariate Fine and Gray competing risk regression analysis\(^{25}\) was done to determine if the evaluated ECG predictors for the risk of SCD differed from those for the risk of non-sudden cardiac death, and if ECG predictors of cardiovascular death differed from those of non-cardiac death. The ECG variables were included one at a time in the multivariate competing risk models (Table 4). Cumulative incidence functions were plotted after competing risk models for QTIVI and LVEF groups with remaining covariates held at their mean values (Figure 3). Schoenfeld-like residuals were evaluated to test an assumption of the subhazards proportionality. STATA function \texttt{nlcheck}, which employs a joint Wald test for the added parameters, was used to test the linearity assumption of the predictors. Interaction between LVEF and QTIVI was tested in the competing risk regression models. A \(P\)-value of \(<0.05\) was considered significant. Data were analyzed using SAS 9.2 (SAS Institute Inc, Cary, NC) and STATA 12 (StataCorp LP, College Station, TX).

Results

\textit{MUSIC study population}

Clinical characteristics of MUSIC study participants have been previously described\(^{16}\). We analyzed high resolution ECGs of 924 MUSIC study participants. Patients with ECGs not eligible for QT variability analysis (due to atrial fibrillation/flutter, frequent premature beats,
[n=346], or noise; [n=45]) were excluded from this study, and data of remaining 533 patients were further analyzed. Mean age was 62.8±12.0 years. The majority of patients were males (N=377; 70.7%), in NYHA HF class II (N=428; 80.3%), with LVEF > 35% in about half (N=254; 47.7%), and history of myocardial infarction (MI) in 238 (44.7%) patients. There were 125 deaths overall during median 44-months follow-up, including 105 cardiac deaths, 20 non-cardiac death, 53 non-sudden cardiac deaths and 52 cases of SCD. Amongst 254 HF patients with LVEF>35%, 39 died during follow-up, cardiovascular cause of death was established in 32 patients, and SCD- in 15 patients.

**IDEAL study population**

We analyzed data of 181 healthy subjects in the IDEAL database (mean age 38.7±15.7; range of age 18-82; males 51%; 93.8% whites), predominantly non-smokers (71.4%) with a mean body mass index of 24.1±4.5.

**Beat-to-beat QT variability**

QTVI was significantly higher in MUSIC HF patients than in healthy IDEAL participants (-1.56 [95%CI from-2.61 to-0.42] vs. -2.23 [95%CI from-3.39 to-1.05]; P<0.00001) (Figure 1). To determine threshold of abnormally amplified QTVI, which would separate healthy individuals from HF patients at risk, we compared percentiles of QTVI in HF patients and healthy subjects. Threshold of the highest QTVI quartile in HF patients (above -1.19; 95 %CI from -1.27 to –1.13) corresponded to the threshold of QTVI above the 97.5th percentile of healthy individuals’ values (above -0.97; 95%CI from -1.32 to -0.42).

Interestingly, HF patients with QTVI in the highest quartile had smaller LV mass and narrower QRS (Table 1). As expected, the highest QTVI quartile was characterized by significantly increased QTVN, faster heart rate, decreased QTm, diminished LogHRV, and
reduced coherence (Table 2). Even though the heart rate at rest was slower in patients with LVEF >35%, there were no significant differences in QT variability parameters between HF patients with LVEF ≤35% and those with LVEF >35% (Table 2).

**Predictive value of QT variability: competing risk analyses**

Overall mortality was almost twice as high in patients with QTVI in the highest quartile [42 deaths (31.6%, mean survival time 40.4 [95% CI 38.0-42.8] months) vs. 74 deaths (18.5%, mean survival time 44.8 [95% CI 43.6-46.0] months); P=0.002]. In competing risk analysis, neither QT variability nor HRV predicted non-cardiac death (Table 4). However, QTVI was a strong, independent predictor of cardiovascular mortality (Figures 2A and 3A). In competing risk analysis QT and heart rate variability strongly predicted non-sudden cardiac death (Figures 2D and 3D). However, no association between SCD and QTVI was found (Figure 3C, Table 4). There was no significant interaction found between the highest QTVI quartile and LVEF above or below 35% (P=0.162 for non-sudden cardiac mortality, and P=0.426 for cardiovascular mortality), which confirmed that QTVI predicts cardiac death across the continuum of left ventricular dysfunction equally well.

Additional analysis was performed to assess whether combination of the predictors (QTVI and LVEF) would further improve risk stratification. As expected, patients with the highest QTVI quartile and LVEF ≤35% had the highest risk (Figures 2A-D and 3A-D), whereas patients with QTVI in 3 lower quartiles and LVEF >35% had the lowest risk.

In order to separately examine the predictive value of the numerator and denominator in the QTVI formula one-by-one, we evaluated the predictive values of QTVI, QTVN, LogHRV, and coherence in univariate and multivariate competing risk analyses. Surprisingly, even in univariate analysis the highest quartile of QTVN did not predict any end-point (Table 4),
whereas the lowest quartile of LogHRV was significantly associated with cardiovascular mortality and specifically, non-sudden cardiac death. Therefore, in this study, the predictive value of QTVI was due to the denominator in the QTVI formula, due to decreased heart rate variability. Importantly, we have found a similar risk for HF patients with the highest QTVI quartile and for patients with QTVI above the 97.5th percentile of healthy individuals’ values (Table 4).

**Excluded from QT variability analysis ECG recordings**

In univariate survival analysis risk of all-cause death was higher in patients, excluded from QTVI analysis due to arrhythmia at baseline (Figure 4A). However, in multivariate Cox regression after adjustment for age, gender, history of MI, NYHA HF class status of “analyzable” ECG did not carry independent predictive value \([HR 0.79 (95\% CI 0.60-1.03); P=0.085]\). Cardiovascular mortality (Figure 4B) and SCD (Figure 4C) outcomes did not differ in included and excluded from QT variability analysis subjects.

**Discussion**

To the best of our knowledge, this is the first study, which showed that increased QTVI predicts cardiovascular mortality and in particular, non-sudden cardiac death, but neither non-cardiac death nor SCD across a continuum of LV dysfunction in HF patients with LVEF either below or above 35%. For the first time we showed that abnormally amplified QTVI separates 97.5% of healthy individuals from HF patients at risk, and therefore could be considered in future investigation to develop strategy of the screening of cardiovascular death risk in the general population. In addition, we demonstrated incremental improvement of risk stratification if QTVI was combined with LVEF.
Increased QT variability index: absolute increase in repolarization lability or predominantly decreased heart rate variability?

Berger et al. \(^{12}\) in 1997 proposed QTVI as a measure of repolarization lability. During next 15 years, increased QTVI was shown to be a strong predictor of increased risk of cardiovascular death, SCD, and ventricular arrhythmia in patients with ischemic and non-ischemic cardiomyopathy \(^{13-15}\). Elevated QTVI has also been shown in ischemia\(^{26}\), hypertrophic cardiomyopathy\(^{27}\), and long QT syndrome\(^{28}\). Importantly, marked elevation of QT variance, rather than a drop in heart rate variance, was responsible for increased QTVI in these conditions. At the same time, increased QTVI was observed in a wide variety of other conditions.

Unfortunately, not every study reported data of QTVI formula numerator and denominator. Two scenarios could result in increased QTVI: (1) true dramatic increase in absolute beat-to-beat QT variability [e.g., as reported in MADIT II males\(^{13}\)] and (2) predominantly decreased heart rate variability and out-of-proportion unchanged or mildly increased QT variance [e.g., as reported in MADIT II females\(^{29}\)]. The second scenario was observed in MUSIC HF patients in this study.

As we see in this study, elevated QTVI predominantly due to depressed heart rate variability is associated with increased risk of cardiovascular and specifically non-sudden cardiac death, but not SCD. Depressed heart rate variability is a well-known predictor of all-cause mortality and cardiovascular death. Importantly, competing risk analysis demonstrated that low heart rate variability is a specific predictor of cardiovascular, but not non-cardiac death.

Mechanisms of repolarization lability

The mechanisms and arrhythmogenic potential of elevated QT variability have been recently reviewed\(^{30}\). Experimental and theoretical study\(^{31}\) showed that stochastic fluctuations of \(I_{Kr}\) gating in the presence of \(I_{Ks}\) block and cell-to-cell uncoupling lead to beat-to-beat variability of QT
interval on pseudo-ECG. In another experiment, QTVI correlated directly with integrated left stellate-ganglion nervous activity in a heart failure dog model\textsuperscript{32}. In the study of hypertensive patients, QT variability significantly correlated with cardiac norepinephrine spillover into the coronary sinus\textsuperscript{33}. Increased intracardiac QT variability on bipolar near-field ICD electrogram confirmed that repolarization lability is present throughout the ventricles\textsuperscript{15}. Elevated repolarization lability leads to frequent afterdepolarizations, an important mechanism of arrhythmogenesis\textsuperscript{31}. Degree of beat-to-beat QT variability in humans observed in experiments is modest\textsuperscript{31}. In our study, QTVN was not elevated in HF patients with SCD outcome.

**Methods of QT variability measurement**

A previous study by Haigney et al.\textsuperscript{29} underscored the importance of the U-wave inclusion in the repolarization template. QT variability method by Berger\textsuperscript{12} measures repolarization lability by stretching or compressing the JT interval (from the J-point to the end of repolarization (end of T wave or end of U wave, if present), but does not precisely delineate the end of the T wave. In this study we used a slightly different approach, developed in Tereshchenko’s laboratory. We measured precisely QT interval from the beginning of Q (if present) or R wave to the end of T or U wave (if present). Comparison of these 2 methods showed slight advantage of new approach\textsuperscript{34}. Importantly, U wave is included in analysis by both methods. U-wave is an arch of the T-loop and has to be analyzed accordingly, as a part of repolarization.

In our previous study\textsuperscript{35} we have shown that both QTVI and STV have similar predictive value for ventricular arrhythmia. There is a minor difference in QTVI and STV methodologies: while STV quantifies absolute differences in QT interval duration between consecutive beats, QTVI quantifies normalized QT variance over a time epoch.

Importantly, in this study we showed that risk of cardiovascular death and SCD is similar
in patients with eligible and non-eligible for QT variability analysis ECGs.

**QTVI separates 97.5% of healthy individuals from HF patients at risk**

Our study showed that QTVI separates 97.5% of healthy individuals from HF patients at risk of cardiovascular and in particular, non-sudden cardiac death. The predictive value of QTVI is independent of LVEF. Therefore, assessment of repolarization lability could be a very valuable tool in future for screening for the risk of cardiovascular death in the general population.

Additional studies are needed to confirm its predictive value.

**Prediction of mortality in patients with LVEF >35%**

Very few studies have explored the predictive value of ECG-parameters in HF patients with LVEF >35%. In a GISSI-HF study QTVI predicted cardiovascular and all-cause death. The prognostic significance of clinical and ECG parameters for SCD was previously investigated in the MUSIC study. A decreased heart rate turbulence slope was shown to be associated with an increased risk of SCD in multivariate Cox regression analysis, after adjustment for gender, LVEF, NYHA class, and history of MI. A combination of ≥2 abnormal markers (turbulence slope, QT/RR slope, or SDNN) was associated with increased SCD risk. In the ISAR-Risk study severe autonomic failure predicted SCD in patients with LVEF above and below 30%. In contrast with successful prediction of SCD by markers of autonomic failure, markers of repolarization heterogeneity were not always helpful for prediction of SCD in HF with LVEF >35%. Contradictory results of T-wave alternans predictive power in HF patients with LVEF >35% were previously reported, although recent analysis of MUSIC study showed predictive value of TWA for SCD.

**Limitations**

This was an ad-hoc analysis of a prospectively conducted cohort study. Difficulties in
adjudication of SCD are well recognized. It was previously shown that in HF patients with relatively preserved LVEF, cases of non-arrhythmic death are frequent. The racial and ethnic composition of the MUSIC study may affect extrapolation of study findings to the entire US population. Specific characteristics of SCD in a Mediterranean Spanish population were recently described.

**Acknowledgments:** We thank all investigators of the MUSIC study.

**Conflict of Interest Disclosures:** Ronald Berger holds a patent on the technology for QT variability analysis. The THEW initiative is supported by NIH grant U24HL096556 (Jean-Philippe Couderc). MUSIC study was supported by the Grant no. G03/078 from the Instituto de Salud Carlos III, Madrid, Spain.

**References:**


5. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *European Heart Journal* 2011.


**Table 1. Clinical characteristics of MUSIC heart failure patients with QTVI, dichotomized at the 75th percentile**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>QTVI &lt;75th percentile (n=400)</th>
<th>QTVI ≥75th percentile (n=133)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ±SD, y</td>
<td>63.4±11.3</td>
<td>62.3±12.7</td>
<td>0.434</td>
</tr>
<tr>
<td>Female, n(%)</td>
<td>110(27.5)</td>
<td>46(34.6)</td>
<td>0.120</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy, n(%)</td>
<td>196(49.0)</td>
<td>70(52.6)</td>
<td>0.468</td>
</tr>
<tr>
<td>History of MI, n(%)</td>
<td>176(44.0)</td>
<td>61(45.9)</td>
<td>0.708</td>
</tr>
<tr>
<td>LVEF ≤35%, n(%)</td>
<td>213(53.3)</td>
<td>66(49.6)</td>
<td>0.468</td>
</tr>
<tr>
<td>Mean LVEF</td>
<td>38±13</td>
<td>40±15</td>
<td>0.291</td>
</tr>
<tr>
<td>LV mass, g/m²</td>
<td>166±53</td>
<td>151±39</td>
<td>0.012</td>
</tr>
<tr>
<td>Restrictive filling pattern, n(%)</td>
<td>29(7.3)</td>
<td>15(11.3)</td>
<td>0.144</td>
</tr>
<tr>
<td>NYHA class II, n(%)</td>
<td>327(81.8)</td>
<td>102(76.7)</td>
<td>0.202</td>
</tr>
<tr>
<td>NYHA class III, n (%)</td>
<td>73(18.3)</td>
<td>31(23.3)</td>
<td>0.202</td>
</tr>
<tr>
<td>Beta-blockers use, n(%)</td>
<td>283(70.8)</td>
<td>84(63.2)</td>
<td>0.101</td>
</tr>
<tr>
<td>Heart rate±SD, bpm</td>
<td>65.5±10.9</td>
<td>78.5±13.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>123±32</td>
<td>112±27</td>
<td>0.001</td>
</tr>
</tbody>
</table>

MI = myocardial infarction. LVEF = left ventricular ejection fraction. NYHA class = New York Heart Association heart failure class.
<table>
<thead>
<tr>
<th></th>
<th>QTVI &lt;75&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>QTVI ≥75&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>P</th>
<th>LVEF ≤35% (n=279)</th>
<th>LVEF &gt;35% (n=254)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRm±SD, bpm</td>
<td>65.5±10.9</td>
<td>78.5±13.5</td>
<td>&lt;0.00001</td>
<td>70.3±12.7</td>
<td>66.9±13.0</td>
<td>0.001</td>
</tr>
<tr>
<td>LogHRV±SD</td>
<td>6.60±0.95</td>
<td>5.00±0.79</td>
<td>&lt;0.00001</td>
<td>6.21±1.14</td>
<td>6.22±1.16</td>
<td>0.932</td>
</tr>
<tr>
<td>QTm±SD, ms</td>
<td>439.7±47.8</td>
<td>413.4±46.7</td>
<td>&lt;0.00001</td>
<td>432.3±48.4</td>
<td>434.1±49.4</td>
<td>0.528</td>
</tr>
<tr>
<td>QTVN±SD</td>
<td>0.230±0.024</td>
<td>0.245±0.027</td>
<td>&lt;0.00001</td>
<td>0.234±0.025</td>
<td>0.233±0.027</td>
<td>0.528</td>
</tr>
<tr>
<td>Coherence±SD</td>
<td>0.297±0.111</td>
<td>0.252±0.090</td>
<td>&lt;0.00001</td>
<td>0.283±0.109</td>
<td>0.288±0.107</td>
<td>0.414</td>
</tr>
<tr>
<td>QTVI±SD</td>
<td>-1.83±0.50</td>
<td>-0.66±0.37</td>
<td>&lt;0.00001</td>
<td>-1.56±0.71</td>
<td>-1.52±0.66</td>
<td>0.328</td>
</tr>
</tbody>
</table>

HRm = mean heart rate. LogHRV = log-transformed heart rate variance. QTm = mean QT interval duration. QTVN = QT variance, normalized by mean QT interval. QTVI = QT variability index.
Table 3. Cox regression hazards ratios of the demographic and clinical predictors of outcomes in eligible for QT variability analysis MUSIC heart failure patients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate hazard ratio (95% CI)</th>
<th>P value</th>
<th>Multivariate hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>1.77 (1.19-2.62)</td>
<td>0.005</td>
<td>1.39 (0.92-2.09)</td>
<td>0.120</td>
</tr>
<tr>
<td>NT-proBNP&gt;1000ng/L</td>
<td>3.47 (2.33-5.17)</td>
<td>&lt;0.001</td>
<td>2.21 (1.41-3.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR&lt;60mL/min/1.73m²</td>
<td>1.91 (1.30-2.82)</td>
<td>0.001</td>
<td>1.02 (0.67-1.57)</td>
<td>0.939</td>
</tr>
<tr>
<td>Prior AVE</td>
<td>1.68 (1.12-2.49)</td>
<td>0.010</td>
<td>1.26 (0.53-2.99)</td>
<td></td>
</tr>
<tr>
<td>LVEF≤35%</td>
<td>2.42 (1.60-3.68)</td>
<td>&lt;0.001</td>
<td>1.88 (1.22-2.89)</td>
<td>0.004</td>
</tr>
<tr>
<td>History of MI</td>
<td>2.09 (1.41-3.08)</td>
<td>&lt;0.001</td>
<td>1.51 (1.01-2.26)</td>
<td>0.041</td>
</tr>
<tr>
<td>NYHA HF class</td>
<td>1.64 (1.11-2.42)</td>
<td>0.012</td>
<td>1.14 (0.49-2.66)</td>
<td>0.760</td>
</tr>
<tr>
<td>Troponin-positive</td>
<td>2.57 (1.71-3.87)</td>
<td>&lt;0.001</td>
<td>1.68 (1.10-2.59)</td>
<td>0.017</td>
</tr>
<tr>
<td>Non-sudden cardiac death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>2.54 (1.41-4.57)</td>
<td>0.002</td>
<td>2.05 (1.13-3.72)</td>
<td>0.018</td>
</tr>
<tr>
<td>NT-proBNP&gt;1000ng/L</td>
<td>5.09 (2.80-9.26)</td>
<td>&lt;0.001</td>
<td>3.61 (1.94-6.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF≤35%</td>
<td>2.27 (1.28-4.04)</td>
<td>0.005</td>
<td>1.81 (1.00-3.30)</td>
<td>0.047</td>
</tr>
<tr>
<td>NYHA HF class</td>
<td>2.92 (1.67-5.13)</td>
<td>&lt;0.001</td>
<td>2.05 (1.16-3.63)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

* Adjusted for left ventricular ejection fraction below 35%, New York Heart Association heart failure class, NT-proBNP>1000ng/L, positive Troponin, NSVT and frequent PVCs. # Adjusted for age >65 years, left ventricular ejection fraction below 35%, New York Heart Association heart failure class, and NT-proBNP>1000ng/L.

Q4 QTVI = the highest quartile of QT variability index. 97.5% QTVI = QT variability index above the 97.5th percentile of healthy individuals’ values. Q4 QTVN = the highest quartile of normalized QT variance. Q1 LogHRV = the lowest quartile of log-transformed heart rate variance. Q1 Coherence = the lowest quartile of coherence between heart rate variability and QT variability.

Table 4. Competing risks subhazard ratios of the QT variability and heart rate variability parameters in MUSIC heart failure patients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unadjusted sub-hazard ratio (95% CI)</th>
<th>P value</th>
<th>Adjusted subhazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 QTVI</td>
<td>1.94(1.32-2.85)</td>
<td>0.001</td>
<td>1.67(1.14-2.47)*</td>
<td>0.009</td>
</tr>
<tr>
<td>97.5% QTVI</td>
<td>1.80(1.21-2.68)</td>
<td>0.004</td>
<td>1.57(1.04-2.35)*</td>
<td>0.031</td>
</tr>
<tr>
<td>Q4 QTVN</td>
<td>1.05(0.68-1.62)</td>
<td>0.832</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 LogHRV</td>
<td>1.99(1.33-2.97)</td>
<td>0.001</td>
<td>1.67(1.11-2.49)*</td>
<td>0.013</td>
</tr>
<tr>
<td>Q1 Coherence</td>
<td>1.57(1.03-2.39)</td>
<td>0.035</td>
<td>2.25(0.81-1.92)*</td>
<td>0.309</td>
</tr>
<tr>
<td>Extra-cardiac death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 QTVI</td>
<td>0.76(0.28-2.09)</td>
<td>0.596</td>
<td></td>
<td></td>
</tr>
<tr>
<td>97.5% QTVI</td>
<td>0.99(0.36-2.71)</td>
<td>0.980</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 QTVN</td>
<td>1.10(0.40-3.04)</td>
<td>0.850</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 LogHRV</td>
<td>0.59(0.17-2.02)</td>
<td>0.404</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 Coherence</td>
<td>1.18(0.43-3.23)</td>
<td>0.747</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-sudden cardiac death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 QTVI</td>
<td>3.21(1.87-5.51)</td>
<td>&lt;0.001</td>
<td>2.91(1.69-5.01)#</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>97.5% QTVI</td>
<td>2.83(1.65-4.84)</td>
<td>&lt;0.001</td>
<td>2.58(1.13-3.78)#</td>
<td>0.001</td>
</tr>
<tr>
<td>Q4 QTVN</td>
<td>0.92(0.51-1.67)</td>
<td>0.786</td>
<td></td>
<td></td>
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<tr>
<td>Q1 LogHRV</td>
<td>2.30(1.33-4.00)</td>
<td>0.003</td>
<td>2.00(1.15-3.48)#</td>
<td>0.014</td>
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<tr>
<td>Q1 Coherence</td>
<td>1.90(1.08-3.35)</td>
<td>0.026</td>
<td>1.52(0.85-2.72)#</td>
<td>0.157</td>
</tr>
<tr>
<td>SCD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 QTVI</td>
<td>1.02(0.57-1.84)</td>
<td>0.945</td>
<td></td>
<td></td>
</tr>
<tr>
<td>97.5% QTVI</td>
<td>0.99(0.53-1.85)</td>
<td>0.971</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 QTVN</td>
<td>1.22(0.64-2.33)</td>
<td>0.542</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 LogHRV</td>
<td>1.53(0.85-2.77)</td>
<td>0.157</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 Coherence</td>
<td>1.20(0.64-2.25)</td>
<td>0.569</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for left ventricular ejection fraction below 35%, New York Heart Association heart failure class, NT-proBNP>1000ng/L, positive Troponin, NSVT and frequent PVCs. # Adjusted for age >65 years, left ventricular ejection fraction below 35%, New York Heart Association heart failure class, and NT-proBNP>1000ng/L. Q4 QTVI = the highest quartile of QT variability index. 97.5% QTVI = QT variability index above the 97.5th percentile of healthy individuals’ values. Q4 QTVN = the highest quartile of normalized QT variance. Q1 LogHRV = the lowest quartile of log-transformed heart rate variance. Q1 Coherence = the lowest quartile of coherence between heart rate variability and QT variability.
Figure Legends:

**Figure 1.** Histograms showing QTVI distribution. Histograms showing the distribution of the QTVI in healthy IDEAL subjects (empty bars) and heart failure participants of MUSIC study patients (full bars).

**Figure 2.** Survival in heart failure. Nelson-Aalen cumulative hazard estimates for the cardiovascular death (A), non-cardiac death (B), sudden cardiac death (C) and non-sudden cardiac death (D) in 4 categories of patients: those with the highest QTVI quartile and LVEF ≤35%, patients with the highest QTVI quartile and LVEF >35%, those with the lower 3 QTVI quartiles and LVEF ≤35%, patients with the lower 3 QTVI quartiles and LVEF >35%.

**Figure 3.** Cumulative incidence functions for the cardiovascular death (A), non-cardiac death (B), sudden cardiac death (C) and non-sudden cardiac death (D) in 4 categories of patients.

**Figure 4.** Kaplan-Meier curves for the probabilities of all-cause death (A), cardiovascular death (B), and sudden cardiac death (C) in patients with available QT variability results (Included), and those who were excluded from QT variability analysis as non-analyzable.