# Ultra-Short Beat-to-Beat Repolarization Variability Predicts Cardiovascular Events in Individuals Without Cardiovascular Disease

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## Abstract

*The beat-to-beat variability of the QT interval (QTV) is thought to be a measure of sympathetic activity directed to the heart and it has predictive value in cardiac patients, but its predictive value in the general population is unclear. This study aimed to determine the association between ultra-short QTV from 15-second ECGs and future major adverse cardiovascular events (MACE) in a large cohort of middled aged individuals without previous cardiovascular disease. QTV was measured using the QTV index (QTVI), and the short-term QTV (STVQT) in n=55,765 UK Biobank participants (54% female, 56.6±8.2 years old). The temporal variability of Q-Tpeak and Tpeak-Tend intervals was also assessed, and heart rate variability (RMSSD) was estimated for comparison. After a median follow-up of 12.5 years, n=2,542 (4.6%) MACE occurred. QTVI and STVQTV were associated with MACE and the association remained significant after adjusting for age, sex, bmi, diabetes, hypertension, smoking, beta-blockers, and, for STVQTV only, QT interval, resting heart rate, heart rate variability. QTVI showed the higher hazard ratio (1.10 (1.06, 1.15), p<0.01) and it was associated with MACE also when based on Q-Tpeak and Tpeak-Tend intervals. This study demonstrates for the first time that in the general population ultra-short repolarization variability from 15-sec ECG predicts MACE independently of traditional risk factors.*

## 1. Introduction

The beat-to-beat variability in the duration of ventricular repolarization, typically measured non-invasively from the electrocardiogram as QT interval variability (QTV), is an established risk factor in cardiac patients [1], [2]. QTV is thought to be a marker of sympathetic activity directed to the ventricles [3] and increased QTV has been associated with increased risk of sudden and non-sudden cardiac death in patients with structural heart disease, heart failure or post myocardial infarction [4]–[6]. It is however unclear if QTV can predict increased risk of cardiovascular events in the general population. Furthermore, it is not clear if QTV from ultra-short ECG recordings with a duration of 10-30 seconds would maintain its predictive value. This would allow extracting prognostic information from standard clinical ECGs or even wearable-ECG devices (smartwatches and mobile phone apps), which have a typical duration of 10-30 seconds, with important ramifications for implementing novel preventative strategies.

The aim of this study was to address these knowledge gaps and determine the association between ultra-short QTV from 15-second single-lead ECGs and future major adverse cardiovascular events (MACE) in a large cohort of middle-aged individuals without known cardiovascular disease. We implemented strategies for automated analysis of tens of thousands of ECGs and conducted statistical analysis in the UK Biobank.

## 2. Methods

### 2.1. Population study

Participants from the UK Biobank who underwent an ECG test during 2009-2010 and 2012-2013 were included in this study (as part of UK Biobank application number 8256). The UK Biobank study has approval from the North West Multi-Centre Research Ethics Committee, and all participants provided informed consent.

The ECG (GE CardioSoft, Lead I, sampling frequency 500 Hz) was measured at rest for 15 seconds in sitting position. Data was recorded in 66,178 participants. As part of a previous study [7], extensive semi-automatic revision was conducted to ensure that only ECGs in normal sinus rhythm were included in the analysis. Exclusion criteria for this study included: previous self-reported or diagnosed cardiovascular events identified through Hospital Episode Statistics (as in previous studies [7]–[9]); signal quality insufficient to confirm normal sinus rhythm; abnormal rhythm (atrial or ventricular ectopic, atrial fibrillation,

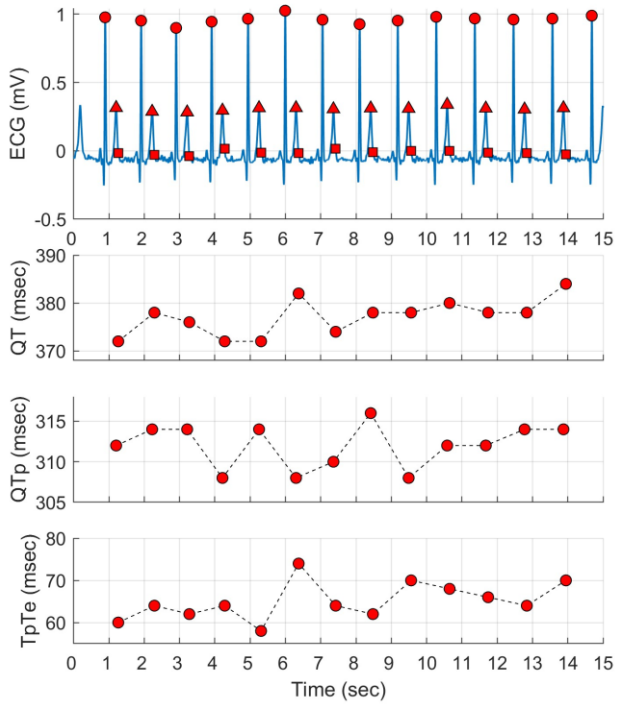


**Figure 1.** Example of 15-second single-lead ECG and time-series of R-Tend (QT), R-Tpeak (QTp) and Tpeak-Tend (Tpe) intervals.

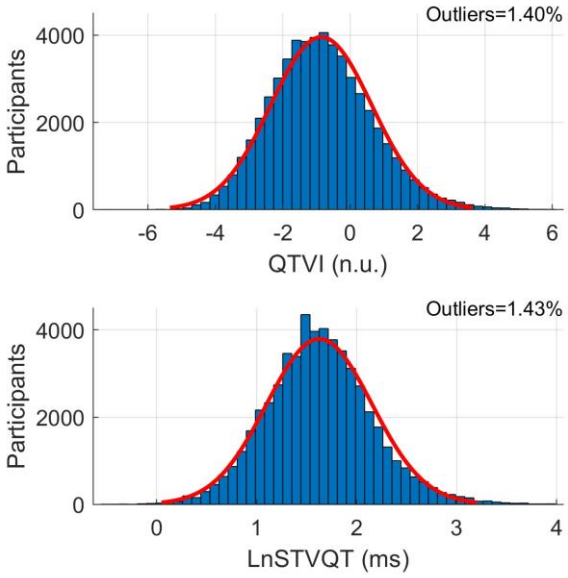


**Figure 2.** Histograms of QT variability indices QTVI and log transformed STVQT. The red lines represent a Gaussian interpolation. The number of participants automatically excluded from the distribution is shown in the panels.

conduction block) and bundle branch block morphology. After exclusions, N=55,765 individuals were included in the study.

## 2.2. ECG analysis

The 15-second single-lead ECGs were analyzed using software developed and tested by our group [10]–[12]. After identification of R-waves, ECG signals were band-pass filtered between 0.5 – 20 Hz and the T-peak was identified as the local maximum of the T-wave, while the end of the T-wave was measured using the tangent method [1]. Automatic correction was conducted by iteratively searching for markers (T-peak and $dV/dt_{min}$) in 80-ms temporal windows centered on their median occurrence. ECGs with signal-to-noise ration < 7 dB (where signal and noise were defined within the 0.5-40 Hz and 40-250 Hz, respectively), a ratio between T-wave and QRS aplitude <10%, and a median RT<250 ms were excluded. Furthermore, individuals for which an index was $<q_1$-$3x(q_3-q_1)$ and $>q_3+3x(q_3-q_1)$, with $q$ indicating a quartile, were considered outliers and excluded.

The RT interval was used as a robust surrogate of the QT intervals.

The QTV index (QTVI) and the short-term QT variability index (STVQT) were measured as follows:

$$QTVI = \frac{\sigma_{RT}^2/m_{RT}^2}{\sigma_{HR}^2/m_{HR}^2} \text{ and } STVQT = \sum \frac{|RT_n - RT_{n-1}|}{N\sqrt{2}}$$

where $\sigma$ and $m$ represent the variance and the mean of RT intervals and heart rate (in bpm) along the recording, and $N$ is the total number of beats. Repolarization variability parameters based on R-Tpeak and Tpeak-Tend intervals were measured using the same definitions and denoted $QTVI_{QTp}$ and $STVQT_{QTp}$ if using the RTpeak interval and $QTVI_{TpTe}$ and $STVQT_{TpTe}$ if using the TpTe interval. Heart rate variability was measured using the root mean square of successive differences (RMSSD) for comparison.

## 2.3. Statistical analysis

Distributions are reported as median (interquartile range). Cox regressions were used to determine the association between exposures (repolarization variability parameters) and MACE, which was defined based on Hospital Episode Statistics diagnostic codes as an aggregate outcome including myocardial infarction, ischemic heart disease, heart failure and life-threatening ventricular arrhythmia. STVQT indices were log-transformed to account for right-sided skewness. All continuous variables were normalized so that hazard ratios and 95% confidence intervals are provided per 1 standard deviation increase. All models were adjusted for traditional risk factors including age, sex, body mass index, hypertension, diabetes, smoking and use of beta-blockers. Additionally, RMSSD was adjusted for resting RR-interval; STVQT was adjusted for resting RR-interval, RMSSD and average QT interval; QTVI was not adjusted for average QT, heart rate variability or resting RR-interval

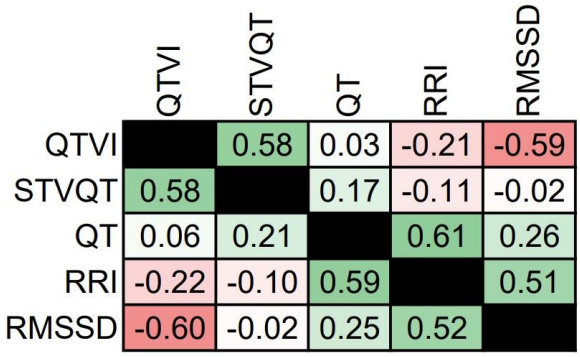


**Figure 1**. Heatmap showing Spearman's (upper part) and Pearson's (lower part) correlation coefficients between ECG markers.

because they are all part of its definition. Only completed cases were analyzed and participants with missing data in the risk factors were excluded.

## 3. Results

A representative example of 15-second single-lead ECG and the time series of QT, QTp and TpTe intervals is shown in Figure 1. Histograms of QTVI and log transformed STVQT are shown in Figure 2. As can be observed, thanks to the fully automated correction of ECG markers and exclusion of outliers (about 1.7% of total participants), both indices show an almost Gaussian distribution (red line). The distribution of all ECG indices is reported in Table 1. Figure 3 shows a heatmap reporting the Spearman's and Pearson's correlation coefficients between QTVI, STVQT, QT, RRI and RMSSD. QTVI and STVQT were moderately correlated (cc=0.58). QTVI was moderately inversely correlated to RMSSD (-0.59). Correlation of QTVI and STVQT with underlying QT and RRI were low (-0.21<cc<0.17). Hazard ratios (95% confidence intervals) of unadjusted and fully adjusted models are reported in Table 2. Increase in QT and QTp, and decrease in TpTe and RRI (i.e. heart rate increase) were associated with increased risk of MACE. In the fully adjusted models, both QTVI and STVQT were positively associated with increased risk of MACE, with QTVI showing the largest hazard ratio, equal to 1.11 (1.06-1.17), p<0.01 per 1 SD increase. When the QTp and TpTe intervals were used instead of the QT interval, QTVI remained significantly associated with MACE in both the unadjusted and adjusted model, whereas the association between STVQT and MACE was attenuated.

## 4. Discussion and Conclusions

The aim of this study was to assess the predictive value of beat-to-beat repolarization variability from 15-second single-leads ECGs in the general population. The main finding is that in over 55 thousand middle aged individuals,

**Table 1**: Distribution of ECG parameters across all participants. Sub-indices QTp and TpTe represent repolarization variability indices based on R-Tpeak and Tpeal-Tend intervals, respectively. IQR: Interquartile range. Ln: Log-transformation.

| Parameter | Units | Median (IQR) |
|---|---|---|
| RRI | ms | 854 (767, 950) |
| QT | ms | 319 (302, 336) |
| QTp | ms | 256 (238, 272) |
| TpTe | ms | 62 (58, 68) |
| LnRMSSD | ms | 3.05 (2.64, 3.45) |
| QTVI | n.u. | -0.92 (-1.89, 0.11) |
| LnSTVQT | ms | 1.61 (1.28, 1.96) |
| $QTVI_{QTp}$ | n.u. | -0.48 (-1.55, 0.62) |
| $LnSTVQT_{QTp}$ | ms | 1.65 (1.20, 2.06) |
| $QTVI_{TpTe}$ | n.u. | 3.21 (2.20, 4.26) |
| $LnSTV_{TpTe}$ | ms | 2.12 (1.75, 2.46) |

**Table 2**. Associations between ECG markers and major adverse cardiovascular events (MACE). P-values <0.05 are reported in bold. HR: Hazard ratio; CI: Confidence intervals. Ln: Log-transformation.

| | Unadjusted Models | | Adjusted Models | |
|---|---|---|---|---|
| | HR (95% CI) | P | HR (95% CI) | P |
| RRI | 0.94 (0.91, 0.98) | **5.4E-03** | 0.87 (0.82, 0.92) | **7.3E-06** |
| QT | 1.05 (1.01, 1.09) | **2.5E-02** | 1.18 (1.12, 1.25) | **8.1E-09** |
| QTp | 1.05 (1.01, 1.09) | **1.8E-02** | 1.22 (1.15, 1.29) | **4.7E-12** |
| TpTe | 0.90 (0.86, 0.95) | **7.6E-05** | 0.86 (0.82, 0.91) | **1.2E-08** |
| LnRMSSD | 0.76 (0.73, 0.79) | **3.4E-41** | 0.98 (0.94, 1.03) | 5.1E-01 |
| QTVI | 1.31 (1.26, 1.36) | **4.1E-43** | 1.10 (1.06, 1.15) | **1.8E-06** |
| LnSTVQT | 1.09 (1.04, 1.13) | **8.3E-05** | 1.06 (1.01, 1.10) | **1.0E-02** |
| $QTVI_{QTp}$ | 1.24 (1.19, 1.29) | **1.2E-27** | 1.08 (1.04, 1.12) | **2.0E-04** |
| $LnSTVQT_{QTp}$ | 1.01 (0.97, 1.05) | 5.9E-01 | 1.02 (0.98, 1.06) | 3.2E-01 |
| $QTVI_{TpTe}$ | 1.29 (1.24, 1.34) | **1.7E-36** | 1.09 (1.04, 1.13) | **4.5E-05** |
| $LnSTV_{TpTe}$ | 1.02 (0.98, 1.07) | 2.7E-01 | 1.05 (1.01, 1.10) | **1.7E-02** |

standard QT variability indices QTVI and STVQT were significantly associated with MACE and that this association was independent of traditional risk factors and heart rate variability, which was not linearly associated with MACE. To the best of our knowledge, this is the first study to demonstrate an association between QTV and increased risk of MACE in the general population and the largest in assessing QT variability predictive value. The analysis of repolarization variability based on QTpeak and Tpeak-Tend showed that QTVI maintained a significant

association with MACE, whereas the association was attenuated for STV. Future study could assess the predictive value of indices that estimate QTV unrelated to heart rate variability through spectral decomposition [13] as well as other established QTV markers [1]. The fact QTV was measured from ultra-short 15-second single-lead ECGs has important ramifications because it demonstrates that clinical ECGs, which are typically recorded over 10-20 seconds could be used to identify individuals at risk of MACE, and it suggests that even wearable-ECGs, which are typically recorded over a similar period of time in the same configuration used in this study (Lead I), may be used for risk stratification. Other ECG markers from 15-second single-lead ECGs have been recently shown to predict cardiovascular events [7], [14], and future studies should try to derive a risk score from wearable-format ECGs with the aim of transforming risk stratification for cardiovascular disease prevention.

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