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Electrocardiographic Intervals Associated with Incident Atrial Fibrillation: Dissecting the QT-interval

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Abstract

Background: Prolongation of the QT-interval has been associated with an increased risk for developing atrial fibrillation (AF), but the responsible mechanism remains unknown.

Objective: To sub-divide the QT-interval into its components and identify the resultant lectrocardiographic interval(s) responsible for the association with AF.

Methods: Pre-defined QT-interval components were assessed for association with incident AF in the Atherosclerosis Risk in Communities (ARIC) Study using Cox proportional hazards models. Hazard ratios were calculated per 1-standard deviation increase in each component. Among QT-interval components exhibiting significant associations, additional analyses evaluating long extremes, defined as greater than the 95th percentile, were performed.

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Conflicts of Interest: Nil to report.

Results: Among 14,625 individuals, 1,505 (10.3%) were diagnosed with incident AF during a mean follow-up period of 17.6 years. Following multivariable adjustment, QT-interval components involved in repolarization, but not depolarization, exhibited significant associations with incident AF, including a longer ST-segment (Hazard Ratio [HR]: 1.27; 95% Confidence Interval [CI]: 1.14–1.41], p<0.001) and a prolonged T-wave onset to T-wave peak (T-onset to T-peak) (HR: 1.13; 95% CI: 1.07–1.20, p<0.001). Marked prolongation of the ST-segment (HR: 1.31; 95% CI: 1.04–1.64, p=0.022) and T-onset to T-peak (HR: 1.36, 95% CI: 1.09–1.69, p=0.006) was also associated with an increased risk of incident AF.

Conclusions: The association between a prolonged QT-interval and incident AF is primarily explained by components involved in ventricular repolarization; prolongation of the ST-segment and T-onset to T-peak. These observations suggest that prolongation of Phases 2 and 3 of the cardiac action potential drives the association between the QT-interval and AF risk.

Keywords

atrial fibrillation; QT-interval; electrocardiography; epidemiology; arrhythmia

Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, carries substantial clinical burdens, including debilitating palpitations and increased risks of heart failure, stroke, myocardial infarction, and death.[1–4] Its economic burden is also staggering with costs linked to treatment of the arrhythmia and its sequelae being estimated to approximate 26 billion dollars annually in the United States alone.[5] The impact of the arrhythmia on patients and health care systems is anticipated to surge in the coming years owing to its expanding prevalence, a phenomenon that is partially attributed to an aging population.[6]

These worrisome prospects are further aggravated by the limited efficacy of current treatments, including anti-arrhythmic drugs and catheter ablation, which likely stems from our limited insight into AF pathophysiology.[7–10] Improved treatment of affected patients will require novel insights into mechanisms underlying the development and maintenance of the arrhythmia.[11] Recent work has revealed that prolongation of the electrocardiographic QT-interval is associated with an increased risk of developing AF.[12,13] Notably, these findings are consistent with observations that patients with congenital long-QT syndrome (LQTS) have a markedly higher prevalence of the arrhythmia relative to the general population.[14] Mechanisms accounting for the increased risk of AF among LQTS patients are unknown, however experts have hypothesized that they may suffer from a pathophysiologic sub-phenotype of the arrhythmia reflective of atrial torsades.[15,16]

The QT-interval encompasses Phases 0–3 of the ventricular cardiac action potential and hence involves both depolarizing and repolarizing currents.[17] Although it is now clear that prolongation of the QT-interval in the general population is associated with an increased risk of AF, the precise component(s) within the interval responsible for this association remain unknown. In order to leverage this recent insight to help guide the development of novel treatment strategies and facilitate more effective identification of individuals at risk of developing the arrhythmia, it is imperative to identify the individual component(s) within the

QT-interval responsible for the association. By identifying the most specific ECG components responsible, we might begin to understand and study distinct mechanistic "sub-phenotypes" of AF to identify optimal therapies personalized to the particular type of AF. Accordingly, we sought to characterize associations of the components of the QT-interval with the risk of incident AF in a large population-based cohort.

Methods

Assessment of the relationship between components of the QT-interval and the risk of incident AF was performed using the Atherosclerosis Risk in Communities (ARIC) Study, a prospective population-based cohort study.

Atherosclerosis Risk in Communities Study (ARIC)

Recruitment, characterization, and outcome ascertainment in ARIC has been described in detail previously.[18] ARIC enrolled 15,792 adults aged 45–64 years between 1987 and 1989 from 4 US communities: the northwest suburbs of Minneapolis, MN; Washington County, MD; Jackson, MS; and Forsyth County, NC. For the current analysis, study participants were excluded in the presence of: known prevalent AF, major intra-ventricular conduction defects (complete left bundle branch block, complete right bundle branch block, QRS duration ≥ 120 ms), ventricular pre-excitation, Vaughan-Williams class I or III antiarrhythmic drug use, artificial pacing, or extremes of absolute QT interval duration (>600 or <200 ms) at baseline. Major intra-ventricular conduction defects were excluded as they are felt to represent a separate disease process, while exclusion of extremes of absolute QT interval duration was utilized to ensure integrity of the data and avoid including outliers most likely reflective of data errors. Written informed consent was obtained, and all procedures were conducted under institutionally approved protocols for human subjects research. Certification to use de-identified ARIC data was obtained from the University of California, San Francisco Institutional Review Board.

Baseline Examinations and Event Ascertainment

Comprehensive baseline evaluations were performed, followed by annual phone interviews and 3 repeat examinations spaced approximately 3 years apart.[18] Hypertension was defined as current use of antihypertensive medications or systolic and/or diastolic blood pressure greater than or equal to 140 and 90mm Hg, respectively. Participants were classified as diabetic if they had a fasting glucose concentration greater than or equal to 126 mg/dL, any glucose measurement greater than 200mg/dL, use of glucose-lowering medication, or self-reported physician diagnosis of diabetes. Methods for ascertaining prevalent coronary heart disease and heart failure have been described previously.[18]

Prevalent AF was identified from the baseline ECG, while incident AF was documented using study visit ECGs, hospital discharge diagnoses, and death certificates. Previous work on selected ARIC subgroups evaluating AF ascertainment by hospital discharge diagnoses revealed a sensitivity and specificity of 85% and 99% in whites and corresponding values of 80% and 99% in blacks, respectively.[19]

Electrocardiographic procedures and QT interval ascertainment

Standard resting 12-lead ECGs were performed at each visit using MAC PC (Marquette Electronics, Milwaukee, Wisconsin) in each clinical center. ECG parameters, including the QT-interval, were automatically processed in a central ECG laboratory, initially using the Dalhousie Novacode ECG program and then were reprocessed with the GE Marquette 12-SL program (GE Marquette, Milwaukee, Wisconsin) at the Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston Salem, NC. The QT-interval was then sub-divided into the following components: Intrinsicoid R-wave (onset of R-wave to R-wave peak), R-peak to R-end (R-wave peak to R-wave end), ST-segment (J-point to the onset of the T-wave), T-onset to T-peak (T-wave onset to T-wave peak), and T-peak to T-end (T-wave peak to T-wave end).

Statistical Analysis

Normally distributed continuous variables are presented as means ± standard deviation and were compared using the Student's t-test. Comparison of categorical values was performed using the Chi-squared test.

Time-to-event analyses using Cox proportional hazards models were employed to evaluate for an association between each of the QT-interval components and incident AF. QT-interval components initially were treated as continuous variables and the median value among the 12 individuals leads was utilized. The QT-interval components were evaluated with histograms and each was noted to exhibit a normal distribution. The hazard ratios were calculated per 1-standard deviation increase in each component. Ventricular rate was included as a covariate in all models in order to adjust for the association between the QT-interval and heart rate. Sensitivity analyses using lead V5 in isolation were also performed. Covariates included in the multivariable Cox regression models were baseline age, gender, race, body mass index, hypertension, diabetes, heart failure, and coronary artery disease. Cox regression analyses simultaneously adjusting for the different components of the QT-interval were also performed using the same covariates. Additional analyses were performed to evaluate the impact of long extremes of the QT-interval components, defined as greater than the 95^{th} percentile. Similar Cox regression models were utilized for these analyses with identical covariates. Each Cox regression model satisfied the proportional hazards assumption when evaluated using log-minus-log curves and the Schoenfeld test. For the adjusted survival curves, categorical covariates were set at 0 and continuous covariates were set at their median values.

To assess the discrimination afforded by the ST-segment and T-onset to T-peak intervals, we used the C-index, an extension of the C-statistic for logistic models to censored survival data. We first calculated the C-index for a base Cox model for time to AF, with the previously specified covariates. We then added each of the new variables in turn to this base model, re-estimated the C-index, and informally compared these to the C-index for the base model.

For the C-statistic, we used logistic models for AF incidence within 20 years of baseline. Participants who died or were lost to follow-up before 20 years were omitted from these

analysis. To minimize selection bias, we used inverse probability weighting. In brief, we fit a logistic model for retention in the analysis, using the same covariates as in the baseline Cox model, then weighted the retained observations by the inverse of the fitted probability of retention. Using these weights, we first estimated a base logistic model for AF within 20 years, with the same covariates as in the base Cox model, then estimated augmented logistic models also including each of the ST-segment and T-onset to T-peak intervals. In a final step, we calculated the C-statistic for each of these models and formally tested the differences between the C-statistics for the base and augmented models.

In order to adjust for multiple hypothesis testing in the initial set of analyses evaluating for associations between the QT-interval components treated as continuous variables and incident AF, a Bonferroni correction was utilized corresponding to a p-value for significance of 0.05/5 = 0.01. For the remaining analyses, two-tailed p-values < 0.05 were considered statistically significant. Statistical analyses were performed using Stata version 12 (College Station, Tx, USA).

Results

ARIC Participant Characteristics

A total of 14,625 individuals from the ARIC cohort were included in the analysis. At baseline, the mean age of the cohort was 54.1 ± 5.8 years, 44.3% were male, and 73.9% were classified as White. The remaining baseline clinical characteristics, Bazett-corrected QT-intervals, and QT-interval components of the cohort, stratified by the presence or absence of incident AF, are summarized in Table 1. During a mean follow-up period of 17.6 years, 1,505 (10.3%) individuals were diagnosed with incident AF.

QT-interval Components and the Risk of Incident AF

Among the 5 QT-interval components evaluated, 2 were found to have statistically significant associations with incident AF following adjustment for multiple hypothesis testing with the Bonferroni correction ($p<0.01$). When treated as continuous variables, both the ST-segment and the T-onset to T-peak were associated with an increased hazard of incident AF on unadjusted and adjusted analyses (Figure 1). Every standard deviation increase in the ST-segment length predicted a statistically significant 27% greater hazard of AF after multivariable adjustment (HR 1.27, 95% CI: 1.14–1.41, $p<0.001$). Also after multivariable adjustment, every standard deviation increase in T-onset to T-peak predicted a 13% increased hazard of AF (HR 1.13, 95% CI: 1.07–1.20, $p<0.001$). None of the remaining QT-interval components exhibited statistically significant associations following multivariable adjustment (Figure 1). When each of the 5 QT-interval components were included together within the same multivariate Cox regression model, both the ST-segment (HR: 1.34, 95% CI: 1.20–1.50, $p<0.001$) and T-onset to T-peak (HR: 1.17, 95% CI: 1.10–1.25, $p<0.001$) remained significantly associated with incident AF. No significant differences were observed in the sensitivity analyses utilizing values derived from lead V5.

Assessment of the discriminatory capacity of the Cox regression models for predicting incident AF revealed that the base model containing the pre-specified covariates exhibited a

C-index of 0.7219. Addition of either the ST-segment or T-onset to T-peak intervals resulted in an increase of the C-index to 0.7234. In a similar manner, the C-statistic for the base model was 0.7481. Addition of ST-segment length and T-onset to T-peak to the base model resulted in non-significant increases to the C-statistic of 0.7491 (p=0.231) and 0.7494 (p=0.2187), respectively.

Additional analyses were undertaken to evaluate the risk of incident AF among individuals with markedly prolonged values of the 5 QT-interval components, defined as greater than the 95th percentile. Individuals with a markedly prolonged ST-segment experienced a 1.31-fold increased hazard (95% CI: 1.04–1.64, p=0.022) of developing the arrhythmia (Figure 2) relative to the remainder of the cohort, while a markedly prolonged T-onset to T-peak was also associated with a statistically significant increased risk of AF (HR: 1.36, 95% CI: 1.09–1.69, p=0.006) (Figure 3). No statistically significant associations were observed for the remaining 3 QT-interval components on unadjusted and adjusted analyses (Table 2).

Discussion

Our investigation involving 14,625 individuals from the ARIC cohort identified the ST-segment and T-onset to T-peak as the primary electrocardiographic intervals responsible for the documented association between a prolonged QT-interval and incident AF. Prolongation of both the ST-segment and T-onset to T-peak durations was associated with a greater risk of developing the arrhythmia when the ECG intervals were treated as continuous variables. In addition, individuals with marked prolongation of the ST-segment and the T-onset to T-peak, defined as greater than the 95th percentile, also exhibited a statistically significant increased risk of incident AF. Our findings provide further insight into the relationship between the QT-interval and AF, which may guide additional mechanistic investigations into the arrhythmia, potentially identify novel treatment targets, and may help identify particular sub-phenotypes of AF patients more or less amenable to various therapeutic strategies.

Recognition that prolongation of the QT-interval is associated with an increased risk of AF in the general population represents a potentially important mechanistic insight into the pathogenesis of the arrhythmia.[12,13] Given that the QT-interval is comprised of multiple different phases of the cardiac cycle, including depolarization and repolarization, identification of the specific components within the QT-interval responsible for the association is critical for guiding subsequent mechanistic investigations. Indeed, as highlighted by their being upwards of 15 genetic culprits for congenital long QT syndrome, there are multiple potential causes of QT-interval prolongation.[20] The ability to focus on a limited set of ionic currents within the cardiac action potential as putative therapeutic targets offers a greater likelihood of success for developing more effective treatment strategies.

Our findings suggest that prolongation of the depolarizing currents responsible for the QRS complex do not account for the association between a prolonged QT-interval and an increased risk of AF. Instead, the primary electrocardiographic intervals responsible for the relationship were prolongation of the ST segment and T-onset to T-peak, which occur during Phase 2 and the early component of Phase 3 of the cardiac action potential. The primary currents operative during this period within the ventricular myocardium include the inward

calcium current (I_{Ca}) that occurs through L-type calcium channels and the rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed rectifier potassium current.[17] It should also be noted that a prolonged ST-segment is classically observed with LQT3, which develops secondary to an *SCN5A* gain-of-function mutation that results in delayed closing of the late inward sodium current.[21]

In contrast to the increase in late inward sodium current that results in LQT3, a reduction in the aforementioned calcium and potassium currents can result in QT prolongation. Although the mechanisms through which these alterations predispose to AF are unclear, as noted previously, it has been hypothesized that individuals with LQTS may suffer from a sub-phenotype of AF reflective of atrial torsades.[14–16] In addition to the early afterdepolarizations that classically occur in the setting of delayed cardiac repolarization, previous work has also suggested that delayed afterdepolarizations may also be operative in this context and could potentially serve as a critical factor responsible for the initiation and maintenance of the arrhythmia.[22,23] It is conceivable that prevention of this triggered activity, either via its direction inhibition or through normalization of cardiac repolarization, could potentially serve as an effective therapeutic strategy. Notably, a recent study has suggested that eleclazine, an inhibitor of the late inward sodium current, is effective at reducing autonomically induced atrial premature beats and vulnerability to AF in a porcine model.[24]

While our findings provide additional insight into the association between QT-interval prolongation and AF risk, at present they suggest a limited role for utilizing ST-segment and T-onset to T-peak durations for discriminating among patients at risk of developing AF as evidenced by their minimal impact on the C-index and C-statistic values relative to a model containing known clinical predictors. It is also important to note that treatments that normalize the QT-interval through shortening of the ST-segment and T-onset to T-peak are unlikely to serve as panaceas for AF management. It has become increasingly clear that AF is a heterogeneous arrhythmia that is likely comprised of multiple different pathophysiological sub-phenotypes.[25,26] Although prolonged atrial repolarization likely predisposes to a particular sub-phenotype, potentially reflective of atrial torsades, genetic findings have alluded to the existence of additional sub-phenotypes, including those associated with a shortened atrial action potential duration, conduction velocity heterogeneity, and cellular hyper-excitability, to name a few.[25,27] Indeed, this notion is reflected by the variable clinical response to different anti-arrhythmic drugs and catheter ablation.[28–30] These data may be used in either subsequent prospective studies or retrospective analyses of pre-existing datasets to determine if patients with a prolonged QT, ST segment, or T-onset to T-peak may predict a better (or worse) response to particular antiarrhythmic drugs or particular ablation approaches.

Limitations

AF was ascertained in a prospective, systematic fashion with prior work from ARIC indicating that use of hospital discharge diagnoses alone conferred a sensitivity of approximately 80–85% for detecting the arrhythmia, however it is probable that some cases of incident AF may not have been detected.[19] Although under-ascertainment of the outcome

has the potential to introduce bias, in the current study it would be anticipated to be non-differential in relation to the baseline QT-interval. As a result, any bias introduced would be anticipated to be towards the null and hence should not account for the positive associations identified in the present study. Although the intrinsicoid R-wave was associated with incident AF only on unadjusted analysis and the association was lost after multivariable adjustment, we may have had inadequate power to detect all relationships. As a result, we cannot exclude the possibility that depolarizing currents may yet be an important contributor to AF in some individuals. While we performed multiple tests, the statistically significant results revealed P values well below our conservative *a priori* identified Bonferonni corrected alpha value. Finally, our study was restricted to Black and White individuals and our findings may not be generalizable to other races.

Conclusions

Our study involving 14,625 individuals from the ARIC cohort revealed that the previously documented association between a prolonged QT-interval and an increased risk of incident AF is primarily mediated by prolongation of the ST segment and T-onset to T-peak. Insight into the specific components of the QT-interval that predispose to arrhythmia development may help identify patients at risk for the disease, lead to more effective treatment strategies of affected patients, and help to identify AF patients more or less amenable to various therapies.

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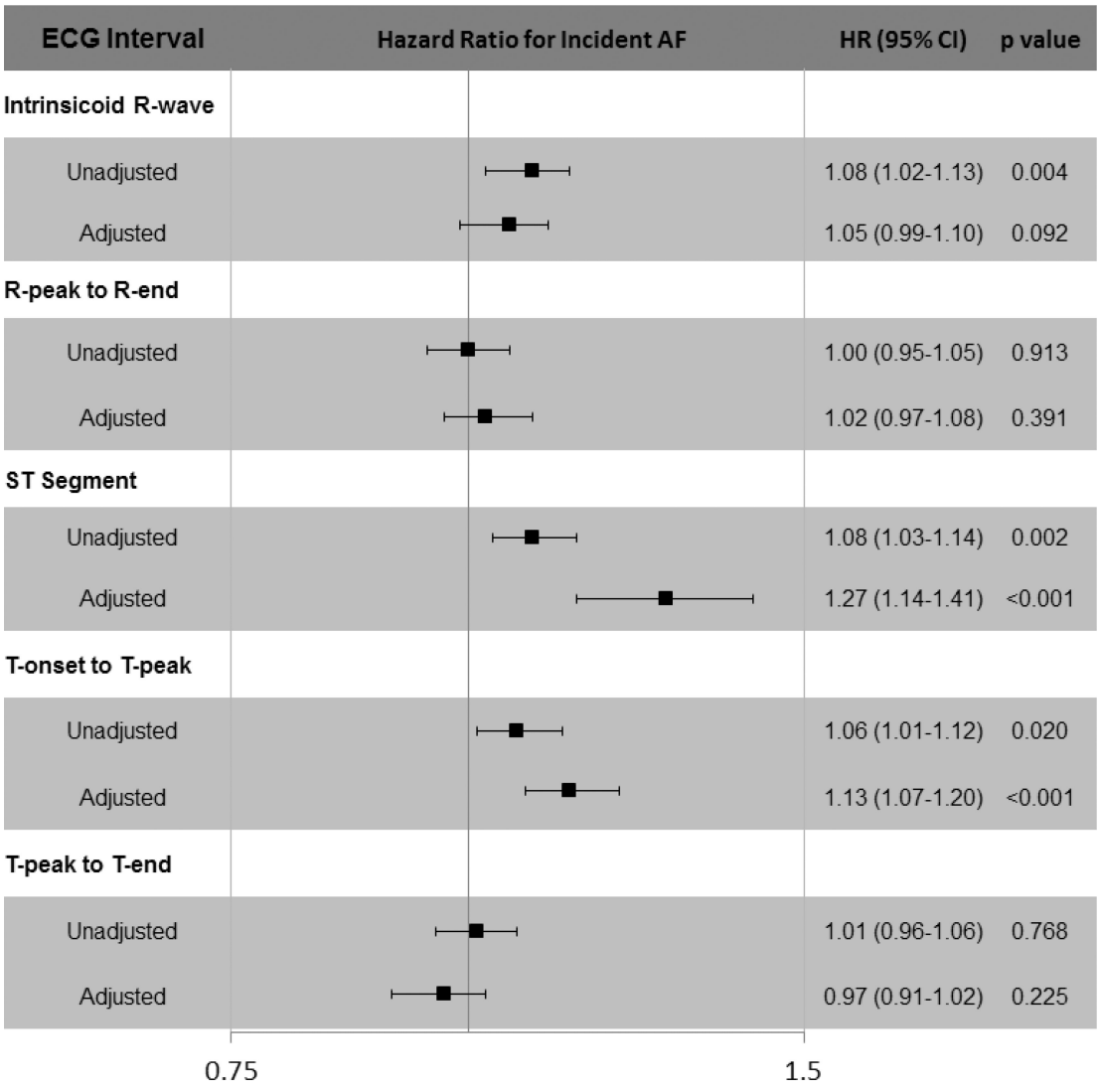

Figure 1:

Association of QT-interval components with Incident Atrial Fibrillation.

Hazard ratios and 95% confidence intervals per 1-standard deviation increase in the component.

Covariates used for adjustment include baseline age, gender, race, body mass index, hypertension, diabetes, heart failure and coronary artery disease, and ventricular rate.

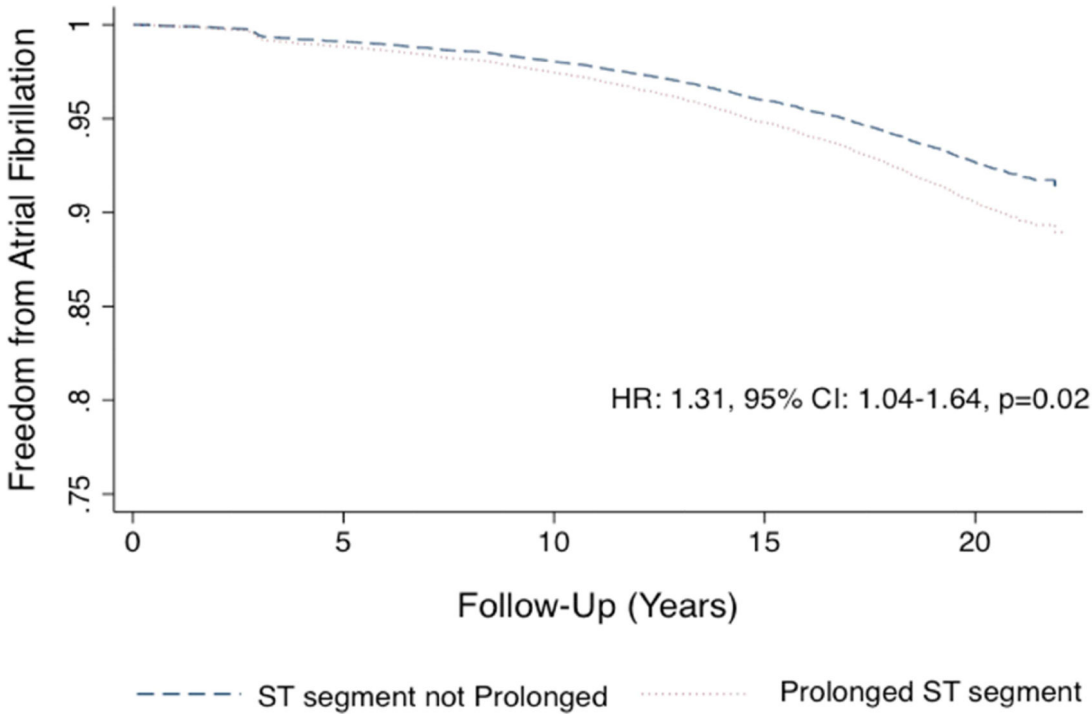

Figure 2:

Adjusted Survival Curves of Incident Atrial Fibrillation among Study Participants with and without a Prolonged ST segment.

A Prolonged ST segment was defined as above the 95th percentile.

Covariates used for adjustment include baseline age, gender, race, body mass index, hypertension, diabetes, heart failure and coronary artery disease, and ventricular rate.

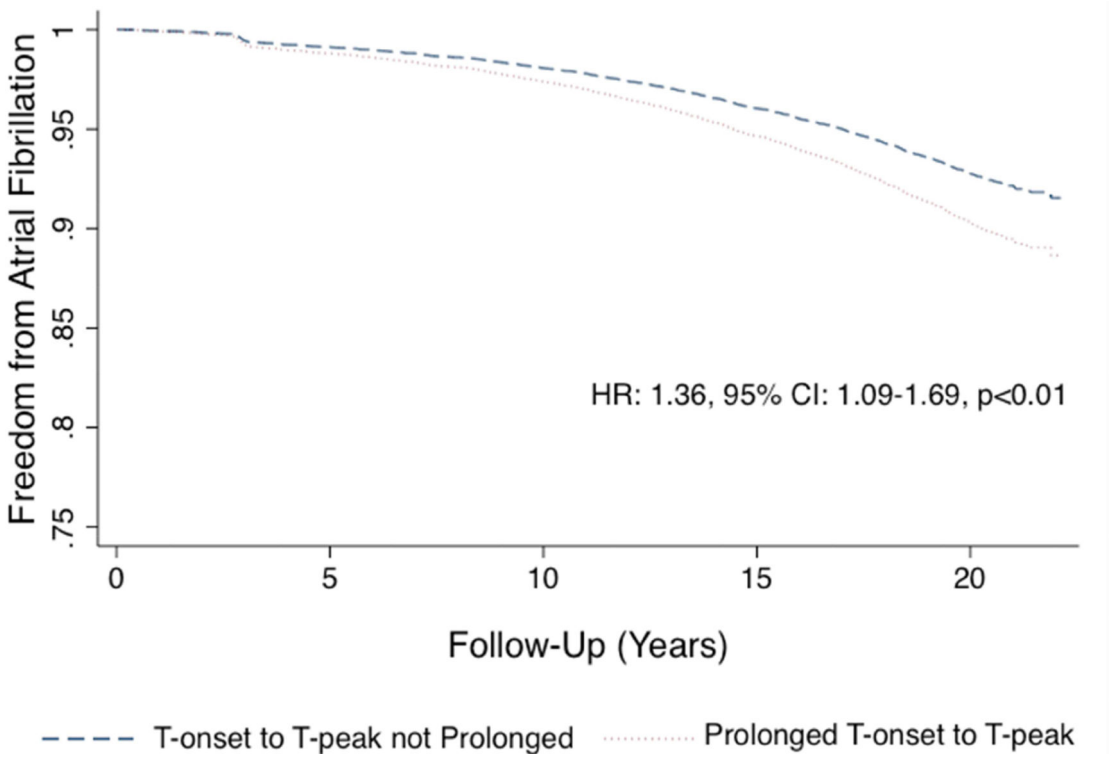

Figure 3:

Adjusted Survival Curves of Incident Atrial Fibrillation among Study Participants with and without a Prolonged T-wave onset to T-wave peak.

A Prolonged T-wave onset to T-wave peak was defined as above the 95th percentile. Covariates used for adjustment include baseline age, gender, race, body mass index, hypertension, diabetes, heart failure and coronary artery disease, and ventricular rate.

Table 1:

Baseline Characteristics of Study Participants with and without Incident AF

	Overall n = 14,625	Incident AF n = 1,505	No AF n = 13,120	p value
Age (years)	54.1 ± 5.8	56.8 ± 5.4	53.8 ± 5.7	<0.001
Male (%)	6,474 (44.3)	817 (54.3)	5,657 (43.1)	<0.001
White Race (%)	10,808 (73.9)	1,243 (82.7)	9,565 (73.1)	<0.001
Hypertension (%)	4,922 (33.8)	693 (46.3)	4,229 (32.4)	<0.001
Diabetes Mellitus (%)	1,677 (11.6)	261 (17.4)	1,416 (10.9)	<0.001
Body Mass Index (kg/m^2)	27.7 ± 5.3	28.9 ± 6.0	27.5 ± 5.3	<0.001
Coronary Artery Disease (%)	640 (4.5)	144 (9.8)	496 (3.8)	<0.001
Congestive Heart Failure (%)	647 (4.5)	129 (8.8)	518 (4.0)	<0.001
QT_c (ms)	408.1 ± 27.3	412.6 ± 29.7	407.5 ± 27.3	<0.001
Intrinsicoid R-wave (ms)	25.9 ± 5.3	26.2 ± 5.6	25.9 ± 5.3	0.020
R-peak to R-end (ms)	23.7 ± 11.2	23.7 ± 10.9	23.7 ± 11.2	0.958
ST segment (ms)	114.6 ± 18.1	116.4 ± 20.0	114.4 ± 17.9	<0.001
T-onset to T-peak (ms)	101.8 ± 21.8	103.0 ± 22.4	101.7 ± 21.7	0.022
T-peak to T-end (ms)	97.6 ± 16.6	97.9 ± 17.2	97.6 ± 16.5	0.488

Data are n (%) or mean ± standard deviation, AF = atrial fibrillation. p-value is for comparison of study participants with and without incident AF, ms = milliseconds

Table 2:

Association of Marked Prolongation (above the 95th Percentile) of QT-interval Components with Incident Atrial Fibrillation

QT-interval component	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Intrinsicoid R-wave	1.20 (1.00–1.44)	0.056	1.17 (0.97–1.41)	0.099
R-peak to R-end	0.88 (0.71–1.09)	0.233	0.95 (0.76–1.18)	0.655
ST-segment	1.49 (1.19–1.87)	<0.001	1.31 (1.04–1.64)	0.022
T-onset to T-peak	1.29 (1.04–1.59)	0.018	1.36 (1.09–1.69)	0.006
T-peak to T-end	1.11 (0.91–1.36)	0.298	1.02 (0.83–1.26)	0.819

HR = hazard ratio, CI = confidence interval