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Electrocardiographic Predictors of Sudden and Non-Sudden Cardiac Death in Patients with Ischemic Cardiomyopathy

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Abstract

Objective—This study evaluated the prognostic value of electrocardiogram (ECG)-based predictors in the primary prevention of sudden cardiac arrest (SCA) among ischemic cardiomyopathy patients with depressed left ventricular ejection fraction (LVEF < 35%).

Background—The prediction of cause-specific mortality in high-risk patients offers the potential for targeting specific therapies (i.e., implantable cardioverter-defibrillator [ICD]).

Methods—Subjects were recruited from the Prediction of Arrhythmic Events with Positron Emission Tomography (PAREPET) study. Continuous Holter 12-lead ECG recordings were obtained at the start of study and used to compute 15 clinically-important ECG abnormalities (e.g., atrial fibrillation).

Results—Among 197 patients (age 67 ± 11 years, 93% male, mean follow-up 4.1 years) enrolled, 30 (15%) were SCA cases and 35 (18%) cardiac non-sudden deaths (C/NS). In multivariate analysis, only heart-rate-corrected QT interval (QTc) predicted SCA (hazard ratio 2.9 [1.2–7.3]) and only depressed heart rate variability (HRV) predicted C/NS (hazard ratio 5.0 [1.5–17.1]) independent of demographic and clinical parameters.

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Conclusions—Among patients with depressed LVEF, prolonged QTc suggests greater potential benefit from ICD therapy to prevent SCA; depressed HRV suggests potential benefit from bi-ventricular pacing to prevent C/NS.

Keywords

sudden cardiac arrest; electrocardiogram; implantable cardioverter defibrillator; ischemic cardiomyopathy

INTRODUCTION

Non-invasive risk stratification to identify and manage high-risk populations is a clinical priority.¹ Fatal tachyarrhythmias (i.e., sustained ventricular tachycardia [VT] or ventricular fibrillation [VF]) and heart failure complications are very common in patients with ischemic cardiomyopathy, which can lead to sudden cardiac death (SCD) or cardiac non-sudden death (C/NS), respectively. Secondary prevention of fatal complications in ischemic cardiomyopathy emphasizes (1) early termination of VT/VF using implantable cardioverter-defibrillator (ICD) shocks after successful resuscitation from sudden cardiac arrest (SCA) or (2) aggressive treatment using bi-ventricular (BiV) pacing for cardiac resynchronization to prevent heart failure mortality in selected high-risk patients. Elaborate guidelines advocate not only the use of a differential approach according to multiple diagnostic parameters, but also the consideration of the clinical status of the patient in order to risk-stratify different cardiac populations. Nevertheless, depressed left ventricular ejection fraction (LVEF) remains the only clinically-used tool to identify ischemic cardiomyopathy patients at the greatest risk for SCA or C/NS and, therefore, most in need of preventive treatment. This limited-sensitivity approach, which primarily relies on LVEF to identify those who will benefit the most from targeted ICD or BiV pacing, has been found to be fallible in the prevention of SCA or C/NS.^{2, 3} Continued efforts for accurate risk stratification are still warranted in ischemic cardiomyopathy.

The 12-lead electrocardiogram (ECG) is widely known to provide valuable prognostic information in different cardiac populations and widely used as an easily accessible and noninvasive diagnostic tool.^{4, 5} The value of the ECG in predicting cardiac events has been repeatedly assessed and validated in many clinical populations. In particular, abnormalities seen on standard 10-second, 12-lead ECG strips (referred to as resting ECG parameters) have been described as promising clinical tools to predict cardiovascular death.⁶ In addition, abnormalities seen during continuous Holter ECG recordings (e.g., ST segment monitoring and transient tachyarrhythmia alarms) have been previously described to provide more insights about the pathogenesis of cardiovascular death.⁷ Despite the abundant literature concerning the value of resting and continuous Holter ECG parameters in post-acute myocardial infarction patients,^{8, 9} limited data exist on the prognostic value of these parameters in ischemic cardiomyopathy patients who are deemed eligible, according to their LVEF, for ICD therapy for the secondary prevention of SCA. Evaluating the incremental value of the resting and continuous Holter ECG, beyond that of the LVEF, might improve the optimal targeting of ICD and other more invasive therapies in high-risk cardiac populations.

We have previously reported¹⁰ that the ubiquitous presence of ECG confounders (i.e., pacing, left bundle branch block [LBBB], QRS widening, and atrial fibrillation) among chronic heart failure patients substantially interferes with the interpretation of the ECG. A classic example of this interference in the ECG literature is the inability to evaluate ST deviation in the presence of LBBB. Previous reports have excluded patients with interpretation confounders from further analysis,¹¹ which limits the clinical value of many important ECG parameters for widespread clinical utility. Evaluating the presence or absence of ECG confounders as potential markers of risk, rather than excluding patients with such confounders, could provide a tool to account for the role of confounders that preclude all means of analyzing important ECG parameters. In this study, we sought to determine the prognostic value of resting and continuous Holter ECG parameters, in relation to presence of ECG confounders, for cause-specific mortality in subjects with ischemic cardiomyopathy who were eligible for the secondary prevention of SCA with ICD therapy.

METHODS

Setting and Subjects

Patients for this study were recruited from an NIH-funded study known as Prediction of Arrhythmic Events with Positron Emission Tomography (PAREPET). The PAREPET study was prospective in nature and designed to determine whether or not denervated or hibernating myocardium assessed with positron emission tomography could predict SCA among subjects with ischemic cardiomyopathy who were eligible for ICD therapy (pre-enrollment LVEF < 35% for Class II–VI and < 30% for Class I).¹² Therefore, enrolled subjects exhibited coronary artery disease, pre-enrollment LVEF less than or equal to 35%, and New York State Heart Association Functional Class (NYHA) I–III heart failure symptoms. Although all patients were clinically eligible for ICD therapy, only 81% had an ICD implanted prior to a coronary event. The study design and methods featured in PAREPET have been reported in detail.¹³ In short, patients eligible for PAREPET first underwent a baseline echocardiogram, PET scan, and 24-hour continuous Holter ECG recording. Next, they received follow-up assessment by phone in 3-month intervals. There were no modifications to the standard care received by enrollees. Patients reporting ICD shocks were seen in a clinic where they had their ICDs interrogated. Medical records of patients meeting any study endpoints (i.e., SCA or C/NS) were collected and reviewed periodically. The PAREPET study complies with the Declaration of Helsinki and was approved by the appropriate institutional review boards. All subjects included in the PAREPET study consented to participate.

Endpoints and Clinical Data

Our analysis included consecutive outpatients from the PAREPET study (n = 197). Those who were lost to follow up (n = 1) or did not complete continuous Holter ECG monitoring (n = 6) were not included in our analysis. Clinical data was collected from electronic medical charts at the beginning of the study that included clinical presentation, past medical history, medications, and laboratory and other diagnostic tests. Endpoints were screened at regular intervals and were classified using modified Hinkle-Thaler criteria.^{14, 15} The primary endpoint was SCA, which was defined as either arrhythmic death (i.e., abrupt collapse with

pulse cessation without prior circulatory collapse) or documented ICD discharge for VF or rapid VT (i.e., > 240 beats/min). The secondary endpoint was non-arrhythmic cardiovascular death (i.e., cardiac non-sudden death [C/NS]), which was defined as circulatory failure (i.e., pulse cessation only after the peripheral circulation had collapsed) or cardiac transplantation with end stage heart failure or hospice care. Medical records, witnesses, death certificates, and symptoms before death were reviewed by two independent cardiologists, and cause of death was determined after review of all available data. In the event of disagreement, a consensus was reached by a third cardiologist.

Electrocardiographic Methods

Upon enrollment in our study, each patient underwent a continuous Holter 12-lead ECG recording using H12+ recorders (V3.12, Mortara Instrument, Milwaukee, WI). These recorders obtain ECG signals at a high-resolution sampling rate of 1,000 samples per second. Leads were placed using the Mason-Likar configuration in which limb leads are placed on the body to allow full mobility during the 24-hour recording period. We previously confirmed that ECG waveform morphologies do not significantly change between the Mason-Likar lead configuration and the standard lead configuration.¹⁶ The first 5 minutes of the continuous Holter ECG recording were obtained while the patient was resting supine in the clinic; for the remainder of the recording period, the patient was instructed to resume normal activity. Recordings were then downloaded to a computer and processed using H-Scribe with Eli-link software (Mortara Instrument). After the automated processing, ECG streams were manually annotated by a reviewer who was blinded to all clinical data to ensure that the quality of ECG signals were adequate for analysis. Noise and artifacts were deleted from the analysis, which resulted in an average monitoring period of 23 hours.

Next, from the initial 5 minutes of continuous Holter ECG recording that were completed with the patient resting supine, a 10-second, 12-lead ECG strip was exported using Eli-link and printed on standard ECG paper. Eli-link uses the raw (i.e., unfiltered) waveform ECG signal to retrieve a standard ECG strip using a filter setting of 0.05–150 Hz, which is essential for the accurate measurement of rapid upstroke velocity, peak amplitude, and waves of small duration (e.g., Q wave, QRS fragmentation, and QRS duration).¹⁷ These resting and continuous Holter ECG files were then used to compute 15 high-risk ECG parameters that have been previously reported and validated in the literature (Table 1). The importance and relevance of each of these parameters have also been discussed.¹⁰ Finally, the presence of ECG confounders was assessed in relation to each of the 15 high-risk ECG parameters as follows.

1. Left Bundle Branch Block (LBBB): This confounder precluded the analysis of (1) ST depression (STd), (2) heart-rate-corrected QT interval (QTc), (3) QT-RR slope, and (4) spatial QRS-T Angle (QRSTA).
2. Atrial Fibrillation (AF): This confounder precluded the analysis of (1) minimum heart rate (minHR), (2) heart rate variability (HRV), (3) premature ventricular contractions (PVC), (4) QRS duration (QRSd), (5) QTc, (6) QT-RR slope, and (7) QRSTA.

3. Persistent ventricular pacing: This confounder precluded the analysis of (1) Q waves, (2) left ventricular hypertrophy (LVH), (3) LBBB, (4) STd, (5) minHR, (6) HRV, (7) PVC, (8) QRSd, (9) QTc, (10) QT-RR slope, and (11) QRSTA.
4. Widened QRSd greater than 120 milliseconds (ms): This confounder precluded the analysis of QRSTA.

Statistical Analysis

All analyses were conducted using Statistical Package for Social Sciences (SPSS v 19.0 for Windows), and $p < 0.05$ was considered statistically significant. Dynamic measures are reported as mean $\pm$ standard deviation (SD), and categorical variables as n (%). Demographic and clinical characteristics of groups were compared using analysis of variance (ANOVA) with Bonferroni adjustment for dynamic measures and chi-square for categorical measures. Each ECG predictor was coded for each patient as *Normal*, *Abnormal*, or *Cannot Assess (N/A)* due to confounders. Optimal cutoff points for continuous Holter ECG variables (i.e., minHR, QRSd, HRV, QTc, QT/RR slope, and QRSTA) were selected using the receiver operator characteristics (ROC) curve. The independent relationship between each ECG predictor and time-to-event data was evaluated using Cox proportional-hazards regression models.¹⁸ Hazard ratios (HR) were calculated for the *Abnormal* and *N/A* categories against the *Normal* category as the reference group. To minimize Type II error, variables significant at $p < 0.1$ in the univariate analysis were entered simultaneously in a multivariate model with a backward selection technique to identify independent ECG predictors.¹⁹ The following clinical and demographics variables were correlated with outcomes and included as covariates only if they were significant at the univariate level: age, sex, body mass index (BMI), and LVEF. Significant ECG predictors from the multivariate analysis were analyzed using Kaplan-Meier events probability curves, and a log rank test was used to compare the curves. To identify statistically significant ECG predictors in each comparison with Type I and II errors of 5% and 20%, a minimum event rate of $n = 26$ for each endpoint was needed, which was satisfied in our analysis.

RESULTS

Baseline Characteristics

This analysis consisted of 197 subjects (67 ± 11 years of age, 93% male, LVEF = 28 ± 9). Over half of these patients (52.3%) were classified as having Class II NYHA heart failure symptoms. They were optimally managed with β -blockers (96%) and angiotensin inhibition therapy (90%). Men and women who took part in the study were similar regarding age, LVEF, NYHA class, and β -blockers versus angiotensin inhibition therapies. After a mean follow-up time of 4.20 years (range 2.5–7.2 years), 30 patients (15%) were classified as SCA, 35 (18%) as C/NS, and 132 (67%) with no cardiac mortality. No demographic or clinical differences (e.g., age) were observed between those who experienced arrhythmic death ($n = 20$) versus those displaying ICD discharges ($n = 10$). While patients in the C/NS group were more likely to be older and have diabetes, there were no differences in the other baseline clinical and demographic characteristics between patients with and without endpoints (Table 2).

ECG Predictors

The intrinsic rhythm was sinus in 170 patients (86%) and AF in the remaining 27 (14%). Most patients had a pacemaker present ($n = 175$; 89%), but only a quarter ($n = 42$; 25%) of them had persistent pacing during the Holter ECG recording. As illustrated in Figure 1, high-risk ECG parameters were frequently present in this population with ischemic cardiomyopathy. There were 3.4 ± 1.8 (range 0–8) abnormal parameters per subject, and at least one abnormal parameter was present in 191 subjects (97%). Due to the high prevalence of confounding factors (i.e., prolonged QRSd [$n = 114$, 58%], persistent ventricular pacing [$n = 42$, 21%], AF [$n = 27$, 14%], and LBBB [$n = 11$, 6%]), only four high-risk ECG parameters could be assessed in all subjects, and the assessment of the other 11 ECG parameters was limited by one or more ECG confounders (Figure 1).

The univariate hazard ratios (HR) for each high-risk ECG parameter are shown in Table 3. An ROC analysis determined that prolonged QTc greater than 440 ms (both sexes) optimized the prediction of SCA (HR = 2.9, $p = 0.02$). In multivariate analysis, prolonged QTc remained a significant and independent predictor of time-to-SCA (Table 4 and Figure 2, panel 1A). This cutoff value (i.e., QTc > 440 ms) had a sensitivity of 65% and specificity of 66% to predict the incidence of SCA. There were no clinical or demographic variables that were predictive of time-to-SCA.

Similarly, the ROC-optimized cutoff point for HRV (SDNN < 80 ms) was predictive of C/NS (HR = 2.4, $p < 0.05$; Table 3). In multivariate analysis, depressed HRV remained a significant predictor of time-to-C/NS, independent of age and diabetes (Table 4 and Figure 2, panel 2B). This cutoff value (SDNN < 80 ms) had a sensitivity of 56% and specificity of 67% to predict the incidence of C/NS. Additionally, there was a consistent pattern of strong correlation between the presence of confounders and C/NS, which seemed to be attributable to persistent bi-ventricular (BiV) pacing (Table 4 and Figure 2, panel 2C). Further analyses demonstrated that, unlike RV pacing, persistent BiV pacing was strongly correlated with lower LVEF ($22 \pm 7\%$ vs. $29 \pm 10\%$, $p < 0.05$). Intermittent pacing (either RV or BiV) was not predictive of C/NS.

DISCUSSION

This study evaluates the prognostic value of 15 high-risk factors seen in the resting as well as the continuous Holter 12-lead ECG in patients with heart failure and ischemic cardiomyopathy. In contrast to previous studies that assessed patients at low to moderate risk, we applied these 15 ECG parameters to patients at high-risk of cardiac mortality. Furthermore, we specifically assessed the ability of ECG parameters to predict cause-specific mortality (SCA vs. C/NS). Although our subjects were primarily older, white males, this demographic homogeneity is consistent with other clinical trials of patients with ischemic cardiomyopathy.²⁰ Furthermore, our high mortality rate is consistent with previous reports.²¹

Electrocardiographic Prediction of Cause-Specific Mortality

Compared to low-to-moderate risk groups in which the current ECG parameters were previously validated, most of the ECG parameters we analyzed failed to predict death in our high-risk cohort of patients. However, sensitivity analysis using data from this cohort suggested that only the presence of prolonged QTc (> 440 ms) was predictive of SCA, which increased the risk of death by a factor of approximately 3 (multivariate HR = 2.9), independent of other ECG parameters. Such a finding should not be surprising because prolonged cardiac repolarization is already known to play an important role in the genesis of arrhythmic death.²² What this finding does suggest, however, is that QTc can predict SCA independently from poor LVEF, which has an interesting application: the further sub-stratification of ICD candidates into low-risk and high-risk groups for optimally prioritizing ICD therapy targeting.

Similarly, sensitivity analysis of our data suggests that depressed HRV not only predicted C/NS, but also increased the risk of death by a factor of approximately 5 (multivariate HR = 5.0) independent of age, diabetes mellitus, and other ECG parameters. This finding confirms previous reports that baroreflex sensitivity strongly correlates with total cardiac mortality,²³ which may suggest that more aggressive medical therapy and invasive approaches (i.e., BiV pacemaker for cardiac resynchronization) are warranted in these patients to reduce the risk of pump failure deaths.

Assessment of ECG Predictors in Ischemic Cardiomyopathy—In previous studies,¹¹ the presence of confounding ECG factors (i.e., prolonged QRSd, persistent ventricular pacing, AF, and LBBB) has been addressed by simply excluding affected subjects. Unfortunately, doing so results in the exclusion of a majority of subjects with ischemic cardiomyopathy and limits the clinical value of the ECG in this high-risk patient population.¹⁰ In an effort to determine the validity of these previous exclusions, we included patients with confounders in the statistical model as a separate subgroup (i.e., the *Cannot Assess* category; Table 3), and compared that subgroup to the *Normal* reference category. This approach improved the predictive power and the fitness of the final regression model. Although our approach did not result in any novel insights for the prediction of SCA, it did reveal the frequent association of the ECG confounding factors with C/NS death (e.g., *Cannot Assess*, Table 3). Careful examination of data reveals that the role of ECG confounders in the prediction of C/NS death was not mediated by other high-risk ECG parameters but rather the presence of persistent ventricular pacing—specifically BiV pacing (Table 2 and Figure 2). Although BiV pacing has been convincingly shown to improve mortality,²⁴ those with persistent BiV pacing in the current analysis had significantly lower LVEF compared to those with intermittent or no pacing ($22 \pm 7\%$ vs. $29 \pm 10\%$ and $28 \pm 9\%$, respectively; $p < 0.05$), which suggests that BiV pacing therapy was retained for sicker patients to begin with.

Also noteworthy is that ICD therapy not only correlates with a relevant incidence of complications and adverse events, but also poses a heavy burden on every patient. Moreover, BiV pacing is the more invasive procedure and is more prone to technical complications. However, if ICD therapy and BiV pacing are used together (i.e., ICD-P), the

potential for adverse events is considerably lower compared with classical ICD therapy. Accordingly, new guidelines have been expanded to include administering BiV pacing to either patients with earlier stages of heart failure or patients with pacemakers and frequent or constant RV-pacing. We suspect that retaining the BiV pacing therapy for patients with significantly lower LVEF—who are, therefore, more symptomatic—is the likely explanation for the unexpected, negative prognosis associated with BiV pacing in our analysis; however, it is difficult to draw precise conclusions from the relatively small, highly-selected patient cohort in our study.

An alternate strategy to reduce confounding factors for high-risk ECG parameters would be to adjust the criteria to expand the population in which the parameter could be assessed. Such modified criteria have been successfully applied to the assessment of fQRS, and alternate criteria have been formulated for those with prolonged QRSd or ventricular pacing.²⁴ In a similar vein, we attempted to assess QTc in the 14% of our patient cohort with AF by correcting for heart rate based on the averaged RR intervals in a 10-second ECG strip among AF patients (n = 27). However, the ability of QTc prolongation to predict time-to-SCA was no longer significant after including AF patients (Table 5), which supports the contention that QTc in the setting of AF is not a reliable predictor of risk.²²

CONCLUSIONS

Risk stratification and medical-decision making are extremely important and challenging; therefore, the continued effort to improve predictive criteria is imperative. In this study, we analyzed 15 ECG risk factors of cardiac death, taking into account the presence of other interpretation confounders. Our results suggest that a prolonged QTc interval on the 12-lead ECG can further stratify depressed LVEF patients into high-risk and low-risk subgroups for prioritizing ICD therapy for the secondary prevention of SCA. Moreover, we found no difference in risk between those who had normal QTc interval and those who could not have their QTc interval assessed due to confounders. These results have two important implications for clinical cardiologists. First, patients with low LVEF who have prolonged QTc interval require closer follow-up prior to and after ICD implantation. Second, patients who cannot have their ECG interpreted for QTc do not need further evaluation. Since nearly one fifth of patients who are eligible to receive an ICD might not get one prior to a fatal event, special attention needs to be paid to those who display a prolonged QTc interval.

Additionally, we found that a depressed HRV on a continuous Holter ECG can not only predict C/NS, but also serve as a potential tool for targeting BiV pacing and aggressive medical therapy. Those patients who could not have their HRV assessed were also at excess risk for C/NS. In contrast, our results also show that those with severely depressed LVEF were less likely to benefit from BiV pacing. This demonstrates that clinical cardiologists can utilize HRV analysis very early in the risk stratification process to identify those who will benefit the most from such therapies. If the clinician is unable to analyze HRV for a given patient due to particular confounders, then that patient still might be at high risk for heart failure death and should undergo further evaluation (e.g., PET imaging for quantifying myocardial sympathetic denervation).

Future research of ECG-based predictors in the primary prevention of SCA among high-risk patients should emphasize developing novel approaches to analyze important ECG parameters (e.g., QTc, and HRV) in the presence of interpretation confounders.

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Highlights

- The ECG is a simple and valuable tool to identify patients at greater risk for adverse cardiac events
- Novel approaches to analyze the ECG in the presence of interpretation confounders are needed

Figure 1. Prevalence of High Risk ECG Parameters

An illustration of the prevalence of high-risk ECG parameters within the groups. Refer to Table 2 for abbreviations.

Figure 2. Probability Curves for Predicting Sudden Cardiac Arrest and Cardiac Non-Sudden Death

Panel 1: Kaplan-Meier events probability curves showing that QTc interval (< 440 ms), not HRV or persistent pacing, predicts sudden cardiac arrest or the equivalent.

Panel 2: Kaplan-Meier events probability curves showing that HRV (SDNN < 80 ms) and persistent pacing, not QT interval, predict cardiac non-sudden death.

Table 1

The Definitions of High-risk ECG Parameters Used in This Study

#	ECG Parameter	Definition
1	QRS Duration ¹	Duration from QRS onset to QRS offset averaged among all leads over 10 seconds
2	Heart-Rate Corrected QT Interval ¹	Duration from QRS onset to T offset averaged among all leads over 10 seconds then corrected for heart rate using Bazett's formula ($QT/RR^{1/2}$)
3	Fragmented QRS ²⁵	(1) RSR morphology 2 R' or (2) notching in the nadir of S wave with a narrow QRS (< 120 ms) or (3) 2 R' or 2 notches in the nadir of S wave with a widened QRS
4	Q Waves ²⁶	The presence of pathologic Q waves (> 40 ms) in at least two leads corresponding to the same coronary territory
5	Left Bundle Branch Block ⁶	The presence of this pattern as per American Heart Association guidelines
6	Left Ventricular Hypertrophy ⁶	The presence of this pattern as per Cornell voltage criteria
7	Spatial QRS-T Angle ²⁷	The three-dimensional spatial angle between the mean R and T vectors estimated directly from the 12-lead ECG
8	Minimum Heart Rate ²⁸	The minimum 5-minute averaged heart rate during the 24-hour Holter monitoring period
9	Heart Rate Variability ¹	The standard deviation of normal-to-normal R-R intervals of all R-R intervals averaged over 24 hours
10	Atrial Fibrillation ⁶	A heart rhythm with irregular RR interval with absent P wave at any time during the 24-hour Holter recording
11	Non-Sustained Ventricular Tachycardia ¹	At least one episode of 3 consecutive ventricular beats at a rate of 120 beats/minute
12	Ventricular Ectopic Activity ²⁸	The presence of frequent premature ventricular contractions at rate of 10/hour for the duration of the Holter recording
13	ST Depression ²⁹	The presence of at least one episode of ST depression of 0.5 mm in leads V2-V3 or 1 mm in all other leads in 2 contiguous leads for at least 5 minutes at any time during the Holter recording
14	QT/RR Slope ³⁰	The linear regression slope between all beat-to-beat QT and R-R intervals over a 24-hour period
15	Persistent Pacing ³¹	100% of the total monitoring period with prolonged QRS complexes due to single chamber right ventricular (RV) pacemaker spikes. Bi-ventricular pacing, although it limits the interpretation of other ECG parameters, was not considered a high-risk parameter.

TABLE 2
Clinical and Demographic Characteristics in Patients with and without Endpoints

Parameter	All Patients (n = 197)	Endpoint		
		SCA (n = 30, 15%)	C/NS (n = 35, 18%)	Without Endpoints (n = 132, 67%)
Age (years)	67.2 ± 11.4	66.2 ± 8.3	72.3 ± 9.5 **	66.1 ± 12.1
Sex (male)	183 (93%)	33 (100%)	30 (83%)	120 (89%)
NYHA Class	2.1 ± 0.8	2.3 ± 0.6	2.1 ± 0.7	2.1 ± 0.9
Diabetes Mellitus	95 (47%)	17 (52%)	23 (64%) *	55 (41%)
Beta Blockers	189 (96%)	32 (97%)	34 (94%)	129 (96%)
Angiotensin Inhibition Therapy	177 (90%)	26 (79%)	33 (92%)	124 (92%)
LVEF (%)	28 ± 9	25 ± 9	25 ± 9	29 ± 9

Note. Values are mean ± standard deviation (SD), or n (%). SCA: sudden cardiac arrest or equivalent; C/NS: cardiovascular non-sudden death; NYHA: New York State Heart Association Functional Class; ACE: angiotensin converting enzyme; LVEF: left ventricular ejection fraction.

(*) p < 0.05 and

(**) p < 0.01 against survivors using analysis of variance analysis (ANOVA) with Bonferroni post-hoc comparisons and 3-group chi-square comparison for continuous and categorical variables, respectively.

TABLE 3

The Prognostic Value of ECG Predictors in Patients with and without Endpoints

ECG Parameters (n = 197)		Univariate Model HR (95% CI)			
		SCA		C/NS	
		HR (95% CI)	P	HR (95% CI)	P
1. Prolonged QRSd (> 120 ms)	Normal	Reference	-	Reference	-
	Abnormal	2.2 (1.0–5.0)	NS	1.1 (0.4–2.8)	NS
	Cannot Assess	1.0 (0.4–2.8)	NS	2.8 (1.3–6.3)	0.01
2. Prolonged QTc (> 440 ms)	Normal	Reference	-	Reference	-
	Abnormal	2.9 (1.2–7.4)	0.02	0.6 (0.2–1.8)	NS
	Cannot Assess	1.7 (0.8–4.9)	NS	2.1 (1.0–4.4)	NS
3. fQRS	Normal	Reference	-	Reference	-
	Abnormal	1.2 (0.6–2.5)	NS	1.3 (0.6–2.5)	NS
	Cannot Assess	-	-	-	-
4. Q waves	Normal	Reference	-	Reference	-
	Abnormal	1.3 (0.6–2.7)	NS	0.8 (0.3–2.1)	NS
	Cannot Assess	0.3 (0.3–2.0)	NS	2.5 (1.2–5.3)	0.02
5. LBBB	Normal	Reference	-	Reference	-
	Abnormal	1.9 (0.6–5.3)	NS	1.4 (0.5–5.4)	NS
	Cannot Assess	0.3 (0.3–1.8)	NS	2.8 (1.4–5.6)	0.01
6. LVH	Normal	Reference	-	Reference	-
	Abnormal	1.0 (0.3–3.2)	NS	0.4 (0.1–2.5)	NS
	Cannot Assess	0.3 (0.2–1.7)	NS	2.5 (1.2–5.0)	0.01
7. Wide QRSTA (Angle > 100°)	Normal	Reference	-	Reference	-
	Abnormal	1.6 (0.3–7.2)	NS	1.3 (0.4–4.6)	NS
	Cannot Assess	2.7 (0.9–9.6)	NS	2.0 (0.8–4.7)	NS
8. Elevated min HR (> 65 beats/minute)	Normal	Reference	-	Reference	-
	Abnormal	0.5 (0.1–3.7)	NS	1.4 (0.4–7.2)	NS
	Cannot Assess	0.6 (0.4–1.8)	NS	2.8 (1.4–5.5)	0.01
9. Depressed HRV (SDNN < 80 ms)	Normal	Reference	-	Reference	-
	Abnormal	0.5 (0.2–1.8)	NS	2.4 (1.0–6.2)	0.05
	Cannot Assess	0.6 (0.4–1.7)	NS	3.6 (1.6–8.1)	0.01
10. AF	Normal	Reference	-	Reference	-
	Abnormal	1.2 (0.3–2.8)	NS	1.1 (0.4–2.5)	NS
	Cannot Assess	-	-	-	-
11. NSVT	Normal	Reference	-	Reference	-
	Abnormal	1.2 (0.6–2.5)	NS	1.0 (0.5–2.0)	NS

ECG Parameters (n = 197)		Univariate Model HR (95% CI)			
		SCA		C/NS	
		HR (95% CI)	P	HR (95% CI)	P
Cannot Assess		-	-	-	-
12. Frequent PVCs	Normal	Reference	-	Reference	-
	Abnormal	1.4 (0.7–3.3)	NS	2.0 (0.8–5.3)	NS
	Cannot Assess	0.8 (0.4–2.5)	NS	3.8 (1.6–9.4)	0.01
13. Dynamic STd	Normal	Reference	-	Reference	-
	Abnormal	0.9 (0.4–2.0)	NS	1.0 (0.4–2.6)	NS
	Cannot Assess	0.7 (0.2–1.8)	NS	2.3 (1.0–5.7)	NS
14. Steep QTRR slope (slope coefficient > 0.22)	Normal	Reference	-	Reference	-
	Abnormal	1.5 (0.7–3.8)	NS	2.2 (0.8–6.3)	NS
	Cannot Assess	1.1 (0.6–3.0)	NS	3.7 (1.5–8.7)	0.01
15. Persistent Pacing	No Pacing	Reference	-	Reference	-
	RV Pacing	0.2 (0.0–1.5)	NS	0.7 (0.2–2.3)	NS
	BiV Pacing	0.5 (0.1–3.7)	NS	12.5 (5.5–28.4)	0.01

Note. NS: not significant; HR: hazard ratio; CI: confidence interval; SCA: Sudden Cardiac Arrest or equivalent; C/NS: Cardiovascular Non-Sudden Death; QRSd: QRS duration; fQRS: fragmented QRS; LBBB: left bundle branch block; LVH: left ventricular hypertrophy; QRSTA: QRS-T Angle; minHR: minimum heart rate; HRV: heart rate variability; SDNN: standard deviation of normal-to-normal R-R intervals; AF: atrial fibrillation; NSVT: non-sustained ventricular tachycardia; PVCs: premature ventricular contractions; STd: ST segment depression; RV: right ventricular; BiV: bi-ventricular. Italics: cutoff points selected using the ROC curve from current dataset.

Table 4

Multivariate Cox Regression for Predicting Endpoints*

ECG Parameter	HR (95% CI)	P
<i>SCA (n = 30)</i> Prolonged QTc (> 440 ms)	2.9 (1.2–7.3)	0.02
<i>C/NS (n = 35)</i>		
Age (years)	1.1 (1.0–1.1)	< 0.01
Diabetes (present)	3.5 (1.6–7.7)	< 0.01
Depressed HRV (SDNN < 80 ms)	5.0 (1.5–17.1)	0.01
Persistent BiV Pacing	7.7 (1.5–39.9)	0.02

* *Note.* Using backward Wald selection by entering ECG predictors significant at $p < 0.10$ in the univariate model. HR: hazard ratio; CI: confidence interval; SCA: sudden cardiac arrest or equivalent; C/NS: cardiovascular non-sudden death; HRV: heart rate variability.

Table 5

Impact of Analyzing QTc in Patients with Atrial Fibrillation

ECG Parameter (n = 197)		SCA (n = 30)					
		AF group excluded			AF group included		
		n	HR (95% CI)	p	n	HR (95% CI)	p
Prolonged QTc	Normal	77	Reference	-	87	Reference	-
	Abnormal	48	2.9 (1.2–7.3)	0.02	65	2.1 (0.9–4.9)	0.08
	Cannot Assess	72	1.6 (0.6–4.3)	0.32	45	1.4 (0.5–3.9)	0.53

Note. SCA: sudden cardiac arrest or equivalent; AF: atrial fibrillation; HR: hazard ratio