MAYO CLINIC

ORIGINAL ARTICLE

Institution-Wide QT Alert System Identifies Patients With a High Risk of Mortality

Kristina H. Haugaa, MD, PhD; J. Martijn Bos, MD, PhD; Robert F. Tarrell, MS; Bruce W. Morlan, MS; Pedro J. Caraballo, MD; and Michael J. Ackerman, MD, PhD

Abstract

Objectives: To determine the phenotype and outcome of patients with QTc of at least 500 ms and to create a pro-QTc risk score for mortality.

Patients and Methods: An institution-wide computer-based QT alert system was developed and implemented at Mayo Clinic in Rochester, Minnesota. This system screens all electrocardiograms (ECGs) performed and alerts the physician if the QTc is 500 ms or greater. Between November 10, 2010, and June 30, 2011, 86,107 ECGs were performed in 52,579 patients. Clinical diagnoses, laboratory abnormalities, and medications known to influence the QT interval were collected from the medical records and summarized in a new pro-QTc score. Survival was compared with that of the 51,434 Mayo Clinic patients with a QTc less than 500 ms during the same period.

Results: QT alerts were sent for 1145 patients (2%); of these, 470 (41%) had no other identifiable ECG reason for QT prolongation (eg, pacing). All-cause mortality during a mean ± SD of 224±174 days of follow-up was 19% in those with QTc of 500 ms or greater compared with 5% in patients with QTc less than 500 ms (log-rank $P<.001$). The pro-QTc score was an age-independent predictor of mortality (pro-QTc score: hazard ratio, 1.18; 95% CI, 1.05-1.32; $P=.006$; age: hazard ratio, 1.02; 95% CI, 1.01-1.03; $P=.004$.). QT-prolonging medications accounted for 37% of the pro-QTc score.

Conclusion: This novel institution-wide QT alert system identified patients with a high risk of mortality. The pro-QTc score, reflecting patients' multimorbidity and multipharmacy, was an independent predictor of mortality. The QT alert system may increase a physician's awareness of a high-risk patient. Potentially lifesaving interventions can be facilitated by reducing the modifiable factors of the pro-QTc score.

 ■ Mayo Clin Proc. 2013;88(4):315-325

QT prolongation is an independent risk factor for sudden death in patients with and without congenital long QT syndrome (LQTS) and is also a predictor of all-cause cardiovascular mortality and stroke.[1-9] Sudden death secondary to drug-induced QT prolongation and torsades de pointes ventricular arrhythmias continues to be a major problem[10-12] and is the most common reason for withdrawal of medications after approval, including terolidine in 1991, astemizole in 1998, mibefradil in 1998, terfenadine in 1998, grepafloxacin in 1999, cisapride in 2000, levomethadyl in 2004, and propoxyphene in 2010.[13]

Presently, there are more than 100 Food and Drug Administration–approved medications with either known QT-prolonging or torsadogenic potential.[14] These medications cross all disciplines of medicine, and yet the average health care professional's awareness of QTc as a predictor of death is lagging. In fact, the American Heart Association and the American College of Cardiology have called for the need for early identification of the QT at-risk host and improved monitoring of such patients when exposed to medications with significant QT-prolonging or torsadogenic potential.[7] The effect of a QT-prolonging medication can be aggravated when combined with electrolyte disturbances and other comorbidities in the QT-vulnerable host.[15] Importantly, several of the QT-prolonging conditions are modifiable, and the risk of death can, therefore, be reduced if detected.

Given this American Heart Association/American College of Cardiology recommendation to identify a QT-vulnerable host as early as possible, we developed and implemented an institution-wide QT alert system at the Mayo

For editorial comment, see page 309

From the Division of Cardiovascular Diseases (K.H.H., M.J.A.), Department of Molecular Pharmacology and Experimental Therapeutics (J.M.B.), Department of Biomedical Statistics and Informatics (R.F.T.), Division of Health Care Policy and Research (B.W.M.), Division of General Internal Medicine (P.J.C.), and Division of Pediatric Cardiology (M.J.A.), Mayo Clinic, Rochester, MN.

Clinic in Rochester, Minnesota, in November 2010 whereby the ordering physicians receive an electronic alert of their patients' prolonged QTc value coupled with a link to the website "AskMayoExpert" to inform and guide them regarding the potential significance of this electrocardiographic (ECG) finding. Herein, we report our early experience with respect to this system, the frequency of alerted ECGs, the phenotypic profiles of patients with an alerted ECG, and their mortality outcome. Furthermore, we introduce a pro-QTc score as a clinical tool for detecting patients at increased risk for death in whom the risk of mortality may be modifiable.

PATIENTS AND METHODS

Performance and Analyses of ECGs

Between November 10, 2010, and June 30, 2011, 86,107 ECGs for 52,579 unique patients were performed at Mayo Clinic in Rochester, Minnesota. The ECG analyses were performed using a 12-lead ECG and the 12SL ECG analysis program from GE Marquette Medical Systems or Cardiology Org@nizer from Esaote. All electronically generated reports were evaluated by an ECG technician trained in ECG interpretation and, where needed, corrected.[16] Pediatric and questionable abnormal ECG findings were evaluated subsequently by a pediatric/adult cardiologist. In cases of high-risk ECGs, the ECG laboratory assigned a "semi-urgent finding" (Marquette Code 1707) to the ECG. This retrospective study was approved by the Mayo Clinic Institutional Review Board.

QT Alert System Algorithm

Mayo Clinic in Rochester uses Centricity Enterprise (GE Healthcare) as the main component of the electronic medical record (EMR). Blaze Advisor (FICO) is a commercial knowledge-based decision support system that has been integrated into the Centricity Enterprise applications to enhance their capabilities by using rules management technology. This system allows experts at Mayo Clinic to represent knowledge and to develop, deploy, and maintain clinical rules integrated into the clinical workflow. Via an interface, the EMR receives all the ECG reports as images and as elemental data.

The ECGs and ECG reports from the ECG laboratory were surveyed, and values were extracted for the following variables: age, heart rate, QRS duration, and QTc interval by the Bazett formula[17] and an indicator for the presence of atrial fibrillation or atrial flutter. These measures were analyzed by the algorithm to determine whether an ECG showed marked QT prolongation (Figure 1). If the algorithm was satisfied, an automatic "semi-urgent finding" alert notification was sent to the ordering physician. Independent of the algorithm, a semi-urgent finding related to the QTc followed by physician notification could also be assigned to an ECG manually by the ECG laboratory based on the ECG interpretation by the ECG technician and cardiologist. Pediatric and adult ECGs were evaluated separately.

Pediatric Patients

The ECGs from patients younger than 18 years were defined as pediatric and were analyzed separately. Pediatric ECGs with QRS duration of 120 ms or less and QTc of 470 ms or more were evaluated for heart rate. If heart rate was less than 150 beats/min, the defined pediatric alert criteria were met and a QT alert was sent. All ECGs with QRS duration greater than 120 ms and heart rate less than 150 beats/min were QT alerted if QTc was at least 550 milliseconds. The ECGs with a heart rate of 150 beats/min or greater were not further evaluated (Figure 1).

Adult Patients

All ECGs with QRS duration of 120 ms or less and QTc of 500 ms or greater were evaluated for heart rate. If heart rate was less than 100 beats/min, the defined alert criteria were met and a QT alert was sent. All ECGs with QRS duration greater than 120 ms and heart rate less than 100 beats/min were QT alerted if QTc was 550 ms or greater. The ECGs with a heart rate of 100 beats/min or greater were not further evaluated (Figure 1).

Analyses of ECGs by a Cardiologist

All alerted ECGs were reviewed additionally by a research cardiologist (K.H.H.) blinded to the QT interval measurements by the ECG laboratory. For patients with more than 1 alerted ECG during the study period, the first alerted ECG was chosen. The QT interval was

Mayo Clin Proc. ■ April 2013;88(4):315-325 ■ http://dx.doi.org/10.1016/j.mayocp.2013.01.013
www.mayoclinicproceedings.org

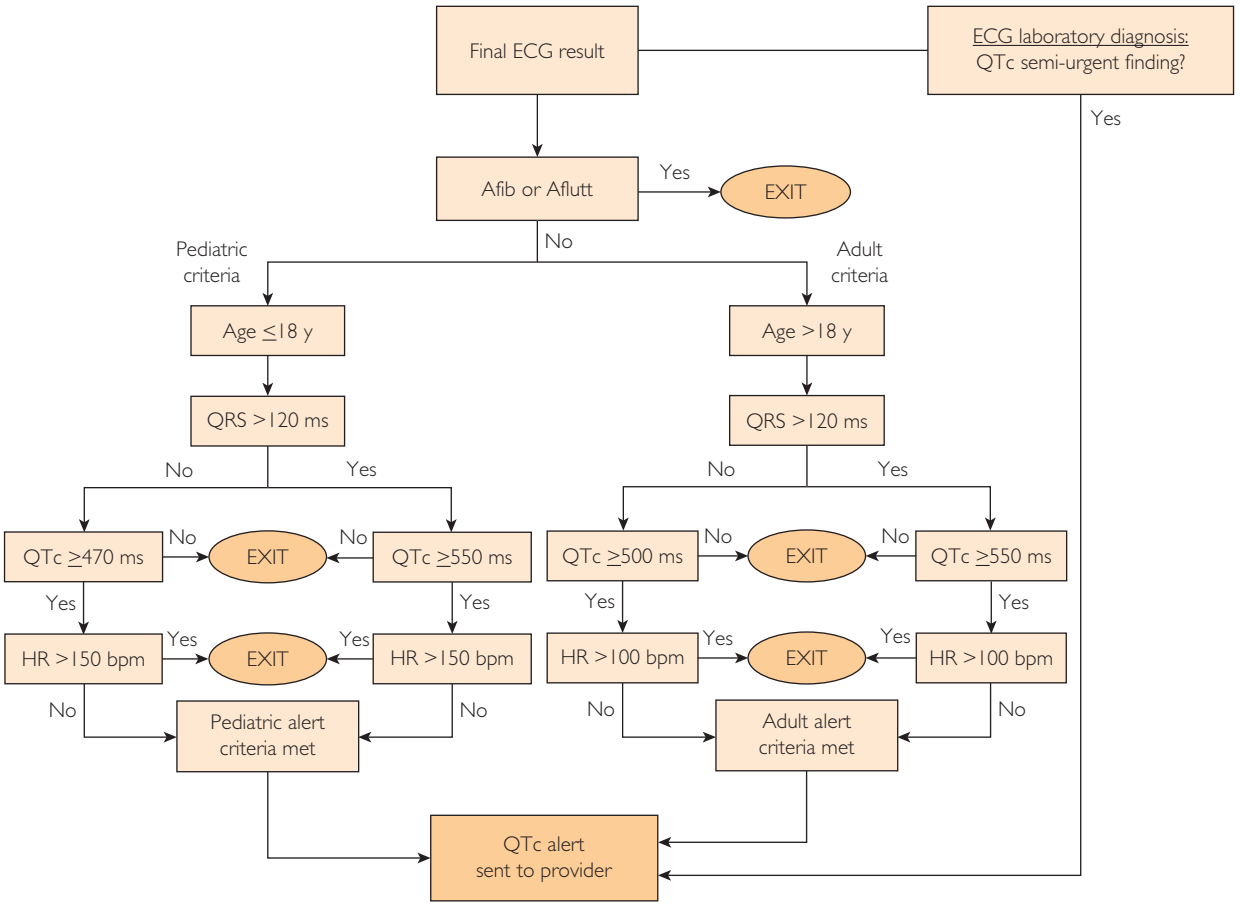

FIGURE 1. Algorithm showing the decision process of the QTc alert system. Electrocardiograms (ECGs) with atrial fibrillation were not analyzed by the algorithm. Different QTc thresholds were used for pediatric and adult ECGs. The ECGs with QRS duration greater than 120 ms required higher QTc values to meet the alert criteria. The ECGs with tachycardia were not evaluated. Afib = atrial fibrillation; Aflutt = atrial flutter; bpm = beats/min; HR = heart rate.

measured manually in the lead showing the longest QT interval as a mean of 3 consecutive beats. The end of the T wave was determined by the tangent method, and U waves were not included if they were distinct from T waves.[18]

In addition, every alerted ECG was evaluated manually regarding the presence of the following factors that affect the QT interval: bundle branch block, ventricular pacing, atrial fibrillation, atrial flutter or other supraventricular tachycardias, ST-T changes of typical ischemic origin, and left ventricular hypertrophy by Sokolow-Lyon[19] and Cornell[20] voltage criteria. These ECGs were excluded from further analyses. If none of these ECG diagnoses were present, the ECG was defined as ECG isolated QTc of at least 500 ms.

Comparison of QTc Values by the Cardiologist and the ECG Laboratory

The QT interval measured by the cardiologist was defined as being in agreement with the QT interval from the ECG laboratory/automated measurement if it was within ±10 ms. If the ECG laboratory QTc differed by more than 10 ms from the cardiologist's manually derived QTc, the latter was used in further analyses.

Clinical Data

For patients with ECG isolated QTc of 500 ms or greater, clinical data were obtained from the EMRs. All the records were reviewed manually, and the following variables were recorded. (1) Main admission diagnosis; diagnoses were collected in all available notes and letters and then were categorized into 9 groups: cardiovascular,

infectious, malignancy, pulmonary, renal, gastrointestinal, psychiatric (including intoxications), neurologic, and traumatic. (2) Presence of any condition or factor influencing the QTc as defined in Table 1. (3) Mortality and cause of death if death was in-hospital or if a death certificate was obtained. If death occurred out of the hospital, a death diagnosis was recorded if a physician or the patient's relatives had communicated cause of death to Mayo Clinic. Otherwise, the cause of death was recorded as unknown.

Laboratory Data

For patients with an ECG isolated QTc of 500 ms or greater, laboratory data regarding serum potassium (K), magnesium (Mg), calcium (Ca), and creatinine were extracted from the EMR. For K, Mg, and Ca, data were collected from 48 hours before to 48 hours after the alerted ECG. If multiple data points were present, the data closest to and before the ECG was chosen. Values below the reference values for Mayo Clinic were defined as hypo-K (<3.6 mmol/L), hypo-Mg (<1.7 mg/dL [to convert to mmol/L, multiply by 0.411]), and hypo-Ca (<4.65 mg/dL [to convert to mmol/L, multiply by 0.25]). For Ca, only ionized Ca^{2+} was used. Creatinine values were collected up to 30 days before the date of ECG. The value closest in time to the ECG was selected. If no creatinine level was available before ECG, values up to 2 days after the ECG time point were included.

TABLE 1. QT-Prolonging Diagnoses and Conditions With a Pro-QTc Score of 1[a,b]

Diagnosis/condition	No. (%) of patients (n=470)
Acute coronary syndrome (≤7 d)	26 (6)
Anorexia nervosa or starvation	6 (1)
Bradycardia (heart rate <45 beats/min)	3 (<1)
Cardiac heart failure (EF <40%)	47 (10)
Diabetes mellitus (types 1 and 2)	88 (19)
Female sex	263 (56)
Hypertrophic cardiomyopathy	6 (1)
Hypoglycemia (documented and in the absence of diabetes)	1 (<1)
Intoxication with QT-prolonging drug (≤24 h)	8 (2)
Long QT syndrome	45 (10)
Pheochromocytoma	2 (<1)
Renal dialysis	25 (5)
Status after AF conversion (7 d after cardioversion, radiofrequency ablation, or the Maze procedure)	4 (1)
Status after cardiac arrest (24 h)	8 (2)
Status after syncope or seizure (24 h)	9 (2)
Stroke, SAH, head trauma (≤7 d)	16 (3)
Electrolyte disturbances	
Hypocalcemia (calcium <4.65 mg/dL)	131 (28)
Hypokalemia (potassium <3.6 mmol/L)	121 (26)
Hypomagnesemia (magnesium <1.7 mg/dL)	74 (16)
QT-prolonging medication	
≥1 Medication from CredibleMeds during the previous 7 d	310 (66)
Pro-QTc score ≥1	465 (99)

[a]AF = atrial fibrillation; EF = ejection fraction; SAH = subarachnoidhemorrhage.
[b]SI conversion factor: To convert calcium values to mmol/L, multiply by 0.25; to convert magnesium values to mmol/L, multiply by 0.411.

Medication Data

Medication data for each patient with isolated QTc of 500 ms or greater were collected from the EMRs. All the medications within 7 days before the alerted ECG were reviewed, and all the QT-prolonging medications were recorded. QT-prolonging medications were defined as medications present on the Arizona CredibleMeds QT drug list.[14]

Pro-QTc Score

QT-prolonging conditions and factors were summarized in a pro-QTc score. This score included female sex, QT-affecting clinical diagnoses and conditions, QT-prolonging electrolyte disturbances, and QT-prolonging medication(s) present on the Arizona CredibleMeds QT drug list (Table 1). For the purposes of this study, each QT-prolonging data point, drug, or medical condition was considered equipotent and was designated 1 point.

Statistical Analyses

Continuous data are presented as mean ± SD or as median (range). Comparisons of means were analyzed by the unpaired *t* test and proportions by the χ^2 test (SPSS, version 19; SPSS Inc). Cox regression analysis was performed to identify predictors of mortality. Significant predictors ($P<.05$) from univariable analyses were included in the multivariable model. The variables pro-QTc score and pro-QTc score categorized into less than 4 or 4 or greater were analyzed separately in the multivariable Cox regression model. Kaplan-Meier analyses were used to create survival curves. Two-sided $P<.05$ was considered significant.

RESULTS

Performed ECGs and ECG Diagnoses

Of the 86,107 ECGs performed in 52,579 unique patients, 1145 unique patients (2%)

Mayo Clin Proc. ■ April 2013;88(4):315-325 ■ http://dx.doi.org/10.1016/j.mayocp.2013.01.013
www.mayoclinicproceedings.org

had one or more ECGs that received a QT alert (Figure 2). Electronic alerts were sent to 684 different physicians (>20% of Mayo Clinic's physician staff) across all disciplines of medicine. Computer-derived vs manual QTc concordance was 93% for the 1145 patients with a QT-alerted ECG (data not shown). The QTc was adjusted manually to higher values in 48 of 1145 patients (4.2%) and to lower values in 39 (3.4%), with an intraclass correlation coefficient between manually and automatically measured QTc values of 0.60. Electrocardiographically isolated QTc of 500 ms or greater was present in 470 of 1145 patients (41%). In addition, obtained ECG diagnoses known to affect QTc and not included for further analyses included ventricular pacing in 213 (19%), bundle branch block in 140 (12%), ST-T changes of ischemic origin in 115 (10%), left ventricular hypertrophy in 102 (9%), incomplete right bundle branch block in 41 (4%), and other ECG findings in 64 (6%).

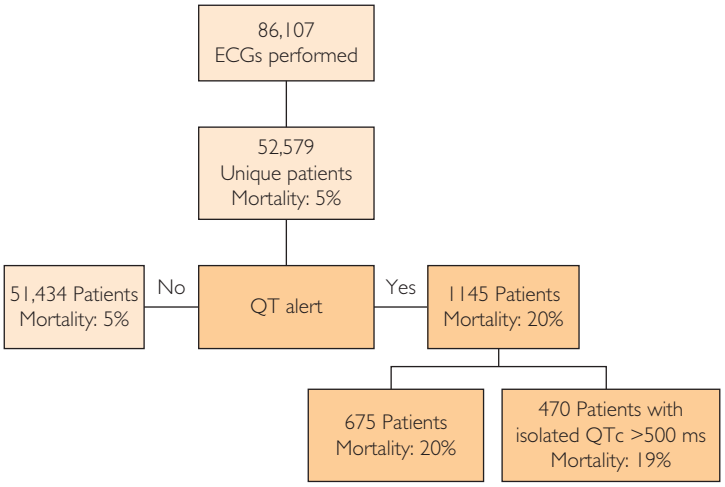

FIGURE 2. Flowchart of electrocardiograms (ECGs) performed at Mayo Clinic during the study period. Of the 52,579 unique patients, 1145 (2%) received a QT alert. The mortality rate for patients with a QT alert was markedly higher than that for patients without a QT alert. Of the alerted ECGs, 470 showed ECG isolated QT prolongation, and QT prolongation was explained by ventricular pacing, bundle branch block, ischemic ST-T changes, etc, in 675 ECGs.

Patients With ECG Isolated QTc of 500 ms or Greater and Their Pro-QTc Scores

The demographic characteristics of the 470 patients with ECG isolated QTc of 500 ms or greater are given in Table 2. Cardiovascular diagnoses were the most frequent main admission diagnoses (214/470, 46%) and included 45 patients (10%) having a clinical/genetic diagnosis of congenital LQTS. The next most common admission diagnoses were infectious and gastrointestinal diseases (64/470, 13% each). At least 1 diagnosis associated with QT prolongation was present in 271/470 (58%) of patients (Figure 3, A). By including female sex as a QTc risk factor (n=263), at least 1 known QTc risk factor was present in 99% of patients. The mean number of diagnoses was 0.7 (range, 0-3). The most common single QT-prolonging diagnosis was diabetes mellitus, which was present in 88 patients (19%). In all, 251 patients (53%) had decreased K, Mg, or Ca^{2+} levels or a combination of these, whereas normal electrolytes regarding K, Mg, and Ca^{2+} were present in 219 (47%). The mean number of electrolyte disturbances was 0.7 (range, 0-3).

In all, 310/470 (66%) of patients received at least 1 QT-prolonging medication (Figure 3, B), and the mean number of QT-prolonging medications was 1.1 (range, 0-5). Of the QT-prolonging medications, antidepressants were most common (143/533 medications given, 27%), followed by antiarrhythmics (109/533 medications given, 20%) and antibiotics/antifungals (107/533 medications given, 20%). After summing female sex, QT-prolonging diagnoses and conditions, laboratory/electrolyte abnormalities, and medications into a pro-QTc score, the mean pro-QTc score was 3.1 (range, 0-9) (Figure 3, D). Only 5 unique patients (1%) had a pro-QTc score of 0. Excluding female sex (n=263), medications were the greatest contributors to the pro-QTc score, with a score-proportion of 533/1455 (37%), followed by QT-prolonging diagnoses (330/1455, 23%) and electrolyte abnormalities (326/1455, 22%).

Mortality

Mortality in Patients With ECG Isolated QTc of 500 ms or Greater. During the study period, all-cause mortality for the 470 patients with ECG isolated QTc of at least 500 ms was 19% (n=87) and was increased markedly compared with 5% mortality in the 51,434 patients with QTc less than 500 ms (log-rank $P<.001$) (Figure 4, A) despite being significantly younger (mean ± SD age = 55±24 vs 61±17 years;

TABLE 2. Demographic Characteristics of the 470 Patients With Electrocardiographically Isolated QTc of at Least 500 ms[a,b,c]

Characteristic	Total (N=470)	Survivors (n=383)	Nonsurvivors (n=87)	*P* value[d]
Age (y)	55±24	53±25	65±17	<.001
Female sex	263 (56)	221 (58)	42 (48)	.11
White race	430 (91)	346 (90)	84 (97)	.60
Heart rate (beats/min)	80±17	80±17	80±15	.99
QRS duration (ms)	92±14	91±14	95±14	<.01
QRS duration excluding patients with LQTS (ms)	93±14	92±13	95±14	.10
QTc (ms)	517±33	516±32	521±34	.17
Serum creatinine (mg/dL)	1.5±1.7	1.4±1.7	1.9±1.6	.03
Hypokalemia (potassium <3.6 mmol/L)	121/408 (30)	90/324 (28)	31/84 (37)	.10
Hypomagnesemia (magnesium <1.7 mg/dL)	74/328 (23)	53/251 (21)	21/77 (27)	.25
Hypocalcemia (calcium <4.65 mg/dL)	131/228 (57)	98/172 (57)	33/56 (59)	.80
Cardiovascular main diagnosis	214 (46)	192 (50)	22 (25)	<.001
Cardiovascular main diagnosis excluding patients with LQTS	169 (36)	147 (38)	22 (25)	.002
LQTS	45 (10)	45 (12)	0	.001
Pro-QTc score	3.1±1.6	3.0±1.6	3.8±1.9	<.001
Pro-QTc score excluding patients with LQTS	3.2±1.7	3.1±1.6	3.8±1.9	.001

[a]LQTS = long QT syndrome.
[b]Values are mean ± SD for continuous variables and No. (percentage) for categorical variables.
[c]SI conversion factors: To convert creatinine values to μmol/L, multiply by 88.4; to convert calcium values to mmol/L, multiply by 0.25; to convert magnesium values to mmol/L, multiply by 0.411.
[d]By unpaired *t* test or χ^2 test.

P<.001; data not shown). Mortality at 6 months was 14% in those with isolated QTc of 500 ms or greater and 3% in those with QTc less than 500 ms (*P*<.001), and mortality at 1 year was 18% and 5%, respectively (*P*<.001).

A death diagnosis was obtained in 77 of 87 of these decedents (89%). The most frequent death diagnosis was malignancy in 23 patients (26%), followed by cardiovascular death in 18 (21%) and infectious disease/sepsis in 17 (20%). The 23 patients who died of malignancy received an even higher mean ± SD number of QT-prolonging medications compared with those who died of other causes (2.0±1.3 vs 1.3±1.1 medications; *P*=.02), whereas QTc and age did not differ. However, there is no way of knowing whether a drug-induced torsadogenic environment was being created for these patients, thereby accelerating their malignancy-related mortality, or whether the QTc and the patient's higher pro-QTc score were simply a surrogate of an extremely unwell host about to succumb to the malignancy. Of the 18 patients with a cardiovascular death diagnosis, 7 died suddenly, 8 died of progressive heart failure, 2 died of cardiac amyloidosis, and 1 died of an unspecified cardiovascular disorder.

The pro-QTc score, age, and noncardiovascular diagnoses were independent predictors of mortality. A pro-QTc score of 4 or greater predicted mortality with a hazard ratio (HR) of 1.72 (95% CI, 1.11-2.66; *P*<.001) (Table 3). Kaplan-Meier analysis showed that patients with a pro-QTc score of 4 or greater had significantly higher mortality than did patients with a pro-QTc score less than 4 (log-rank *P*<.001) (Figure 4, B and C). Mortality was 22% (37 of 167 patients) at 6 months and 27% (45 of 167 patients) at 1 year in those with a pro-QTc score of 4 or greater compared with 10% (30 of 303 patients) at 6 months and 13% (38 of 303 patients) at 1 year for those with a pro-QTc score less than 4 (*P*<.001 for both).

Analyses of the pro-QTc score subcomponents (female sex, QT-prolonging diagnoses and conditions, QT-prolonging electrolyte abnormalities, and QT-prolonging medications) by Cox multivariable analyses showed that only number of QT-prolonging medications (HR, 1.20; 95% CI, 1.03-1.40; *P*=.02) and electrolyte abnormalities (HR, 1.39; 95% CI,

Mayo Clin Proc. ■ April 2013;88(4):315-325 ■ http://dx.doi.org/10.1016/j.mayocp.2013.01.013
www.mayoclinicproceedings.org

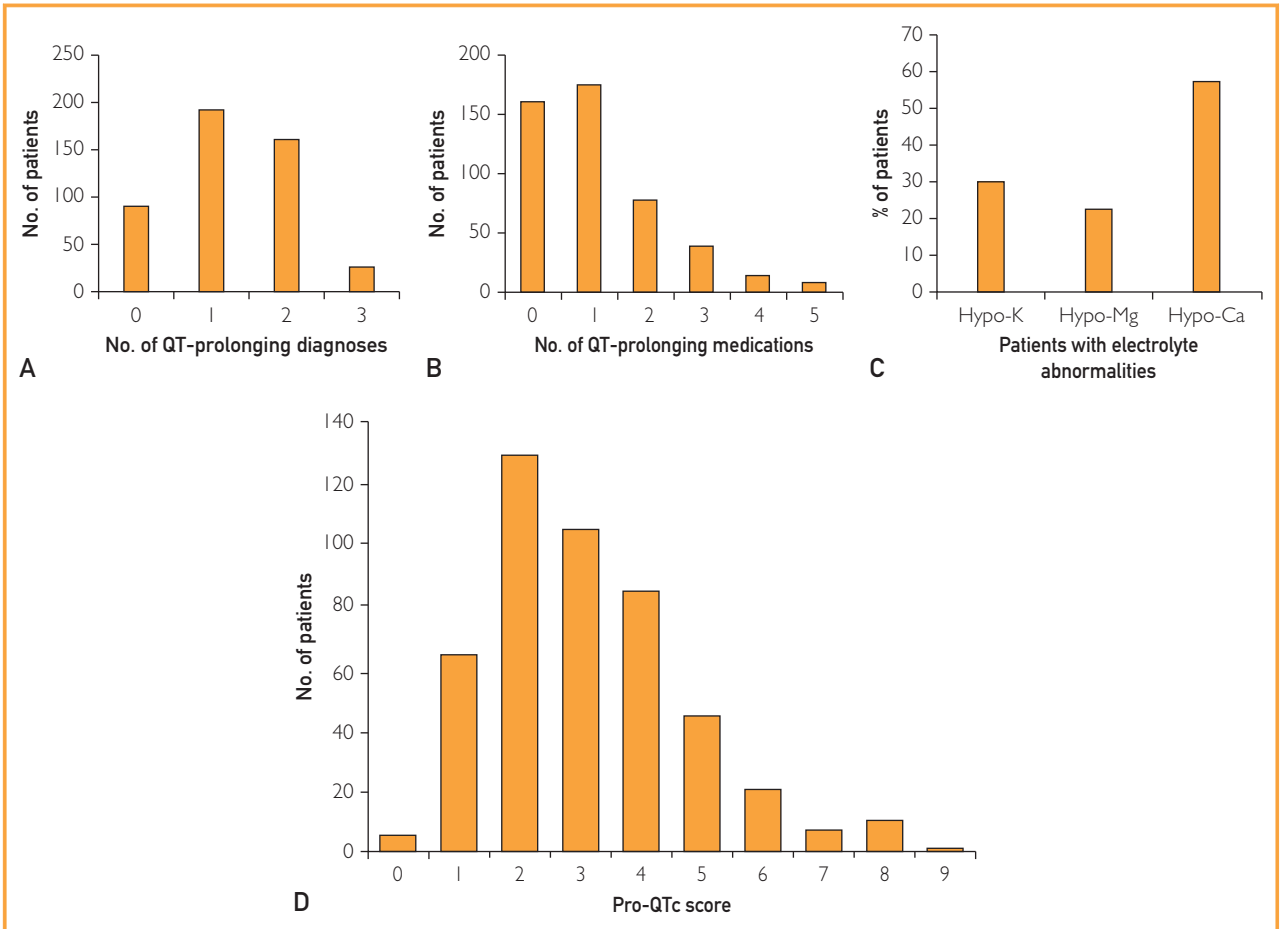

FIGURE 3. Bar charts of components of the pro-QTc score. A, Number of patients with QT-prolonging diagnoses. B, Number of patients taking QT-prolonging medications. C, Proportion of patients with electrolyte abnormalities. D, The number of patients with pro-QTc scores. The mean pro-QTc score was 3.1 (range, 0-9). Ca = calcium; K = potassium; Mg = magnesium.

1.10-1.75; *P*=.005) were significant predictors of death, whereas female sex and number of QT-prolonging diagnoses were not (HR, 0.92; 95% CI, 0.71-1.18; *P*=.49).

By using a pro-QTc score including QT-prolonging electrolyte abnormalities and medication only (Figure 4, D) in the multivariable Cox regression model together with age, creatinine level, QRS duration, and cardiovascular admission diagnosis, the predictive value of mortality was even higher (HR, 1.26; 95% CI, 1.10-1.44; *P*=.001) than with a pro-QTc score that included female sex and diagnoses and conditions known to affect the QT interval (Table 3).

Mortality analyses by main hospital admission diagnoses showed that patients with cardiovascular diagnoses (n=214) had better survival compared with patients with noncardiovascular diagnoses (log-rank *P*<.001) (Table 3). Patients with cardiovascular diagnoses were younger (mean ± SD age = 51±28 vs 59±21 years; *P*<.001) and had lower mean ± SD pro-QTc scores (2.7±1.5 vs 3.4±1.7; *P*<.001), higher mean ± SD levels of K (4.0±0.5 vs 3.7±0.6 mmol/L; *P*<.001) and Mg (2.0±0.3 vs 1.9±0.4 mg/dL; *P*=.001), and a lower mean ± SD heart rate (77±18 vs 82±16 beats/min; *P*<.001) but similar QTc (*P*=.16) and QRS duration (*P*=.38) compared with patients with noncardiovascular diagnoses. Patients with cardiovascular diagnoses also had better survival when patients with LQTS were excluded from the analyses (log-rank *P*<.008) (Table 3). Congenital LQTS did not contribute risk to the pro-QTc score because there were no deaths in the subset of patients with LQTS and an alerted QTc (n=45).

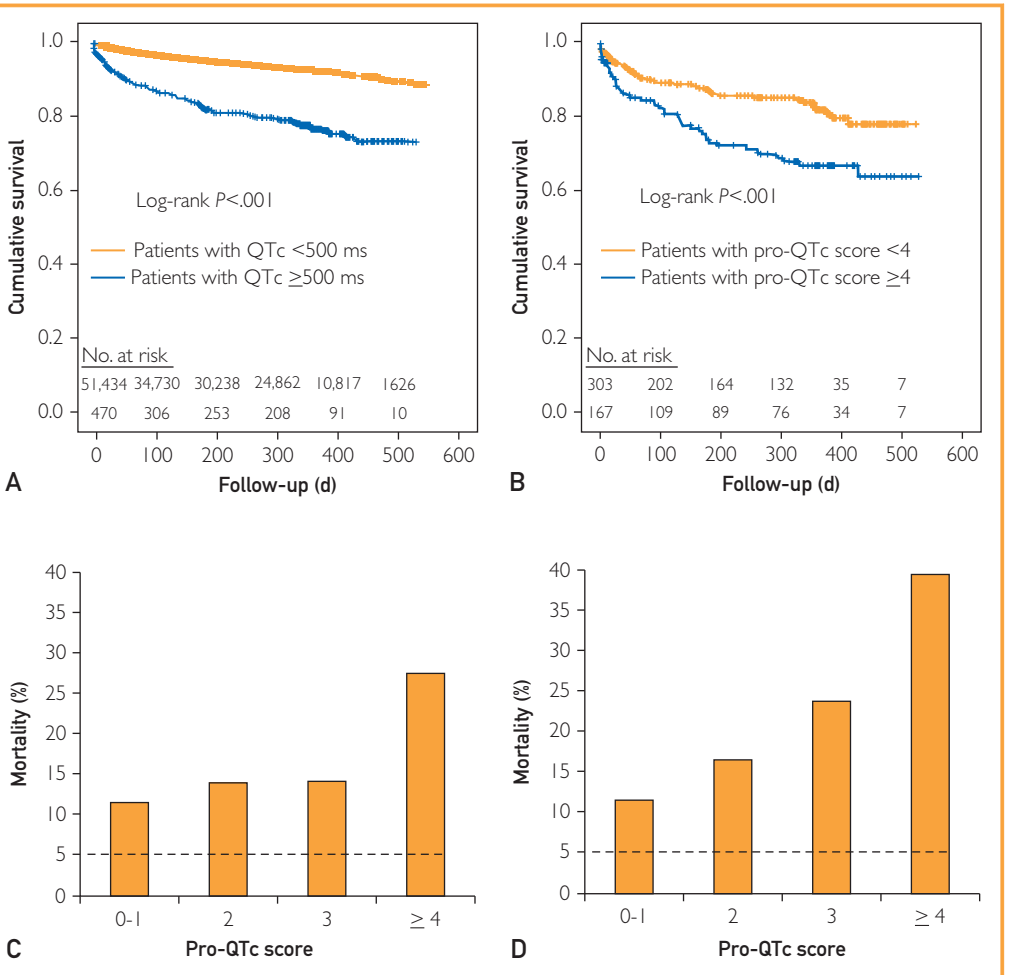

FIGURE 4. A, Kaplan-Meier analyses of 51,343 patients who underwent electrocardiography (ECG) at Mayo Clinic during 7 months' registration with QTc less than 500 ms compared with 470 patients with ECG isolated QTc of 500 ms or greater. Patients with QTc of 500 ms or greater show significantly higher mortality. B, Kaplan-Meier analyses of 470 patients with ECG-isolated QTc of 500 ms or greater. Patients with a pro-QTc score of at least 4 show significantly higher mortality compared with those with a pro-QTc score less than 4. Bar charts of pro-QTc score and relation to mortality (C) and (D) pro-QTc score including medication and laboratory data only and relation to mortality in 470 patients with ECG isolated QTc of 500 ms or greater (D). The charts display increasing mortality in a dose-dependent manner along with increasing pro-QTc scores. The dashed lines represent the 5% mortality for those with QTc less than 500 ms.

Mortality in the Total Population of 52,579 Unique Patients. In the total sample, all-cause mortality was 5% (2875 of 52,579 patients) during mean ± SD follow-up of 224±173 days. QTc was a significant predictor of mortality (HR, 1.13; 95% CI, 1.12-1.14; per 10-ms increase, $P<.001$), independently of age and sex. Females had a lower mortality risk compared with males in the total sample (HR, 0.9; 95% CI, 0.79-0.91; $P<.001$; data not shown).

DISCUSSION

A QTc of at least 500 ms is a powerful risk predictor of total mortality. Herein, we present an institution-wide tool for detecting patients with marked QT prolongation who are being treated by physicians across all disciplines of medicine. Furthermore, we present a pro-QTc score representing multimorbidity and multipharmacy in patients with extremely prolonged QT. Mortality rates were increased clearly by increasing pro-QTc scores, and because most components

Mayo Clin Proc. ■ April 2013;88(4):315-325 ■ http://dx.doi.org/10.1016/j.mayocp.2013.01.013
www.mayoclinicproceedings.org

of the pro-QTc score are modifiable, a QT alert system that increases physician awareness of QT-predicted mortality may help the physician not only to identify an at-risk patient but also to intervene by addressing the conditions contributing to a patient's pro-QTc score.

QTc: A Powerful Risk Predictor of Mortality

This study confirmed QTc as a potent risk predictor of mortality. Previous studies have shown the ability of QTc to predict sudden cardiac arrest, cardiovascular mortality, and stroke.[1-7] Herein, we demonstrate a markedly increased all-cause mortality rate in patients with QTc of at least 500 ms compared with patients with QTc less than 500 ms. As a noninvasive, widely available clinical tool, ECG is performed in millions of patients daily. However, despite the profound evidence of QTc as a risk predictor, awareness of prolonged QTc is still lagging. Based on this background, we developed and implemented an institution-wide QT alert system. During the study period, 2% of all administered ECGs received a QT alert, and nearly 700 unique physicians were informed electronically of their patient's marked QT prolongation. Nearly one-quarter of our faculty, practicing in essentially every specialty of medicine and pediatrics, has received at least one QT alert.

Mortality and QT-Prolonging Conditions

Mortality rates increased in a dose-dependent manner with increasing pro-QTc scores. Medication was the main contributor to increased pro-QTc scores, with as many as 5 QT-prolonging drugs identified in some patients. This finding is in line with previous studies showing increased mortality risk in multimorbid patients with multipharmacy.[6,10] Documentation of antidepressants and antibiotics with a known QT-prolonging adverse effect contributed to the high pro-QTc scores in this study, as also shown by others.[11] Antidepressants can be well tolerated under normal conditions but can be potentially lethal when combined with other medications and situations. A typical example is a patient receiving an antidepressant medication who is treated for an infection with an antibiotic agent having QT-prolonging potential and who may have concomitant electrolyte abnormalities. An emerging "QT perfect storm" like this can be overseen easily, and physician awareness of these potentially dangerous scenarios is required. When a physician is aware of a patient's prolonged QT and, therefore, the possibility of such a scenario, QT-related sudden death preventive measures can be initiated.

TABLE 3. Predictors of Mortality by Cox Regression Multivariable Analyses[a,b]

Predictor	HR	95% CI	*P* value
470 Patients with ECG isolated QTc ≥500 ms			
Age (per year)	1.02	1.01-1.03	.004
QRS duration (per ms)	1.01	0.99-1.03	.22
Serum creatinine (per 1 mg/dL)	1.11	1.01-1.23	.04
Cardiovascular diagnosis (yes vs no)	0.54	0.33-0.90	.02
Pro-QTc score (per point)[c]	1.18	1.05-1.32	.006
Pro-QTc score ≥4[c]	1.72	1.11-2.66	<.001
425 Patients with ECG isolated QTc ≥500 ms excluding patients with LQTS			
Age (per year)	1.02	1.01-1.03	.005
Serum creatinine (per 1 mg/dL)	1.12	1.02-1.24	.02
Cardiovascular diagnosis (yes vs no)	0.58	0.35-0.95	.02
Pro-QTc score (per point)[c]	1.17	1.04-1.31	.008
Pro-QTc score ≥4[c]	1.70	1.10-2.63	.02

[a]ECG = electrocardiographically; HR = hazard ratio; LQTS = long QT syndrome.
[b]SI conversion factor: To convert creatinine values to μmol/L, multiply by 88.4.
[c]Pro-QTc score (per point) and pro-QTc score of 4 or greater were analyzed separately.

In this study, the patient's pro-QTc score was a significant predictor of mortality, with medications and electrolyte abnormalities as the most important components. In fact, if the QTc was 500 ms or greater and there were at least 4 QT-prolonging medications or QT-prolonging electrolyte abnormalities present, mortality was 40%. Choice of medications is clearly modifiable because an alternative medication without an unwanted QT effect is almost always available. Awareness of a vulnerable patient identified by the QT alert system, risk stratification by the pro-QTc score, and information about alternative non–QT-prolonging medications may lead to lifesaving changes in treatment and medication. Furthermore, its institution-wide implementation raises QT-related awareness in physicians across all disciplines. At Mayo Clinic, a physician receiving a QT alert is guided to a website providing information about the risk of QT prolongation and about risk-reducing interventions to facilitate lifesaving changes in treatment and medication.

Patients with cardiovascular diagnoses had better survival compared with patients with

noncardiovascular diagnoses independent of age, sex, QTc, and creatinine concentration. Patients with cardiovascular diagnoses had lower pro-QTc scores, including lower numbers of QT-prolonging medications and electrolyte abnormalities. However, the number of medical conditions associated with QT prolongation in patients with cardiovascular diagnoses was even higher compared with that in patients with noncardiovascular diagnoses. We speculate that cardiologists may be the ones taking care of the patients with cardiovascular diagnoses and, as such, might have more QTc respect/awareness and, therefore, might be less likely to stack up/add on/rack up QTc-aggravating factors. These results strengthen the finding that QT-prolonging medications and electrolyte abnormalities have a greater effect on mortality rates compared with QT-prolonging diagnoses as defined in this study and underscore the potentially modifiable character of mortality risk.

In this study, 45 of 470 patients with QTc of 500 ms or greater were patients with clinically diagnosed and genetically confirmed LQTS who were evaluated in Mayo Clinic's LQTS clinic. Therefore, the prevalence of patients with LQTS in the current population was nearly doubled (1.7 per 2000) compared with the estimated prevalence of LQTS in the general population (1 per 2000)[21] owing to likely referral bias. Furthermore, a substantial proportion of patients with LQTS have QTc values below 500 ms, and, therefore, the prevalence of LQTS was even higher. Prognosis in patients with congenital LQTS differs from that in patients with acquired QT prolongation by the absence of QT-prolonging medications and low mortality if sufficiently treated. Every main result presented in this study was analyzed with the 45 patients with LQTS included and excluded with no significant changes in results (Table 3).

Limitations

This study has the inherent limitations of its retrospective design. Prospective studies are necessary to determine whether implementation of the QT alert system precipitates better survival in patients with prolonged QTc and high pro-QTc scores. Also, each condition of the pro-QTc score was considered equipotent owing to lack of specific data for each point. Future research might be able to carefully attribute different potency, resulting in an even more powerful risk stratification tool.

CONCLUSION

This novel institution-wide QT alert system identified patients with a high risk of mortality. Patients with QTc of 500 ms or greater had a nearly 4-fold higher mortality rate compared with patients with QTc less than 500 ms. Among those with such marked QT prolongation, mortality increased further with increasing pro-QTc scores, and medications and electrolyte abnormalities having QT-prolonging effects were the chief contributors to increased pro-QTc scores. QT-prolonging medications can be changed easily in patients with multiple risk factors and prolonged QTc. The institution-wide QT alert system presented in this study may increase physician awareness and prevent life-threatening multipharmacy in multimorbid patients by reducing the amount of QT-prolonging stressors.

Abbreviations and Acronyms: **Ca** = calcium; **ECG** = electrocardiography; **EMR** = electronic medical record; **HR** = hazard ratio; **K** = potassium; **LQTS** = long QT syndrome; **Mg** = magnesium

Grant Support: This study was supported partially by a generous gift from the Frederick W. Smith family and by the Mayo Clinic Windland Smith Rice Comprehensive Sudden Cardiac Death Program. Its contents are solely the responsibility of the authors. Dr Haugaa was funded by the South-Eastern Norway Regional Health Authority and Center for Heart Failure Research, Oslo, Norway.

Potential Competing Interests: Dr Ackerman is a consultant for Transgenomic and chairs their FAMILION Medical/Scientific Advisory Board (approved by Mayo Clinic's Medical-Industry Relations Office and Conflict of Interests Review Board). In addition, "cardiac channel gene screen" and "know-how relating to long QT genetic testing" license agreements, resulting in consideration and royalty payments, were established between Genaissance Pharmaceuticals (then PGxHealth, and now Transgenomic) and Mayo Medical Ventures (now Mayo Clinic Health Solutions) in 2004. Furthermore, Dr Ackerman is a consultant for Boston Scientific Corp, Medtronic, and St Jude Medical Inc.

Correspondence: Address to Michael J. Ackerman, MD, PhD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (ackerman.michael@mayo.edu).

REFERENCES

1. Hobbs JB, Peterson DR, Moss AJ, et al. Risk of aborted cardiac arrest or sudden cardiac death during adolescence in the long-QT syndrome. *JAMA*. 2006;296(10):1249-1254.

2. Zhang Y, Post WS, Blasco-Colmenares E, Dalal D, Tomaselli GF, Guallar E. Electrocardiographic QT interval and mortality: a meta-analysis. *Epidemiology*. 2011;22(5):660-670.
3. Montanez A, Ruskin JN, Hebert PR, Lamas GA, Hennekens CH. Prolonged QTc interval and risks of total and cardiovascular mortality and sudden death in the general population: a review and qualitative overview of the prospective cohort studies. *Arch Intern Med*. 2004;164(9):943-948.
4. Straus SM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol*. 2006;47(2):362-367.
5. Dekker JM, Crow RS, Hannan PJ, Schouten EG, Folsom AR. Heart rate-corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: the ARIC study. *J Am Coll Cardiol*. 2004;43(4):565-571.
6. Soliman EZ, Howard G, Cushman M, et al. Prolongation of QTc and risk of stroke: The REGARDS (REasons for Geographic and Racial Differences in Stroke) Study. *J Am Coll Cardiol*. 2012;59(16):1460-1467.
7. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*. 2010;121(8):1047-1060.
8. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med*. 2003;348(19):1866-1874.
9. Schwartz PJ, Stramba-Badiale M, Segantini A, et al. Prolongation of the QT interval and the sudden infant death syndrome. *N Engl J Med*. 1998;338(24):1709-1714.
10. De Bruin ML, Langendijk PN, Koopmans RP, Wilde AA, Leufkens HG, Hoes AW. In-hospital cardiac arrest is associated with use of non-antiarrhythmic QTc-prolonging drugs. *Br J Clin Pharmacol*. 2007;63(2):216-223.
11. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med*. 2009;360(3):225-235.
12. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med*. 2012;366(20):1881-1890.
13. Drug safety and availability. US Food and Drug Administration website. http://www.fda.gov/Drugs/DrugSafety/default.htm. Accessed July 18, 2012.
14. CredibleMeds website. http://www.qtdrugs.org. Accessed July 18, 2012.
15. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004;350(10):1013-1022.
16. Hammill SC, Andrist EM, Thorkelson LA. Electrocardiogram interpreting technician: training and role in a contemporary electrocardiogram practice. *J Electrocardiol*. 2008;41(5):442-443.
17. Bazett HC. An analysis of the time-relations of electrocardiography. *Heart*. 1920;7:353-370.
18. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram, part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol*. 2009;53(11):982-991.
19. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J*. 1949;37(2):161-186.
20. Casale PN, Devereux RB, Alonso DR, Campo E, Kligfield P. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings. *Circulation*. 1987;75(3):565-572.
21. Schwartz PJ, Stramba-Badiale M, Crotti L, et al. Prevalence of the congenital long-QT syndrome. *Circulation*. 2009;120(18):1761-1767.