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Prolongation of the QTc Interval Predicts Appropriate Implantable Cardioverter-Defibrillator Therapies in Hypertrophic Cardiomyopathy

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Objectives This study sought to determine factors predicting appropriate implantable cardioverter defibrillator (ICD) therapy in a large cohort of patients with hypertrophic cardiomyopathy (HCM).

Background HCM is the leading cause of sudden cardiac death in those age ≤35 years. ICD therapy is offered to select patients at increased risk for sudden cardiac death. Currently, there are no clinical predictors of appropriate ICD therapy in HCM.

Methods Patients attending the HCM clinic in Sydney, Australia, and who had undergone ICD insertion were included. Baseline data on clinical and ICD characteristics were collected. The primary endpoint was the proportion of patients who experienced at least 1 appropriate therapy from the ICD.

Results Of 164 HCM patients included (62% male; mean follow-up, 6 ± 4 years [range, 0 to 19 years]), 21 patients (13%) had at least 1 appropriate therapy. Corrected QT (QTc) interval was the strongest clinical predictor of appropriate ICD therapy (458 ± 30 ms vs. 430 ± 35 ms; p = 0.001). Multivariate logistic regression analysis demonstrated a 1.2-fold increased likelihood of appropriate therapy per 10-ms increase in QTc, independent of left ventricular wall thickness (LVWT) (odds ratio: 1.2; 95% confidence interval [CI]: 1.03 to 1.39; p = 0.02) and sex (odds ratio: 1.2; 95% CI: 1.07 to 1.42; p = 0.003). On analysis of cumulative event-free survival from appropriate ICD therapy, the risk for an appropriate ICD therapy in the subgroup with prolonged QT was >3-fold that in the subgroup without prolonged QT, after adjustment for LVWT (hazard ratio: 3.2; 95% CI: 1.02 to 9.88; p = 0.047) and sex (hazard ratio, 3.7; 95% CI, 1.22 to 11.41; p = 0.02).

Conclusions The findings from this study suggest that QTc interval prolongation is a novel clinical predictor of appropriate ICD therapy in HCM. (J Am Coll Cardiol HF 2013;1:149–55) © 2013 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic disorder characterized by left ventricular hypertrophy in the absence of loading conditions such as hypertension or aortic stenosis (1–3). HCM is a clinically heterogeneous disorder, with presentations ranging from no symptoms to heart failure and sudden cardiac death (SCD) (4–6). HCM affects 1 in 500 of the general population and is the most common structural cause of SCD in patients age ≤35 years, including elite athletes (7).

Prevention of SCD in HCM patients is an important cornerstone of current clinical management. Only implantable cardioverter-defibrillator (ICD) therapy has been reported to effectively prevent SCD at all ages, and specifically in the young (8,9). Of HCM patients in whom an ICD has been implanted, up to one-third have an appropriate therapy within 3 years of implantation (8,10). The current risk-stratification criteria used to identify those with HCM at highest risk for SCD include a history of resuscitated cardiac arrest, severely increased (≥30 mm) left ventricular wall thickness (LVWT), documented nonsustained ventricular tachycardia (NSVT), a family history of SCD due to HCM, and a history of recent unexplained syncope (11). Based on current HCM guidelines, in patients with ≥1 high-risk criterion and a life expectancy of ≥1 year, implantation of an ICD is recommended for the prevention of SCD (12).

Although these risk-stratification criteria for HCM have been extremely helpful in guiding therapies to prevent SCD,

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Abbreviations and Acronyms

AF = atrial fibrillation
ATP = antitachycardia pacing
DCCV = direct current cardioversion
ECG = electrocardiography
HCM = hypertrophic cardiomyopathy
ICD = implantable cardioverter-defibrillator
LQTS = long QT syndrome
LVOT = left ventricular outflow tract
LVWT = left ventricular wall thickness
NSVT = non sustained ventricular tachycardia
SCD = sudden cardiac death
VA = ventricular arrhythmia
VF = ventricular fibrillation
VT = ventricular tachycardia

there remain several outstanding issues. Several reports have suggested that patients with HCM deemed to be at low risk for SCD on the basis of the absence of the established conventional risk factors continue to have SCD events (13). These would suggest that there are other as-yet unidentified risk factors for SCD in HCM (14). Furthermore, no clinical predictors of appropriate ICD therapy during follow-up have been identified. To this end, there are a number of considerations relating to the risk for proarrhythmia in HCM, including severity of left ventricular hypertrophy, extent of cardiac fibrosis, and presence of left ventricular outflow tract (LVOT) obstruction.

Prolongation of the QT interval on electrocardiography (ECG) is an established proarrhythmic factor in familial long-QT syndrome (LQTS) as well as iatrogenic drug-induced QT prolongation (15–17). The role of QT prolongation has also been studied in the context of HCM, with variable findings, although a common feature is the presence of QT prolongation in subsets of HCM patients (18–23). The significance of QT prolongation in HCM remains unresolved. This study was designed to investigate clinical factors predicting appropriate ICD therapy in a large cohort of HCM patients.

Methods

Patients. Patients with a clinical diagnosis of HCM who were assessed at the Hypertrophic Cardiomyopathy Centre at Royal Prince Alfred Hospital, Sydney, Australia, between 1997 and 2011 and who had undergone ICD implantation were included in the analysis. The indications for ICD included the presence of at least 1 of the following risk factors (8): history of resuscitated cardiac arrest; history of SCD in a first-degree relative presumed secondary to HCM; LVWT $\geq$30 mm; documented NSVT, defined as $\geq$3 consecutive beats of VT $\geq$120 beats/min; and a history of recent and unexplained syncope.

Diagnosis of HCM. Diagnosis of HCM was based on conventional echocardiography-based criteria, with the demonstration of a nondilated and hypertrophied left ventricle (LVWT, $\geq$15 mm), in the absence of other loading conditions such as hypertension or aortic stenosis (12).

ECG and echocardiographic analysis. Baseline data, including demographic characteristics, clinical history, medication history, and family history of SCD, were collected. ECG data included corrected QT (QTc) interval, atrial fibrillation (AF), clinically documented NSVT, LVWT, and ST- segment changes. The QT interval was measured in lead II or V_5 and was taken from the earliest onset of the QRS complex to the end of the T-wave, where a line drawn following the down-sloping limb of the T-wave intersected the baseline, and excluding U waves. QT was corrected for heart rate according to the Bazett formula ($QTc = QT/\sqrt{RR}$) and was validated by 2 independent physicians (B.G. and C.M.). The initial ECG at diagnosis was used to measure QTc. Patients were excluded if they had a paced ventricular rhythm. Echocardiographic data included maximal LVWT, left ventricular end-diastolic dimension, presence of LVOT obstruction, and fractional shortening.

ICD therapy analysis. ICD insertion and interrogation data included age at implantation, number of appropriate events, number of inappropriate events, triggering rhythm, and mode of device discharge (i.e., antitachycardia pacing [ATP] or direct-current cardioversion [DCCV]). The primary outcome measure was the proportion of patients with an appropriate ICD event (ATP or DCCV) triggered by ventricular fibrillation (VF) or ventricular tachycardia (VT). These were determined at ICD interrogation by stored intracardiac electrography.

Statistical analysis. Statistical analysis was carried out using SPSS Statistics version 20 (SPSS Inc., Chicago, Illinois) and Prism version 5.0 (GraphPad Software Inc., La Jolla, California). Chi-square analyses and unpaired *t* tests were used to analyze categorical and continuous variables, respectively. Multivariate logistic regression analyses were performed for the investigation of QTc as a predictor of appropriate ICD therapy, with adjustments for LVWT and sex. Pearson correlation was performed to assess the degree of correlation between QTc and LVWT. A receiver-operating characteristics curve was constructed to determine the QT cutoff with highest sensitivity and specificity, where the sum of the sensitivity and specificity is maximized, allowing the creation of a dichotomized QT variable. Multivariate Cox-proportional hazards models were used to assess event-free survival, with adjustments for LVWT and sex. Kaplan-Meier survival analysis and log-rank test for comparison were performed to identify event-free risk by number of ICD risk factors. For continuous variables, mean $\pm$ SD are reported, with p values considered significant at <0.05. For multivariate analysis, adjusted odds ratio (OR) or hazard ratio (95% confidence interval [CI]) was used.

Results

Cohort characteristics. A total of 164 HCM patients were included (Table 1). The mean age at ICD implantation was 42 $\pm$ 17 years and 102 (62%) were male. Over a mean follow-up period of 6 $\pm$ 4 years, 36 patients (22%) received at least 1 discharge from their ICD. This included 21 patients (13%) who received an appropriate discharge and

Table 1 Baseline Characteristics of the Study Population, by Appropriate ICD Therapy

Characteristic	At Least 1 Appropriate ICD Event (n = 21)	No Appropriate ICD Events (n = 143)	p Value
Age at implant, yrs	40 ± 15	42 ± 17	0.74
Male	12 (57)	90 (63)	0.64
Follow-up, yrs	8 ± 4 (1–15)	6 ± 4 (1–19)	0.0002
History			
Primary prevention	17 (81)	132 (92)	0.11
Previous syncope	9 (43)	39 (27)	0.20
Documented NSVT	12 (57)	47 (33)	0.049
Family history SCD	12 (57)	56 (39)	0.09
≥1 risk factor for SCD	10 (48)	38 (27)	0.027
Beta-blocker therapy	14 (67)	89 (62)	0.80

Values are mean ± SD, n (%), or mean ± SD (range).
ICD = implantable cardioverter defibrillator; NSVT = nonsustained ventricular tachycardia; SCD = sudden cardiac death.

Table 2 ECG and Echocardiographic Characteristics of the Study Population

Characteristic	At Least 1 Appropriate ICD Event (n = 21)	No Appropriate ICD Events (n = 143)	p Value
Heart rate, beats/min	69 ± 13	67 ± 11	0.60
Atrial fibrillation	9 (43)	31 (22)	0.05
QRS duration, ms	110 ± 20	105 ± 21	0.40
QTc interval, ms	458 ± 30	430 ± 35	0.001
LV septum, mm	27 ± 9	23 ± 8	0.02
LVOT obstruction at rest	0	6 (5)	1.00

Values are mean ± SD or n (%).
ECG = electrocardiography; ICD = implantable cardioverter defibrillator; LV = left ventricular; OT = left ventricular outflow tract; QTc = corrected QT interval.

18 (11%) who experienced an inappropriate discharge (3 [2%] patients had both). Of those who had appropriate events, 13 (62%) were for VT and 8 (38%) were for VF. In cases with VT, 4 (31%) received successful ATP therapy and 9 (69%) received DCCV. All patients with VF received DCCV therapy. The mean time to first appropriate therapy was 3 ± 3 years.

Clinical predictors of an appropriate ICD therapy. Univariate analyses identified a number of predictors of an appropriate ICD therapy event, including increased LVWT (27 ± 9 mm vs. 23 ± 8 mm; p = 0.02), history of AF (43% vs. 22%; p = 0.05), and documented NSVT (57% vs. 33%; p = 0.049). Family history of SCD events was not associated with a greater proportion of appropriate ICD events (57% vs. 39%; p = 0.09). There were no significant differences in age, sex, indication for ICD (i.e., primary or secondary prevention), history of syncope, or beta-blocker therapy between patients who had experienced an appropriate therapy and those who did not. None of the patients who experienced an appropriate ICD event were on QTc-prolonging medications at the time of the event.

QTc as an independent predictor of an appropriate ICD therapy. Mean QTc on baseline ECG was greater in the group that experienced an appropriate ICD therapy compared to that in those who did not (458 ± 30 ms vs. 430 ± 35 ms; p = 0.001) (Table 2). On logistic regression analysis to determine whether QTc was an independent predictor of an appropriate therapy event, QTc remained significant after adjustments for LVWT (OR: 1.2; 95% CI: 1.03 to 1.39; p = 0.02) and sex (OR: 1.2; 95% CI: 1.07 to 1.42; p = 0.003) (Table 3), with a 1.2-fold increase in likelihood of appropriate ICD therapy per 10-ms increase in baseline QTc. On assessment of additional ECG parameters, the between-group differences in QRS duration and heart rate were not significant (Table 2). QTc remained a strong predictor of appropriate ICD therapies when the data were reanalyzed after the exclusion of patients with a prolonged QRS duration or the exclusion of patients with a history of septal-reduction therapy (surgical myectomy or alcohol septal ablation). Pearson correlation identified a weak but significant association between the 2 continuous variables LVWT and QTc ($r = 0.21$; p = 0.011).

Of those who received an appropriate ICD therapy, 79% had a QTc ≥440 ms (Fig. 1), whereas the corresponding rate in the group with no appropriate events was 40% (p = 0.001). To more accurately determine the appropriate cutoff for QTc interval, a receiver-operating characteristics curve was constructed and a QTc measurement of ≥439 ms was selected, with 79% sensitivity and 61% specificity for predicting an appropriate ICD event (area under the curve, 0.74) (Fig. 2). This cutoff QTc interval was used as a dichotomized variable in subsequent analyses.

Cumulative event-free survival. Patients with a QTc ≥439 ms were 3.2-fold more likely to have an appropriate ICD event as per Cox proportional hazards models adjusted for LVWT (HR: 3.2; 95% CI: 1.02 to 9.88; p = 0.047) (Fig. 3A) and 3.7-fold more likely after adjustment for sex (HR: 3.7; 95% CI: 1.22 to 11.41; p = 0.02) (Fig. 3B).This analysis took into account different follow-up periods after ICD implantation.

Multiple risk factors for SCD. There were 149 patients (91%) who received their ICD for primary prevention of SCD, including 24% with LVWT ≥30 mm, 41% with a family history of SCD, 36% with documented NSVT, and 29% with unexplained syncope. Almost one-third of patients fulfilled multiple high-risk criteria for ICD insertion (29%); these patients were more likely to have experienced an

Table 3 Logistic Regression Analysis of QTc as a Predictor of Appropriate ICD Events

Variable	OR (95% CI)	p Value	R^2
QTc adjusted for LVWT	1.2 (1.03–1.39)	0.02	14%
QTc adjusted for sex	1.2 (1.07–1.42)	0.003	12%

CI = confidence interval; LVWT = left ventricular wall thickness; OR = odds ratio; other abbreviations as in Tables 1 and 2.

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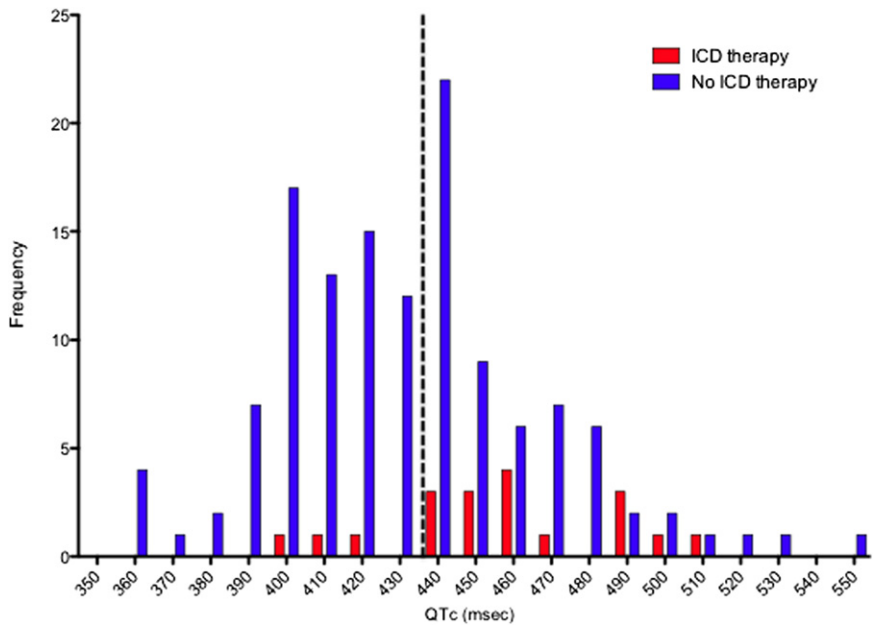


Figure 1 **Frequency Distribution of QTc, by Appropriate ICD Therapy**

Frequency distribution of corrected QT (QTc) measurements for those who had **(red bars)** and had not experienced an appropriate implantable cardioverter defibrillator (ICD) event **(blue bars)**. Of patients with a QTc ≥440 ms, 79% of patients had an appropriate ICD event, whereas 40% of those with no events had a QTc ≥440 ms ($p = 0.001$). NB = significant outlier (QTc 550 ms) in the context of left bundle branch block with severe left ventricular hypertrophy (left ventricular wall thickness [LVWT], 46 mm).

appropriate ICD event (43% vs. 22%; $p = 0.027$) (Fig. 4). However, on Kaplan-Meier survival analysis with log-rank for comparison, the difference in event-free survival over time was not significant (data not shown).

Discussion

This study focused specifically on a cohort of HCM patients at high risk for SCD who had had an ICD implanted on the basis of conventional risk-stratification criteria for primary and secondary prevention. QTc prolongation on baseline ECG was found to be a key clinical predictor of appropriate ICD therapies in patients with HCM. The mean baseline QTc interval was significantly greater in HCM patients who had experienced an appropriate ICD event during follow-up compared with that in those who had no appropriate ICD interventions. Although a number of clinical variables were examined, QTc was the most strongly associated with the occurrence of appropriate events. Importantly, this finding was independent of other key variables, such as LVWT and sex. HCM patients with a QTc ≥439 ms were >3-fold more likely to have experienced an appropriate ICD event after adjustment for LVWT and sex. Collectively, these findings suggest prolongation of the QTc interval as a clinical predictor of an appropriate ICD event in HCM patients after ICD insertion.

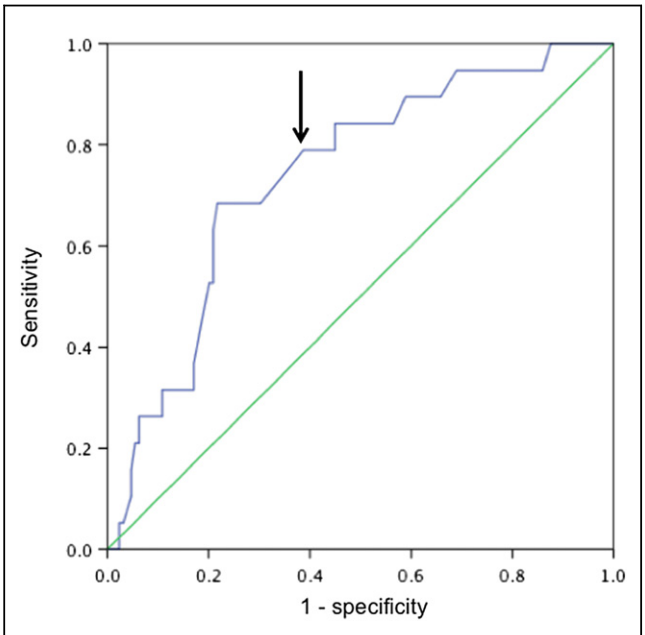
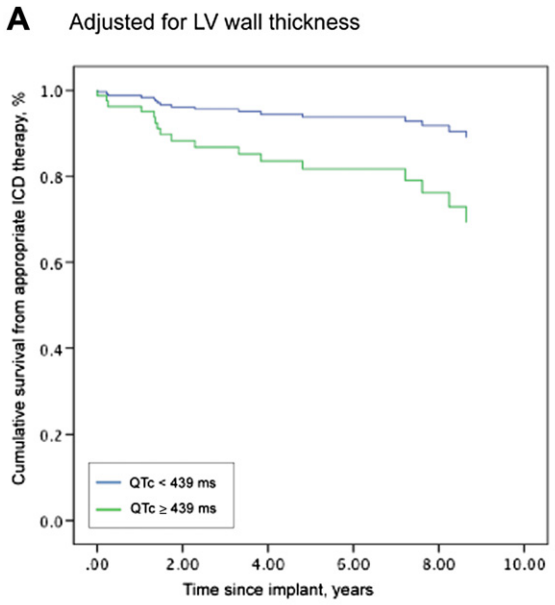
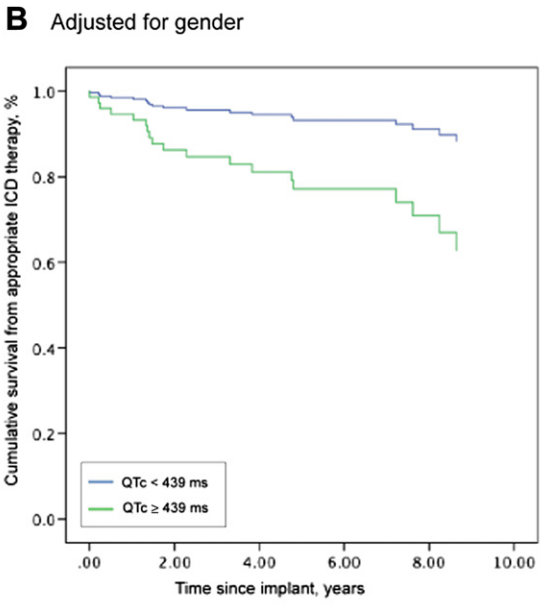


Figure 2 **ROC Curve Analysis of QTc, by Appropriate ICD Therapy**

A corrected QT (QTc) cutoff of 439 ms was selected on the basis of the receiver-operating characteristic (ROC) curve analysis with sensitivity of 79% and specificity of 61% **(arrow)**. The area under the curve (AUC) was 0.74.



Variable	Adjusted HR	95% CI	p value
QTc ≥ 439 msec	3.2	1.02-9.88	0.047



Variable	Adjusted HR	95% CI	p value
QTc ≥ 439 msec	3.7	1.22-11.41	0.02

Figure 3 **Cumulative Event-Free Survival Analysis, by Appropriate ICD Therapy**

Cox proportional hazards models were used to assess the independent cumulative event-free survival from appropriate ICD events by QTc measurement, adjusted for **(A)** LVWT (hazard ratio [HR]: 3.2; 95% confidence interval [CI]: 1.02 to 9.88; p = 0.047) and **(B)** sex (HR: 3.7; 95% CI: 1.22 to 11.41; p = 0.02. Abbreviations as in Figure 1.

Prolongation of the QT interval has been reported in a small number of studies of HCM patients (18,19,22,24). The main contributor of QT prolongation in HCM has been postulated to be the severity of left ventricular hypertrophy with myocyte disarray, which presumably affects both depolarization and repolarization in these patients (19). QT prolongation has also been associated with LVOT obstruction (18). In this study, the investigators found that although there was a weak but significant correlation between QTc and LVWT, multivariate analysis demonstrated that QT prolongation was independent of LVWT in this subgroup of patients at risk for SCD, suggesting other possible contributory factors. The link between QT prolongation and appropriate ICD events suggests that in this setting, QT prolongation is proarrhythmic in HCM patients. This finding of QT prolongation as a predictor of appropriate ICD events in HCM is novel. Maron et al. (22) previously reported that QT interval and QT dispersion were increased in HCM patients compared to control populations but that these increases did not predict SCD. This finding may reflect differences in clinical in the HCM population, genetic background, proportion of patients on QT-modifying drugs, and the primary outcome measure (SCD vs. ICD therapies) compared to the present study. In a recent study by Johnson et al. (18), in a subgroup analysis of QT intervals in HCM patients with an ICD, no correlation between QT-interval prolongation and ICD therapies was reported. However, the study had significantly fewer patients (n = 90 in this subgroup), with fewer events and a shorter mean follow-up

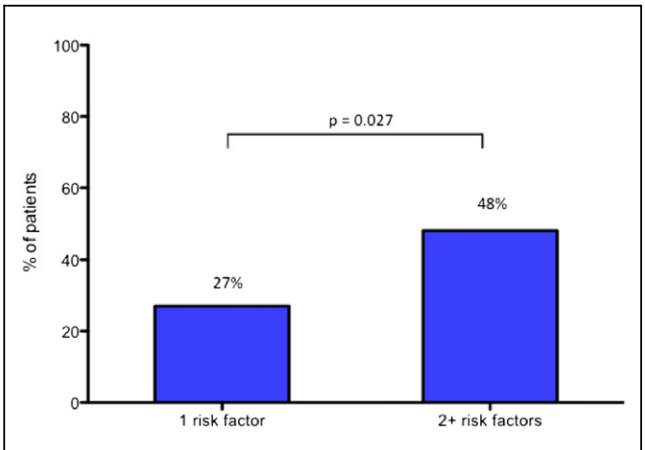


Figure 4 **Proportion of Risk Factors Predicting Appropriate ICD Therapy**

The proportion of patients who experienced at least 1 appropriate implantable cardioverter defibrillator (ICD) event was significantly greater in the subgroup with 2 or more risk factors for sudden cardiac death (SCD)/indication for ICD compared to the subgroup with 1 risk factor/indication (43% vs. 22%; p = 0.027).

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period. Regardless, the conclusion that QTc assessment should be performed in HCM patients, whether they have an ICD or not, is supported by these studies.

One potential explanation unrelated to the severity of LVWT is a mechanistic link between QT prolongation and myocardial fibrosis. It is conceivable that cellular changes in the myocardium of patients with HCM other than hypertrophy (i.e., interstitial fibrosis and myofiber disarray) may contribute to QTc prolongation and combine to produce the proarrhythmic effects observed (25). The extent and severity of myocardial fibrosis and myocyte disarray have been implicated as key substrates for VA in HCM (3,6). The present study did not formally assess fibrosis because cardiac magnetic resonance was not readily available before ICD implantation in the present cohort. Interestingly, a recent magnetic resonance–based study by Delcre et al. (23) in 257 HCM patients reported a numeric but nonsignificant association between QTc prolongation and prevalence of late gadolinium enhancement (83% in patients with QTc prolongation vs. 73% in those without; $p = 0.08$), supporting a possible link between fibrosis and QT prolongation in HCM.

The potential association between QT prolongation and HCM may originate from other factors. The possibility of a genetic underpinning to link the QT interval and HCM is tantalizing because genetic factors that independently cause HCM (3) and familial LQTS (26,27) are well established. Although these 2 sets of causative genes encode proteins in 2 different anatomical regions of the heart (i.e., ion channels in LQTS and sarcomere structures in HCM), findings from recent studies suggest that interactions exist and may be the result of a single genetic cause. For example, mutations in the sodium ion channel gene *SCN5A* may lead to a primary arrhythmogenic disease (Brugada syndrome) (28) as well as a structural disease (dilated cardiomyopathy) (29). It is conceivable that some patients with HCM may have coexisting genetic variants in LQTS genes (30), leading to an increased susceptibility to prolongation of the QT interval and subsequent development of cardiac arrhythmias and SCD. This cumulative effect of 2 or more genetic variants has been linked to disease severity in many cardiovascular genetic diseases (31). In the present study, unfortunately only a limited proportion of the cohort had undergone genetic testing for HCM, and none had undergone any genetic evaluation for the common LQTS genes. However, major advances in genetic technologies will facilitate more extensive and detailed genetic evaluation in future studies.

This study was conducted in a national tertiary referral HCM center in Sydney, Australia, and so this cohort represents a group with generally more severe disease and at higher risk for SCD than a population-based cohort. A further consideration related to the findings of this study, but relevant to all studies and clinical evaluations of QT interval, is the variability in QT intervals within the same patient, due to various factors including the time of day, concurrent illnesses, and medication use. Caution should be exercised in considering these factors, and ECG should be repeated as required to confirm the QT measurements. Furthermore, although patients with 2 or more risk factors were significantly more likely to have experienced an appropriate ICD event (48%), more than one-quarter of patients with a single risk factor experienced VT or VF requiring intervention from their ICD.

The findings of the present study in HCM patients with a high risk for SCD, combined with those from recent key studies focused on general HCM populations (18), have important implications for the clinical management of HCM. The present findings may provide a useful clinical predictor of appropriate ICD therapy events in HCM patients. The issue of the likelihood that the ICD will deliver an appropriate-therapy event is frequently raised by HCM patients after the implantation of an ICD. Although QT prolongation is unlikely to be the only clinical predictor, it is a useful, easily obtained measurement that may influence the management strategy. On the basis of the present findings, a prolonged QT interval of $\geq$440 ms in a patient with HCM who has an ICD in place may guide advice about avoiding QT-prolonging drugs, may influence the introduction and/or dosage of beta-blocker therapy, and may result in modifications of ICD programming in terms of ATP and DCCV algorithms.

Conclusions

Given its proarrhythmic potential, assessment of the QT interval in HCM patients should be performed and considered as an additional piece of clinical information for guiding clinical management. This is of particular significance in the setting of HCM patients at increased risk for SCD who have an ICD in place. Future studies to understand the mechanisms underpinning the link between prolongation of the QT interval and proarrhythmia in HCM will be of key importance.

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