Long-Term Follow-Up of Patients With Short QT Syndrome

This is the author's manuscript

Original Citation:

Availability:
This version is available http://hdl.handle.net/2318/87167 since

Published version:
DOI:10.1016/j.jacc.2011.03.038

Terms of use:
Open Access
Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)
This is an author version of the contribution published on:

Questa è la versione dell’autore dell’opera:

[Journal of the American College of Cardiology, volume 6 (2), 2011, DOI:

10.1016/j.jacc.2011.03.038]

The definitive version is available at:

La versione definitiva è disponibile alla URL:

Long-Term Follow-Up of Patients With Short QT Syndrome

Carla Giustetto, MD*; Rainer Schimpf, MD†; Andrea Mazzanti, MD*; Chiara Scrocco, MD*;
Philippe Maury, MD‡; Olli Anttonen, MD§; Vincent Probst, MD, PhD||; Jean-Jacques Blanc, MD#;
Pascal Sbragia, MD**; Paola Dalmasso, MS††; Martin Borggrefe, MD†; and Fiorenzo Gaita,
MD*.
The first two authors contributed equally to this work.

Total word count: 4455
Follow-up of SQT Syndrome patients

* Cardiology Department, Cardinal Massaia Hospital, Asti and San Giovanni Battista Hospital,
Turin, University of Turin, Italy
† Department of Medicine-Cardiology, University Hospital, Mannheim, Germany
‡ Federation of Cardiology, University Hospital Rangueil, Toulouse, France
§ Division of Cardiology, Lahti Central Hospital, Lahti, Finland;
|| Service de Cardiologie, Institut du Thorax, Université de Nantes, Nantes, France;
# Departement de Cardiologie, Université de Bretagne Occidentale, Hôpital de la Cavale Blanche,
Brest, France
** Division of Cardiology, Hôpital Nord, Marseille, France
†† Medical Statistics Unit, Department of Public Health and Microbiology, Turin, University of
Turin, Italy

This work was supported by a grant from the Foundation Cassa di Risparmio of Asti, Italy.

There was no relationship with industry.
Correspondence to:

Carla Giustetto, MD

Division of Cardiology, Cardinal Massaia Hospital, Asti, Italy

C.so Dante 202, 14100 Asti, Italy.

Phone: +39-0141-487121 Fax: +39-0141-487134

E-mail: carla.giustetto@unito.it
Abstract

Objectives. The aim of this study was to investigate the clinical characteristics and the long-term course of a large cohort of patients with Short QT Syndrome (SQTS).

Background. SQTS is a rare channelopathy characterized by an increased risk of sudden death. Data on the long-term outcome of SQTS patients are not available.

Methods. Fifty-three patients from the European short QT Registry (75% males; median age 26 years) were followed for 64±27 months.

Results. A familial or personal history of cardiac arrest was present in 89%. SD was the clinical presentation in 32%. The average QTc 314±23 ms. A mutation in genes related to SQTS was found in 23% of the probands; most of them had a gain of function mutation in HERG (SQTS1). Twenty-four patients received an implantable cardioverter defibrillator (ICD) and 12 long-term prophylaxis with hydroquinidine (HQ), which was effective in preventing the induction of ventricular arrhythmias. Patients with a HERG mutation had shorter QTc at baseline and a greater QTc prolongation following treatment with HQ. During follow-up, 2 already symptomatic patients received appropriate ICD shocks and one had syncope. Non-sustained polymorphic ventricular tachycardia was recorded in 3 patients. The event rate was 4.9% per year in the patients without antiarrhythmic therapy. No arrhythmic events occurred in patients receiving HQ.

Conclusions. SQTS carries a high risk of SD, in all age groups. Symptomatic patients have a high risk of recurrent arrhythmic events. HQ is effective in preventing ventricular tachyarrhythmias induction and arrhythmic events during long-term follow-up.

Key Words: short-QT syndrome; sudden death; channelopathies; arrhythmias; hydroquinidine; ICD.
Abbreviations and Acronyms

AF = Atrial Fibrillation
CA = Cardiac Arrest
EPS = Electrophysiological Study
ERP = Effective Refractory Period
HQ = Hydroquinidine
ICD = Implantable Cardioverter Defibrillator
QTc = Corrected QT
QTp = Predicted QT
SQTS = Short QT Syndrome
SD = Sudden Death
Introduction

The association between long QT interval and sudden death has been known for over 50 years (1), but only recently the interest has moved to the opposite, a short QT interval. In 1993 Algra et al. (2) observed that both prolonged and shortened QTc intervals were associated with an increased risk of sudden death (SD) compared with intermediate QTc values. In 2000 Gussak et al. (3) reported one family with short QT intervals (QTc <300 ms) and atrial fibrillation (AF) in one of the members and an unrelated woman with similar ECG changes, who died suddenly. Finally, our group in 2003 recognized the Short QT Syndrome (SQTS) as a new clinical entity related to familial SD with an autosomal dominant inheritance (4), and the genetic nature of the disease was confirmed shortly after (5,6,7,8). Although the upper limit of normal QT values is well defined, the lower limit has not been determined to date. In the initial published cases of SQTS, the QT and the QTc were constantly ≤300 ms. In the subsequent years, individuals with SQTS and QTc values below 340 ms were reported in association with SD (9). According to population studies, QTc ≤360 ms or QT ≤88% of the predicted QT (QTp) have been proposed as the lower limit of the “normal” QTc and QT, because these correspond to the mean values – 2 SD in the general population (10).

The first proposed therapy was an implantable cardioverter defibrillator (ICD). Some studies have demonstrated the efficacy of hydroquinidine (HQ) over a short-time period and in a limited number of patients (11,12). As short QT syndrome has only recently been recognized, data regarding the long-term outcome of SQTS patients are not available. The purposes of this study were, firstly, to assess the clinical presentation, the electrocardiographic features, the prevalence of known genetic mutations and their relationship with the long-term prognosis in a large cohort of SQTS patients and, secondly, to verify the efficacy and the side effects of the therapy, including ICD and antiarrhythmic drugs.
Methods

Study Population.
From June 2002, SQTS patients from 7 European Centres were enrolled in the European SQTS Registry (EuroShort). In the present study we included patients with a QTc ≤ 360 ms (or ≤88% of QTp) associated with history of SD/aborted SD or syncope of arrhythmic origin. Subjects with a very short QT interval (QTc ≤ 340 ms) were included even if asymptomatic. Family members of affected patients having a short QT interval were also included in the study. The final study group comprised 53 patients (75% males; median age 26 years; interquartile range [IQR] 17-39), from 29 proband-identified families. Thirty-three patients have already been reported in previous studies (4, 9, 11, 13, 14, 15).

Four patients were included after SD, having ECG documentation of short QT intervals prior to cardiac arrest. There were 27 cases of SD without ECG documentation in the families, which were therefore not included in the present study.

Data Collection and Management.
For each patient, data on personal and family history, cardiac events and therapy were recorded. Between 1 and 8 (median 2) 12-lead ECGs with a paper speed of 25 or 50 mm/s and a gain of 10 mm/mV were available and analyzed for each patient. The ECG parameters were measured with a 400% magnification from the lead with the highest T-wave amplitude, usually V2 or V3, by 3 independent examiners. Analyzed ECG parameters were: heart rate (HR), QRS duration, QT interval, QTc, QTp according to Rautaharju’s formula (16). Moreover, Jpoint-Tpeak, (J-Tp), Q-Tpeak (Q-Tp), Tpeak-Tend (Tp-Te) and Tpeak-Tend/QT ratio (Tp-Te/QT) were evaluated. The QT interval was manually measured according to the tangential method; the Tpeak was measured from the highest point of the T wave. Comparing the mean QT values obtained with tangential (282±39) and threshold (291±42) methods by paired t test, we found a statistically significant difference (-
9.1±14, p=0.0001), however with an excellent agreement between the two methods (Pearson correlation coefficient (r) equal to 0.94). It is already known that the first method slightly underestimates the QT interval, however has a higher reproducibility (17); moreover we consider it particularly appropriate in SQT patients, due to the high voltage T waves.

A baseline electrophysiological study (EPS) was performed in 28 patients off antiarrhythmic drugs. In 8 patients EPS was repeated following oral HQ administration at steady-state concentrations. Altogether, 24 patients received an ICD and 12 patients long-term prophylaxis with HQ. One patient was treated with amiodarone.

**Follow-up.**

The follow-up time comprised historical clinical information from birth to enrolment and the prospective follow-up information at 6-month intervals from enrolment to November 2010. Of the 53 patients, 4 died before clinical evaluation; 1 child died during the follow-up at 4 months of age for non-cardiac causes. The parents of a child presenting with ventricular fibrillation (VF) refused to take part in the follow-up.

**Statistical Analysis.**

Comparisons between groups were done with the chi-square test or Fisher’s exact test for qualitative variables, and the one-way analysis of variance (ANOVA) or the t test for quantitative variables apart for variables which have a skewed distribution and for which the non-parametric Kruskal-Wallis or Mann-Whitney rank-sum tests were used. We applied the Bonferroni correction to address the problem of multiple comparisons. Parameters before and after treatment were compared using the paired t test or the Wilcoxon matched-pairs signed-rank tests. The Kaplan–Meier product-limit estimator was used to compare event incidence between different patient subgroups. The log-rank or Wilcoxon tests were used to test the statistical significance of the observed differences. To exclude that the patients treated with HQ might be at higher or lower risk
based on other characteristics, we performed a comparison of baseline clinical and demographic characteristics (gender, age, previous events and QTc at baseline) between the 2 groups. The multivariate logistic regression was performed with Firth correction to avoid the problem of separation, due to have no event in HQ. All the tests were two tailed. A value of p<0.05 was considered statistically significant.

Results

Demographic and Clinical Data.
Thirty subjects (24 males, 80%; median age 23 years; IQR: 17-34) initially came to the observation for the following reasons: SD (n=4), aborted SD (n=13), syncope (n=4), other symptoms (palpitations n=3, effort dyspnea n=1), family screening for SD (n=3) and ECGs recorded for other reasons (n=2). Fifteen patients had a history of familial SD (50%). After the screening of the related families, 23 subjects were added to the study population, 16 males, with a median age of 32 years (IQR 21-42). Considering the whole population, 33 out of 53 patients presented symptoms (62%): 4 had died suddenly, 13 had an aborted SD (range 3 months to 62 years), 8 syncope, 13 palpitations (6 of whom with documented AF or flutter). Frequent ventricular ectopic beats were documented in 6 patients.

Two pediatric patients were affected by severe congenital multi-organ disease; no cardiac involvement or acquired causes that could determinate a short QT interval were detected in any of these cases.

Cardiac arrest (CA) had a similar prevalence in males and females (35% vs. 30%, p=0.15), and in both genders episodes under 1 year of age were reported. In males more than 90% of CA occurred between 14 and 40 years of age, whereas in females the events were spread across the entire life-span; syncope was observed only in males and had a similar age distribution (Figure 1).
In the patients carrying a HERG mutation a greater proportion of affected females (55% vs. 18%, p=0.04) and a higher prevalence of AF (36% vs. 3.6%, p=0.02) were observed compared to non-HERG patients.

**Genetic analysis.**

Genetic analysis was performed in 22 of the index patients and revealed a mutation in 5. Four families had a mutation in HERG, N588K in two (5) and T618I in the other two, a Chinese family (13) and a Caucasian family (unpublished data from Prof. Antzelevitch group, Masonic Medical Research Laboratory, Utica, NY, USA): both the mutations were in the pore loop of HERG channel. A family had a mutation in CACNB2b (8). The test was negative in 12 index patients, while in 5 cases the analysis was still ongoing at the time of writing.

**ECG.**

In all the available ECGs the average QT was 76±6% of the QTp (range 59-86%); the average QT interval was 282±39 ms and the QTc was 314±23 ms (range 250-350 ms). No differences were found in the ECG parameters between symptomatic and asymptomatic patients (Table 1). A Brugada type 1 ECG and a shorter than normal QT interval were found in 3 patients: in two brothers with a CACNB2b mutation and a history of CA in one, the pattern was observed after ajmaline challenge (8). The third case was a 30-year-old male, who presented after a nocturnal syncope and showed a spontaneous type 1 ECG.

Comparing the ECG parameters between patients with a mutation in HERG and those without, QT interval, QTc, QT/QTp, J-Tp, Tp-Te and Tp-Te/QT ratio were significantly shorter in HERG patients (Table 2).

**Electrophysiological study.**
Twenty-eight patients underwent an EPS. The ventricular effective refractory periods (ERPs) at the right ventricular apex at a cycle length of 600–500 ms were shortened and varied between 140 and 200 ms (mean 166±21 ms). No differences were found between patients with a history of CA or syncope and those without (RVA, S1S1 500 ms: 158±15 ms vs. 148±18 ms, p=0.21). VF was induced in 16 patients (57%): 3 had an aborted SD and 5 syncope. Seven out of the 16 (44%) had “mechanical” induction of VF during catheters positioning. In 12 patients, ventricular tachyarrhythmias were not induced: 5 had an aborted SD and 2 had syncope. Due to the fact that only 3 out of the 8 patients with a history of CA had inducible VF, EPS sensitivity was only 37%, and its negative predictive value 58%. The atrial ERPs were also shortened and ranged between 120 and 200 ms (mean 163±22 ms). AF was induced in 8 patients (36%). Comparing the electrophysiological parameters between patients with a mutation in HERG (7 patients) and those without (12 patients), the ventricular ERPs were shorter in the first group (151±14 ms vs. 176±24 ms, p=0.01).

**Therapy.**

*Hydroquinidine.*

In 22 patients HQ was tested to assess its efficacy in prolonging the QT interval. In 6 cases it was discontinued early due to poor therapeutic compliance, in 2 cases because no effect on the QT was observed, whereas 2 subjects (9%) reported gastro-enteric side effects. Twelve patients (8 adults and 4 children) had been receiving HQ for a mean period of 76±30 months (range 27–105); the mean dosage in adults was 870±186 mg per day (range 600–1000 mg). ECGs before and after drug therapy were available for analysis in 18 patients (Table 3). In 8 patients EPS was repeated after the drug had reached the steady–state concentration, in 6 cases via the ventricular lead of the ICD. Ventricular ERPs were significantly prolonged (from 154±12 ms to 205±23 ms, p=0.02). Seven patients had VF induced at baseline (87%), while none had VF induced following HQ (p=0.016). Comparing the ECG parameters in patients with mutation in HERG and those without, the effect of
HQ on QTc was more relevant and constant in the first group, both in N588K and in T618I carriers (Table 3 and Figure 2).

Other drugs.

Experiences with drugs other than HQ are reported in table 4.

Amiodarone.

Amiodarone was administered in 2 patients. It did not produce any effect on the QT interval in a woman with a HERG mutation. Another patient (male, QTc 350 ms) with documented VF at the age of 26 and unknown genotype (Figures 3 and 4) received amiodarone and metoprolol: QTc prolonged to 400 ms and no arrhythmias were recorded in a six-month follow-up. Previous treatment with sotalol was ineffective both in prolonging the QT interval and in preventing ventricular tachyarrhythmias.

Disopyramide.

Three patients with inducible VF at baseline, an asymptomatic with unknown genotype and 2 with paroxysmal AF and HERG mutation underwent an antiarrhythmic drug trial with oral disopyramide (200 mg - 400 mg per day). VF was still inducible in the patient taking the lower dosage and no changes were observed in the ventricular ERPs. In the patients taking the higher dosage the QTc prolonged slightly (Table 4), and the ventricular ERP prolonged from 160 to 200 ms in one case; these latter data have already been reported (18).

Follow-up.

Forty-seven patients were followed over 64±27 months (Figure 5).
Patients with a previous cardiac arrest.

Twelve patients had an aborted SD. An ICD was implanted in 11. One child with a HERG mutation (4) had CA at the age of 8 months, with severe neurological damage. He was not implanted and received HQ from the age of 6, which effectively prolonged the QT interval. Two patients started HQ at the time of ICD implantation, which was discontinued after a few days in one (9). During follow-up one patient repeatedly received appropriate shocks on VF and was effectively treated with amiodarone. One patient received inappropriate ICD shocks due to atrial flutter; he underwent successful cavo-tricuspid isthmus ablation and was started on oral HQ. One patient had two asymptomatic episodes of polymorphic non-sustained ventricular tachycardia (NSVT).

Patients with a history of syncope.

Eight patients presented with syncope: 4 received an ICD, 3 refused the implant and in one case the patient was judged to be at low risk (23-year-old male with no familial history of SD and probably vaso-vagal syncope). Of the 3 patients who refused the implant, one was a 70-year-old male with permanent AF and familial history of SD who refused any treatment; the others were two brothers with a family history of SD, with an unknown genotype and inducible VF during EPS, who received HQ (9).

The only event during the follow-up occurred in a patient with a HERG mutation (SQTS1), who received an appropriate shock on VF 11 months after the implant. He was a 16 year-old male with a syncope at the age of 8 months and a family history of SD over three generations (4,14).

Patients asymptomatic for CA or syncope.

Twenty-seven patients were asymptomatic for CA and syncope. Eight of them had AF or palpitations. An ICD was implanted in 9, due to a family history of SD and/or induction of VF at EPS (9,13). Seven patients also received HQ, but it was soon interrupted in 5. Oral HQ alone was started in two adult patients with family history of SD, who stopped it early, and in a 25-year-old
patient with permanent AF (15). Moreover, HQ therapy was started in 3 children (two under 1 year of age) and the drug was well tolerated (9).

During follow-up one patient experienced a syncope, and other two patients had episodes of NSVT documented by the ICD: none of them were receiving pharmacological prophylaxis (9).

The event rate in the whole population was 3.3% per year. All the events occurred in patients who were not receiving HQ: in this group the event rate was 4.9% per year, while no arrhythmic events occurred in those receiving HQ (Figure 6). In a multivariate analysis (table 5), only the QTc was significantly different between the 2 groups, with a shorter mean QTc before therapy in the group receiving HQ.

**ICD-related complications.**

Fourteen patients out of 24 (58%) suffered complications related to the ICD. In 8 subjects inappropriate shocks were observed: 4 patients with a HERG mutation received inappropriate shocks shortly after implant (within 2 months) due to T-wave oversensing (19); no recurrences were reported after the new programming of the ICD. The other 4 patients had inappropriate shocks during episodes of supraventricular tachycardia. Three patients had ICD lead replacement due to lead fracture and a fourth patient due to an infection of the ICD system; one patient had early substitution of the ICD due to a recall. One suffered from severe psychological distress.

**Discussion**

In the present study the long-term outcome of 53 patients with SQTS is reported, representing the largest series in the literature. Clinical characteristics, therapy efficacy and the outcome after the diagnosis were analyzed. The follow-up was almost complete, with only one patient not participating. Almost 90% of the patients presented a personal or familial history of SD. A prevalence of males was observed and the mean age was between 20 and 30 years. Over 60% of the
subjects presented with symptoms: the most frequent symptom was CA, which represented the first clinical manifestation in one third of the patients. It was observed also in infants in their first months of life. Most of the events occurred in males, mainly between the second and the fourth decade. This distribution of events corresponds to the age with the highest testosterone plasma levels (20). Androgens, and specifically testosterone, cause a shortening of the QT in boys after puberty, which is responsible for the fact that women exhibit QTc intervals significantly longer than men (21). These hormonal influences may provide relative protection to post-puberal boys and men in the context of the long QT syndrome (22). However, the possible relationship of testosterone with susceptibility for cardiac arrhythmias in the context of SQTS needs to be further investigated.

Syncope was the second most frequent clinical manifestation, in 15% of cases. The finding of several episodes of NSVT recorded by the ICD or during telemetry in our patients seems to confirm that self-terminating episodes of VT or VF may be the cause of syncope in SQTS (Figures 3 and 4). CA and syncope occurred both at rest and during effort, so that it was not possible to identify a uniform trigger for the events. AF or atrial flutter were observed in 15% of the population, also under 35 years.

Concerning the ECG parameters, we considered a consistently short QT interval (QTc ≤ 340 ms) among the inclusion criteria in the study (9), even in the absence of symptoms or family history of SD. Moreover we decided to include also patients with a QTc ≤ 360 ms and a history of SD/aborted SD or syncope of arrhythmic origin. In this larger population it was confirmed the previous observation (9) that the QTc values in a population with short QT did not distinguish between asymptomatic subjects and those with CA. In a recent paper by Anttonen et al. (23) it was shown that parameters such as the J-T peak interval and Tp-Te/QTc may differentiate patients with SQTS and CA from asymptomatic subjects with a shorter than normal QT interval from the general population. None of these indexes, however, could discriminate in our population of patients with SQTS, asymptomatic SQT subjects from those with CA or syncope (Table 1). Furthermore, electrophysiological study was not useful in predicting CA, having a sensitivity of only 37%.
The yield of genetic screening in SQTS was 23% of the investigated index patients. Mutations were predominantly found in KCNH2/HERG (4 of the 5 with a positive genotype), while a loss of function mutation in the gene CACNB2b was found in another family. Patients with a HERG mutation constituted a subgroup with specific characteristics such as a greater proportion of affected females and a higher prevalence of AF compared to non-HERG patients. Moreover, they exhibited shorter QT intervals and ERPs.

Hydroquinidine was tested in 41% of the patients. In the patients with a HERG mutation HQ induced normalization of the QT interval and of the ERPs, while in those without the mutation a weaker effect and a significant variability of responses were observed. HQ prevented the induction of ventricular arrhythmias during EPS in all studied patients and none of the treated patients had arrhythmic events during the follow-up. Drug tolerability was good: only 9% of the patients interrupted it due to side effects (gastro-enteric intolerance or dermatitis). HQ was used in adults mainly as a prophylaxis for AF/flutter, but also in patients who had refused an ICD implant and in children both as primary and secondary prevention after VF. Hydroquinidine served as a valuable bridge to ICD. However, unfortunately quinidine became no longer available in several European countries because of commercial reasons (24).

The incidence of arrhythmic events during the follow-up was 4.9% per year in the patients without pharmacological prophylaxis, while no arrhythmic events occurred in those receiving HQ. VF occurred in already symptomatic patients. No events were recorded among treated patients, even if previously symptomatic. For this reason HQ may be considered as an alternative option to ICD in patients who cannot receive it (children) or who refuse the implant, but it is still underutilized.

Fifty-eight percent of the patients with an ICD had complications related to the device. Many were inappropriate shocks, secondary to T-wave oversensing with double counting of the R and T waves, which occurred early after the implant (19) and were prevented with correct ventricular sensitivity programming for VF detection.
**Future perspectives.**

The current study only included asymptomatic patients if they had very short QT intervals. In the future it would be important to expand this registry, including also asymptomatic subjects with borderline short QT intervals, in order to better understand the prognosis and help guide the management of such patients.

**Acknowledgments**

We would like to thank for their contribution to this study:

- Charles Antzelevitch, PhD, FACC, FAHA, FHRS, Masonic Medical Research Laboratory, Utica, NY, USA;
- Christian Veltmann, MD, Department of Medicine-Cardiology, University Hospital, Mannheim, Germany;
- Yaxun Sun, MD, Division of Cardiology, People's Hospital, Peking University, Beijing, China;
- Riccardo Asteggiano, MD, Cardiology Outpatient Clinic, Hospital of Giaveno, TO, Italy;
- Maurizio Mezzetti, MD, Department of Cardiology, Ospedale degli Infermi, Rimini, Italy;
- Gianpiero Leone, MD, Division of Cardiology, Hospital of Aosta, Italy;
- Fernando Di Monte, PhD, Department of Cardiology, Cardinal Massaia Hospital, Asti, Italy.
References


Figure Titles and Legends

Figure 1. Cardiac events in males and females.
Age distribution of sudden death (top) and sudden death or syncope (bottom) in males (♂) and females (♀).

Figure 2. Different effect of HQ in patients with HERG mutation vs non-HERG.
Effect of hydroquinidine on the QTc in patients with a HERG mutation (on the left), as compared to those without (on the right).
Pre = before treatment, post = during treatment.

Figure 3. Non-sustained ventricular tachycardia.
Polymorphic non-sustained VT recorded in a patient with history of SD and repeated shocks of the ICD (Holter monitoring, paper speed 25 mm/sec).

Figure 4. Ventricular fibrillation recorded by the ICD.
Same patient of figure 3. The arrhythmia is triggered by a short-coupled ventricular extrasystole.

Figure 5. Therapeutic approach.
Schematic representation of therapeutic approach and follow-up of the whole population.
Hq= Hydroquinidine, ICD= implantable cardioverter defibrillator, NSVT = non-sustained ventricular tachycardia, VF= ventricular fibrillation.

Figure 6. Different incidence of arrhythmic events in patients treated with HQ and without therapy.
Kaplan-Meier estimate of survival free from major arrhythmic events during a 5-year follow-up; comparison of patients treated with hydroquinidine with those without therapy. The difference is not statistically significant.
Tables.

**Table 1.** Comparison of ECG parameters between patients with previous cardiac arrest, syncope and asymptomatic patients; values are expressed as mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Cardiac Arrest (18 pts)</th>
<th>Syncope (8 pts)</th>
<th>No cardiac arrest nor syncope (27 pts)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>78 ± 21</td>
<td>79 ± 20</td>
<td>73 ± 14</td>
<td>79 ± 23</td>
<td>0.68</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>82 ± 9</td>
<td>84 ± 5</td>
<td>83 ± 5</td>
<td>80 ± 11</td>
<td>0.22</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>282 ± 39</td>
<td>278 ± 44</td>
<td>289 ± 34</td>
<td>283 ± 38</td>
<td>0.68</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>314 ± 23</td>
<td>311 ± 25</td>
<td>316 ± 23</td>
<td>315 ± 22</td>
<td>0.80</td>
</tr>
<tr>
<td>QT/QTp (%)</td>
<td>76 ± 6</td>
<td>75 ± 6</td>
<td>76 ± 6</td>
<td>77 ± 5</td>
<td>0.46</td>
</tr>
<tr>
<td>J-Tpeak (ms)</td>
<td>121 ± 29</td>
<td>113 ± 35</td>
<td>123 ± 36</td>
<td>126 ± 23</td>
<td>0.51</td>
</tr>
<tr>
<td>Q-Tpeak (ms)</td>
<td>205 ± 34</td>
<td>197 ± 44</td>
<td>210 ± 35</td>
<td>208 ± 28</td>
<td>0.76</td>
</tr>
<tr>
<td>Tp-Te (ms)</td>
<td>77 ± 16</td>
<td>78 ± 14</td>
<td>80 ± 13</td>
<td>75 ± 19</td>
<td>0.79</td>
</tr>
<tr>
<td>Tp-Te/QT (%)</td>
<td>27 ± 5</td>
<td>28 ± 5</td>
<td>28 ± 6</td>
<td>26 ± 5</td>
<td>0.44</td>
</tr>
</tbody>
</table>

J-Tpeak = Jpoint-Tpeak; QTc = corrected QT; QTp = predicted QT; Tp-Te = Tpeak-Tend.
Table 2. Comparison of ECG parameters between patients with mutation in HERG and those without; values are expressed as mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>HERG (n = 11)</th>
<th>Non-HERG (n = 28)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ±SD</td>
<td>Mean±SD</td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>88 ± 21</td>
<td>73 ± 13</td>
<td>0.02</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>85 ± 13</td>
<td>82 ± 4</td>
<td>0.34</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>253 ± 26</td>
<td>292 ± 32</td>
<td>0.0003</td>
</tr>
<tr>
<td>QTc</td>
<td>297 ± 29</td>
<td>319 ± 17</td>
<td>0.01</td>
</tr>
<tr>
<td>QT/QTp (%)</td>
<td>72 ± 7</td>
<td>77 ± 5</td>
<td>0.03</td>
</tr>
<tr>
<td>J-Tpeak (ms)</td>
<td>103 ± 22</td>
<td>125 ± 26</td>
<td>0.007</td>
</tr>
<tr>
<td>Q-Tpeak (ms)</td>
<td>187 ± 35</td>
<td>208 ± 27</td>
<td>0.05</td>
</tr>
<tr>
<td>Tp -Te (ms)</td>
<td>66 ± 10</td>
<td>85 ± 13</td>
<td>0.0002</td>
</tr>
<tr>
<td>Tp-Te / QT (%)</td>
<td>26 ± 6</td>
<td>29 ± 5</td>
<td>0.011</td>
</tr>
</tbody>
</table>

J-Tpeak= Jpoint-Tpeak; QTc =corrected QT; QTp =predicted QT; SD = standard deviation; Tp-Te =Tpeak-Tend.
Table 3. Comparison of ECG parameters before and after initiation of hydroquinidine; data on 18 patients. Values are expressed as mean ± SE.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=18)</th>
<th>HERG (n=8)</th>
<th>Non-HERG (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc pre HQ</td>
<td>307±20</td>
<td>299 ± 23</td>
<td>313 ± 17</td>
</tr>
<tr>
<td>QTc post HQ</td>
<td>384±39</td>
<td>404 ± 30</td>
<td>362 ± 36</td>
</tr>
<tr>
<td>Difference (p value)</td>
<td>105±14</td>
<td>49 ± 9</td>
<td>56±16 (p=0.004)</td>
</tr>
<tr>
<td>QT/QTp pre HQ</td>
<td>73±5</td>
<td>71 ± 5</td>
<td>75 ± 4</td>
</tr>
<tr>
<td>QT/QTp post HQ</td>
<td>91±9</td>
<td>96 ± 7</td>
<td>86 ± 7</td>
</tr>
<tr>
<td>Difference (p value)</td>
<td>25±3</td>
<td>11 ± 2</td>
<td>14±4 (p=0.006)</td>
</tr>
</tbody>
</table>

QTc = corrected QT; QTp = predicted QT; SE = standard error.
Table 4. Patients with available data to compare the efficacy of hydroquinidine with other antiarrhythmic treatments.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Drug</th>
<th>Dosage</th>
<th>HR (bpm)</th>
<th>QT (ms)</th>
<th>QTc (ms)</th>
<th>QT/QTp (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 y, F, HERG</td>
<td>basal ECG</td>
<td></td>
<td>86</td>
<td>250</td>
<td>300</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>amiodarone</td>
<td>200 mg</td>
<td>71</td>
<td>260</td>
<td>284</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>80 mg BID</td>
<td>63</td>
<td>280</td>
<td>287</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>hydroquinidine</td>
<td>250 mg TID</td>
<td>85</td>
<td>360</td>
<td>428</td>
<td>102</td>
</tr>
<tr>
<td>35 y, M, HERG</td>
<td>basal ECG</td>
<td></td>
<td>66</td>
<td>270</td>
<td>283</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>80 mg BID</td>
<td>63</td>
<td>260</td>
<td>266</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>hydroquinidine</td>
<td>250 mg TID</td>
<td>60</td>
<td>380</td>
<td>380</td>
<td>93</td>
</tr>
<tr>
<td>71 y, F, HERG</td>
<td>basal ECG</td>
<td></td>
<td>77</td>
<td>291</td>
<td>329</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>disopyramide</td>
<td>400 mg/day</td>
<td>86</td>
<td>299</td>
<td>358</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>hydroquinidine</td>
<td>500 mg BID</td>
<td>75</td>
<td>342</td>
<td>382</td>
<td>91</td>
</tr>
<tr>
<td>44 y, F, HERG</td>
<td>basal ECG</td>
<td></td>
<td>70</td>
<td>292</td>
<td>315</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>disopyramide</td>
<td>400 mg/day</td>
<td>79</td>
<td>290</td>
<td>333</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>hydroquinidine</td>
<td>500 mg BID</td>
<td>81</td>
<td>318</td>
<td>370</td>
<td>88</td>
</tr>
<tr>
<td>43 y, M</td>
<td>basal ECG</td>
<td></td>
<td></td>
<td>290</td>
<td>338</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>disopyramide</td>
<td>100 mg BID</td>
<td>95</td>
<td>290</td>
<td>365</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>hydroquinidine</td>
<td>300 mg BID</td>
<td>97</td>
<td>270</td>
<td>343</td>
<td>81</td>
</tr>
<tr>
<td>29 y, M</td>
<td>basal ECG</td>
<td></td>
<td>81</td>
<td>300</td>
<td>349</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>80 mg TID</td>
<td>54</td>
<td>350</td>
<td>332</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>amiodarone</td>
<td>200 mg BID</td>
<td>60</td>
<td>400</td>
<td>400</td>
<td>98</td>
</tr>
</tbody>
</table>
QTc = corrected QT; QTp = predicted QT.
Table 5. Comparison of baseline clinical and demographics characteristics between patients receiving hydroquinidined and those without. Data are expressed as mean (±SD) or number (%).

<table>
<thead>
<tr>
<th></th>
<th>HQ (n=12)</th>
<th>no HQ (n=35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>9 (75%)</td>
<td>28 (80%)</td>
<td>0.70*</td>
</tr>
<tr>
<td>Age at 1st visit</td>
<td>27±21</td>
<td>32±18</td>
<td>0.41**</td>
</tr>
<tr>
<td>Symptomatic for CA or syncope (%)</td>
<td>6 (50%)</td>
<td>14 (40%)</td>
<td>0.74*</td>
</tr>
<tr>
<td>CA (%)</td>
<td>3 (25%)</td>
<td>9 (26%)</td>
<td>0.99*</td>
</tr>
<tr>
<td>Syncope (%)</td>
<td>3 (25%)</td>
<td>5 (14%)</td>
<td>0.40*</td>
</tr>
<tr>
<td>Asymptomatic (%)</td>
<td>6 (50%)</td>
<td>21 (60%)</td>
<td>0.74*</td>
</tr>
<tr>
<td>QTc at baseline</td>
<td>302±23</td>
<td>320±20</td>
<td>0.01**</td>
</tr>
</tbody>
</table>

* Fisher’s exact test; ** T test.