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**The QUIDAM Study: hydroquinidine therapy in the management of Brugada syndrome patients at high arrhythmic risk**

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**Short Title:** Quinidine in high-risk patients with Brugada syndrome

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**Abstract**

**Background:** Although the implantable cardiac defibrillator (ICD) remains the main therapy in Brugada syndrome (BrS), it does not reduce life-threatening ventricular arrhythmia. Based on pathophysiological mechanisms, hydroquinidine (HQ) has been suggested for the effective prevention of arrhythmia.

**Objective:** To provide evidence-based data supporting HQ use to prevent life threatening ventricular arrhythmia in high-risk patients with BrS.

**Methods:** We performed a prospective multicentre randomised (HQ vs. placebo) double-blind study with two 18-month cross-over phases in patients with BrS and implanted with an ICD.

**Results:** Among the 50 patients enrolled [mean age  $47.0 \pm 11.4$  years; 42 (84%) male], 26 (52%) fully completed both phases. Thirty-four (68%) presented HQ-related side effects, mainly gastrointestinal, which led to discontinuation of the therapy in 13 (26%). HQ has lengthened the QTc interval ( $409 \pm 32$  vs.  $433 \pm 37$ ms;  $P=0.027$ ) and increased the repolarization dispersion as evaluated by the Tpe max in precordial leads ( $89 \pm 15$  vs.  $108 \pm 27$ ms;  $P<0.0001$ ) with no significant changes in J-point elevation. During the 36-month follow-up, 1 appropriate ICD shock (0.97% event per year), 1 self-terminating ventricular fibrillation and 1 inappropriate ICD shock occurred under placebo therapy. No arrhythmic events were reported under HQ therapy.

**Conclusion:** Although HQ appears to be effective in preventing life-threatening ventricular arrhythmia, it could not be an alternative for ICD implant. Its frequent side effects greatly reduce its probable compliance and therefore do not reveal a significant effect. HQ increases repolarization dispersal with no changes in BrS pattern, which could indicate a more complex action of HQ than its  $I_{to}$  blocking effect alone.

**Keywords:** Brugada syndrome • Quinidine • Arrhythmia • Repolarisation • Implantable  
Cardioverter Defibrillator

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## Introduction

Since the first description of Brugada syndrome<sup>1</sup> (BrS), our understanding of the pathophysiological mechanisms of this inherited arrhythmia disease has constantly progressed.<sup>2-5</sup> Although risk stratification of sudden cardiac death (SCD) has been improved in line with this understanding,<sup>6-8</sup> management of patients affected with BrS remains mainly dependent on an implantable cardioverter defibrillator (ICD) with a high rate of complications.<sup>9</sup>  $\beta$ blockers were evaluated to be an alternative for ICD implant but have failed to prove their efficiency.<sup>10</sup>

Hydroquinidine (HQ), a class I<sub>A</sub> antiarrhythmic, has been used for decades in the management of arrhythmia.<sup>11</sup> Its safety and efficacy in patients with idiopathic ventricular fibrillation (VF)<sup>12</sup>, early repolarization syndrome<sup>2</sup> or BrS have been reported by different retrospective studies but remain a matter of debate since it has never been investigated by randomised and multicenter studies.<sup>13-18</sup>

Our aim was to provide evidence-based data to support HQ use to prevent life threatening ventricular arrhythmia in high-risk patients with BrS in multicenter prospective randomised double-blind study.

## Methods

### Population

Patients were recruited from February 2009 to November 2011, from 13 tertiary French university hospitals. Protocol approval was obtained from institutional ethical committees. Written informed consent was obtained from all patients before their inclusion. This clinical trial was registered at <https://clinicaltrials.gov/> (NCT00927732).

All our BrS study patients were considered at high-risk and all had an ICD implanted due to the following: previous aborted SCD or documented ventricular tachyarrhythmias (group A); previous unexplained syncope supposed to be of an arrhythmic origin (group B); spontaneous type 1 BrS ECG pattern with a positive electrophysiological study (EPS) (group C). Patients in group A or B could display both spontaneous or drug-induced type 1 BrS ECG pattern. EPS were conducted with a maximum of three ventricular extrastimuli with a minimum coupling interval of 200ms from at least one right ventricular site. EPS was considered positive if VF and/or sustained ventricular tachycardia (VT) was induced.

Patients already on daily HQ medication above 900mg or below 300mg were excluded as those with manifestations of HQ hypersensitivity [appearance of hypotension, fever, prolongation of QTc interval >40ms (arbitrarily chosen) or prolongation of QRS duration >25%].<sup>11,19,20</sup> HQ hypersensitivity test (clinical and ECG monitoring for 3 hours after a single intake of HQ 300mg) was performed in every included patient not on chronic HQ therapy before.

After a 7-day washout period, patients were randomised to placebo or HQ. A crossover was performed after 18 months, separated by a second 7-day washout period. Optimal HQ dosages were assessed in each patient to achieve HQ blood level



range from 3 to 6  $\mu\text{mol/L}$ , commonly consider as therapeutic and reported in previous studies.<sup>13,16,17</sup>

A core lab of 3 expert physicians blinded to patient clinical and pharmacological status reviewed ECG at baseline and during follow-up. Quantitative measurements of electrocardiographic parameters were assessed at baseline, after an acute intake and on chronic HQ therapy (*supplementary methods* for ECG measurement's details).

Follow-up consultations, including ECG and ICD interrogation, were planned in each phase of the crossover study at 1, 6, 12 and 18 months. In case of an appropriate ICD shock, the patient was switched to phase 2 after a 7-day washout period or ended the study if he/she had already been in phase 2.

### **Endpoints**

The primary endpoint was the time to the first appropriate ICD shock. Secondary endpoints were evaluation of inappropriate shocks, self-terminating VT/VF episodes, death from all causes, occurrence of supra-ventricular tachycardia (SVT), syncope without arrhythmic events after ICD interrogation and adverse events under HQ therapy.

### **Statistical Analysis**

Data were analysed with SAS packages (SAS Institute Inc., Cary, NC). Chi<sup>2</sup> or Fisher's exact tests were used to compare categorical variables. The *t*-test, Mann-Whitney, Kruskal-Wallis tests were performed to test for differences in continuous parameters. Means with standard deviations or medians with quartile data are presented as appropriate. A two-sided *P*-value<0.05 was considered as statistically significant in all tests.

## Results

### Study population

Among the 78 patients screened, 50 were randomised [mean age:  $47.0 \pm 11.4$  years, 42 (84%) male] as shown in *Figure 1*. The clinical characteristics and baseline ECG parameters for all of the 50 randomized patients and according to their subgroups are summarized in *Table 1*.

Twenty-six (52%) patients were randomised to phase 1 HQ and 24 (48%) to phase 1 placebo. Among the 13 (26%) patients who stopped therapy during phase 1, 8 (62%) were on HQ. Nine (69%) stopped because of adverse events, which were essentially gastrointestinal (n=6). Eleven (22%) patients stopped therapy during phase 2 including 8 (73%) on HQ. The main reason was adverse events (n= 10; 91%), which were essentially gastrointestinal (n=5).

Finally, 26 (52%) patients fully completed both phases (36 months) without discontinuation of medication.

### Occurrence of arrhythmias

Mean follow-up was respectively  $376 \pm 248$  days and  $377 \pm 235$  days under HQ and placebo therapy.

No patient on HQ presented an appropriate ICD shock. One patient (group A) on placebo experienced an appropriate ICD shock (event rate 0.97% per year) without recurrence during the following 18 months while on HQ (900mg daily; HQ blood level:  $3 \mu\text{mol/L}$ ), but he experienced a second appropriate ICD shock 3 days after having stopped his HQ during the washout period (after the end of phase 2). This patient was diagnosed at age 28 after an aborted SCD and presented with a spontaneous BrS type 1 ECG pattern. His specific ECG parameters under placebo then HQ therapy are shown in supplementary material *Table 1*.

One self-terminating VF episode occurred in a patient (group B) while on placebo and one inappropriate ICD shock for SVT in a patient (group C) while on placebo. Fourteen patients (28%) presented SVT during follow-up, of whom 8 (57%) were on HQ therapy and 6 (43%) on placebo ( $P=0.33$ ). Two (4%) patients died during the study, one (group B) from a traumatic brain injury and the other (group A) secondary to a neuromuscular disease.

### **HQ therapy**

The mean HQ daily dosage was  $738\pm 174$ mg with a mean HQ blood level of  $3.14\pm 0.63$  $\mu$ mol/L. Twenty-nine (58%) patients were under HQ 600mg daily, 19 (38%) under 900mg and 2 (4%) under 1200mg with mean HQ blood levels respectively of  $3.44\pm 0.65$  $\mu$ mol/L,  $2.84\pm 0.46$  $\mu$ mol/L and  $3.20\pm 0.71$  $\mu$ mol/L.

Thirty-four (68%) patients reported adverse events during their treatment with HQ. Thirteen (26%) had to stop the medication for HQ-related side effects, which were mainly gastrointestinal ( $n=10$ ; 77%) but also photophobia ( $n=2$ ; 15%) and photosensitivity ( $n=1$ ; 8%). Three stopped HQ for adverse events not related to HQ therapy. Side effects were significantly more frequent with HQ therapy (*Table 2*).

Patients who experienced side effects were on a higher mean daily dosage of HQ ( $768\pm 186$ mg vs.  $675\pm 136$ mg;  $P=0.04$ ) but no differences were found regarding age, sex, clinical presentation, ECG parameters or HQ blood levels ( $3.09\pm 0.46$  $\mu$ mol/L vs.  $3.28\pm 0.82$  $\mu$ mol/L;  $P=0.25$ ).

### **Acute HQ-induced ECG changes**

Among the 50 randomised patients, 48 (96%) underwent a hypersensitivity HQ test whereas 2 (4%) were already on HQ therapy. QT ( $387\pm 27$  vs.  $414\pm 35$ ms;  $P<0.0001$ ), QTc intervals ( $404\pm 29$  vs.  $417\pm 29$ ms;  $P=0.027$ ) and Tpe max ( $95\pm 18$  vs.  $107\pm 22$ ms;  $P<0.001$ ) were significantly longer 3 hours after an acute intake of HQ

300 mg. No significant changes were observed on J-point elevation. Details are provided in *Table 3* and according to subgroup in supplementary material *Table 2*.

### **Chronic HQ-induced ECG changes**

Among the 50 randomised patients who underwent both therapies (HQ and placebo), QT ( $388\pm 29$  vs.  $411\pm 35$ ms;  $P<0.0001$ ), QTc intervals ( $409\pm 32$  vs.  $433\pm 37$ ms;  $P=0.027$ ), Tpe max ( $89\pm 15$  vs.  $108\pm 27$ ms;  $P<0.0001$ ) and Tpe dispersion were significantly longer while on chronic HQ therapy. No significant changes were observed in J-point elevation in any of the right precordial leads. Except for QTc interval [ $417\pm 29$ ms (acute) vs.  $433\pm 37$ ms (chronic);  $P<0.0001$ ], no ECG parameters appeared to be different under acute and chronic HQ therapy. Details are provided in *Table 3* and according to subgroup in supplementary material *Table 3*. Except for QTc ( $421\pm 35$ ms vs.  $443\pm 36$ ms;  $P<0.001$ ), no significant relevant differences were observed comparing patients under 600mg daily of HQ with others (>600mg daily). Details are presented in supplementary material *Table 4*. An example of ECG HQ-induced changes is shown in *Figure 2*.

## Discussion

Since there was no occurrence of any ventricular arrhythmia in patients under HQ, HQ appears to be quite effective in BrS. However, statistical significance compared to placebo was not observed, principally owing to a lower arrhythmic event frequency than expected (only one patient on placebo presenting with ventricular arrhythmia) and to HQ-related adverse events, which were frequent and causing interruption of therapy in a significant number of cases.

### HQ-related side effects

HQ-related side effects, especially gastrointestinal, have been broadly described in the literature but tend to be fewer than those we observed. Belhassen<sup>14</sup> reported a 36% adverse events rate in patients on a mean daily dosage of quinidine bisulfate of  $1483\pm 240$ mg. Among patients on lower HQ dosages ( $618\pm 72$  mg/day), Bouzeman<sup>16</sup> noted a low 6% rate of major HQ intolerance which led to a discontinuance of therapy. Mizusawa<sup>21</sup> observed no major intolerance in the 14 patients on HQ daily dosage between 300 to 600mg (mean HQ blood level:  $1.55\mu\text{g/mL}$ ) with reported success of 44% in preventing VF inducibility.

In our study, with a mean HQ daily dosage of  $738\pm 174$  mg, we observed a larger proportion of 58% HQ-related adverse events that led to a discontinuance of therapy in 26%. Nonetheless, we were still on the lower border of our therapeutic HQ blood level range ( $3.14\pm 0.63\mu\text{mol/L}$ ). One could argue that the lower the dosage used, the lower the side effects rate, but lower HQ efficacy may also be expected. This lower HQ dosage have been suggested to be efficient in case series, but without further evidences, the difficult question of defining optimal HQ daily dosages remain to be assessed<sup>22</sup>.

Apart from higher HQ dosage, we found no differences between patients who suffered from adverse events and others. Thus, our data did not support a genotype or phenotype relation with side-effects.

### **HQ-induced ECG changes**

Aside from its  $I_{Na}$  and  $I_{Kr}$  blocking effect, HQ presents with an  $I_{to}$  blocking effect that has been suggested to support its potential therapeutic role in patients with BrS<sup>13,23</sup>. Indeed, according to Antzelevitch et al.,<sup>23</sup> the transmural heterogeneity of  $I_{to}$  current, which induces repolarization heterogeneity, plays a key role in the occurrence of type 1 BrS ECG pattern as well as in the arrhythmogenicity by facilitating phase 2 re-entry<sup>2,24</sup>. Tpe has been used as an ECG marker of this transmural repolarization dispersion<sup>25</sup> and appears to be a useful tool to evaluate repolarization processes and the effects of HQ in BrS patients. A prolonged Tpe interval should be correlated with increased transmural repolarization heterogeneity that may enhance the substrate for phase 2 re-entry. Confirming this hypothesis, according to Maury,<sup>26</sup> this prolonged Tpe and Tpe max denote a higher risk of arrhythmic events in BrS patients.

The present study showed that HQ-induced ECG changes appear promptly after an acute intake and are maintained under chronic therapy. This correlates the clinical efficacy of HQ observed during electrical storms in BrS patients<sup>27</sup>. We expected a reduction of repolarization heterogeneity in BrS patients who underwent HQ therapy. However, although HQ lengthened QT and QTc interval, it also increased the repolarization dispersion as evaluated by the Tpe and Tpe max. Additionally, in opposition to previous clinical reports,<sup>28</sup> we did not find any significant effect on J-point elevation.

This effect was considered as unexpected based on the idea that BrS pathophysiology involved only a repolarization disorder.<sup>23</sup> However, as we now

know, repolarization and depolarisation disorders are both involved.<sup>29</sup> Therefore, these ECG modifications could denote a more complex role than simply a selective and exclusive  $I_{to}$  blocking effect of HQ in BrS patients. Indeed,  $I_{Kr}$  blocking effect has been demonstrated to prolong Tpe interval with a similar but smaller effect on ST segment interval<sup>19</sup>. Interestingly, the multi-ion channel block of quinidine is concentration-dependent and begins with a  $I_{Kr}$  blocking effect before appearance of significant block in other sodium, calcium and potassium channel including  $I_{to}$ <sup>30</sup>. This could explain the increase in Tpe interval without modification of J wave amplitude that we observed in our study. Among previous studies about BrS, both low and high dosages of HQ have been used, generating various effects on patient's ECGs. In our study, HQ-induced ECG changes were similar (except for QTc) regardless of daily HQ dosage.

Altogether, this suggests that the global ionic effect of HQ may explain the variability in ECG modifications among studies.<sup>13,23</sup> As a consequence, assuming HQ is efficient to prevent arrhythmia in BrS, its effect does not seem to be only and directly due to  $I_{to}$  inhibition.

### **Study Limitations**

When the QUIDAM study was designed, only few databases that included a large number of patients were available and EPS to test for VF inducibility was commonly used as a tool for risk stratification<sup>6,31</sup>. Thence, we expected an arrhythmic event rate to be as high as 1% monthly in our selected population. This was weighted by our proper evaluation data of arrhythmic risk in patients with BrS which was subsequently published in the FINGER study,<sup>6</sup> but that was still overestimated in comparison to current knowledge.

According to Hermida<sup>13</sup> et al., one could initially consider a risk reduction of arrhythmic events up to 70% with HQ with 10% adverse events leading to discontinuation of therapy. On this basis, with an  $\alpha=5\%$  and  $\beta=20\%$ , and based on expected arrhythmic rate at study onset, 200 patients were thought necessary to reach statistical significance within a 24-month follow-up. This was extended to 36 months to reach statistical significance due to the lower than expected arrhythmic event rate. However, when both were combined, the real arrhythmic event rate and HQ-related side effects leading to discontinuation of therapy, the estimated sample size to reach statistical difference was evaluated as high as 1,800 patients. This extremely high and not reasonably achievable number led to the premature termination of the QUIDAM study.

### **The future of HQ**

Despite previous encouraging clinical and experimental studies,<sup>13,14,23</sup> the QUIDAM study was not able to provide evidence-based data to support its efficacy and safety in high-risk BrS patients. The use of HQ has been suggested in lower-risk Brs patients.<sup>16,17</sup> However, considering the low arrhythmic event rate and a similar HQ-related side-effect rate, demonstration of a significant effect appears unachievable in such population.

Still, as shown by our patient who experienced one (two if wash-out period is included) appropriate ICD shock(s) on placebo, our study supports the HQ individual efficacy. Retrospective studies have reported the well-tolerance and the likely efficiency of long-term HQ therapy<sup>17,32</sup>. Anguera<sup>33</sup> et al. noted that quinidine could be useful to reduce, but not suppress, the burden of ventricular arrhythmias with still few patients who experienced ICD shocks.



Considering the progress of defibrillation devices leading to less ICD-related complications (especially with the sub-cutaneous ICD), the development of catheter ablation in BrS patients and the virtual impossibility to demonstrate the efficacy of HQ therapy, it is likely that its use will remain restricted to secondary prevention in patients already implanted with an ICD or who refuses or has no access to one.

According to current evidence based data, HQ could not be considered as an alternative for ICD implant in patients with high-risk BrS, even considering the high rate of ICD-related complications in such population. Define precise daily HQ dose and characteristics of patients whom benefit from HQ therapy would be of a great help.

We advise to consider, if available, the use of an individual well tolerated HQ dosage in BrS patients with ICD and recurrent ventricular arrhythmias. If such a therapy should fail or be badly tolerated, catheter ablation might be an adjuvant. However, several studies are ongoing and will provide data in the future to better place catheter ablation among the therapeutic arsenal for BrS patients.<sup>34</sup>

Finally, in the paediatric BrS population where an ICD implant could be challenging and HQ appears to be well tolerated, this therapy could be a temporary alternative.<sup>35</sup>

## Conclusion

The QUIDAM study was the first prospective randomized double-blind study aiming to provide strong data to support HQ use in the management of high-risk BrS patients. The conductive idea was to be capable of offering a safe alternative to ICD implants. Unfortunately, frequent HQ-related side effects and rare arrhythmic events have made it difficult to conduct large studies to prove HQ efficacy. This has led to a premature termination of the QUIDAM study without demonstrating the efficacy of this drug. According to current data, HQ could not be considered as an alternative to ICD implantation in high-risk patients with BrS.

However, we did observe ECG changes under therapy such as lengthening of the Tpe interval with no effect on J-point elevation, which suggest a more complex role than a selective and exclusive  $I_{to}$  blocker effect of HQ in BrS patients. This supports the idea that BrS pathophysiology involves more complex mechanisms than only a repolarization disorder.

Regardless of these shadow areas, these considerations should not stop its use in daily clinical practice, especially for the management of BrS patients with recurrent ventricular arrhythmia or electrical storms.

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**Figure legends**

*Figure 1:* Flow-chart of the QUIDAM study.

*Figure 2:* Twelve-lead ECG with no medication (baseline), after an acute intake of hydroquinidine (HQ) and under chronic HQ therapy. An increased QTc and Tpe max was observed while on both HQ therapies. ECG-speed 25mm/s and voltage 10mm/mV.

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**Tables**

**Table 1:** Clinical characteristics and ECG parameters on inclusion. Group A: past history of SCD; Group B: past history of syncope; Group C: asymptomatic with spontaneous type 1 ECG pattern and positive electrophysiological study.

	<b>Group A</b> <i>n=6 (12%)</i>	<b>Group B</b> <i>n=26 (52%)</i>	<b>Group C</b> <i>n=18 (36%)</i>	<b>Total</b> <i>n=50 (100%)</i>
<b>Clinical characteristics</b>				
Age on diagnosis, <i>years</i>	43.7±12.6	45.5±11.9	50.6±9.8	47.0±11.4
Male, <i>n (%)</i>	5(83)	22(85)	15(83)	42(84)
Family history of SCD, <i>n (%)</i>	0	6(23)	9(50)	15(30)
Spontaneous Type 1 ECG pattern, <i>n (%)</i>	5(83)	13(50)	18(100)	36(72)
Dual Chamber ICD, <i>n (%)</i>	0	2(8)	1(5)	3(6)
VF zone >200 bpm, <i>n (%)</i>	6(100)	23(88)	18(100)	47(94)
Presence of a VT zone, <i>n (%)</i>	3(50)	3(12)	5(28)	11(22)
SCN5A mutation, (n=43), <i>n (%)</i>	0/5(0)	4/22(18)	5/16(31)	9/43(21)
<b>ECG parameters on inclusion</b>				
Heart Rate ( <i>bpm</i> )	72±11	72±10	67±10	70±11
PR ( <i>ms</i> )	180±13	190±32	180±36	185±32
QRS ( <i>ms</i> )	108±11	112±22	102±36	108±21
QT ( <i>ms</i> )	393±48	382±32	383±31	383±33
QTc Bazett ( <i>ms</i> )	424±42	425±37	397±37	415±39
Maximum J-point elevation ( <i>mm</i> )	4.0±2.3	3.5±1.4	3.2±1.2	3.5±1.5

SCD: sudden cardiac death; ECG: electrocardiogram; ICD: implantable cardioverter defibrillator; VF: ventricular fibrillation; VT: ventricular tachycardia



**Table 2:** Adverse events in the randomised population (n=50) of the QUIDAM study according to placebo or hydroquinidine therapy.

	Placebo	HQ	P-value
Duration of therapy, <i>days</i>	377±235	376±248	0.23
<b>AE leading to stop therapy, n (%)</b>	3(6)	16(32)	0.002
Gastrointestinal, n (%)	1(2)	10(20)	0.008
Other existing AE under HQ, n (%)	0	3(6)	0.24
photophobia	0	2(4)	-
photosensitivity	0	1(2)	-
AE unrelated to HQ, n (%)	2(4)	3(6)	1
<b>AE not leading to stop therapy, n (%)</b>	5(10)	18(36)	0.004
Gastrointestinal, n (%)	2(4)	16(32)	0.0004
Other existing AE on HQ, n (%)	3(6)	9(18)	0.12
photophobia	0	2(4)	-
photosensitivity	0	2(4)	-
tinnitus	0	2(4)	-
headache	0	1(2)	-
vertigo	1(2)	1(2)	-
fatigue	2(4)	1(2)	-
AE unrelated to HQ, n (%)	0	7(14)	0.01

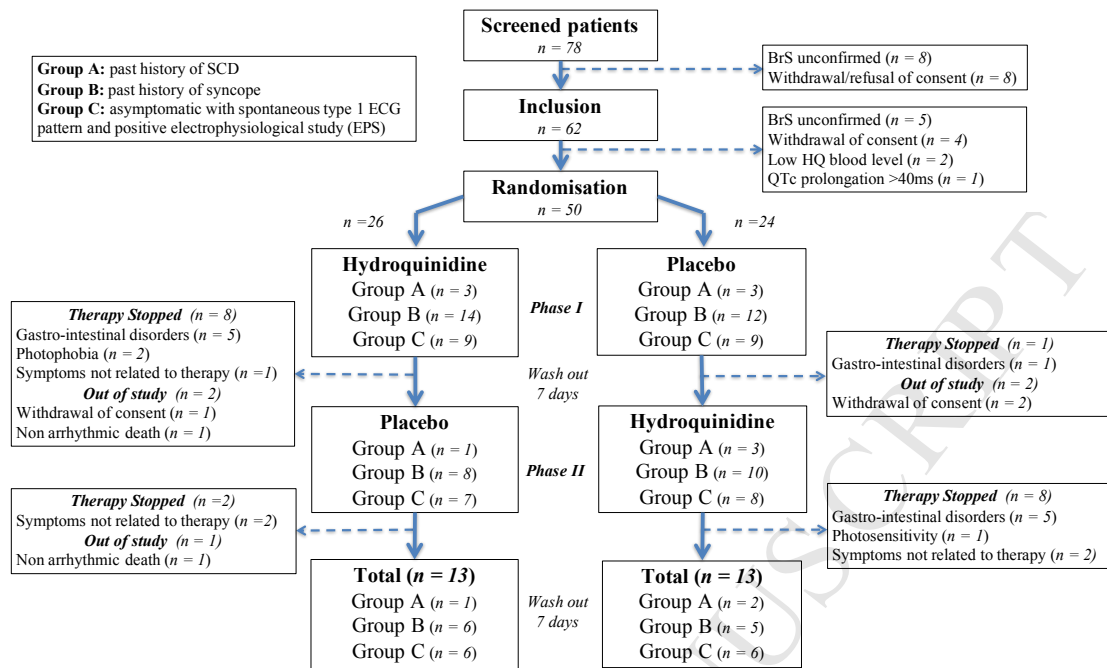
AE: adverse events; HQ: hydroquinidine

**Table 3:** Standard and repolarization dispersion ECG parameters measured before (Before HQ), 3 hours after (Acute HQ) a 300mg intake of hydroquinidine, under placebo and chronic hydroquinidine therapy.

	Before HQ (n=48)	Acute HQ (n=48)	Placebo (n=50)	Chronic HQ (n=50)	P-value
<b>Standard ECG parameters</b>					
Heart Rate ( <i>bpm</i> )	67±10*	62±10*†	68±10	69±10†	*0.032; †0.0004
PR ( <i>ms</i> )	182±31	185±31	182±36	186±31	-
QRS ( <i>ms</i> )	103±17	104±18	103±17	103±16	-
QT ( <i>ms</i> )	387±27*	414±35*	388±29†	411±35†	*†<0.0001
QTc Bazett ( <i>ms</i> )	404±29*	417±29*†	409±32‡	433±37†‡	*0.027; †‡<0.0001
Maximum J-point elevation ( <i>mm</i> )	1.6±1.5	1.7±1.6	1.8±1.4	1.8±1.5	-
<b>Tpe (<i>ms</i>)</b>					
V1	79.3±19.9	84.1±24.5	69.7±16.0*	77.4±20.9*	*0.0055
V2	85.2±19.4*	91.1±25.0*	74.5±16.8†	87.2±21.5†	*0.046; †<0.0001
V3	82.5±15.2*	92.0±18.8*	80.0±17.1†	95.7±29.5†	*0.002; †<0.0001
V4	79.4±15.7*	88.6±20.5*	78.6±13.8†	87.8±25.1†	*0.002; †0.0013
V5	76.6±16.6*	87.2±23.6*	75.4±15.2†	83.8±23.9†	*<0.001; †0.0028
V6	73.4±17.0*	83.4±20.4*	69.5±12.7†	79.0±19.1†	*0.001; †<0.0001
<b>Tpe/QTc</b>					
V1	0.205±0.046	0.205±0.046*	0.176±0.040	0.181±0.043*	0.01
V2	0.218±0.032	0.218±0.032	0.192±0.040	0.208±0.048	-
V3	0.222±0.037	0.222±0.037	0.206±0.046	0.225±0.064	-
V4	0.214±0.036	0.214±0.036	0.201±0.033	0.207±0.053	-
V5	0.205±0.039	0.214±0.047*	0.193±0.034	0.196±0.048*	*0.04
V6	0.197±0.040	0.209±0.048*	0.180±0.030	0.187±0.038*	*0.004
<b>Tpe dispersion (<i>ms</i>)</b>					
	31.0±15.8	36.0±19.0	29.6±13.1*	42.3±23.6*	*<0.0001
<b>Tpe max (<i>ms</i>)</b>					
	94.8±18.3*	106.6±22.4*	89.4±15.2†	107.7±26.6†	*<0.001; †<0.0001

No comparisons were made between acute HQ and Placebo  
ECG: electrocardiogram; HQ: hydroquinidine

Figure 1



**Figure 2**