Atrial fibrillation in a large population with Brugada electrocardiographic pattern: prevalence, management, and correlation with prognosis

Atrial fibrillation in a large population with Brugada electrocardiographic pattern: Prevalence, management, and correlation with prognosis

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Background

A high prevalence of atrial fibrillation/atrial flutter (AF/AFl) has been reported in small series of Brugada patients, with discordant data.

Objective

The purpose of this study was to analyze, in a large population of Brugada patients, the prevalence of AF/AFl, its correlation with prognosis, and the efficacy of hydroquinidine (HQ) treatment.

Methods

Among 560 patients with Brugada type 1 ECG (BrECG), 48 (9%) had AF/AFl. Three groups were considered: 23 patients with BrECG pattern recognized before AF/AFl (group 1); 25 patients first diagnosed with AF/AFl in whom Class IC antiarrhythmic drugs administered for cardioversion/prophylaxis unmasked BrECG (group 2); and 512 patients without AF/AFl (group 3). Recurrence of AF/AFl and occurrence of ventricular arrhythmias were evaluated at follow-up.

Results

Mean age was 47 ± 15 years, 59 ± 11 years, and 44 ± 14 years in groups 1, 2, and 3, respectively. Seven subjects (32%) in group 1 had syncope/aborted sudden death, 1 (4%) in group 2, and 122 (24%) in group 3. Ventricular arrhythmia occurred in three patients in group 1, none in group 2, and 10 in group 3 at median follow-up of 51, 68, and 41 months, respectively. Nine patients in group 1 and nine in group 2 received HQ for AF/AFl prophylaxis; on therapy, none had AF/AFl recurrence.

Conclusion

Prevalence of AF/AFl in Brugada patients is higher than in the general population of the same age. Patients in group 1 are younger than those in group 2 and have a worse prognosis compared to both groups 2 and 3. HQ therapy has proved useful and safe in patients with AF/AFl and BrECG.

Abbreviations

AF, atrial fibrillation; **AFl**, atrial flutter; **aSD**, aborted sudden death; **BrECG**, Brugada type 1 electrocardiographic pattern; **HQ**, hydroquinidine; **ICD**, implantable cardioverter-defibrillator;

IQR, interquartile range; **VF**, ventricular fibrillation

Keywords

Brugada syndrome; Atrial fibrillation; Hydroquinidine; Ventricular arrhythmia; SCN5A; SCN1B; Class IC antiarrhythmic drug

Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia, and its prevalence increases with age.[1, 2 and 3] The correlation between Brugada ECG pattern (BrECG) and atrial flutter (AFl) has been reported, but data about the prevalence of AF/AFl in Brugada patients are highly variable (range 11%–39%),[4, 5, 6, 7 and 8] depending on the sample size, and there are no data concerning its prognostic value and treatment.

In some cases, AF/AFl occur in patients who already have a diagnosis of Brugada syndrome. In other situations, AF/AFl are initially diagnosed and BrECG appears for the first time as a consequence of the pharmacologic therapy given for AF/AFl cardioversion or prophylaxis. In both cases, the choice of the antiarrhythmic treatment can be a concern. Class IC drugs are contraindicated because, by increasing ST-segment elevation, they can predispose to ventricular arrhythmic events. The efficacy of hydroquinidine (HQ) in AF treatment in the general population is known[9 and 10]; however, to our knowledge there are no data about the use of HQ in the subgroup of patients with AF/AFl and concomitant BrECG. Preliminary data suggest that HQ is not harmful in Brugada patients and might even be useful in preventing ventricular arrhythmias, although these data require further confirmation.[11, 12, 13, 14 and 15]

The aim of our study was to verify (1) the prevalence of AF/AFl in a large Brugada population, (2) the possible relation between AF/AFl and prognosis, and (3) the efficacy and safety of HQ therapy in this specific subgroup of patients.

Methods

Study population

Five hundred sixty patients with BrECG consecutively observed at the cardiology divisions of the Piedmont region of Italy between 2001 and 2012 were included in a registry after providing their consent. All of the patients had a BrECG as defined by the Consensus Conferences,[16 and 17] at least in one right precordial lead,[18] including recordings from the second and third intercostal space,[19 and 20] spontaneously or after Class I antiarrhythmic drugs administration. Patients included in the registry were classified as symptomatic for aborted sudden death (aSD; n = 6 [1%]) or syncope (n = 125 [22%]); otherwise, they were considered asymptomatic (n = 427 [76%]). In 2 patients (0.4%), the diagnosis of Brugada syndrome was made postmortem. Mean age was 44 ± 14 years, and 425 (76%) were males.

Genetic test was performed in 182 probands: 33 (18%) had SCN5A and 6 (3%) SCN1B mutation. Transthoracic echocardiography was performed in all the patients and other investigations were performed as appropriate, in order to exclude underlying structural diseases or other conditions that could justify the ST-segment elevation. Implantable cardioverter-defibrillator (ICD) placement was proposed to patients with previous aSD or arrhythmic syncope, according to the method reported in a previous study.[21]

Study design

In this study, we focused on patients with a history of AF/AFl (defined as at least one documented episode of paroxysmal/persistent AF/AFl) divided into three groups: patients in whom AF/AFl were documented after diagnosis of BrECG and inclusion in the Brugada registry (group 1), patients in whom BrECG was unmasked for the first time during Class IC antiarrhythmic therapy given for AF/AFl interruption or prevention (group 2), and the remaining patients in the registry who did not have AF/AFl (group 3).

Age, gender, occurrence of syncope or cardiac arrest, spontaneous type 1 ECG, and mutation in genes encoding for the cardiac sodium channel (SCN5A-SCN1B) were compared in group 1 vs group 2, group 1 vs group 3, and group 2 vs group 3.

AF was defined according to the 2010 European Society of Cardiology guidelines.[1] In patients with AF/AFl, HQ treatment was proposed as prophylaxis when ≥2 paroxysmal AF/AFl episodes or ≥1 episodes of persistent AF/AFl were documented or when inappropriate ICD shocks due to AF/AFl had occurred. In adults, sustained-release HQ was given at a starting dose of 250 mg bid; in children, the galenic formulation was given at a starting dose of 4 mg/kg tid, adjusted according to HQ plasma level (therapeutic range 0.6–2.2 μg/mL), QRS duration, and QT interval. Ablation of AF/AFl was performed in case of inefficacy or intolerance to HQ therapy or based on physician and patient choice. Details of catheter pulmonary vein isolation and inferior vena cava-tricuspid annulus isthmus ablation techniques have been described in our previous publications on these topics.[22 and 23]

Follow-up

All subjects underwent outpatient follow-up with surface 12-lead ECG and, in those with ICD, analysis of stored electrograms every 6 months; 24-hour 12-lead Holter monitoring also was planned once per year. Recurrence of AF/AFl and onset of ventricular arrhythmias were investigated and compared among the groups. Efficacy and safety of HQ treatment in the prevention of AF/AFl recurrences also were evaluated.

Statistical analysis

Continuous variable are reported as mean ± SD or median and interquartile range (IQR) depending on distribution. Between-groups comparison was performed using the χ^2 test (maximum likelihood χ^2 test) or the Fisher exact test for categorical variables and Student's *t* test or Kruskal-Wallis test for continuous variables. All probability values were two-sided, with P <.05 considered significant. Ventricular fibrillation (VF)–free survival time was determined using the life-table method and presented as Kaplan-Meier curves compared by means of log rank test. Analyses were performed using SPSS 20 (IBM, Armonk, NY, USA).

Results

Among the 560 patients of the Brugada Piedmont Registry, 48 (9%) had documented episodes of paroxysmal or persistent AF/AFl and are the object of this study. These patients were divided into three groups: group 1 (G1) consisted of 23 patients in whom AF/AFl were documented after the diagnosis of BrECG (median time elapsed between inclusion in the registry and AF/AFl occurrence 17 months [IQR 4–83]); group 2 (G2) was composed of 25 patients with BrECG pattern unmasked for the first time after Class IC antiarrhythmic therapy, given in 13 patients for AF/AFl interruption and the other 12 for prevention of recurrences; and group 3 (G3) was composed of 512 patients without documented AF/AFl. Baseline characteristics of the three groups are listed in Table 1.

Mean age in group 1 was 47 ± 15 years (range 5–66 years), in group 2 was 59 ± 11 years (range 37–76 years), and in group 3 was 44 ± 14 years (range 2–76 years) (P = .002 G1 vs G2, P <.001 G2 vs G3). In all groups there was a male predominance (P = NS). Group 1 showed a higher prevalence of aSD (2/23 [9%]) compared with group 3 (4/512 [1%], P = .049), whereas none of the group 2 patients experienced aSD. Prevalence of syncope was similar in groups 1 (5/23 [22%]) and 3 (118/512 [23%], P = .981) but was significantly lower in group 2 (1/25 [4%]) than in group 3 (P = .025).

Spontaneous type 1 ECG was observed more frequently in group 1 (16/23 [70%]) than in groups 2 (0/25) and 3 (215/512 [42%]) (P <.001 G1 vs G2, P = .01 G1 vs G3).

Genetic testing was performed in 13 of 23 patients in group 1: 5 (38%) were positive, with a SCN5A mutation found in 4 patients (31%) and a SCN1B mutation in 1 (7%); in group 2, SCN5A mutation was identified in 2 of the 10 patients (20%) who underwent genetic analysis; in group 3, mutations were identified in 32 of 159 (20%): SCN5A in 27 (17%) and SCN1B in 5 (3%). There was no statistically significant difference among the groups.

In group 1, 11 patients (48%) underwent ICD placement: 5 due to a history of aSD or syncope and 6 because of spontaneous type 1 ECG and VF induction at electrophysiologic study. In group 2, an ICD was placed in 1 patient (4%), the only with a history of syncope. In group 3, 96 patients (19%) underwent ICD placement: 57 with a history of aSD/syncope and 39 for VF induction at electrophysiologic study.

Considering echocardiographic data, mean ejection fraction was in the normal range in the three groups. The anteroposterior diameter of the left atrium was available for all group 1 and group 2 patients and for 176 patients (31%) in group 3. It was significantly greater in group 2 than in group 3 (P <.001) and tended to be increased in group 2 compared to group 1, without reaching statistical significance (P = .07; Table 1).

Follow-up and therapeutic management of AF/AFl

Median follow-up in group 1 from the first episode of AF/AFl was 51 months (IQR 26–69); groups 2 and 3 had median follow-up of 68 months (IQR 28–117) and 41 months (IQR 26–86), respectively, from inclusion in the Brugada Registry. In group 1, 11 of 23 subjects (48%) did not receive any antiarrhythmic treatment because they had experienced a single episode of paroxysmal AF/AFl without recurrences. The other 12 patients, who had ≥ 2episodes of AF/AFl or inappropriate ICD shocks due to AF/AFl (5 patients), were treated. Nine patients (39%) received HQ: none had AF/AFl recurrence during therapy at median follow-up of 28 months (IQR 17–50); one had to discontinue the

drug because of gastrointestinal side effects. Three subjects underwent radiofrequency catheter ablation as first therapy: two of these patients had no recurrences at 101 and 32 months of follow-up, respectively; the third patient underwent a redo procedure after 1 year and thereafter remained asymptomatic for AF/AFl at 61 months of follow-up.

In group 2, 13 of the 25 subjects (52%) did not receive any therapy: one developed permanent AF, six had from 1–3 paroxysmal AF/AFl episodes, and six had no recurrences. Nine patients (36%) were treated with HQ, and none experienced AF/AFl recurrences during median follow-up of 28 months (IQR 7–41). Two subjects (18%) had to discontinue HQ because of side effects (erythema in one and gastrointestinal intolerance in the other) and had subsequent sporadic paroxysmal AF/AFl recurrences. Another three patients underwent radiofrequency catheter ablation: two had no recurrences at 85 and 6 months of follow-up, respectively; the third one experienced two brief episodes of paroxysmal AF at 61 months.

HQ mean dosage in the 17 adult patients was 500 mg/day (range 250–750 mg/day); the dosage in the only child was 6 mg/kg tid.

Follow-up and therapeutic management of ventricular arrhythmias

In group 1, at median follow-up of 46 months (IQR 28–130), 3 patients (13%) had VF with appropriate shocks (mean age at event 42 ± 14 years). Of these three patients, two had previous aSD and one had a history of syncope. In these three patients, a spontaneous type 1 ECG pattern was present. Two of these patients were started on HQ therapy: one did not experience ventricular arrhythmia relapses at 70 months of follow-up; the other had a recurrence of VF during a brief period of HQ discontinuation. HQ was restarted after this event, and the patient remained asymptomatic thereafter (15 months of follow-up).

None of the patients in group 2 had spontaneous ventricular arrhythmias at median follow-up of 68 months (IQR 28–117). In this group, a 66-year-old patient had experienced episodes of paroxysmal AF since 2000 that had been treated with propafenone “pill in the pocket.” In 2010, after taking propafenone 600 mg orally, he had a syncopal episode and was hospitalized in a cardiology

department. ECG on admission showed a type 1 Brugada pattern. However; despite that finding, because of AF persistence he was treated with intravenous propafenone infusion. This caused further QRS widening and onset of ventricular premature beats triggering VF, which was interrupted by DC shock. The ECG in sinus rhythm still showed type 1 Brugada pattern (Figure 1). After this episode he came to our observation. HQ therapy was started, and a loop recorder was implanted. Neither AF/AFl recurrences nor ventricular arrhythmias were documented at 28 months of follow-up; in addition, thereafter he never exhibited spontaneous type 1 Brugada ECG.

In group 3, at median follow-up of 41 months (IQR 26–86), arrhythmic events occurred in 10 patients (2%): nine experienced VF with ICD shocks, and one patient who had refused ICD implant suffered sudden cardiac death.

Twenty-six patients in group 3 were treated with HQ. Follow-up of these patients was ended at the beginning of therapy.

The incidence of ventricular arrhythmic events in group 1 was significantly higher than in group 3 (P = .001), whereas a borderline higher incidence of events at follow-up was observed in group 1 compared with group 2 (P = .07; Figure 2A). Group 1 also showed a significantly higher incidence of ventricular events when compared to groups 2 and 3 considered together (P = .001; Figure 2B).

Discussion

The association between BrECG pattern and AF/AFl has been previously reported, with a prevalence of AF/AFl ranging from 25% to 39%[4, 5 and 6] in older studies and from 11%[8] to 19%[7] in the most recent studies. In the Brugada Registry of the Piedmont region, the overall prevalence of AF/AFl is about 9%. If we consider only the patients already included in the Brugada Registry before the onset of AF/AFl (group 1), the incidence of these arrhythmias in our Brugada population reduces to 4% but still remains high compared to the incidence reported in people younger than 55 years in different populations.[2 and 3]

In this study, based on the hypothesis of our previous work that patients who develop BrECG for the first time after administration of Class IC drugs for AF/AFl have different clinical features and a better prognosis,[21] we divided the patients with AF/AFl into two groups: patients in whom the arrhythmia was documented after the diagnosis of BrECG and inclusion in the Brugada Registry (group 1) and those in whom BrECG was unmasked for the first time during Class IC antiarrhythmic therapy given for AF/AFl interruption or prevention (group 2). We compared these two groups between themselves and with the patients in the Registry without AF/AFl (group 3). Our results indicate that patients in group 1 are younger, more often have aSD as the first clinical presentation, have a greater prevalence of spontaneous type 1 ECG, and experience a greater number of ventricular arrhythmic events at follow-up compared to group 2. Their clinical features are much more similar to those of group 3, with an even higher percentage of spontaneous type 1 ECG and a greater incidence of aSD. Moreover, in group 1, the left atrium tends to be smaller than in group 2, probably because the genesis of AF/AFl is linked more to ionic channel dysfunction than to left atrial enlargement. A recent study analyzing 190 patients with lone AF reported a prevalence of BrECG pattern after flecainide treatment of 5.8% (11 patients).[24] The clinical characteristics of the three patients who had ventricular arrhythmias at follow-up were similar to those described for the patients in our group 1 (mean age 47 ± 11 years and persistence of spontaneous type 1 ECG at follow-up). In our study, the onset of AF/AFl in patients with previously documented BrECG pattern seems to be a marker of more advanced disease, as also reported by Bordachar et al.[7] Thus, when lone AF is observed in a young and otherwise healthy subject, the presence of a concealed BrECG pattern should be ruled out because of the not negligible risk of ventricular arrhythmias, as shown in group 1. Moreover, in these subjects, it is important to look for the appearance of a spontaneous type 1 ECG during follow-up.

Similar considerations were also made by Rodríguez-Mañero et al,[25] who recently reported 35 of 611 Brugada patients in whom AF was documented before the diagnosis of BrECG. Their patients are similar to our group 2 in that they had AF before the diagnosis of BrECG pattern; however, they are younger (49 ± 15 years) and some of them previously had syncope or aSD, thus raising the possibility that some of these patients might belong to our group 1.

On the other hand, patients with BrECG pattern unmasked for the first time after Class IC

antiarrhythmic drugs administered for paroxysmal or persistent AF (group 2) are generally older, over the fifth decade of life, and their clinical profile is similar to that of the general population, in which the prevalence of AF increases with age.[2] This study confirms that group 2 is a subgroup of patients with a good long-term prognosis, as hypothesized in our previous work.[21] Nevertheless, in these patients, great attention should be paid to avoiding drugs that may enhance ST-segment elevation in the right precordial leads because they may precipitate life-threatening tachyarrhythmias,[26] as in the patient we described. For the same reason, whenever a self-administered "pill in the pocket" strategy has been chosen for treatment of new-onset AF/AFl, the first drug administration should be performed in the hospital with careful and continuous ECG monitoring.

The overall incidence of ventricular arrhythmic events at follow-up in our population is 2.3% at median follow-up of 41 months, which is lower than in other recent European cohorts. The incidence was 5% in the FINGER study (median follow-up 32 months)[27] and 4.5% in the PRELUDE study[28] (median follow-up 34 months). The incidence of events is lower especially in the asymptomatic patients: 0.5% in our population, 1.5% in the FINGER study, and 2.9% in the PRELUDE study. One reason may be that the Brugada Registry of the Piedmont region collects data on consecutive patients in a small and well-defined geographic area, thus reducing the referral selection bias. Moreover, the particularly good prognosis of our asymptomatic patients also could depend on behavioral recommendations concerning timely treatment of hyperthermia and the drugs to avoid.

Therapy

Pharmacologic therapy of AF/AFl in Brugada patients is still challenging because Class IC antiarrhythmic drugs as well as amiodarone and calcium channel blockers are contraindicated.[29 and 30] Our study demonstrates that HQ is effective and safe in patients with BrECG and concomitant AF/AFl. As a consequence, HQ may be a useful antiarrhythmic therapy alternative in this specific subgroup of patients. Our study also shows that catheter ablation is a good option for treatment of AF/AFl in Brugada patients, as also reported in a previous study.[31]

Genetic analysis

Mutations in SCN5A and SCN1B encoding for the α- and β-subunits of the sodium channel have been

reported in both lone atrial fibrillation and Brugada syndrome.[32, 33, 34 and 35] In our study, we found a mutation in the sodium channel in 38% of patients in group 1, which is about twice that in groups 2 and 3 (20%), although the difference does not reach statistical significance.

Study limitations

A limitation inherent to this kind of study is the difficulty in having a real community-based population, as the probability of observing a subject with BrECG is higher in patients with symptoms, including palpitations. Thus, AF/AFl prevalence might have been overestimated.

Our echocardiographic data were mainly obtained for the purpose of excluding underlying structural heart disease. Thus, we are not able to provide more detailed data on atrial dimensions. In several cases, in the presence of normal atria, dimensions were not specified.

Given the small number of syncopal events, the lack of significant differences between subgroups may be secondary to underlying type II error and should prevent definitive conclusions.

Conclusion

The prevalence of AF/AFl in patients with Brugada ECG is higher than in the general population of the same age. Patients who develop AF/AFl after the diagnosis of BrECG are younger, have a greater prevalence of spontaneous type 1 ECG, and more often experience cardiac arrest, unlike patients in whom BrECG is unmasked for the first time after administration of Class IC antiarrhythmic drugs given for AF/AFl. They also have a worse prognosis compared to Brugada patients without AF/AFl. A history of aSD and the presence of spontaneous type 1 ECG are well-known features of risk in Brugada patients. It is conceivable that AF/AFl is not, *per se,* a risk factor for sudden death but in patients with previously documented BrECG pattern seems to be a marker of more advanced disease. HQ has proved to be a useful and safe treatment for prevention of AF/AFl recurrence in the subgroup of patients with AF/AFl associated with BrECG.

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Table 1.

Clinical features of the three groups considered in the study

				P value		
	G1 (n = 23)	G2 (n = 25)	G3 (n = 512)	G1 vs G3	G2 vs G3	G1 vs G2
Age (years)	47 ± 15	59 ± 11	44 ± 14	.419	<.001	.002
Male gender (%)	19 (83%)	15 (60%)	390 (76%)	.64	.08	.1
Asymptomatic	16 (69%)	24 (96%)	388 (76%)	.497	.02	.035
Symptomatic						
Syncope (%)	5 (22%)	1 (4%)	118 (23%)	.981	.025	.156
Aborted sudden death (%)	2 (9%)	0 (0%)	4 (1%)	.049	.005	.667
Sudden death (%)	–	–	2 (0.4%)			
Spontaneous type 1	16 (70%)	0 (0%)	215 (42%)	.01	.001	<.001
Drug-induced type 1	7 (30%)	25 (100%)	297 (58%)			
Genetic analysis for SCN5A-SCN1B	13 (57%)	10 (40%)	159 (31%)			
Positive	5 (38%)	2 (20%)	32 (20%)	.154	.201	.590
Left atrial anteroposterior diameter (mm)	36 ± 6	40 ± 6	35 ± 3	.452	<.001	.070
Ejection fraction (%)	63 ± 17	62 ± 7	63 ± 5	.724	.711	.989

Values are given as number (percent) or mean ± SD.

G1 = group 1; G2 = group 2; G3 = group 3.

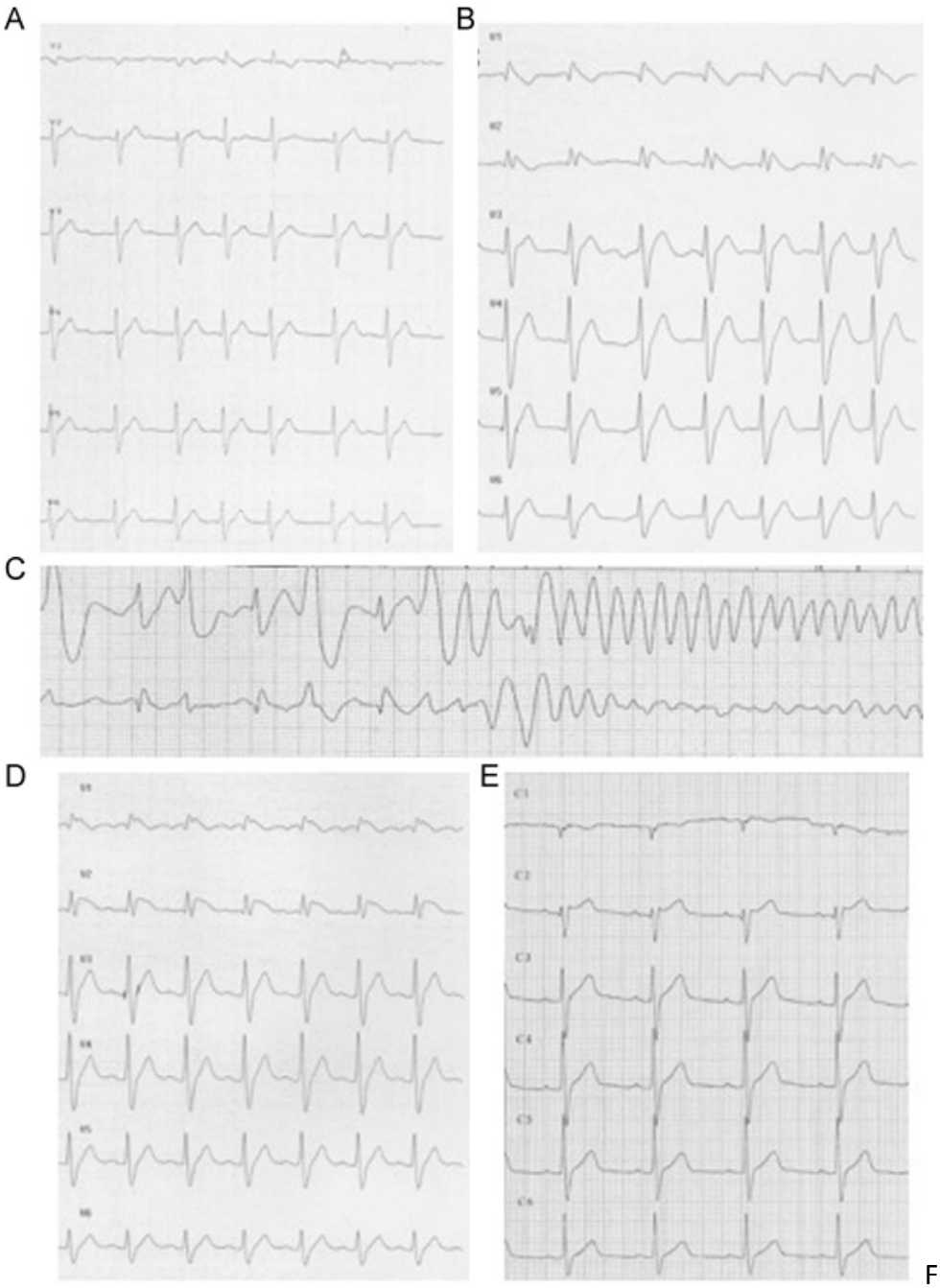

Figure 1.

A: ECG showing atrial fibrillation. There are two aberrant beats with right bundle branch block morphology. **B:** Type 1 Brugada ECG pattern and widening of the QRS after propafenone 600 mg orally. **C:** Premature ventricular beats triggering ventricular fibrillation after intravenous propafenone. **D:** ECG after DC shock showing restored sinus rhythm and persistence of type 1 Brugada pattern. **E:** ECG recorded after 1 month, on hydroquinidine therapy, showing a type 2 Brugada pattern.

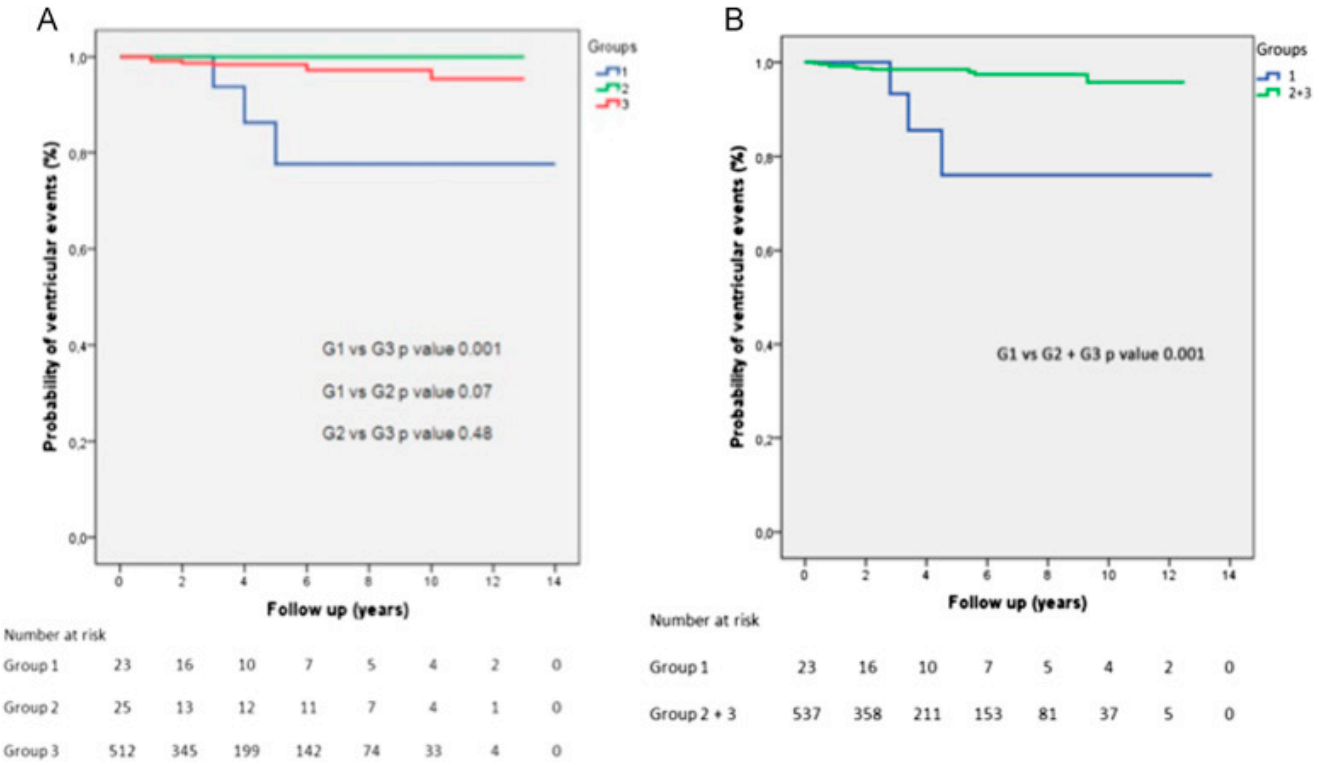

Figure 2.

Cumulative survival curves comparing the occurrence of ventricular arrhythmic events during follow-up in groups 1, 2, and 3 (**A**) and in group 1 vs groups 2 and 3 together (**B**). G1 = group 1; G2 = group 2; G3 = group 3.