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Abstract

Background: Flecainide and propafenone are Class Ic antiarrhythmic drugs that block the cardiac fast inwards Na^+ current and are used for rhythm control in patients with atrial fibrillation (AF). However, data on long-term clinical efficacy and safety of these drugs in a real-world setting are scarce.

Methods: Patients with AF who received chronic flecainide or propafenone therapy were retrospectively studied from the database of a tertiary care center. The primary outcome of the study was clinical efficacy of Class Ic antiarrhythmics, which was assessed based on the improvement of arrhythmia-related symptoms at the time of last follow-up.

Results: Among the 361 patients (261 males, 72.3%) with a mean age of 56 ± 12 years, 287 (79.5%) were using long-term flecainide, and 74 (20.5%) patients propafenone. The majority of the patients had paroxysmal AF (n = 331, 91.7%) and had an atrioventricular-nodal

blocking co-medication (n = 287, 79.5%). A total of 117 (32%) patients discontinued therapy after a median of 210 days (interquartile range 62–855 days). Clinical efficacy was observed in 188 patients (52%). The most common reason for therapy discontinuation was adverse drug effects, particularly proarrhythmic effects (48% for flecainide and 33% for propafenone). Patients who did not clinically benefit from Class Ic antiarrhythmics more often underwent pulmonary vein isolation (p = 0.02).

Conclusions: Long-term therapy with Class Ic antiarrhythmics showed clinical efficacy in approximately half of the patients with paroxysmal or persistent AF. However, these drugs were also associated with a relatively high rate of adverse events, and in particular proarrhythmic effects, which often resulted in therapy discontinuation rendering appropriate patient selection and therapy surveillance essential.

Key words: flecainide, propafenone, antiarrhythmics, atrial fibrillation, clinical outcome

Introduction

The medical treatment of atrial fibrillation (AF) has two main cornerstones: management of arrhythmia by rhythm or rate control and thromboembolic prophylaxis. Rhythm control aims to restore and maintain sinus rhythm (SR) [1]. In contrast, rate control aims to keep the heart rate during the arrhythmia within a desired range. Several antiarrhythmic drugs, such as Vaughan Williams Class Ic, can be used for the purpose of rhythm control.

Flecainide and propafenone are Class Ic antiarrhythmic drugs that block the cardiac fast inwards Na$^+$ current (I_{Na}). As a result, atrial refractoriness is prolonged and intracardiac conduction slows down in a rate-dependent manner [2]. Propafenone has additional minor beta-blocking effects. Both of these drugs are among the first-line therapeutic options for the treatment of AF in patients with no or minimal underlying structural heart disease. Although their long-term efficacy in maintenance of SR have been confirmed in several clinical trials [3–13], Class Ic antiarrhythmic drugs may also exert proarrhythmic effects, such as 1:1 atrioventricular conduction of atrial flutter (Fig. 1). The incidence of reported adverse effects during chronic use of flecainide ranges from 3.6% to 7.6% [14–16]. The aim of this study was to assess the efficacy and safety of flecainide and propafenone over long-term in a real-world setting of a tertiary care center.

Methods

The study enrolled patients with symptomatic, 12-lead electrocardiogram-documented AF who used flecainide or propafenone for at least three months since January 1999 at the University Heart Center in Zurich, Switzerland. Patients with missing follow-up data were excluded from analysis. Patient records were reviewed for baseline characteristics, such as age and gender, arrhythmic profile, co-morbidities, thromboembolic risk profile, use of antiarrhythmic, antiplatelet and anticoagulant co-medications, and echocardiographic parameters including left ventricular ejection fraction (LVEF) and left atrial long-axis diameter.

All patients were followed up every 6 to 12 months as part of a standard of care. The primary outcome of the study was clinical efficacy of Class Ic antiarrhythmics, which was assessed based on the improvement of arrhythmia-related symptoms at the time of last follow-up as compared to before therapy initiation. The incidence of AF ablation during follow-up was assessed as a secondary outcome. In addition, causes of therapy discontinuation were assessed in the study cohort.

Statistical analysis

Categorical variables are reported as frequencies (percentage), continuous variables as means ± standard deviation or as medians (interquartile range [IQR], range). Baseline characteristics between patients taking flecainide and propafenone were compared. Statistical analysis was performed by comparing continuous data using univariate ANOVA or Mann-Whitney U test, as appropriate, and categorical data using the Fisher exact test or chi-square test depending on the number of groups. Correlation was calculated using Pearson's coefficient. A two-sided p value < 0.05 was considered statistically significant. All statistical analyzes were conducted using SPSS version 21 (IBM Corp., Armonk, NY, USA).

Results

A total of 361 patients (261 males, 72.3%) with a mean age of 56 ± 12 years were included in the study. Of these, 287 (79.5%) were using long-term flecainide, and the remaining 74 (20.5%) patients were on propafenone. Most of the patients had paroxysmal AF (n = 331, 91.7%) and had an atrioventricular-nodal blocking co-medication (n = 287, 79.5%). There was a statistically significant difference in the use of antithrombotic therapy between patients taking flecainide and propafenone (p = 0.037). Otherwise, the two groups were similar regarding baseline characteristics (Table 1).

Clinical efficacy

A beneficial clinical effect of Class Ic antiarrhythmics was observed in 188 (52.1%) patients, assuring therapy continuation at the time of last follow-up. Clinical efficacy did not differ significantly whether flecainide or propafenone was used (52.0% and 49.0%, respectively; $p = 0.79$). The remaining 173 patients who did not benefit from Class Ic antiarrhythmics more often discontinued therapy ($p < 0.001$). Patients suffering from paroxysmal and persistent AF experienced similar rates of clinical efficacy ($p = 0.175$). Patients who did not clinically benefit from Class Ic antiarrhythmics more often underwent pulmonary vein isolation for AF ($p = 0.02$).

Therapy duration and discontinuation

The median therapy duration with Class Ic antiarrhythmics was 198 days (IQR 60–731 days). Of the total study population, 117 (32%) patients discontinued therapy with flecainide (99 patients, 27%), and propafenone (18 patients, 5%) after a combined median of 210 days (IQR 62–855 days). There was no significant difference in therapy duration between patients taking flecainide or propafenone ($p = 0.22$). The reason for antiarrhythmic drug discontinuation differed significantly among patients taking flecainide or propafenone ($p = 0.002$). The most common reason for therapy discontinuation for patients taking flecainide was an adverse drug effect ($n = 48$, 48%) and for patients taking propafenone a clinical inefficacy with subsequent change to a different antiarrhythmic drug ($n = 6$, 33%) (Fig. 2). Furthermore, patients discontinuing Class Ic antiarrhythmic therapy were significantly older ($p = 0.04$). The most common adverse drug effects for both flecainide and propafenone were proarrhythmic side effects such as wide complex tachycardia (Fig. 3A) or QRS broadening (Fig. 4) (see Table 2 for full list).

Atrioventricular-nodal blocking co-medication

Atrioventricular-nodal conduction slowing co-medications were taken by 287 (80%) patients, which was evenly distributed between patients taking flecainide and those taking propafenone ($p = 0.24$) (Fig. 5). These medications did not have a significant effect on the prevalence of proarrhythmic adverse events ($p = 0.92$), clinical inefficacy ($p = 0.25$ and 0.56 for flecainide, and for propafenone, respectively) or the reason for discontinuing flecainide or propafenone ($p = 0.57$).

Discussion

According to available research, this is the first observational study, , that evaluated the long-term use of flecainide or propafenone for maintenance of SR in patients suffering from AF in the real-world setting of a tertiary care center. Herein, it was shown that Class Ic antiarrhythmics were a viable long-term therapy option in approximately half of the patients for whom these medications were prescribed. The present study suggests an acceptably good long-term clinical efficacy using these drugs. On the other hand, adverse drug effects, and in particular proarrhythmias, were relatively common and were the most frequent cause of drug discontinuation.

Symptomatic arrhythmia burden is a key outcome parameter in assessing antiarrhythmic drug efficacy of AF. Our findings reflect standard clinical practice in which therapeutic responses are assessed in ambulatory follow-up consultations. Data on long-term flecainide and propafenone use are scarce. In the literature, there are studies with shorter follow-ups showing response rates ranging from 46% to 84% [10, 14, 16–18]. In the Euro Heart Survey on AF, the prevalence of flecainide or propafenone use for paroxysmal and persistent AF among all rate and rhythm control drugs was only 17% and 13%, respectively [19]. This is comparable to recent data reported in the United States where only electrophysiologists were found to prescribe these drugs [20]. The use of Class Ic antiarrhythmics had greatly decreased after the publication of the Cardiac Arrhythmia Suppression Trial (CAST) in 1991 [21], which showed increased mortality when these drugs were used for suppression of premature ventricular beats in ischemic heart disease. Following the CAST study, however, with more careful selection of patients, no mortality increase could be demonstrated any more [22]. Another population-based study in AF patients similarly could not show an increased mortality in the rhythm control arm (using Class Ic antiarrhythmics) versus rate control [23].

In the current study, patients who did not clinically benefit from Class Ic antiarrhythmics discontinued drug therapy significantly more often, as expected. The most common reasons for therapy discontinuation were adverse drug effects, particularly proarrhythmias. Data addressing the incidence of proarrhythmic adverse effects of flecainide and propafenone are limited. A Cochrane review and meta-analysis investigating the use of AAD for maintenance of SR in AF examined all controlled clinical trials assessing this question. The authors found a high rate of therapy discontinuation due to adverse effects and a high rate of adverse proarrhythmic events for the use of flecainide with odds ratios of 9.14 (95% confidence interval [CI] 1.94–42.9) and 5.25 (95% CI 1.76–15.6), respectively [22]. In

this report, adverse effect rates for propafenone were markedly lower (odds ratio of 1.69 for therapy discontinuation and of 1.52 for adverse effects). Thus, propafenone seemed to have a more favorable adverse effect profile than flecainide. In more recent trials, the incidence of proarrhythmic side effects with the use of flecainide were more reassuring, ranging from 3.2 to 3.6 per year (the latter value also included other major cardiovascular and cerebrovascular events, possibly overestimating the incidence) [14, 16]. The lower rate of proarrhythmic adverse effects with the use of propafenone may be attributed particularly to its Class II (beta-blocker) effects [24]. On the other hand, in the French-AF study, patients taking propafenone more often reported gastrointestinal and neurological side effects, rather than proarrhythmias. Likewise, in the present study, approximately half the patients under long-term propafenone experienced neurological (headache and dizziness) side effects.

There was a high incidence of proarrhythmic events reported for patients taking flecainide, the most common being atrial flutter with rapid AV conduction. Despite the fact that drugs slowing AV-nodal conduction were frequently prescribed to reduce this complication, the majority of proarrhythmic side effects still arose in patients using a concomitant beta-blocker. Similar findings were also reported in another retrospective observational study conducted in Sweden [25]. However, due to the lack of a control group, potential confounders could not be excluded in the Swedish cohort, as well as in the present study.

The current patient cohort was young and mostly without accompanying structural heart disease. Despite this, a significant association was demonstrated of antiarrhythmic drug discontinuation with the increasing age of patients. This underlines the importance of continuous reassessment of patients not to miss subclinical cardiovascular disease while on flecainide or propafenone. Other adverse effects included dizziness, fatigue or visual disturbances, similar to reports of early prospective trials [10, 17].

One-fourth of all patients in the present cohort with an adequate therapy response to Class Ic antiarrhythmics stopped the medication and underwent catheter ablation during the follow-up period. Current European Society of Cardiology guidelines promote patient choice for the selection of an appropriate long-term rhythm control strategy in the absence of structural heart disease [1]. For this purpose, Class Ic antiarrhythmics and catheter ablation are given Class IA and IIA recommendations, respectively. The MANTRA-PAF trial showed the benefit of catheter ablation after 5 years of follow-up with a safety profile comparable to

antiarrhythmic drug therapy [26]. The CABANA trial, on the other hand, did not show a benefit of ablation compared to antiarrhythmic drugs in the per-protocol analysis [27].

The current study has the limitation of having a retrospective design without predefined follow-up evaluations. Therefore, data on further co-morbidities are lacking. Furthermore, loss of follow-up is an innate issue with this trial design making an estimate of mortality not possible.

Conclusions

Long-term therapy with Class Ic antiarrhythmics showed clinical efficacy in approximately half of the patients with paroxysmal or persistent AF. However, these drugs were also associated with a relatively high rate of adverse events, and in particular proarrhythmic effects, which often resulted in therapy discontinuation rendering appropriate patient selection and therapy surveillance essential.

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Table 1. Clinical characteristics of the 361 patients treated with Class Ic antiarrhythmics.

Antiarrhythmic therapy	Flecainide (n = 287)	Propafenone (n = 74)	P value
Age [years]	56 ± 12	56 ± 11	0.625
Women	78 (27)	22 (30)	0.663
Arrhythmia frequency:			0.548
Paroxysmal	264 (92)	67 (90)	
Persistent	23 (8)	7 (10)	
Daily antiarrhythmic dose [mg]	166 ± 77	359 ± 155	
Antiarrhythmic co-medication:			0.563
Beta-blocker	202 (70)	46 (62)	
Calcium channel blocker	30 (10)	6 (8)	
Digoxin	2 (1)	1 (1)	
CHA_2Ds_2-VASc Score:	0.8 ± 1.1	0.7 ± 0.9	0.4
0-1	219 (76)	59 (80)	
2	41 (14)	11 (15)	
3	18 (6)	4 (5)	
4	2 (1)	0 (0)	
≥ 5	4 (1)	0 (0)	
Antithrombotic therapy:			0.037
Acetylsalicylic acid	51 (18)	10 (14)	
Vitamin K antagonist	110 (38)	41 (55)	
Direct oral anticoagulant	35 (12)	2 (3)	
Low molecular weight heparin	1 (1)	0 (0)	
Structural heart disease:			0.611
Hypertrophic	14 (5)	6 (8)	
Valvular	13 (4)	14 (19)	
Aortic	8 (3)	0 (0)	
Congenital	2 (1)	1 (1)	
Ischemic heart disease	1 (1)	0 (0)	
Other	10 (4)	4 (5)	
Left ventricular ejection fraction [%]	60 ± 7	58 ± 7	0.059
Left atrial diameter [cm]	4.2 ± 0.7	4.5 ± 0.7	0.062

Echocardiographic parameters were available in 249 (68%) patients. Data are shown as mean ± standard deviation or number (percentage).

Table 2. Adverse drug effects leading to drug discontinuation (n = 52).

Adverse drug effects	Flecainide (n = 48)	Propafenone (n = 4)
Arrhythmia and electrocardiogram-changes:		
Atrial flutter with rapid ventricular	9 (19)	1 (25)

conduction		
Symptomatic bradycardia	5 (11)	
Broadening QRS complex	5 (11)	
Ventricular tachycardia	3 (6)	
Palpitations without documented arrhythmia	1 (2)	1 (25)
Isolated QT prolongation	1 (2)	
Other adverse effects:		
Neurologic	12 (25)	2 (50)
Syncope without arrhythmia	3 (6)	
Dermatologic	3 (6)	
Gastrointestinal	3 (6)	
Other	3 (6)	

Data are shown as number (percentage).
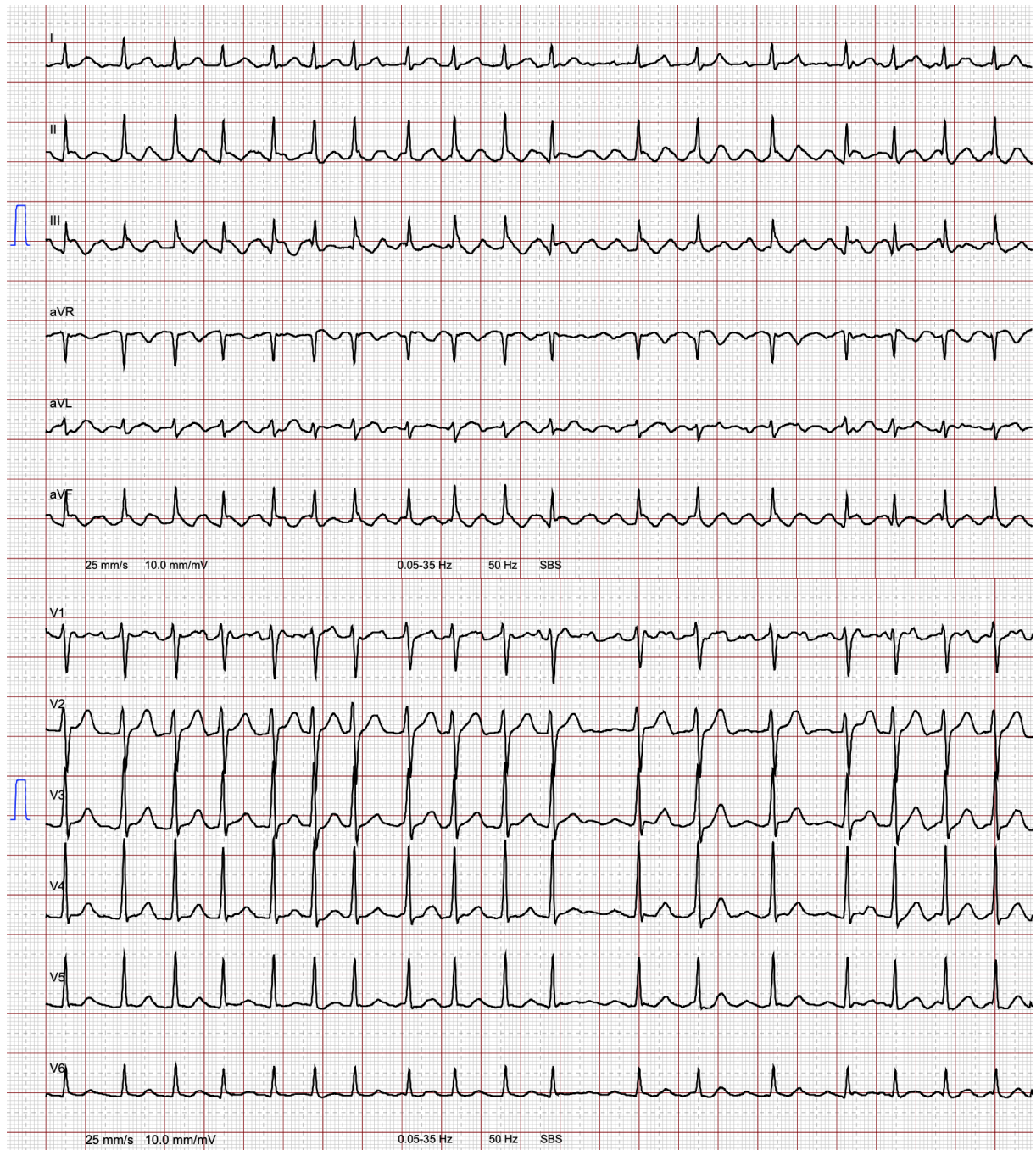
Figure 1. Atrial flutter with rapid atrioventricular (2:1 to 3:1) conduction.
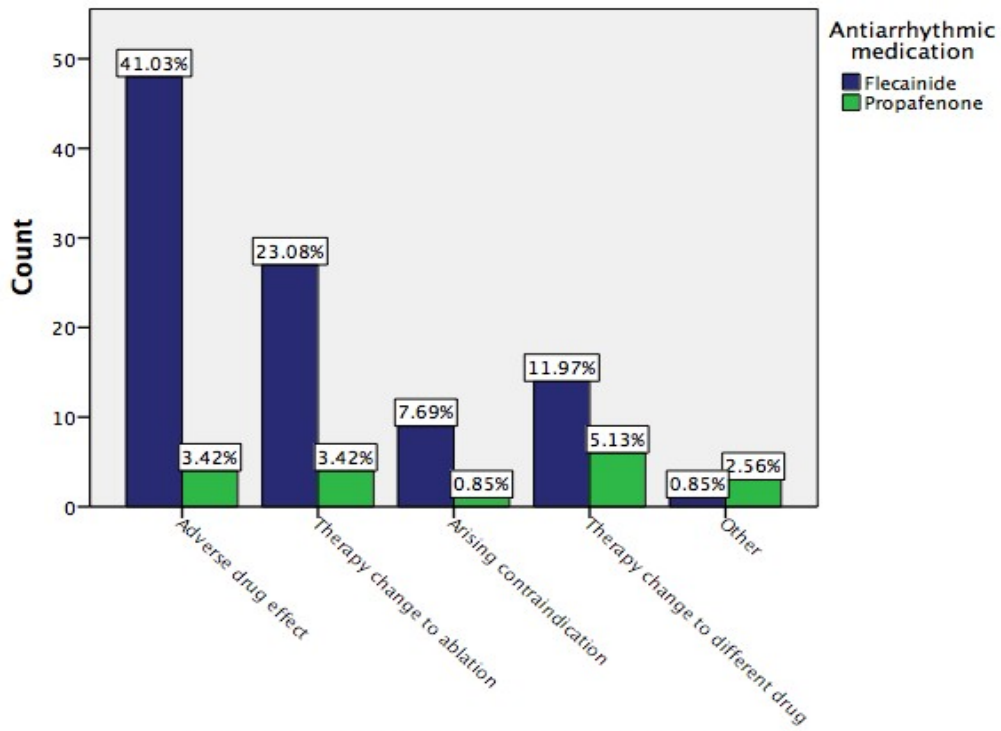
Figure 2. Reasons for Class Ic antiarrhythmic drug discontinuation (flecainide, n = 99; propafenone, n = 19). There is a significant difference between the distributions of the two groups (p = 0.002).

Figure 3. A. Narrow-complex supraventricular tachycardia (atrial fibrillation/flutter) transforming into wide-complex tachycardia due to phase 3 aberration with a long-short sequence; **B.** Atrial fibrillation/flutter with wide QRS complexes in response to flecainide treatment.
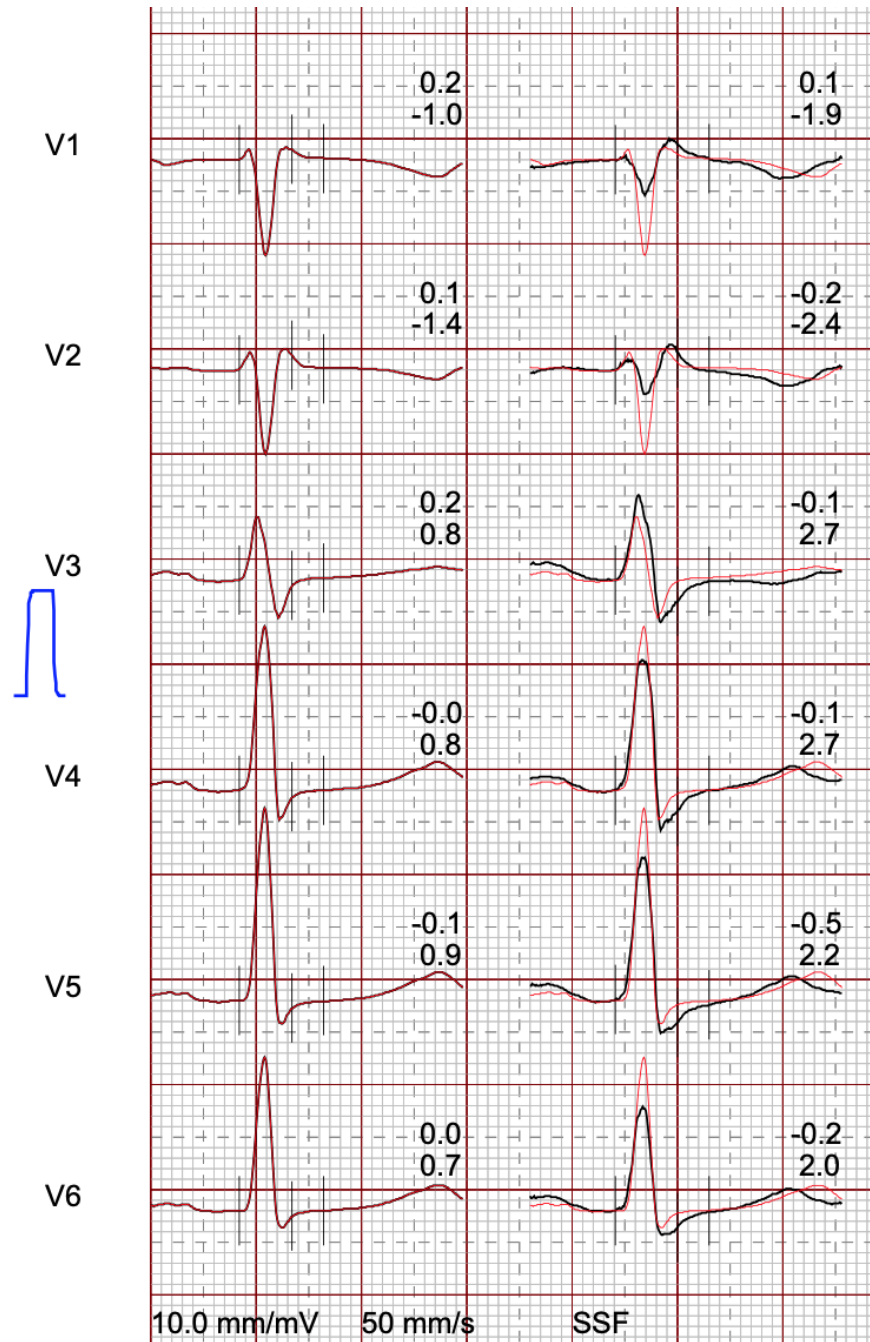
Figure 4. Broadening of QRS complex during exercise stress test in a patient under flecainide treatment. QRS widening is more prominent on right precordial leads (V1/V2) along with a pseudo-Brugada pattern.
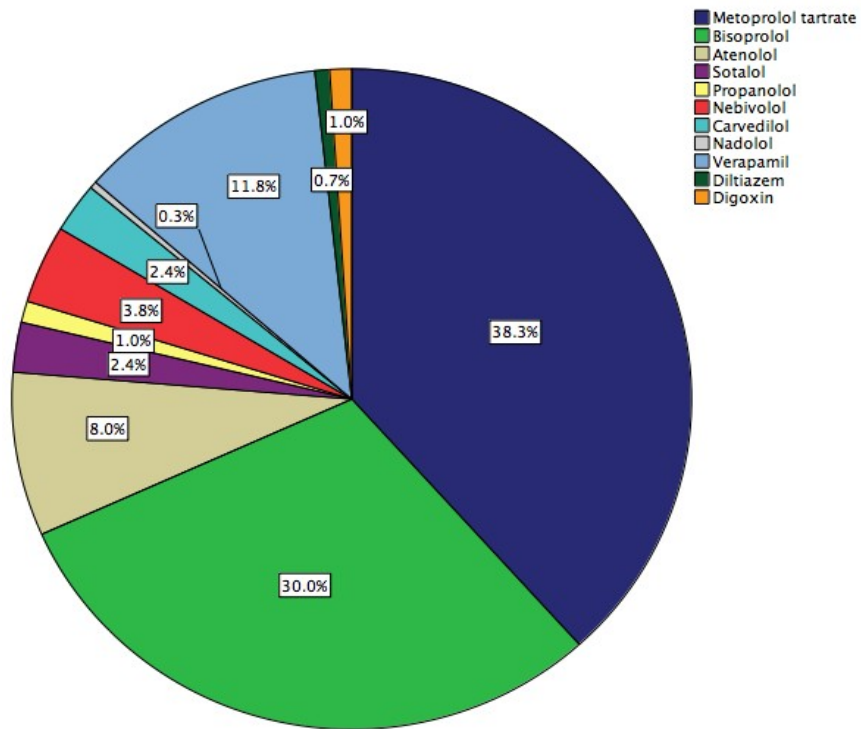
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