SCN5A promoter haplotype affects the therapeutic range for serum flecainide concentration in Asian patients

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SCN5A Promoter Haplotype Affects Therapeutic Range for Serum Flecainide Concentration in Asian Patients

Short title: SCN5A, and therapeutic range of flecainide

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Abstract

Objective: An increased slowing of cardiac conduction induced by sodium channel blockers is remarkably observed in carriers of an Asian-specific promoter haplotype (haplotype B, HapB) of the cardiac sodium channel (SCN5A) gene. We investigated the effect of HapB on the therapeutic range for serum flecainide concentration in Asian patients.

Methods: We examined the serum concentration and anti-arrhythmic efficacy of flecainide, together with the *SCN5A* promoter haplotype, in 146 patients with supraventricular tachyarrhythmias. Trough serum flecainide concentrations were determined by HPLC. The anti-arrhythmic efficacy of flecainide was assessed for at least 2 months through examination of symptomatology, electrocardiograms, and Holter monitoring.

Results: Serum flecainide concentration did not differ between wild-type haplotype A (HapA) homozygotes and HapB carriers under the treatment with usual dose. A genetic difference in the anti-arrhythmic efficacy of flecainide was observed between the HapA homozygotes and HapB carriers at serum flecainide concentrations <300 ng/mL (42.9% vs. 68.8%; $P = 0.02$). PR prolongation and QRS widening appeared more excessively in the HapB carriers with serum flecainide concentrations ≥300 ng/mL than in the HapA homozygotes (PR, 210 ± 25 vs. 195 ± 25 ms; $P = 0.036$; and QRS, 112 ± 10 vs. 105 ± 9 ms; $P = 0.030$).

Conclusions: These findings suggest that the therapeutic range for serum flecainide concentration is lower in HapB carriers than in HapA homozygotes.

Key words: SCN5A; Promoter haplotype; Flecainide; Arrhythmia; Blood concentration; Therapeutic range

Introduction

The voltage-gated cardiac sodium channel type V alpha (SCN5A) is responsible for the fast depolarization upstroke of the cardiac action potential. It acts as a molecular target for anti-arrhythmic drugs [1]. Mutations in the SCN5A gene result in long QT syndrome, Brugada syndrome, atrial fibrillation, dilated cardiomyopathy, and sick sinus syndrome [2-10]. A haplotype B (HapB) consisting of 6 individual *SCN5A* promoter polymorphisms has been shown to produce lower *SCN5A* transcription activity in Asians (allele frequency 24%) [11]. Increased slowing of cardiac conduction induced by a sodium channel blocker challenge test was remarkably observed in HapB carriers compared with that in wild-type haplotype A (HapA) homozygotes [11]. Thus, *SCN5A* promoter haplotype status may modify a patient's response to sodium channel blockers by modulating the activity of SCN5A [12]. The influence of HapB on the anti-arrhythmic efficacy of the daily dosage of sodium channel blockers is unclear.

Flecainide acetate, a potent sodium channel blocker, is a class Ic anti-arrhythmic agent commonly used for treatment of a variety of supraventricular tachyarrhythmias [13-15]. Maintaining the serum flecainide concentration within the recommended therapeutic range (200–1000 ng/mL) provides proven efficacy without the development of severe adverse events such as proarrhythmia [16-18]. Severe adverse events have occasionally occurred in patients whose serum flecainide concentration exceeded 1000 ng/mL [19]. The lower limit of the recommended therapeutic range for serum flecainide concentration, which remains somewhat controversial, varies from 200 to 400 ng/mL for suppression of ventricular arrhythmia [16, 18, 20]. We previously reported that the serum flecainide concentration was recommended to maintain ≥300 ng/mL in patients with supraventricular tachyarrhythmias [21-23]. However, according to a previous

report, some patients showed sufficient effectiveness of flecainide at concentrations <300 ng/mL [21]. We hypothesized that interindividual differences in the flecainide therapeutic concentration may result from differences in the activity of the drug target, such as reduction in sodium current density due to the presence of *SCN5A* promoter HapB. To confirm this hypothesis, we examined the effects of *SCN5A* promoter haplotype status on the therapeutic range for serum flecainide concentrations in Asian patients with supraventricular tachyarrhythmias.

Methods

Patients

Patients treated with oral flecainide for supraventricular tachyarrhythmias were enrolled in this study during an outpatient visit to our hospital (Table 1). Exclusion criteria were as follows: history of unstable angina or myocardial infarction, recent cardiac surgery, higher-degree atrioventricular nodal block, pacemaker-dependent rhythms, permanent atrial fibrillation, Brugada syndrome, concomitant therapy including other class I anti-arrhythmic drugs or amiodarone, and left ventricular dysfunction (i.e., ejection fraction <50% or history of heart failure or both). The patients had received oral flecainide (1.2–5.0 mg/kg/day as flecainide acetate) for 2–100 months (mean, 18 ± 24 months). They received other drugs as per requirement: digoxin, β-blockers (carvedilol, atenolol, nadolol, bisoprolol, metoprolol, propranolol), Ca^{2+} antagonists (verapamil, diltiazem, nifedipine, amlodipine, nisoldipine, nicardipine), angiotensin-converting enzyme inhibitors (enalapril, lisinopril, temocapril), angiotensin II receptor blockers (valsartan, telmisartan, olmesartan, losartan, candesartan), anti-coagulants (warfarin, aspirin, ticlopidine), H_2-blockers (famotidine, ranitidine), or other drugs (lipid-decreasing drugs,

HMG–CoA reductase inhibitors). This study was approved by the ethical committee of the University of Tsukuba (approval number, 63-1). Written informed consent was obtained from all patients.

Sample collection and determination of serum flecainide

The patients had received flecainide for at least 2 months prior to the study. Blood draws for determining flecainide trough levels were performed between 8:30 and 11:00 during an outpatient visit. On sample collection days, the patients postponed taking their morning flecainide until after the collection. The last dose of flecainide before sample collection was 19:00–21:00. Serum samples separated from whole blood were stored at −20 °C until analysis.

Flecainide acetate and an internal standard [N-(2-piperidinylmethyl)-2,3-bis(2,2,2-trifluoroethoxy)benzamide acetate] were kindly supplied by Eisai Co. (Tokyo, Japan). Serum flecainide was determined by HPLC on a conventional octadecylsilyl silica column with a fluorescence detector, as described previously [24]. Assay precision was evaluated by intra- and inter-day validation at 200 and 1000 ng/mL flecainide. The coefficients of variation for intra- and inter-day assays were 2.7%–5.3% and 7.0%–8.4%, respectively

Clinical evaluation of anti-arrhythmic efficacy

The anti-arrhythmic efficacy of flecainide was assessed for at least 2 months through examination of symptomatology, 12-lead electrocardiograms, and Holter monitoring. At discharge, the patients were given a form and asked to record the incidence of subjective symptoms (e.g., palpitation, chest oppression, chest pain, shortness of breath,

and presyncope). Reported subjective symptoms and an electrocardiogram were recorded at each patient visit. For evaluation of arrhythmias (n = 49), Holter monitoring was performed for 24 h. Presence of arrhythmias was defined as occurrence of symptoms suggestive of tachycardia and an episode of arrhythmias documented on electrocardiogram or Holter monitoring during the assessment period.

Genotyping of *SCN5A* promoter polymorphism and *CYP2D6* polymorphism

Genomic DNA was isolated from peripheral blood with an extraction kit (Takara Bio, Shiga, Japan).

Genotyping for *SCN5A* T-1418C and T-1062C was performed by restriction fragment length polymorphism analysis, as described previously [11]. The corresponding *SCN5A* gene fragments were amplified using the primers 5′-ACC TAA GGC GTC CAA CGA AGC-3′ (forward) and 5′-CCA GGG TCT CAG AGG GCA CAG-3′ (reverse) for T-1418C and 5′-CCC TGA TGG CCT GTT TTG TTT-3′ (forward) and 5′-ACT CAG AGA CAT GGT CAC AGG CA-3′ (reverse) for T-1062C. PCR amplification conditions were as follows: 94 °C for 4 min (initial denaturation); followed by 30 cycles of 94 °C for 30 s (denaturation), 59 °C for 30 s (annealing), and 72 °C for 30 s (extension); and 72 °C for 2 min (final extension). DNA fragments generated after restriction enzyme (*Ear*I for T-1418C and *Hae*III for T-1062C) digestion were separated on a 4% agarose gel. These SNPs were used to assign *SCN5A* promoter haplotypes: A (-1418T and -1062T), B (-1418C and -1062C), and C (-1418C and -1062T).

Genotyping for the *SCN5A* H558R polymorphism (1673A>G) was performed by restriction fragment length polymorphism analysis, as described previously, with minor

modifications [6]. The corresponding *SCN5A* gene fragment was amplified using the primers 5′-GAG ACC TGG GTT CTG AAG CA-3′ (forward) and 5′-TCA GTT TGG GAG ACC AGA CC-3′ (reverse). PCR amplification conditions were as follows: 94 °C for 4 min (initial denaturation); followed by 30 cycles of 94 °C for 30 s (denaturation), 59 °C for 30 s (annealing), and 72 °C for 30 s (extension); and 72 °C for 2 min (final extension). DNA fragments generated after restriction enzyme (*Aci*I) digestion were separated on 4% agarose gel.

*CYP2D6*1*, **2* (C2850T), **4* (G1846A), **5* (*CYP2D6* gene deletion), **10* (C100T), **14* (G1758A), **21* (2573 C insertion), **36* (*CYP2D6* gene conversion to *CYP2D7P* in exon 9), and *CYP2D6xN* (*CYP2D6* gene duplication) were determined using allele-specific polymerase chain reaction (PCR) with mismatch primers (ASPCR-MP) and step-down PCR [25]. SNP typing kits for cytochrome P450 (STK-121, 122, 124, 125, 126 for ASPCR-MP; STK-123, 127, 128 for step-down PCR) were obtained from Toyobo (Tokyo, Japan). We designated *CYP2D6*1* and **2* alleles as extensive metabolizer (EM) alleles, **10* as an intermediate metabolizer (IM) allele, and **4*, **5*, **14*, **21*, and **36* as poor metabolizer (PM) alleles.

Statistical analyses

Patient characteristics and pharmacokinetic and electrocardiographic data were compared between the HapA homozygotes and HapB carriers using Student's *t*-test, Welch's *t*-test, or the Mann–Whitney *U*-test. Comparison of proportions was performed using the chi-square test, Fisher's exact probability test, or the Mann–Whitney U test. Observed haplotype pair frequencies were compared with those expected under the

Hardy–Weinberg equilibrium. *P* values <0.05 were considered statistically significant.

Results

SCN5A promoter polymorphisms and patient characteristics

SCN5A promoter polymorphisms were examined in 146 patients treated with oral flecainide for supraventricular tachyarrhythmias. The frequencies of *SCN5A* promoter haplotype A, B, and C were 0.788, 0.205, and 0.007, respectively. The overall frequency of haplotypes genotyped in this study was comparable to that reported for the Japanese population [11]. The numbers of patients with each haplotype pair were as follows: 91 with AA, 47 with AB, 6 with BB, 1 with BC, and 1 with AC. The frequencies of haplotype pair were not different from the Hardy–Weinberg equilibrium ($P = 0.78$).

The 91 *SCN5A* promoter HapA homozygotes and 54 HapB carriers were used in the comparison. The lone patient with haplotype pair AC was excluded from the analysis. Patient characteristics for each haplotype group are summarized in Table 1. Sex, age, body weight, diagnosis of supraventricular tachyarrhythmias, and comorbidities did not significantly differ between the HapA homozygotes and HapB carriers (Table 1). The frequency of R558 polymorphism, a major *SCN5A* coding region polymorphism, did not differ significantly between the HapA homozygotes and HapB carriers (7.7% vs. 12.0%; $P = 0.21$). The frequencies of *CYP2D6* polymorphisms did not differ between the HapA homozygotes and HapB carriers (Table 1). The flecainide daily dose did not differ between *CYP2D6* EM allele homozygotes and IM/PM allele carriers in both HapA homozygotes (2.3 ± 0.8 vs. 2.4 ± 0.8 mg/kg; $P = 0.49$) and HapB

carriers (2.4 ± 0.8 vs. 2.4 ± 0.8 mg/kg; $P = 0.77$).

SCN5A promoter haplotype and anti-arrhythmic efficacy of flecainide

The flecainide daily dose and serum flecainide concentration did not differ significantly between the HapA homozygotes and HapB carriers (Table 2). Tachyarrhythmias were well controlled in 63.0% of the HapB carriers and 51.6% of the HapA homozygotes; this difference was not significant ($P = 0.18$; Table 2). The influence of the *SCN5A* promoter haplotype on the anti-arrhythmic efficacy of flecainide was compared between the patients with serum flecainide concentrations <300 ng/mL and ≥300 ng/mL according to the previous reports [21-23]. The HapB carriers achieved clinically relevant flecainide efficacy more frequently (68.8%) when the serum flecainide concentrations were <300 ng/mL, compared with the HapA homozygotes (42.9%; $P = 0.022$; Table 2). The efficacy of flecainide at serum concentrations ≥300 ng/mL did not differ significantly between the 2 groups (54.5% vs. 61.9%; $P = 0.57$; Table 2).

The serum concentration–cumulative efficacy rate curves for prevention of supraventricular arrhythmias in the HapA homozygotes and HapB carriers are shown in Fig.1. The concentration–efficacy curve in the HapB carriers had a sharper increase at serum flecainide concentrations <300 ng/mL than that in the HapA homozygotes. The concentration–efficacy curve was shifted to the left in the HapB carriers compared with that in the HapA homozygotes; the cumulative efficacy rate (24%) at 300 ng/mL in the HapA homozygotes was achieved at around 200 ng/mL in the HapB carriers (Fig. 1).

Electrocardiographic data in sinus rhythm and the absence of bundle branch block under treatment with flecainide were compared between the HapA homozygotes (n = 59) and HapB carriers (n = 39) (Table 3). No significant difference was observed in

heart rate, PR interval, QRS duration, and QTc interval between the HapA homozygotes and HapB carriers at serum flecainide concentrations <300 ng/mL (Table 3). In contrast, the PR interval and QRS duration were significantly prolonged in the HapB carriers compared with that in the HapA homozygotes at serum flecainide concentration ≥300 ng/mL ($P = 0.036$ and $P = 0.030$, respectively, Table 3); however, the heart rate and QTc interval did not differ between the HapA homozygotes and HapB carriers.

Discussion

The present study revealed that an Asian-specific *SCN5A* promoter haplotype influences the anti-arrhythmic efficacy of daily doses of flecainide. HapB carriers obtained clinically relevant flecainide efficacy even at drug concentrations <300 ng/mL (Table 2 and Fig. 1). This finding suggests that the therapeutic range for serum flecainide concentration was lower in the HapB carriers because of their low expression of SCN5A. Thus, a *SCN5A* promoter haplotype is an important factor for explaining the difference in flecainide efficacy at lower serum drug concentrations in Asian patients.

We previously reported that the serum flecainide concentration should be maintained at ≥300 ng/mL to control the paroxysms of supraventricular tachyarrhythmias [21-23]. The recommended serum flecainide concentration in Hap B carriers, however, is likely to be ≥200 ng/mL because the cumulative efficacy rate at around 200 ng/mL was similar to that at 300 ng/mL in the HapA homozygotes (Fig. 1). In contrast, electrocardiographic data associated with the risk of cardiovascular side effects [20] showed an excess of cardiac conduction slowing in the HapB carriers with serum flecainide concentrations ≥300 ng/mL; the PR interval (210 ± 25 ms) and QRS duration (112 ± 10 ms) were significantly longer than those in the HapA homozygotes

(Table 3). These values were also remarkable when compared with the data from postmarketing surveillance of flecainide acetate in Japanese patients with atrial fibrillation/flutter (PR interval: 183 ± 34 ms, and QRS duration: 102 ± 20 ms) [26]. The upper limit of the therapeutic range for serum flecainide concentration may also be lower in HapB carriers because of excess slowing in cardiac conduction.

Many factors can influence the anti-arrhythmic effects of sodium channel blockers. The variability in SCN5A function due to polymorphisms in the *SCN5A* coding region may be a genetic factor explaining the interindividual difference in the anti-arrhythmic efficacy. A common polymorphism in the *SCN5A* coding region such as H558R, a risk factor for lone atrial fibrillation, may contribute to the drug response observed with sodium channel blockers. [6, 7] However, in the present study, the frequency of the R558 polymorphism is similar between the HapA homozygotes and HapB carriers. The other genetic factor may be the variant in MOG1, a cofactor of the cardiac sodium channel, which regulates the channel expression on surface of the cardiomyocytes and reduces the sodium current. [27, 28] Although other factors such as concomitant anti-arrhythmic drugs can influence the prevention of supraventricular tachyarrhythmias, coadministration of digoxin, β-blockers, and Ca^{2+} antagonists did not differ between the 2 groups in the present study (Table 1).

Our study has several limitations for assessment of clinical efficacy and a gene-dose effect in ECG parameter. Firstly, asymptomatic atrial fibrillation could not be detected in every patient because Holter monitoring was available in one-third of the present patients. Second, a clear gene-dose effect in PR interval and QRS duration was not found in the present study because the number of HapB homozygotes was insufficient.

In Japan, the flecainide acetate package insert recommends an initial dose of 100 mg/day. This recommendation may be reasonable because one-third of Japanese patients are HapB carriers in whom clinically relevant flecainide efficacy is obtained at lower serum concentrations. Another Asian-specific genetic factor affecting flecainide efficacy is *CYP2D6*10*, a polymorphism in the gene encoding the main metabolic enzyme for flecainide. Since about 60% of Japanese patients were reported to be *CYP2D6*10* carriers [29], this variant as well as the SCN5A promoter HapB may result in a lower flecainide dose requirement in this population [30, 31].

In conclusion, HapB carriers more frequently achieve clinically relevant flecainide efficacy even at lower concentrations. The present study suggests that the therapeutic range for serum flecainide concentration in HapB carriers is likely to be lower than that in HapA homozygotes.

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Figure legend

Fig. 1 Serum concentration–cumulative efficacy rate curves for prevention of supraventricular arrhythmias in HapA homozygotes and HapB carriers. The cumulative efficacy rate was calculated as the percentage of effective patients accumulated up to each serum flecainide concentration in each patient group.

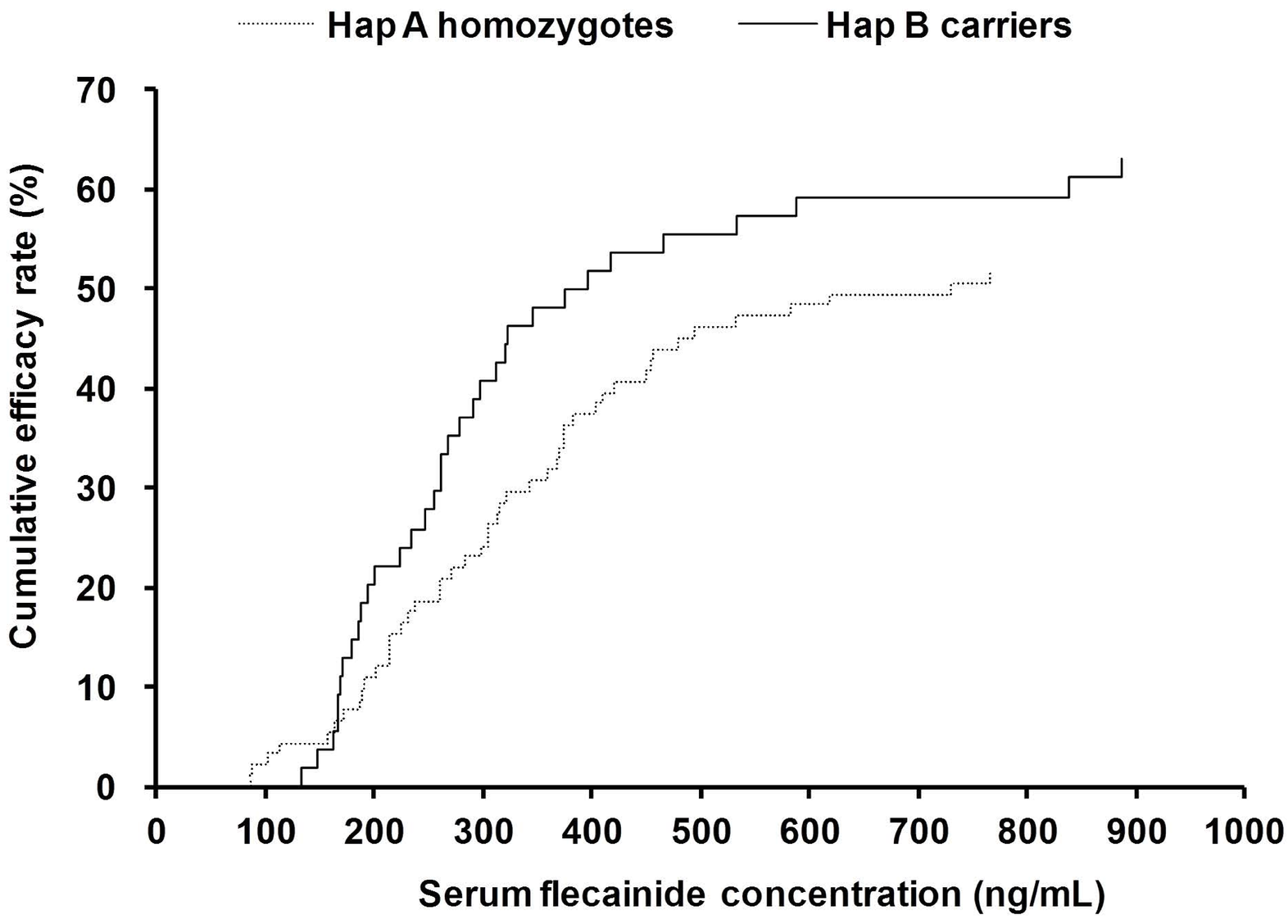

Figure 1

Serum concentration–cumulative efficacy rate curves for prevention of supraventricular arrhythmias in HapA homozygotes and HapB carriers. The cumulative efficacy rate was calculated as the percentage of effective patients accumulated up to each serum flecainide concentration in each patient group.

Table 1 Patient characteristics

	Hap A homozygotes	Hap B carriers	*P*-value
Number of patients	91	54	
Female sex	20 (22.0%)	11 (20.4%)	0.82
Age (y)	61.2 ± 11.3	60.4 ± 14.0	0.91
Weight (kg)	67.2 ± 10.7	64.1 ± 10.8	0.096
Diagnosis			
Paroxysmal atrial fibrillation	67 (73.6%)	46 (85.2%)	0.42
Persistent atrial fibrillation	7 (7.7%)	4 (7.4%)	
Paroxysmal atrial fibrillation and atrial flutter	10 (11.0%)	2 (3.7%)	
Paroxysmal supraventricular tachycardia	6 (6.6%)	2 (3.7%)	
Wolff-Parkinson-White syndrome	1 (1.1%)	0 (0%)	
Comorbidities			
Hypertension	49 (53.8%)	20 (37.0%)	0.050
Hyperlipidemia	24 (26.4%)	14 (25.9%)	0.95
Diabetes mellitus	17 (18.7%)	8 (14.8%)	0.55
Chronic kidney disease	18 (19.8%)	10 (18.5%)	0.85
Concomitant anti-arrhythmic drugs			
Digoxin	7 (7.7%)	8 (14.8%)	0.17
β blockers	51 (56.0%)	26 (48.1%)	0.36
Ca^{2+} antagonists	17 (18.7%)	8 (14.8%)	0.55

CYP2D6 allele frequency			
EM allele	60.4%	57.4%	0.88
IM allele	36.2%	38.9%	
PM allele	3.3%	3.7%	

Data are presented as number (percentage), mean ± SD or percentage. *CYP2D6*1* and **2* alleles, extensive metabolizer (EM) alleles; **10*, an intermediate metabolizer (IM) allele; **4*, **5*, **14*, **21*, and **36*, poor metabolizer (PM) alleles.

Table 2 Effect of *SCN5A* promoter haplotype on anti-arrhythmic efficacy of flecainide

	Hap A homozygotes	Hap B carriers	*P*-value
Number of patients	91	54	
Flecainide daily dose (mg/kg)	2.34 ± 0.78	2.39 ± 0.83	0.81
Seurm flecainide concn. (ng/mL)	300 ± 154	309 ± 161	0.74
Efficacy of flecainide (effective / ineffective)			
Overall	47 / 44 (51.6%)	34 / 20 (63.0%)	0.18
Serum flecainide concn. of <300 ng/mL	21 / 48 (42.9%)	22 / 10 (68.8%)	0.022
Serum flecainide concn. of ≥300 ng/mL	26 / 16 (61.9%)	12 / 10 (54.5%)	0.57

Data are presented as number, mean ± SD or number (efficacy rate).

Table 3 Effects of *SCN5A* promoter haplotype on ECG data in sinus rhythm under treatment with flecainide

	Hap A homozygotes	Hap B carriers	*P*-value
Number of patients with ECG data in sinus rhythm	59	39	
Serum flecainide concn. of <300 ng/mL	27	23	
Heart rate (beats/min)	61 ± 8	63 ± 10	0.47
PR interval (ms)	178 ± 20	181 ± 25	0.66
QRS duration (ms)	101 ± 8	102 ± 8	0.63
QTc	422 ± 29	419 ± 27	0.90
Serum flecainide concn. of ≥300 ng/mL	32	16	
Heart rate (beats/min)	60 ± 10	62 ± 10	0.57
PR interval (ms)	195 ± 25	210 ± 25	0.036
QRS duration (ms)	105 ± 9	112 ± 10	0.030
QTc	437 ± 23	434 ± 24	0.69

Data are presented as number or mean ± SD. ECG, electrocardiogram.