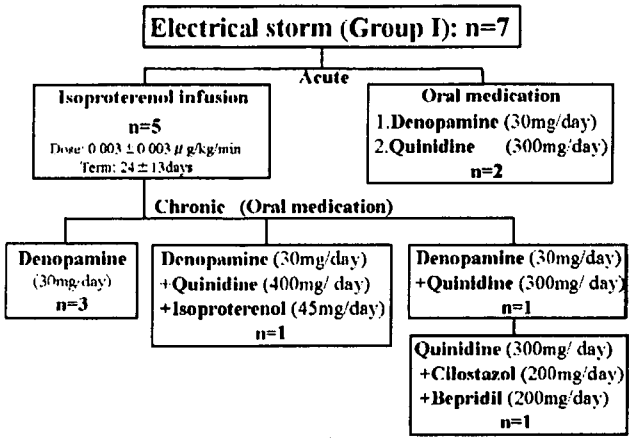

Figure 2 Summary of acute and subsequent chronic treatment in the seven patients associated with electrical storm of ventricular fibrillation.

of SCD, duration after ICD placement, *SCN5A* mutation, and serum potassium level among the three groups. There were no significant differences in previous VF or aborted cardiac arrest before diagnosis and previous syncope alone before diagnosis between groups I and II. Four patients had a history of VF or aborted cardiac arrest before diagnosis, and 3 patients in group I had previous syncope alone before diagnosis. An ICD was implanted before electrical storm of VF in all 7 patients.

No significant differences were observed among the three groups in the electrocardiographic characteristics at diagnosis with regard to J-point amplitude, QRS duration, PQ interval, and incidence of spontaneous coved-type ST elevation, late potentials, and augmentation of ST elevation at early recovery phase after exercise testing.

No significant differences in the frequency and mode of VF induction and HV interval during electrophysiologic study were observed among the three groups.

No significant differences were observed among the three groups during follow-up after diagnosis. However, arrhythmic events during follow-up after diagnosis and number of arrhythmic events/patients were significantly higher in group I vs groups II and III. Average duration between diagnosis and first electrical storm in group I was 4.6 ± 4.7 years. Subsequent arrhythmic events after electrical storm were observed in 5 of the 7 group I patients.

Acute and chronic treatment for electrical storm of VF

At the electrical storm in the 7 group I patients, no intravenous antiarrhythmic agents (e.g., lidocaine or amiodarone) or sedation had been used before starting isoproterenol infusion. ST-segment elevation was augmented at the electrical storm compared with that at baseline (V_1: 0.14 ± 0.07 vs 0.09 ± 0.04 mV; V_2: 0.38 ± 0.09 vs 0.29 ± 0.07 mV). However, this difference did not reach statistical significance.

Figure 1 shows the acute effect of isoproterenol infusion on the electrical storm of VF in a representative patient with Brugada syndrome. Continuous infusion of isoproterenol (0.002 μg/kg/min) decreased the J-point amplitude and changed coved-type to saddleback-type ST-segment elevation in lead V_2. Increasing dose of isoproterenol (0.004 μg/kg/min) normalized ST-segment elevation in lead V_2 and completely suppressed repetitive episodes of VF.

Figure 2 summarizes the acute and subsequent chronic treatment of the 7 patients with electrical storm of VF. Isoproterenol infusion was used as acute treatment in 5 of the 7 patients with electrical storm. Average dose of isoproterenol infusion was 0.003 ± 0.003 μg/kg/min. Average term of isoproterenol infusion (24 ± 13 days) was required because of difficulty in discontinuing or decreasing isoproterenol infusion because of VF recurrence. Isoproterenol completely suppressed electrical storm of VF in all 5 patients. The remaining 2 patients were prescribed oral medication (denopamine 30 mg/day and quinidine 300 mg/day, respectively) because no additional VF episodes occurred after admission.

Isoproterenol infusion was successfully replaced with oral medication in the first 5 patients: 3 with denopamine (30 mg/day), 1 with a combination of denopamine (30 mg/day), quinidine (400 mg/day), and isoproterenol (45 mg/day), and 1 with a combination of denopamine (30 mg/day) and quinidine (300 mg/day).

Average follow-up duration after electrical storm in the 7 group I patients was 5.0 ± 1.5 years. In the 3 patients discharged with denopamine alone following isoproterenol infusion, two VF episodes were recorded in ICD memory for 68 months in 1 patient but no VF episodes in the remaining 2 patients (51 months and 77 months, respectively). Four VF episodes were recorded for 76 months in the patient who was discharged with a combination of denopamine, quinidine, and isoproterenol. The last patient, who was discharged with a combination of denopamine and quinidine, experienced another electrical storm of VF 6 months later after discontinuation of denopamine due to palpitation. Isoproterenol infusion was used again after readmission, and a combination of quinidine (300 mg/day), cilostazol (200 mg/day), and bepridil (200 mg/day) could successfully replace the isoproterenol infusion. VF did not recur for 18 months after readmission in this case. In the 2 patients in whom isoproterenol infusion was not used as an acute treatment, 1 patient who was discharged with denopamine experienced 6 VF episodes for 47 months, and the other patient who was discharged with quinidine had 7 VF episodes for 72 months.

Discussion

The major findings of this study were as follows: (1) no specifically clinical, laboratory, electrocardiographic, and electrophysiologic characteristics were recognized in patients with Brugada syndrome associated with electrical storm of VF, (2) continuous infusion of isoproterenol normalized ST-segment elevation and completely suppressed the electrical storm of VF as an acute treatment, and (3) oral medications including denopamine, quinidine, isoprotere-

nol, cilostazol, and bepridil successfully replaced isoproterenol infusion as a chronic treatment.

Characteristics of Brugada patients associated with electrical storm of VF

Identification of high-risk patients with Brugada syndrome associated with electrical storm of VF and elucidation of their clinical characteristics are important issues. Brugada syndrome usually manifests during adulthood, with a mean age at sudden death of 41 ± 15 years.[14] It is reported that a family history of unexplained sudden death is present in approximately 20%–40% of Brugada Probands in Western countries and less (15–20%) in Japan, and that *SCN5A* mutations account for only 18%–30% of clinically diagnosed Brugada patients.[8,14–16] Low serum potassium level is suggested to be a predisposing factor for VF in patients with Brugada syndrome.[14] However, no significant differences in these clinical characteristics were observed between patients with and without a history of electrical storm of VF. Moreover, 12-lead electrocardiographic parameters and HV interval during electrophysiologic study were no different between patients with and those without an electrical storm of VF. Approximately 60%–70% of patients with Brugada syndrome show late potentials detected by signal-averaged ECG.[14,17] During treadmill exercise testing, augmentation of ST-segment elevation in the right precordial leads compared with that at baseline occasionally is recorded at early recovery phase after exercise (1 or 2 minutes) in Brugada patients. VF or sustained polymorphic VT is induced in approximately 50%–70% of Brugada patients during electrophysiologic study.[8,15,16,18] However, in the present study, frequency of late potentials and ST-segment augmentation after exercise, and inducibility of VF were no different between patients with and those without a history of electrical storm of VF. Although triggering or predisposing factors for electrical storm of VF and characteristics of Brugada patients associated with an electrical storm of VF remain unclear, in this study all 7 patients who experienced electrical storm of VF had arrhythmic events during follow-up after diagnosis. Therefore, our data provided further support for the requirement of ICD placement in Brugada patients with previous episodes of arrhythmic events.

Acute management of Brugada patients associated with electrical storm of VF

Experimental studies have suggested that isoproterenol, a β-adrenergic agonist, decreases ST-segment elevation and suppresses VF by strongly augmenting $I_{Ca\text{-}L}$ in an experimental model of Brugada syndrome.[19,20] Several clinical studies reported the protective effect of isoproterenol in normalizing ST-segment elevation and suppressing episodes of VF.[8–12] Watanabe et al[21] systematically reported that isoproterenol suppressed repetitive ventricular arrhythmia in patients with Brugada syndrome. In the present study, continuous infusion of isoproterenol attenuated ST-segment elevation and completely prevented repetitive episodes of VF in all 5 patients treated and therefore is considered to be first-line acute treatment of electrical storm of VF in Brugada syndrome.

Adjunctive chronic oral treatment

Although isoproterenol infusion is effective in preventing repetitive episodes of VF at electrical storm, discontinuation or decrease of isoproterenol infusion often is difficult because of VF recurrence. In such cases, chronic oral medication usually is required to decrease and discontinue isoproterenol infusion. Several oral agents can be candidates as adjunctive chronic treatment to replace isoproterenol infusion and reduce the incidence of VF episodes subsequently in patients with Brugada syndrome associated with electrical storm of VF.

In the present study, several oral agents, including denopamine, quinidine, isoproterenol, cilostazol, and bepridil alone or in combination, were effective in replacing isoproterenol infusion. Especially, oral denopamine, an α+β–adrenergic stimulant, was effective as a chronic treatment, probably by increasing $I_{Ca\text{-}L}$. Quinidine, a class IA sodium channel blocker, has a relatively strong effect in blocking I_{to} and has been proved effective in suppressing a spontaneous episode of VF in patients with Brugada syndrome.[2–26] Cilostazol, a phosphodiesterase III inhibitor that increases $I_{Ca\text{-}L}$, is reported to be effective in suppressing VF in Brugada syndrome.[2–7] More recently, bepridil is reported to suppress the incidence of VF episodes, probably by blocking I_{to}.[2–8] Although there was small number of Brugada patients associated with electrical storm of VF in whom adjunctive chronic effect of these agents could be examined, each agent alone or in combination was effective as an oral chronic treatment. Further systematic evaluation of the usefulness of these oral agents in larger numbers of Brugada patients is required to make a definitive conclusion.

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Comparison of Long-Term Follow-Up of Electrocardiographic Features in Brugada Syndrome Between the SCN5A-Positive Probands and the SCN5A-Negative Probands

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To investigate changes of electrocardiographic parameters with aging and their relation to the presence of SCN5A mutation in probands with Brugada syndrome (BS), we measured several electrocardiographic parameters prospectively during long-term follow-up (10 ± 5 years) in 8 BS probands with SCN5A mutation (SCN5A-positive group, all men; age 46 ± 10 years) and 36 BS probands without SCN5A mutation (SCN5A-negative group, all men; age 46 ± 13 years). Throughout the follow-up period, depolarization parameters, such as P-wave (lead II), QRS (leads II, V_2, V_5), S-wave durations (leads II, V_5), and PQ interval (leads II) were all significantly longer and S-wave amplitude (II, V_5) was significantly deeper in the SCN5A-positive group than in the SCN5A-negative group. The SCN5A-positive group showed a significantly longer corrected QT interval (lead V_2) and higher ST amplitude (lead V_2) than those in the SCN5A-negative group. The depolarization parameters increased with aging during the follow-up period in both groups; however, the PQ interval (lead II) and QRS duration (lead V_2) were prolonged more prominently and the QRS axis deviated more to the left with aging in the SCN5A-positive group than in the SCN5A-negative group. In conclusion, conduction slowing was more marked and more progressively accentuated in Brugada probands with SCN5A mutation than in those without SCN5A mutation. (Am J Cardiol 2007; 100:649–655)

Brugada syndrome (BS) is characterized by a ST-segment elevation in the right precordial leads V_1 to V_3 and is associated with sudden cardiac death (SCD) secondary to a rapid polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).[1–9] It has been suggested that a transient outward current-mediated action potential notch and a loss of action potential dome in the epicardium of the right ventricular outflow tract (RVOT) give rise to a transmural voltage gradient, resulting in ST-segment elevation in the right precordial lead in BS.[8] Conversely, the SCN5A gene encoding the cardiac sodium channel has been reported to be linked to BS,[10] and mild conduction abnormalities and QRS prolongation have been described.[5,11] Smits et al[12] have compared these electrocardiographic parameters between SCN5A mutation carriers and those who do not carry the mutation. Probst et al[13] meticulously studied aging-associated electrocardiographic parameters in SCN5A-related BS.[13] However, progressive changes of the depolarization and repolarization parameters on the electrocardiogram (ECG) with aging during long-term follow-up in relation to the SCN5A mutation have not been fully evaluated. In the present study, we prospectively measured several electrocardiographic parameters during long-term follow-up periods and compared them between patients with BS with and without SCN5A mutation.

Methods

The study population consisted of 44 probands with BS admitted to the National Cardiovascular Center in Suita, Japan, due to history of aborted SCD, syncope, or evaluation of electrocardiographic abnormality, who could be prospectively followed up for >5 years (average 10 ± 5 years) at regular outpatient clinics in our hospital. All probands were men, and their age on admission (i.e., at early period) ranged from 20 to 72 years (mean 46 ± 12 years). BS was diagnosed when a type 1 coved-type ST-segment elevation (≥0.2 mV at J point) was observed in >1 of the right precordial leads (V_1 to V_3) in the presence or absence of a sodium channel blocker in conjunction with 1 of the following: (1) documented VF or polymorphic VT, (2) a family history of SCD at <45 years of age, type 1 ECG in family members, (3) inducibility of VF or polymorphic VT with programmed electrical stimulation, and (4) history of aborted cardiac arrest with or without documentation of VF,

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Table 1
SCN5A mutations, common variants and promotor haplotype

Coding*	No. of Patients	Type	Coding	No. of Patients	Type
	SCN5A Positive Group (n = 8)			SCN5A Negative Group (n = 36)	
Mutation					
A735V	1	Missense			
P1719fsX1786	1	Frameshift			
L276Q	1	Missense			
V1764fsX1786	1	Frameshift			
L136P	1	Missense			
R367H	2	Missense			
T1709M	1	Missense			
Common variant					
H558R	1	Missense	H558R	4	Missense
Promotor haplotype					
AA	5		AA	12	
AB	2		AB	4	
BB	0		BB	1	

* The numbers and letters refer to the amino acid coding of the mutant channel protein.
AA = haplotype A (common alleles) homozygotes; AB = haplotype A/haplotype B (minor alleles) heterozygotes; BB = haplotype B homozygotes. See detail in Bezzina et al.[14]

syncopal episodes of unknown origin, or nocturnal agonal respiration.[4]

We divided the 44 Brugada probands into 2 groups according to the presence or absence of an SCN5A coding region mutation: SCN5A-positive group (n = 8) and SCN5A-negative group (n = 36).

The standard 12-lead ECGs were recorded at least every 6 months prospectively at regular outpatient clinics with a paper speed of 25 mm/s and an amplitude of 10 mm/mV. The ECGs were magnified to 150%, and several electrocardiographic parameters were measured manually by an investigator (MY) blinded to clinical and genetic information. As depolarization parameters, P-wave duration (lead II), PQ interval (lead II), QRS duration (leads II, V_2, and V_5), S-wave duration and amplitude (leads II, V_5), and QRS axis were measured. Conversely, corrected QT interval (QTc, leads II, V_2, and V_5), corrected JT interval (JTc, leads II, V_2, and V_5), and ST amplitude at the J point and 40 ms after theJ point (STJ and STJ40, lead V_2) were measured as repolarization parameters. The absolute values of these parameters and the change of each parameter between early and late periods were compared between the 8 probands in the SCN5A-positive group and the 36 in the SCN5A-negative group.

In all patients, we screened SCN5A mutation in all 28 exons of SCN5A gene by a direct sequencing method using an ABI 3700 system (Applied Biosystems, Foster City, California). An SCN5A mutation was defined when the mutation was not identified in any of the 100 control subjects. We also screened the SCN5A promoter haplotype, which we have recently identified in an Asian population,[14] in 7 recent SCN5A-positive probands and 17 SCN5A-negative probands.

Numeric values were expressed as means ± SD. Comparisons of each electrocardiographic parameter between the SCN5A-positive group and the SCN5A-negative group and between the early and the late periods were made using 2-way repeated-measures analysis of variance (ANOVA) followed by the Scheffe multiple-comparison test. Comparisons of changes in each parameter between the SCN5A-positive group and the SCN5A-negative group were made using 1-way ANOVA followed by Scheffe test. Comparisons of the clinical, electrophysiologic, and follow-up data between the SCN5A-positive group and the SCN5A-negative group were made using chi-square test or 1-way ANOVA followed by Scheffe test. A p value <0.05 was considered significant.

Results

The SCN5A mutations, which were identified at a coding region in the SCN5A-positive group, are shown in Table 1. Five missense mutations and 2 frameshift mutations were identified. A missense mutation, R367H, was identified in 2 unrelated Brugada probands. The common variant and SCN5A promoter haplotype[14] in both groups are also shown in Table 1. There were no significant differences in the frequency of the common variant and the promoter haplotype between the 2 groups.

The comparison of the clinical and electrophysiologic characteristics between the 8 SCN5A-positive probands and the 36 SCN5A-negative probands are shown in Table 2. There were no significant differences in the age on admission, when the clinical diagnosis of BS was made, between the 2 groups. No significant differences were observed in the incidence of spontaneous type 1 ECG, documented VF until the early period, family history of SCD, implantation of implantable cardioverter defibrillator, complete right bundle branch block (RBBB) at the early period and the latest follow-up period (i.e., late period), and late potentials. The HV interval during the electrophysiologic study was significantly longer in the SCN5A-positive group than in the SCN5A-negative group. There were no significant differ-

Table 2
Clinical and electrophysiologic characteristics and follow-up

Characteristic	SCN5A-Positive Group (n = 8)	SCN5A-Negative Group (n = 36)	p Value
Clinical characteristics			
Age on admission (yrs)	46 ± 10	46 ± 13	0.938
Spontaneous type 1 ECG	6 (75%)	25 (69%)	0.755
Documented VF until early period	2 (25%)	17 (47%)	0.251
Family history of SCD	3 (38%)	4 (11%)	0.065
ICD implantation	8 (100%)	26 (72%)	0.090
Complete RBBB at early period	1 (13%)	2 (5%)	0.481
Complete RBBB at late period	1 (13%)	6 (17%)	0.771
Late potentials	7/7 (100%)	24/33 (73%)	0.117
Electrophysiologic characteristics			
Induction of VF	5/8 (63%)	25/33 (76%)	0.658
Mode (triple/double/single)	1/3/1	12/11/2	–
HV interval (ms)	65±5 (n=7)	41±8 (n=27)	<0.001
Follow-up			
Follow-up period (yrs)	10 ± 5	10 ± 4	0.993
Arrhythmic events during follow-up periods	4/8 (50%)	12/36 (33%)	0.375
Previous VF	2/2 (100%)	8/17 (47%)	0.156
No previous VF	2/6 (33%)	4/19 (21%)	0.539

EPS = electrophysiological study; HV = His-ventricular interval; ICD = implantable cardioverter-defibrillator.

ences in the frequency and mode of VF induction between the 2 groups.

Figure 1 illustrates the standard 12-lead ECGs at early and late periods during the follow-up period in representative patients with BS in the SCN5A-positive group (Figure 1) and the SCN5A-negative group. Table 3 shows composite data of the electrocardiographic parameters at the early and late periods in the 8 SCN5A-positive probands and 36 SCN5A-negative probands during the follow-up period.

As depolarization parameters, the P-wave duration (lead II), PQ interval (lead II), and QRS duration (lead II) significantly increased with aging from early to late periods in both groups and were all significantly longer in the SCN5A-positive group than in the SCN5A-negative group at both early and late periods. The QRS duration (lead V_2) in the SCN5A-positive group and the S-wave duration (leads II and V_5) in the SCN5A-negative group significantly increased with aging. The QRS duration (leads V_2 and V_5) and the S-wave duration (leads II and V_5) were significantly longer, and the S-wave amplitude (leads II and V_5) was significantly deeper in the SCN5A-positive group at early and late periods. The QRS axis was not different between the 2 groups at the early period; however, it was significantly smaller (i.e., deviated to the left) at the late period in the SCN5A-positive group.

As a repolarization parameter, the corrected QT interval (lead V_2) was significantly prolonged from the early period to the late period in the SCN5A-positive group, and was significantly longer in the SCN5A-positive group than in the SCN5A-negative group at the early and late periods. However, the QTc intervals (leads II and V_5) did not change from the early period to the late period in both groups and were not different between groups at the early and late periods. Conversely, no JTc intervals (leads II, V_2, and V_5) changed from the early period to the late period in both groups, and the JTc interval (lead V_2) at the late period was significantly longer in the SCN5A-positive group. The STJ amplitude (lead V_2) and STJ40 amplitude (lead V_2) did not change throughout the follow-up period in both groups, but were significantly greater in the SCN5A-positive group than in the SCN5A-negative group at the early and late periods. Even if we eliminated probands with BS with complete RBBB (1 SCN5A-positive proband and 2 SCN5A-negative probands at the early period, 1 SCN5A-positive proband and 6 SCN5A-negative probands at the late period), the main results and statistical differences were not significant.

Table 4 depicts comparison of the change of the electrocardiographic parameters from early to late periods between the SCN5A-positive group and the SCN5A-negative group.

The changes in PQ interval (lead II) and QRS duration (lead V_2) were significantly longer in the SCN5A-positive group than in the SCN5A-negative group. The change in QRS axis was greater (i.e., deviated more to the left) in the SCN5A-positive group than in the SCN5A-negative group.

There were no significant differences in the duration of follow-up period and the incidence of arrhythmic events during the follow-up period between the 2 groups (Table 2). Because a history of documented VF (until the early period) was proven to be the strongest predictor for subsequent arrhythmic events, arrhythmic events were compared between the 2 groups separately in probands with previous VF and those without previous VF, but no significant differences were observed (Table 2).

Discussion

The present study includes what is, to our knowledge, the longest follow-up of changes of electrocardiographic parameters in SCN5A-positive probands and SCN5A-negative probands with BS.

Mild conduction abnormalities, such as widening of the P wave, prolongation of QRS duration and PQ and HV intervals, and higher incidence of RBBB, have been described in patients with BS, especially those with

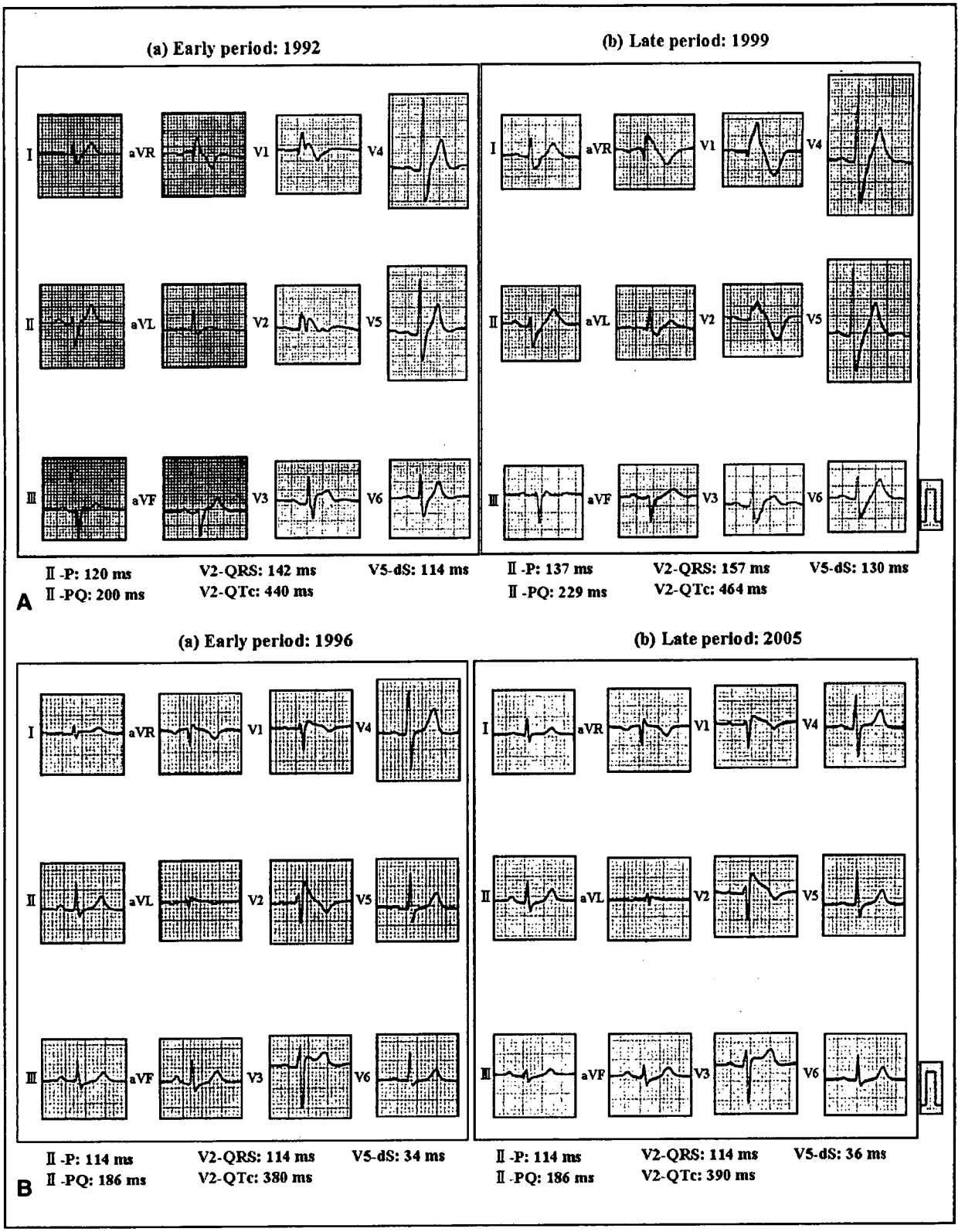

Figure 1. Standard 12-lead ECG at early and late periods during follow-up in representative cases of BS. *A*, in an *SCN5A*-positive proband (follow-up period, 7 years), the P-wave (lead II), QRS (lead V_2), and S-wave (lead V_5) durations and PQ interval (lead II) were prolonged even at the early period (47 years of age, *a*). The S-wave amplitude (lead V_5) was also deep, and the QRS axis deviated to the left. The QTc interval (lead V_2) was borderline prolonged. At the late period (*b*), all these parameters further increased. *B*, in an SCN5A-negative proband (follow-up period, 9 years), the P-wave (lead II), QRS (lead V_2), and S-wave (lead V_5) durations, PQ interval (lead II), and QTc interval (lead V_2) were less prolonged compared with those in an SCN5A-positive proband at the early period (51 years of age, *a*). At the late period (*b*), these parameters did not change significantly. V_5-dS = S-wave duration in lead V_5.

Table 3
Electrocardiographic parameters during follow-up period

ECG Parameter (leads)	Early Period			Late Period		
	SCN5A-Positive Group (n = 8)	SCN5A-Negative Group (n = 36)	p Value	SCN5A-Positive Group (n = 8)	SCN5A-Negative Group (n = 36)	p Value
Heart rate (beats/min)	66 ± 11	64 ± 10	0.924	60 ± 6	67 ± 12	0.194
P-wave duration (II) (ms)	137 ± 21	110 ± 12	<0.001	155 ± 19†	119 ± 16†	<0.001
PQ interval (II) (ms)	227 ± 31	179 ± 18	<0.001	257 ± 22*	190 ± 22†	<0.001
QRS duration (II) (ms)	125 ± 22	102 ± 18	<0.001	142 ± 41‡	111 ± 19‡	<0.001
QRS duration (V_2) (ms)	135 ± 15	110 ± 13	<0.001	157 ± 28*	115 ± 16	<0.001
QRS duration (V_5) (ms)	130 ± 28	101 ± 15	<0.001	147 ± 42	108 ± 17	<0.001
S-wave duration (II) (ms)	65 ± 38	35 ± 24	<0.001	77 ± 54	43 ± 26‡	<0.001
S-wave duration (V_5) (ms)	69 ± 40	37 ± 19	<0.001	78 ± 50	49 ± 17*	<0.001
S-wave amplitude (II) (mV)	0.37 ± 0.23	0.23 ± 0.24	0.005	0.43 ± 0.24	0.21 ± 0.17	<0.001
S-wave amplitude (V_5) (mV)	0.83 ± 0.47	0.34 ± 0.25	<0.001	0.88 ± 0.48	0.47 ± 0.27†	<0.001
QRS axis (°)	44 ± 81	49 ± 43	0.954	10 ± 76‡	43 ± 41	0.001
QTc interval (II) (ms)	409 ± 37	396 ± 28	0.535	432 ± 40	410 ± 34	0.164
QTc interval (V_2) (ms)	427 ± 51	392 ± 37	0.038	471 ± 38‡	405 ± 38	<0.001
QTc interval (V_5) (ms)	401 ± 43	389 ± 29	0.593	408 ± 39	398 ± 36	0.746
JTc interval (II) (ms)	279 ± 32	290 ± 30	0.554	292 ± 44	293 ± 34	0.100
JTc interval (V_2) (ms)	285 ± 39	279 ± 35	0.960	316 ± 42	283 ± 38	0.044
JTc interval (V_5) (ms)	265 ± 26	286 ± 30	0.108	262 ± 42	283 ± 32	0.105
STJ amplitude (V_2) (mV)	0.42 ± 0.19	0.29 ± 0.13	0.014	0.37 ± 0.23	0.24 ± 0.17	0.011
STJ40 amplitude (V_2) (mV)	0.38 ± 0.14	0.23 ± 0.12	<0.001	0.34 ± 0.17	0.21 ± 0.15	0.006

Data are presented as means ± SD.
* p <0.001 versus early period.
† p <0.01 versus early period.
‡ p <0.05 versus early period.
ECG = electrocardiographic; JTc = corrected JT; QTc = corrected QT; STJ amplitude = ST amplitude at J point; STJ 40 amplitude = ST amplitude 40 ms after J point.

Table 4
Comparison of the change of electrocardiographic parameters during follow-up

Change in ECG Parameter (leads)	SCN5A-Positive Group (n = 8)	SCN5A-Negative Group (n = 36)	p Value
Heart rate (beats/min)	−7 ± 10	3 ± 13	0.046
P-wave duration (II) (ms)	19 ± 12	9 ± 13	0.077
PQ interval (II) (ms)	30 ± 22	11 ± 14	0.004
QRS duration (II) (ms)	17 ± 22	8 ± 15	0.163
QRS duration (V_2) (ms)	22 ± 20	6 ± 11	0.003
QRS duration (V_5) (ms)	17 ± 29	8 ± 14	0.161
S-wave duration (II) (ms)	12 ± 17	8 ± 13	0.423
S-wave duration (V_5) (ms)	9 ± 15	12 ± 14	0.604
S-wave amplitude (II) (mV)	0.06 ± 0.10	−0.02 ± 0.14	0.152
S-wave amplitude (V_5) (mV)	0.05 ± 0.27	0.13 ± 0.18	0.331
QRS axis (°)	−34 ± 55	−6 ± 16	0.010
QTc interval (II) (ms)	22 ± 32	15 ± 34	0.562
QTc interval (V_2) (ms)	44 ± 49	13 ± 40	0.064
QTc interval (V_5) (ms)	6 ± 37	9 ± 30	0.845
JTc interval (II) (ms)	13 ± 27	3 ± 28	0.339
JTc interval (V_2) (ms)	31 ± 48	5 ± 38	0.094
JTc interval (V_5) (ms)	−3 ± 29	−3 ± 29	0.990
STJ amplitude (V_2) (mV)	−0.05 ± 0.18	−0.05 ± 0.12	0.949
STJ40 amplitude (V_2) (mV)	−0.04 ± 0.16	−0.02 ± 0.11	0.642

Abbreviations as in Table 3.

SCN5A mutation.[5,11] Smits et al[12] observed significantly longer PQ and HV intervals at baseline and a larger increase in PQ and QRS intervals after administration of sodium channel blockers in patients with BS with SCN5A mutations than in those without SCN5A mutations. Age-dependent variability in the conduction parameters was evidenced in SCN5A-positive patients with BS.[13,15] Moreover, this concept has been mechanistically investigated in vivo in heterozygous SCN5A mice, which showed progressive impairment with aging of atrial and

ventricular conduction associated with myocardial rearrangements and fibrosis.[16] Meregalli et al[17] showed prolongation of S-wave duration in leads II and III after administration of sodium channel blockers. Their group suggested that these electrocardiographic signs included reciprocal changes in the inferior leads, mirroring the conduction slowing in the RVOT,[17,18] which may progress with aging and relate to the pathogenesis of BS. In the present study, the P-wave, QRS, S-wave durations, and PQ intervals were all significantly longer, and the S-wave amplitude was significantly deeper in the SCN5A-positive group than in the SCN5A-negative group. In addition, the PQ interval and QRS duration in lead V_2 were more markedly prolonged, and the QRS axis deviated more to the left with aging in the SCN5A-positive group than in the SCN5A-negative group during the follow-up period. The results of previous clinical studies and the present study suggest that progressive depolarization abnormalities (i.e., conduction slowing) with aging may play a key role in the pathogenesis of BS.

It has been argued recently that arrhythmic events may occur when a sufficient degree of cell damage has been reached as a result of the severity of ion channel protein mutation. Frustaci et al[19] showed that myocyte apoptosis at the right and left ventricular myocardium was significantly higher in patients with BS with SCN5A mutations than in control subjects on histologic study. They suggested that abnormalities in the function of sodium channels may lead to cellular damage because intracellular sodium homeostasis has a relevant role in myocellular function.[19] Experimentally, Aiba et al[20] used a high-resolution optical mapping system in a pharmacologic BS model and demonstrated that depolarization abnormalities (i.e., conduction slowing) is required for the maintenance of VF in BS, although the initiating premature beats were a result of a phase 2 reentry mechanism. These histologic and experimental studies also support that progressive conduction abnormalities with aging may explain why an initial VF episode appears at middle to older ages, usually 40 to 50 years, in BS. It is generally accepted that SCN5A mutation is not associated with a higher risk of cardiac events, suggesting that genetic analysis is a useful diagnostic parameter but is not helpful for risk stratification.[7] Similarly, in the present study, the presence of SCN5A mutation did not predict subsequent arrhythmic events (Table 2). Most clinical studies have reported that induction of VF by programmed electrical stimulation did not predict the clinical outcome or clinical severity in patients with BS.[6,21,22] If the progressive conduction slowing with aging often observed in patients with BS, especially SCN5A-positve patients, are really linked to VF appearance, conduction parameters, such as QRS widening, late potentials, or inducibility of VF, may still have a potential to predict new or subsequent cardiac events.[23] A much larger patient population is required to make a definitive conclusion regarding the predictive value of SCN5A mutation and the conduction parameters for cardiac events.

Several clinical studies have suggested a localized QT prolongation, a repolarization parameter, in the right precordial leads (mainly lead V_2) in patients with BS.[24,25] Castro Hevia et al[25] have suggested that a QTc >460 ms in lead V_2 was a significant risk factor for subsequent cardiac events. We recently used 87-lead body surface ECGs and reported that a corrected recovery time, another repolarization parameter, was significantly longer in the right precordial body surface ECGs, reflecting the potentials of the RVOT, than in other body surface ECGs.[26] Similarly, in the present study, the longest QTc interval was observed in lead V_2 in most patients with BS with SCN5A mutation, who usually also had a coved-type ST-segment elevation and a terminal negative T wave. The fact that the QTc interval in lead V_2 was significantly longer in the SCN5A-positive patients than in the SCN5A-negative patients at the early and late periods can be explained by more frequent and higher coved-type ST-segment elevation with a terminal negative T wave in the SCN5A-positive patients. The QTc interval in lead V_2 was significantly prolonged from the early period to the late period in the SCN5A-positive patients; however, the JTc interval in lead V_2 did not change from the early period to the late period, suggesting that the significant QTc prolongation in lead V_2 with aging occurred mainly as a result of a significant prolongation of the QRS duration in lead V_2.

There are several limitations to the present study. First, because a small number of patients with BS with SCN5A mutation could be included in a single-center study, a larger number of patients with SCN5A mutation will be required to make a definitive conclusion. Second, the study population included 44 Brugada probands who could be prospectively followed up for average of 10 ± 5 years in our hospital. Therefore, the probands represent a severely affected population, but not a consecutively referred population. Third, Veltmann et al[27] recently reported the prevalence of fluctuations between diagnostic and nondiagnostic ECGs in patients with BS, which may influence the measurement of some electrocardiographic parameters, especially QT, JT interval, and ST amplitude, and should be taken into account. However, the influence of the fluctuations on depolarization parameters such as QRS duration is expected to be less pronounced.

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The Common Long-QT Syndrome Mutation *KCNQ1*/A341V Causes Unusually Severe Clinical Manifestations in Patients With Different Ethnic Backgrounds

Toward a Mutation-Specific Risk Stratification

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Background—The impressive clinical heterogeneity of the long-QT syndrome (LQTS) remains partially unexplained. In a South African (SA) founder population, we identified a common LQTS type 1 (LQT1)–causing mutation (*KCNQ1*-A341V) associated with high clinical severity. We tested whether the arrhythmic risk was caused directly by A341V or by its presence in the specific ethnic setting of the SA families.

Methods and Results—Seventy-eight patients, all with a single *KCNQ1*-A341V mutation, from 21 families and 8 countries were compared with 166 SA patients with A341V and with 205 non-A341V LQT1 patients. In the 2 A341V populations (SA and non-SA), the probability of a first event through 40 years of age was similar (76% and 82%), and the QTc was 484±42 versus 485±45 ms (P=NS). Compared with the 205 non-A341V patients with the same median follow-up (30 versus 32 years), the 244 A341V patients were more likely to have cardiac events (75% versus 24%), were younger at first event (6 versus 11 years), and had a longer QTc (485±43 versus 465±38 ms) (all $P<0.001$). Arrhythmic risk remained higher ($P<0.0001$) even when the A341V patients were compared with non-A341V patients with mutations either localized to transmembrane domains or exhibiting a dominant-negative effect. A341V patients had more events despite β-blocker therapy.

Conclusions—The hot spot *KCNQ1*-A341V predicts high clinical severity independently of the ethnic origin of the families. This higher risk of cardiac events also persists when compared with LQT1 patients with either transmembrane or dominant-negative mutations. The identification of this high-risk mutation and possibly others may improve the risk stratification and management of LQTS. (***Circulation***. **2007;116:2366-2375.**)

Key Words: arrhythmia ■ death, sudden ■ genetics ■ long-QT syndrome ■ risk factors

Heterogeneity of clinical manifestations is a well-known feature among patients affected by the long-QT syndrome (LQTS). The extent of this phenomenon became evident with the first large survey of LQTS as indicated by the presence within the same families of symptomatic and asymptomatic affected family members.[1] It was, however, only in the molecular era that scientific attempts were initiated to explain this puzzling clinical observation that also carries implications for patient management.

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The identification of the 3 main genes for LQTS prompted, within a few years, a series of relevant observations. On the basis of a relatively small number of genotyped patients, it

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was first suggested that LQTS type 3 (LQT3) was associated with less frequent but more lethal events.[2] Subsequently, in a larger number of genotyped families, it was shown that patients with either LQT2 or LQT3 were more likely to develop cardiac symptoms, but largely because of the higher incidence of LQT1 patients having a normal resting QTc (ie, <440 ms).[3] The shift of focus from the genes to the actual position of the various mutations within a given gene was the consequence of a study by Moss et al[4] that called attention to the fact that LQT2 patients with mutations in the pore region had a higher risk for cardiac events. However, the possibility that a discrete mutation could be associated with significantly higher risk for life-threatening cardiac events has so far remained unexplored or unproven, in part because the vast majority of LQTS-causing mutations are private, family-specific mutations. In LQTS, relatively few so-called mutational hot spots exist.

In 2005, we reported an LQT1-causing mutation, *KCNQ1*-A341V, in a South African (SA) founder population that was associated with unusual clinical severity.[5] Originated from a Dutchman who traveled to South Africa in 1670, this founder mutation comprises 22 *KCNQ1*-A341V genotype–positive SA families.[5] Although we assumed that this unexpected clinical phenotype was caused directly by this particular missense mutation, we could not exclude the possibility that the clinical severity was mediated not by the *KCNQ1*-A341V mutation per se but by some other probably genetic or epigenetic factors present in these families all living in South Africa for >300 years.

To answer this question and to determine whether the high arrhythmic risk observed in the SA families was indeed due solely to the *KCNQ1*-A341V mutation, one of relatively few "hot spot" missense mutations, we performed the present study on non-SA patients with LQT1 secondary to A341V.

Methods

Study Population

The study population was obtained through an international collaborative project involving 10 centers from 8 countries worldwide (Finland, France, Germany, Italy, Japan, the Netherlands, Russia, and the United States). Genetic and clinical data, collected on prespecified forms, included genotype status, demographic information, personal and family history of disease, type and timing of symptoms, ECG measurements, treatment, and response to therapy.

Data were recorded for a total of 84 patients from 24 unrelated, non-SA families harboring the *KCNQ1*-A341V mutation. Among them, 6 individuals from 3 families were compound heterozygotes (A341V plus an additional mutation on LQTS-related genes) and were excluded from analysis because individuals with 2 independent mutations are more likely to be symptomatic.[6,7]

A341V genotype–positive patients were classified as either symptomatic or asymptomatic on the basis of a previous experience of cardiac events (syncope, cardiac arrest [CA], sudden cardiac death [SCD]) as defined previously.[5] SCDs that occurred through 40 years of age in first-degree relatives and were judged to be LQTS-related according to an established policy[8] were assumed to have occurred in A341V mutation carriers and consequently were included, even in the absence of direct genotyping and/or ECG documentation.

Clinical Severity

The main objective of the study was to evaluate the clinical severity of LQTS among A341V genotype–positive patients with a heterogeneous ethnic background (non–SA-A341V) and to compare it with that of the SA founder population (SA-A341V) previously reported.[5] In addition, we compared the clinical course of all A341V patients with that of an LQT1 population derived from the LQTS database maintained at our institution in Pavia, Italy. As markers of clinical severity, we considered the proportion of symptomatic mutation carriers, the incidence of life-threatening arrhythmias, age at first cardiac event, QTc interval duration, and event-free survival by Kaplan-Meier cumulative estimates. The cumulative probability of a first event was considered, both for any event and for CA/SCD, before the institution of β-blocker therapy and through 40 years of age.

Furthermore, we took into account the disparity in the extent of genetic testing and clinical evaluation among the family members of the 2 A341V populations under study (non-SA and SA) because the SA pedigrees underwent extensive genetic testing. The inclusion of small nuclear families could have biased the results toward an overestimate of the clinical severity, so we also performed 3 different sensitivity analyses according to a priori established exclusion criteria to limit this potential selection bias. Specifically, all the analyses were repeated by (1) limiting the study population to 54 non-SA mutation carriers from 9 unrelated families and to 146 SA mutation carriers from 14 families with at least 4 affected individuals each; (2) excluding all probands, regardless of the number of affected individuals per family; and (3) combining these 2 criteria.

On the basis of recent findings that both transmembrane mutations[9] and dominant-negative functional mutations in *KCNQ1*[8] were associated with increased disease severity, we also considered the possible effect of the mutation site (transmembrane-spanning or pore-forming domains versus C- and N-terminal domains) and the possibility that the clinical severity of A341V might be a consequence of its dominant-negative nature. Therefore, we compared all A341V genotype–positive patients with the LQT1 population stratified for mutation site and the LQT1 patients with dominant-negative mutations.

Therapy

Data were collected on the administration and effectiveness of the treatment modalities applied to these LQTS patients: β-blockers, left cardiac sympathetic denervation, pacemaker, and implantable cardioverter-defibrillator. The assessment of the effectiveness of β-blockers was limited to those subjects with precise information on therapy and outcome and with at least 1 year of follow-up after initiation of treatment. To avoid the confounding role of possible comorbidities, we excluded from analysis those patients who started β-blocker therapy after 40 years of age. With the only exception of long-standing withdrawals (defined as a withdrawal of β-blocker therapy >1 week) or refusal of the prescribed β-blocker by the patient, all the events occurring during sporadic omission of the treatment were counted.

Statistical Analysis

The clinical characteristics of the genotyped groups were compared by Student *t* test or the Mann-Whitney *U* test as appropriate for continuous variables, which were expressed as mean and SD or as median and interquartile range (IQR). Categorical variables were presented as absolute and relative frequencies and compared by χ^2 test with Yates continuity correction. Event-free survival was described by Kaplan-Meier cumulative estimates, with comparisons performed by the log-rank test. Time from birth to first event through 40 years of age was considered both for any event and for CA/SCD. Survival analyses also were performed by gender. To represent the natural history of the disease and to avoid the confounding role of β-blockers, observations were censored at initiation of β-blocker therapy in survival analyses. Multivariate Cox proportional-hazards model was used to evaluate the significant and independent contribution of clinical and genetic factors to the risk of a first cardiac event. SPSS version 13 (SPSS Inc, Chicago, Ill) was used for computation. Values of $P<0.05$ (2 sided) were considered statistically significant.

Table 1. Clinical Characteristics of the Study Population and Comparison Between the 2 A341V Groups

	Non-SA-A341V Population	SA-A341V Population	*P*
Genotype-positive patients, n	78	166	...
Families, n	21	22	...
Female gender, n (%)	43 (55)	89 (54)	0.9
Symptomatic (any first event before 40 y of age), n (%)	53 (68)	131 (79)	0.09
Median age at onset, y (IQR)	6 (5–9)	6 (4–10)	0.82
CA/SCD, n (%)	19 (24)	55 (33)	0.21
SCD, n (%)	10 (13)	24 (14)	0.88
Asymptomatic, n (%)	25 (32)	35 (21)	...
≤15 y of age, n (%)	13 (17)	9 (5)	<0.01
ECG off β-blocker therapy, n	63	90	...
QTc, ms	484±42	485±45	0.89
≤440 ms, n (%)	5 (8)	11 (12)	0.56
≥500 ms, n (%)	15 (24)	30 (33)	0.27
Median follow-up, y (IQR)	21.5 (11–40)	33 (17–56)	0.001

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Clinical Severity

We report data on 78 *KCNQ1*-A341V genotype–positive patients originating from 21 worldwide families with a mean of 3.7±2.8 affected subjects per family.

Table 1 displays the clinical characteristics of this population. A slight but nonsignificant female gender predominance (55%) was present. During a median observation time of 21.5 years (IQR, 11 to 40 years) from birth to last contact, 53 patients (68%) became symptomatic before 40 years of age. Among these, 35 (45%) had syncope only, 9 (11.5%) had CA, and 10 (13%) suffered SCD. All the SCDs occurred while patients were off therapy; 7 occurred before 20 years of age. Exercise was the triggering factor for all (4 of 4) the episodes of witnessed SCD with available information on the circumstances associated with the terminal event. Overall, 19 patients (24%) suffered fatal or near-fatal events. Only 25 A341V patients (32%) were asymptomatic during the first 4 decades. Importantly, approximately half of these individuals are still ≤15 years of age and thus are too young to be considered truly asymptomatic with certainty because they are still at risk of a first cardiac event.

Table 1 also compares the occurrence of symptoms during follow-up from birth between the non-SA A341V patients and the SA-A341V population. The proportion of patients who experienced at least 1 cardiac event was not significantly different (68% in the non-SA population versus 79% in the SA population, $P=0.09$). However, the mean age at last contact was significantly different, with the non-SA population being younger (median, 21.5 years [IQR, 11 to 40 years] versus 33.5 years [IQR, 17 to 56 years]; $P=0.001$); furthermore, a higher number of asymptomatic subjects ≤15 years of age were in the non-SA population compared with the SA group (13 [17%] versus 9 [5%]; $P<0.01$). For this reason, the clinical status between the 2 groups also was compared following the exclusion of all A341V patients ≤15 years of age. The proportions of patients very likely to remain asymptomatic during comparable lengths of their clinical course remained small and very similar between the 2 A341V groups (25% and 19%, respectively, for non-SA versus SA group; $P=0.5$).

The median age at first event through 40 years of age was the same (6 years [IQR, 5 to 9 years] and 6 years [IQR, 4 to 10]; $P=0.82$), as was the incidence of LQTS-related fatal or near-fatal events (24% and 33%, respectively; $P=0.21$).

An ECG recorded in the absence of β-blocker therapy was available in 63 (81%) of the 78 non-SA A341V patients and in 90 (54%) of the 166 SA-A341V. Basal QTc was almost identical between the 2 groups (484±42 versus 485±45 ms, respectively; $P=0.89$). The QTc was ≤440 ms for 8% and 12% ($P=0.56$) of the 2 populations, respectively, whereas 24% and 33% had a QTc ≥500 ms ($P=0.27$).

Kaplan-Meier curves describing the cumulative survival to any first cardiac event (syncope, CA, SCD) before the institution of β-blocker therapy and through 40 years of age are shown for the entire non-SA population compared with the SA cohort in Figure 1. The median survival time (ie, the time by which at least 50% of the population has already had a first cardiac event) was 8 and 9 years, respectively (all together, 8 years; 95% confidence interval, 6.9 to 9.1). By 5 years of age, the cumulative event-free survival was 76% and 70%, respectively; by 10 years of age, it dropped to 38% and 35%. By the end of the observation period, no significant difference in survival was observed (24% versus 18%, $P=0.25$). However, because a slight trend toward a lower probability of a first cardiac event after 10 years of age was observed in the non-SA population, we also focused on those patients who had no cardiac events until 10 years of age and who were followed up through 40 years of age. Once again, no significant difference existed in event-free survival be-

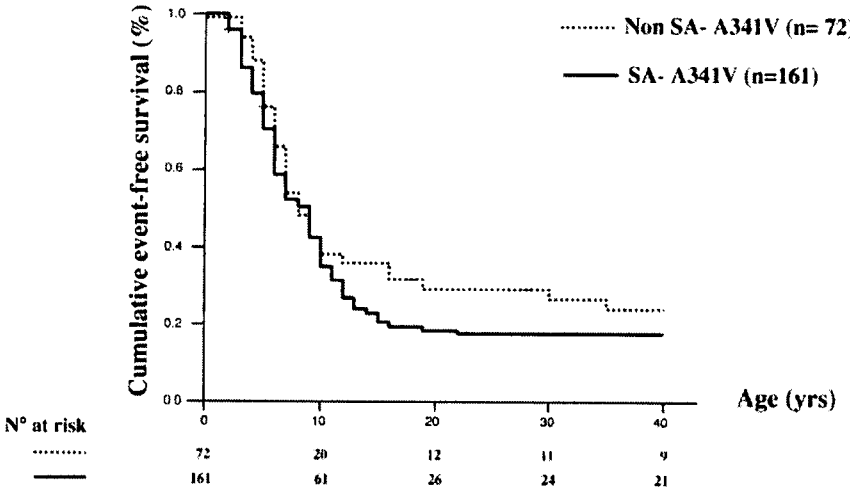

Figure 1. Unadjusted Kaplan-Meier estimate of the cumulative event-free survival in the non-SA and SA-A341V groups. Any cardiac event (syncope, CA, or LQTS-related SCD), whichever occurred first, was considered from birth through 40 years of age and before β-blocker therapy. Numbers at risk are indicated.

tween the 2 populations (data not shown; $P=0.11$). Notably, by 20 years of age, regardless of ethnic subgrouping, all A341V patients destined to become symptomatic had already experienced a first cardiac event, with very few events occurring after 20 years of age. No significant difference was observed between male and female patients among both the non-SA ($P=0.61$) and the SA A341V carriers ($P=0.19$).

When the end point for the comparison of the cumulative survival was limited to CA/SCD (Figure 2), Kaplan-Meier curves described an almost identical pattern between the 2 A341V populations. By 40 years of age, the cumulative probability for combined fatal/near-fatal events was 35% and 31%, respectively ($P=0.93$). The 3 sensitivity analyses confirmed the results reported above, and no significant differences were observed between the SA and non-SA populations.

Comparison Between A341V and Non-A341V LQT1 Populations

Because the SA and non-SA populations showed no significant difference in any of the markers of severity analyzed, all patients genotype positive for A341V were combined to compare the clinical expression of this specific mutation with that of a genetically heterogeneous non-A341V LQT1 group derived from our own LQTS database in Pavia (Table 2). The LQT1 A341V population (n=244) had a significantly greater percentage of symptomatic patients, earlier age at first cardiac event, higher incidence of life-threatening arrhythmias, more prolonged mean QTc, lower frequency of silent mutation carriers, and twice the proportion of subjects with a QTc ≥500 ms compared with the non-A341V LQT1 group (n=205).

When the combined A341V population was plotted against the LQT1 non-A341V group, a significant difference in the cumulative event-free survival emerged in that by 40 years of age, 80% of the A341V population (SA and non-SA) but only 30% of the LQT1 non-A341V group had already experienced a first cardiac ($P<0.0001$; Figure 3). A multivariate Cox model adjusted for gender and QTc showed that A341V patients were at higher risk of a first cardiac event compared with the LQT1 non-A341V group, with a hazard ratio of 4

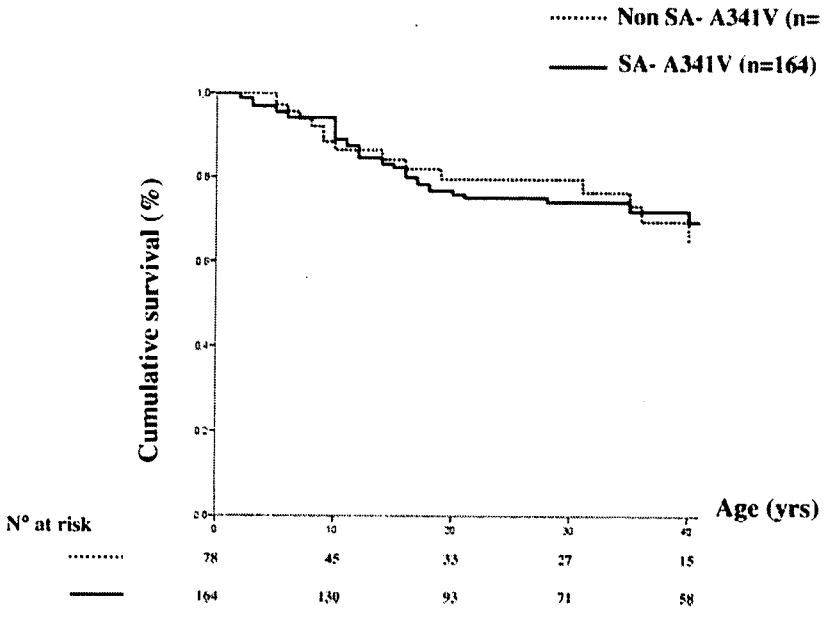

Figure 2. Unadjusted Kaplan-Meier estimate of the cumulative survival in the non-SA and SA-A341V groups. Only life-threatening cardiac events (CA or LQTS-related SCD) were considered from birth through 40 years of age and before β-blocker therapy. The SA group comprises 164 patients because of the lack of precise information on the exact time of the event in relation with therapy in 2 subjects. Numbers at risk are indicated.

Table 2. Clinical Characteristics of the Entire A341V Population and Comparison With a LQT1 Non-A341V Group

	All A341V	LQT1 Non-A341V	P
Genotype-positive patients, n	244	205	...
Female gender, n (%)	132 (54)	122 (59.5)	0.29
Symptomatic (any first event before 40 y of age), n (%)	184 (75)	49 (24)	<0.001
Median age at onset, y (IQR)	6 (5–10)	11 (4–17)	0.001
CA/SCD, n (%)	74 (30)	14 (7)	<0.001
ECG, n (%)	153 (63)	190 (93)	...
QTc, ms	485±43	465±38	<0.001
≤440 ms, n (%)	16 (10.5)	45 (24)	0.002
≥500 ms, n (%)	45 (29)	26 (14)	0.001
Median follow-up, y (IQR)	30 (15–51)	32 (14–46)	0.35

(95% confidence interval, 2.7 to 5.8; $P<0.001$). QTc was a significant and independent ($P=0.004$) predictor of cardiac events with a 6% increase in risk for each 10-ms increase in QTc. This pattern was confirmed when the comparison with the LQT1 population was performed according to the specific intragenic site of mutations and their functional effect. *KCNQ1*-A341V was associated with a much higher probability of experiencing a first cardiac event compared with the group comprising all other LQT1 non-A341V mutations, regardless of their being located in the transmembrane domain or in the C- and N-terminal regions of the protein ($P<0.0001$; Figure 4).

We then compared our 2 A341V populations with the non-A341V group comprising only mutations with a dominant-negative effect functionally demonstrated (Figure 5). Even in this case, patients with the dominant-negative A341V mutation had a significantly higher probability of becoming symptomatic than patients with other dominant-negative LQT1-causing mutations ($P<0.0001$). We also wanted to compare the A341V mutation with another dominant-negative mutation (*KCNQ1*-G314S) producing a significantly greater ($P<0.05$) loss in repolarizing current (≈55% versus 70%)[5] and found that the probability of experiencing a first cardiac event was still significantly higher for A341V ($P=0.03$; Figure 6).

β-Blocker Therapy

For 67 of the 78 non-SA A341V patients (86%), adequate information on therapy and outcome was available. Of them, 34 (51%) received β-blocker therapy and fulfilled the prespecified criteria for the evaluation of the response to treatment. Their median age at initiation of therapy was 7.5 years (IQR, 6 to 27 years).

During a median observation time on β-blocker therapy of 7.5 years (IQR, 5 to 11 years), 14 A341V genotype–positive patients (41%) suffered at least 1 cardiac event, including 3 CAs but no SCD. Six patients also received an implantable cardioverter-defibrillator, and 1 of them received appropriate shocks. Thus, life-threatening events on β-blocker therapy occurred in 4 of 34 LQT1 patients with A341V (12%).

When the same inclusion criteria for analysis were applied to the SA group, it was observed that 70 of 150 patients (47%) were on β-blocker therapy, with a median age at initiation of therapy of 10 years (IQR, 4 to 18 years). During a median follow-up on β-blocker therapy of 12.5 years (IQR, 6.5 to 22.5 years), 34 of 70 carriers (49%) suffered at least 1

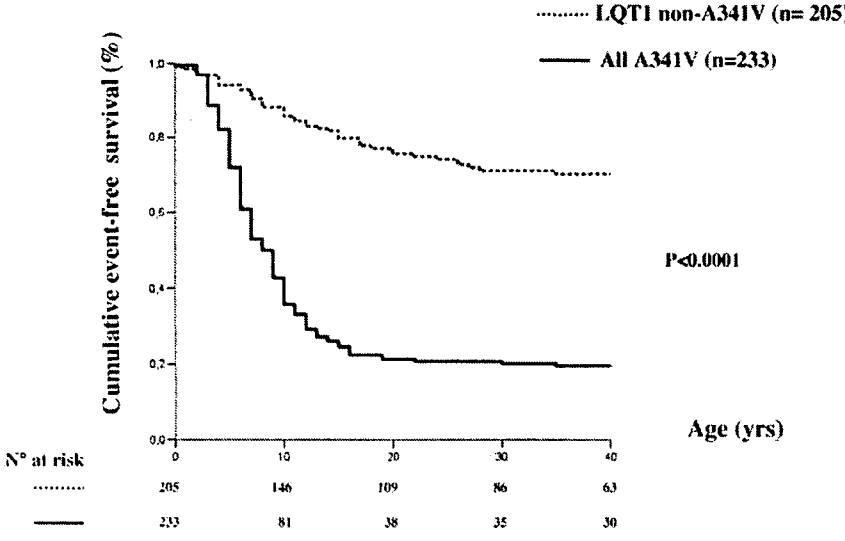

Figure 3. Unadjusted Kaplan-Meier estimate of the cumulative event-free survival (any first event) in the whole (non-SA+SA) A341V population plotted vs the LQT1 non-A341V group. Any cardiac event, whichever occurred first, was considered from birth through 40 years of age and before β-blocker therapy. Numbers at risk are indicated.

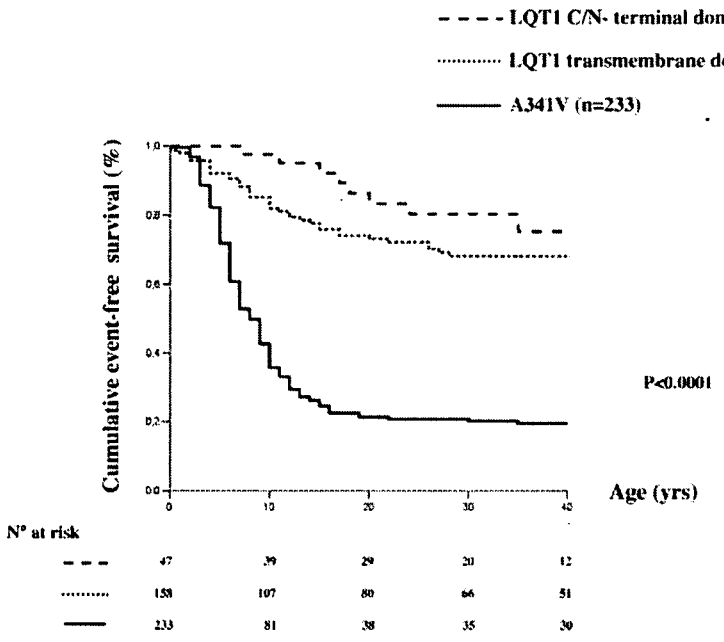

Figure 4. Unadjusted Kaplan-Meier estimate of the cumulative event-free survival (any first event) in the entire A341V and in the LQT1 non-A341V groups according to specific mutation site. Any cardiac event, whichever occurred first, was considered from birth through 40 years of age and before β-blocker therapy. Numbers at risk are indicated.

cardiac event, including 15 CAs and 5 SCDs, for a total of 20 life-threatening events on therapy (29%).

Among the 104 patients with A341V who were on β-blocker therapy, 19 (18%) life-threatening events occurred (18 CA and 1 implantable cardioverter-defibrillator shock) and 5 SCDs (5%). In comparison, among the 76 non-A341V assessable patients, a 7% incidence was shown of any cardiac event while on β-blockers; of note, no CAs and only 1 SCD (1%) occurred.

Discussion

We previously reported that *KCNQ1*-A341V, a mutation with a mild dominant-negative effect,[5] was associated with an unusually severe clinical phenotype in an SA founder population.[5] To determine whether this clinical severity was specific to the SA families or was related directly to the A341V mutation per se, we have collected data on A341V mutation carriers from 21 unrelated families originating from different parts of the world and having a different ethnic background.

We assume that the A341V mutation arose independently in different and unrelated families for 2 main reasons. First, this mutation was found in families living for centuries in very different parts of the world. Second, this mutation occurs in the context of a CpG dinucleotide, a known molecular hot spot for transition mutations.[10]

The major findings of the present study are that (1) the hot spot A341V on the *KCNQ1* gene is indeed associated with an unusual clinical severity independently of the origin of the families, (2) patients with this mutation are at higher risk for cardiac events compared with a more general LQT1 population, and (3) this clinical phenotype is not fully explained by the biophysical properties of the mutation. This evidence should now be taken into account in the risk stratification

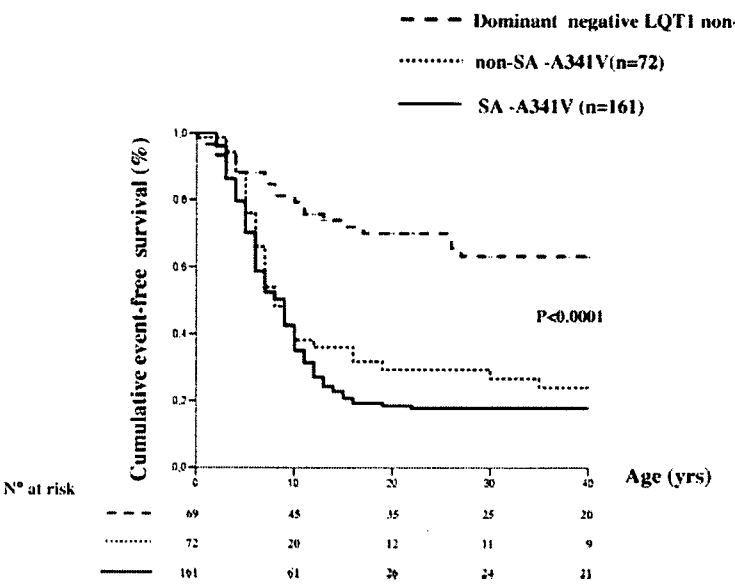

Figure 5. Unadjusted Kaplan-Meier estimate of the cumulative event-free survival (any first event) only in patients with LQT1 secondary to dominant-negative *KCNQ1* mutations; the 2 A341V groups are plotted vs the LQT1 non-A341V group. Any cardiac event, whichever occurred first, was considered from birth through 40 years of age and before β-blocker therapy. Numbers at risk are indicated.

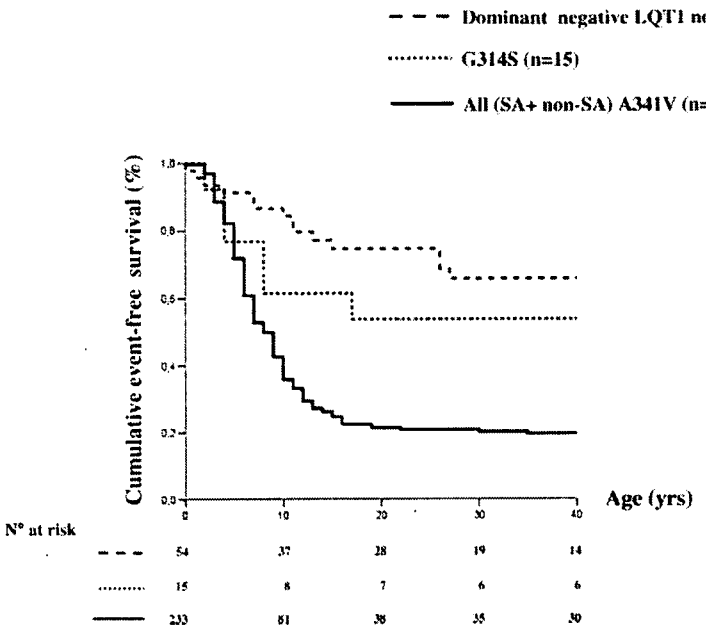

Figure 6. Unadjusted Kaplan-Meier estimate of the cumulative event-free survival (any first event) among patients with a mild (A341V) and strong (G314S) dominant-negative mutation. The entire A341V population (mild dominant-negative effect) is compared with a G314S population (strong dominant-negative effect) and the LQT1 non-A341V group. Numbers at risk are indicated.

process. We also unexpectedly found that recurrences of cardiac events despite β-blocker therapy were more frequent among *KCNQ1*-A341V patients than among LQT1 patients without this specific mutation.[11–15] Accordingly, we recommend careful follow-up and management of the A341V patients.

Mutation Site, Functional Effects, and Clinical Severity

Risk stratification for LQTS is important for the therapeutic decision-making process, especially when dealing with young asymptomatic patients, but despite significant progress compared with 20 to 30 years ago,[1,16] it is still in a developmental phase. In 2003, a risk stratification approach was proposed[3] that was based on gender, genotype, and degree of QT prolongation. However, this approach could not take into account the by-then only initial evidence that within the same genetic subgroup, important differences in the phenotypic manifestations of the disease may reflect the specific site of the mutations.

The first reports in this area came in 1997 by Donger et al[17] and in 2001 by Piippo et al[18] who called attention to the fact that the *KCNQ1*-R555C and *KCNQ1*-G589D mutations, respectively, both located in the C-terminal region, were associated with a somewhat less severe clinical phenotype. In 2002, Moss et al,[4] in a relatively large collaborative study, indicated that LQT2 patients with a mutation in the pore region of KCNH2 were at higher risk for cardiac events compared with patients with a mutation on the same gene but in different regions of the protein. This was followed in 2003 and 2004 by 2 studies[9,19] on the clinical impact of mutation site in LQT1 patients that reached opposite conclusions, thus complicating the attainment of a uniform interpretation.

Zareba et al[19] reported on 294 LQT1 patients from the International LQTS Registry[20] who had been classified into 3 groups according to their mutation site (prepore, pore, postpore) and found no significant differences in clinical presentation, ECG parameters, and cardiac events. Relevant here is the fact that in this cohort, *KCNQ1*-A341V, considered a pore mutation, represented only 6% (6 of 101 cases) of the entire "pore-region" population.

Shimizu et al[9] reported on 95 LQT1 Japanese patients from 37 different families who were classified according to the mutations being part of the transmembrane or of the C-terminal regions. Their main finding was a statistically significant greater risk of cardiac events for patients with mutations in the transmembrane region. Relevant here is the fact that in this investigation, at variance with the Zareba et al study, *KCNQ1*-A341V represented an impressive 29% (19 of 66 cases) of the entire "transmembrane" population.

We believe that an important contributing factor to the apparently very different results reported by Zareba et al and Shimizu et al lies in the large and significantly different representation of *KCNQ1*-A341V in their 2 reports (6% versus 29%; $P<0.001$). The striking clinical severity of this mutation, demonstrated in the present study, is probably sufficient to explain the more severe clinical picture associated with the Shimizu et al transmembrane mutations that included *KCNQ1*-A341V. Indeed, when following the same classification used by Shimizu et al, we divided our non-A341V LQT1 population according to the mutation site (transmembrane domain versus N and C terminal) and still observed a large difference between both these LQT1 genetic subgroups and the entire A341V population ($P<0.0001$).

Very recently, Moss et al[8] demonstrated in 600 LQT1 patients that both the transmembrane location of the mutations and their dominant-negative effect are independent risk factors for cardiac events. Accordingly, we took into consideration the biophysical properties of *KCNQ1*-A341V to verify whether they could explain our findings.

Initially, A341V had been regarded as a simple loss-of-function mutation without dominant-negative effect.[21,22] Later, Brink et al[5] demonstrated that this mutation was associated with a mild dominant-negative effect with a loss in

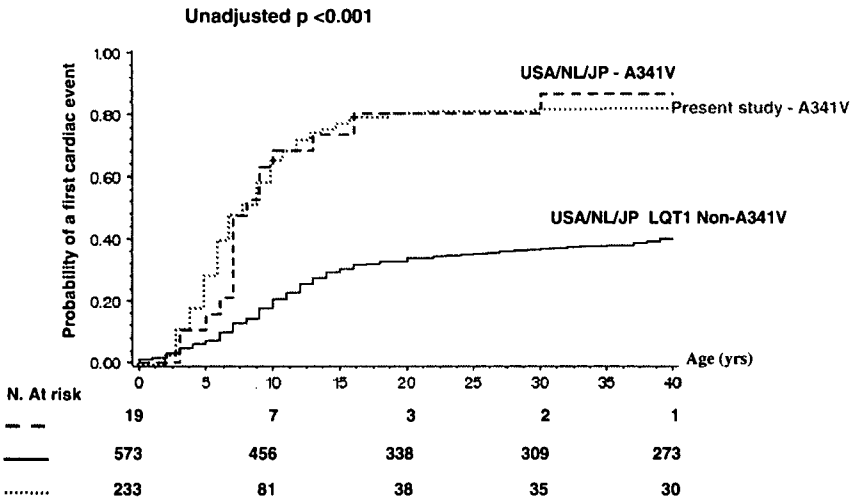

Figure 7. Unadjusted Kaplan-Meier estimate of the cumulative probability of a cardiac event (syncope, CA, or LQTS-related SCD, whichever occurred first) in the LQT1 population from the US-Netherlands-Japan collaborative study.[8] Carriers of A341V mutation are compared with all the other LQT1 non-A341V patients. Superimposed is the curve representing the cumulative probability of a first cardiac event in the entire (SA+non-SA) A341V population from the present study. Numbers at risk are indicated.

repolarizing current slightly exceeding 50% when coexpressed with wild type. When A341V was compared with our non-A341V LQT1 mutations with a dominant-negative effect, it was evident that A341V was associated with a significantly higher arrhythmic risk. Furthermore, when A341V was compared with a stronger dominant-negative mutation, G314S, that produced a loss of current of ≈70%,[5] the pattern indicating a higher risk among patients with A341V was again documented.

Because our own non-A341V population appeared to be somewhat less symptomatic than other LQT1 populations previously reported, for the sake of safety, we also made a comparison with the largest non-A341V population available to us, namely the 573 patients who were part of the recent study by Moss et al.[8] Figure 7 shows Kaplan-Meier curves for these 573 patients, for the 19 A341V patients from the same study, and for our own 233 A341V patients. Two important points become apparent. The first is that the probability of arrhythmic symptoms is twice as large (80% versus 40%; $P<0.0001$) among the A341V compared with the non-A341V patients. The second is the very impressive and practically identical Kaplan-Meier curves of the 19 A341V patients studied by Moss et al[8] and of the 233 A341V patients from our study.

These data conclusively demonstrate the striking clinical severity associated with the A341V mutation and, at variance with a major recent publication,[8] prove that cellular electrophysiological studies cannot always predict the clinical phenotype. Indeed, in the A341V patients, neither the location (transmembrane) nor the functional consequence of the mutation (dominant-negative effect) fully explains the unusually high clinical severity. We surmise that the current biophysical assessments of the electrophysiological effects of LQTS-causing mutations do not provide the whole gamut of information necessary to make a complete genotype-phenotype correlation.

Response to β-Blocker Therapy

In agreement with the evidence that among LQT1 patients, most cardiac events occur under conditions of increased sympathetic activity,[12] treatment with β-blockers is extremely effective in these LQTS patients who represent the largest genetic subtype.[11–15] Indeed, in LQT1 study populations with a percentage of symptomatic patients between 50% and 70%, the combined incidence of CA and SCD during rather long follow-up periods is only 1%.[13,15]

We were therefore surprised by observing what appears to be a rather incomplete protection for patients with A341V. A degree of caution is necessary in the interpretation of these data for which we do not have a ready explanation. It seems appropriate, however, to assess these patients very carefully with frequent follow-up visits to ensure that β-blockers are administered at full dose and to stress the importance of compliance. In addition, with QTc duration factored in as a known risk factor, the responsible physicians should be ready to consider the additional preventive steps represented by left cardiac sympathetic denervation[23] and by implantable cardioverter-defibrillators.

A341V Patients

The present data on a uniquely large population of patients carrying the same genetic defect (*KCNQ1*-A341V) demonstrate that within LQTS patients, mutation-specific behaviors exist independently of different genetic backgrounds and ethnicities. When we compared the clinical severity present in the SA and in the non-SA A341V population, we found that it was very similar. The sensitivity analyses, performed by excluding the probands and by including only those families with at least 4 affected individuals, confirmed these findings. Therefore, all A341V genotype–positive patients (n=244) were compared with a genetically heterogeneous LQT1 non-A341V population (n=205) and were shown to be more likely to have longer QT intervals, to suffer more arrhythmic events, and to be somewhat less protected by β-blockers from life-threatening events. Clearly, they represent a group at much higher risk compared with other LQT1 patients.

Study Limitations

The study had 2 potential limitations that we tried to obviate. In general, the SA families are larger than the non-SA families. For this reason, we performed sensitivity analyses that confirmed the validity of the data. The study of the SA

families goes back many more years and includes periods when the data collection cannot be accurately verified. Accordingly, we have excluded from the analysis of β-blocker therapy those older patients for whom precise information on dosage, compliance, and severity of the cardiac events could not be obtained with sufficient reliability.

Conclusions

The present study provides the largest data set on patients affected by LQTS who carry the exact same mutation. The data unequivocally show that *KCNQ1*-A341V is a mutation associated with unusual clinical severity. This finding, together with the recent evidence that genetically mediated neural control of heart rate may modulate arrhythmic risk in LQT1 patients,[24] begins to unravel the old and puzzling observation of the large heterogeneity in the clinical manifestations of LQTS. We do not believe that this mutation is unique in its clinical phenotype, and we believe that other mutations, more likely to be located in functionally important areas probably within the transmembrane region and close to the pore or in the S4 domain, confer a risk for life-threatening arrhythmias higher than that associated with other mutations. Thus, one can envision not only genotype-specific treatment algorithms but even mutation-specific considerations.

We were able to document these features because of the observations in the large SA founder population and because A341V is a relatively common LQT1-causing mutation. This has allowed us to pull together an adequate number of patients with this mutation from different parts of the world and to confirm the initial observation.[5] The severity of other specific mutations has probably escaped notice so far because they are less common and therefore their clinical impact has been lost within the large series of patients with more frequent mild mutations. The clinical message from our study is that in the future attention should be paid to families with a high percentage of symptomatic individuals and that, once the disease-causing mutations have been identified, collaborative studies similar to ours should be undertaken to test the possibility of identifying other clinically severe mutations. This will contribute to the development of a more accurate risk stratification grid for patients affected by LQTS.

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Disclosure

Dr Ackerman is a consultant for PGxHealth with respect to their FAMILION genetic test for cardiac channel mutations. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

The impressive clinical heterogeneity characteristic of the long-QT syndrome (LQTS) remains puzzling and hinders accurate risk stratification and targeted management. In a South African founder population, we identified a common LQTS type 1 (LQT1)–causing mutation (*KCNQ1*-A341V) associated with high clinical severity. We have now tested whether the arrhythmic risk was caused directly by A341V or by its presence in the specific ethnic setting of the South African families. We compared 78 patients from 10 countries, all with a single *KCNQ1*-A341V mutation, with 166 South African patients with A341V and 2 different populations of non-A341V LQT1 patients. In the 2 A341V populations, the probability of a first event before 40 years of age was similar (76% and 82%), and the QTc was similar. Compared with the LQT1 non-A341V patients, the A341V subjects were significantly more likely to have cardiac events, to be younger at first event, and to have a longer QTc. Arrhythmic risk remained higher even when the A341V group was compared with 573 LQT1 non-A341V patients. Thus, the hot spot *KCNQ1*-A341V predicts high clinical severity independently of the ethnic origin of the families. Neither the location (transmembrane) nor the functional consequence of the mutation (dominant-negative effect) fully explains the clinical phenotype. The identification of this high-risk mutation and possibly others may improve risk stratification and management of LQTS.

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