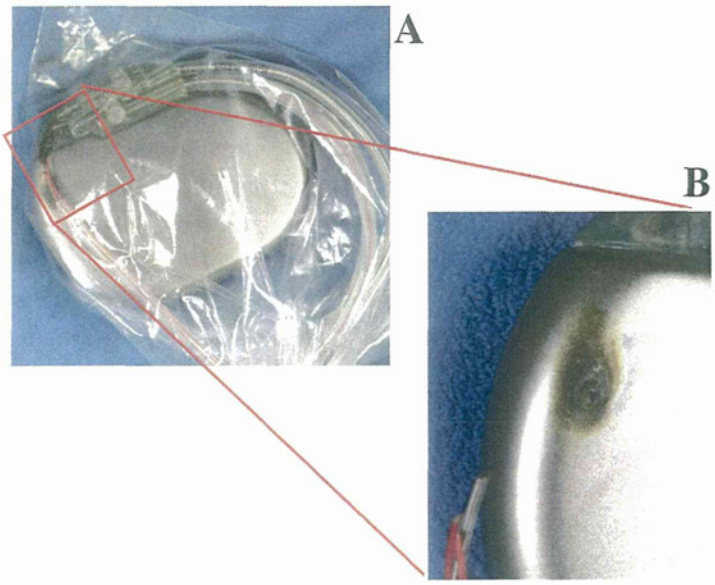

Figure 1. Charring and crater formation on the surface of the ICD.
A: The ICD had been placed in a vinyl bag with the damaged leads still attached.
B: A magnified view of the uncovered ICD surface. Significant craters and charring are observed where the edge of the damaged shock lead came in contact with the ICD can.

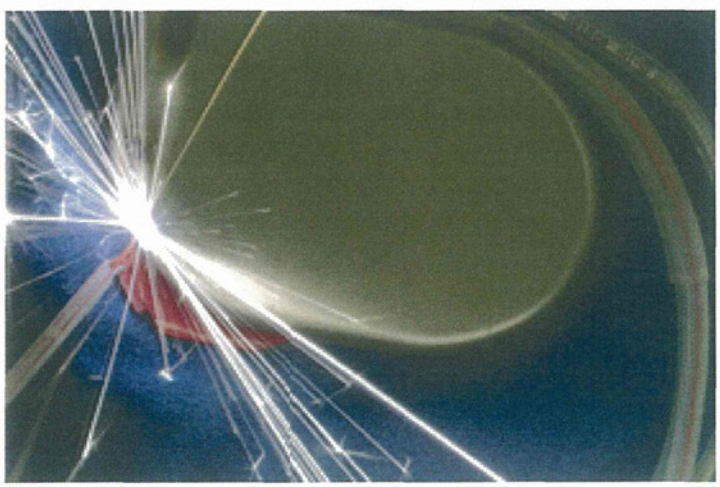

Figure 2. A maximum shock of 31 Joules produced significant sparks emanating from the surface of the ICD.

within approximately 20 minutes (from 14:49 to 15:11 on January 26, 2007), and ICD therapies (antitachycardia pacing and defibrillation shocks) in response to each episode were delivered. After the terminal shock therapy, back-up ventricular pacing with a cycle length of 1000 ms was present. From 21:21 on the same day, frequent events were detected during the coroner's inquest with manipulation of the device during its removal and the ICD delivered many shocks that were triggered by sensing noise. Many events were also recorded on the 26th and 28th of February. Charring and crater formations were observed on the surface of the ICD where the edge of the injured shock lead had come in contact with the can, probably because of the frequent shock deliveries (Figure 1).

In order to observe the conditions in which the shock deliveries occurred during the noise detection, we programmed the ICD to deliver the maximum shock energy via a programmer while keeping continuous contact between the device surface and shock lead. As shown in Figure 2, a maximum shock of 31 Joules produced significant sparks from the surface of the ICD, which resulted in fusion of the lead wire to the ICD surface.

Discussion

We report a patient with idiopathic dilated cardiomyopathy and a history of VT/VF in whom an ICD and the leads were destructively removed by an unaware coroner after the sudden cardiac death of the patient. Because the electrograms during the fatal event had disappeared due to successive detections of noise, the exact cause of the sudden death remained unknown. However, the remaining stored data logs and event markers (showing frequent VT/VF episodes followed by continuous back-up pacing) suggested that the terminal defibrillation shock was either unsuccessful in terminating the tachycardia due to degenerating it to fine (undetectable) VF or induced a nonresponsive cardiac electrical standstill. A postmortum ICD extraction by an uninformed person could lead to the loss of important information.

Furthermore, the present case demonstrated that unstable contact between the uncovered edge of a lead and the surface of the ICD may cause dangerous electric discharges. The melting point of titanium (the material on the surface of ICD generators) is reported to be approximately 1600 °C. If a person were to touch anywhere close to the edge of the lead during a shock discharge, it may cause severe injury.

Even in the United States where the deceased are usually buried, inactivation and removal of an ICD for analysis has been recommended by manufacturers.

To avoid both deletion of the therapy history and dangerous electrical dis-

charges from the ICD, the following procedures are recommended. 1) Careful disconnection of the lead from the ICD using a special screwdriver. 2) Inactivation of the device by changing the previous settings using a compatible programmer. 3) When a coroner or pathologist does not have special implements to perform the above procedures, he or she has no choice but to remove the device by cutting the ICD leads after placing insulation between the edges of the injured leads and the surface of the ICD in order to prevent electrical shock. 4) After removal of the device, the coroner or police department should inform the patient's doctor about the death as soon as possible. 5) The device should be sent to an appropriate medical center or the manufacturer so they can analyze the terminal episode. In order to ensure widespread and consistent notification about the handling of ICDs after death, education through appropriate scientific societies, such as a guideline from the Japanese Heart Rhythm Society, is highly recommended.

Acknowledgment

We would like to thank Mr. Hajime Ideno, Technical Service Manager, Boston Scientific, Guidant Japan, KK for his support in preparing Figure 2 which demonstrates significant sparks from an ICD.

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QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

Genotype-Phenotype Aspects of Type 2 Long QT Syndrome

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Objectives The purpose of this study was to investigate the effect of location, coding type, and topology of *KCNH2(hERG)* mutations on clinical phenotype in type 2 long QT syndrome (LQTS).

Background Previous studies were limited by population size in their ability to examine phenotypic effect of location, type, and topology.

Methods Study subjects included 858 type 2 LQTS patients with 162 different *KCNH2* mutations in 213 proband-identified families. The Cox proportional-hazards survivorship model was used to evaluate independent contributions of clinical and genetic factors to the first cardiac events.

Results For patients with missense mutations, the transmembrane pore (S5-loop-S6) and N-terminus regions were a significantly greater risk than the C-terminus region (hazard ratio [HR]: 2.87 and 1.86, respectively), but the transmembrane nonpore (S1–S4) region was not (HR: 1.19). Additionally, the transmembrane pore region was significantly riskier than the N-terminus or transmembrane nonpore regions (HR: 1.54 and 2.42, respectively). However, for nonmissense mutations, these other regions were no longer riskier than the C-terminus (HR: 1.13, 0.77, and 0.46, respectively). Likewise, subjects with nonmissense mutations were at significantly higher risk than were subjects with missense mutations in the C-terminus region (HR: 2.00), but that was not the case in other regions. This mutation location–type interaction was significant ($p = 0.008$). A significantly higher risk was found in subjects with mutations located in α-helical domains than in subjects with mutations in β-sheet domains or other locations (HR: 1.74 and 1.33, respectively). Time-dependent β-blocker use was associated with a significant 63% reduction in the risk of first cardiac events ($p < 0.001$).

Conclusions The *KCNH2* missense mutations located in the transmembrane S5-loop-S6 region are associated with the greatest risk. (J Am Coll Cardiol 2009;54:2052–62) © 2009 by the American College of Cardiology Foundation

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Long QT syndrome (LQTS) is a congenital disorder caused by mutations of several cardiac ion channel genes and is diagnosed clinically by a prolonged QT interval on the electrocardiogram (ECG) and variable clinical outcomes including arrhythmia-related syncope and sudden death (1,2). Mutations involving the *KCNH2* gene (*hERG* [human ether-a-go-go-related gene]), which codes for the pore-forming α-subunit of a cardiac K^+ channel, have been linked to the type 2 LQTS, the second most common variant of LQTS (3). The *KCNH2* mutations lead to a reduction in the rapid component of the delayed rectifier repolarizing current (I_{Kr}), which contributes to lengthening of the QT interval (4). The *KCNH2* subunits oligomerize to form a tetramer that inserts into the cell membrane to form the functional K^+ channel. Each subunit comprises 6 α-helical transmembrane segments (S1 to S6), where the K^+-selective pore is found between S5 and S6. The transmembrane segments are flanked by amino (N)- and carboxyl (C)-terminus regions (5–8). In a previous study of patients with type 2 LQTS, mutations in the pore region were associated with an increased risk for arrhythmia-related cardiac events when compared with patients with nonpore mutations (9). However, this study was limited by population size in its ability to examine the phenotypic effect of mutations within distinct domains of the nonpore region.

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There are several coding types of mutations in genes that form the functional K^+ channel: missense, nonsense, splice site, in-frame deletion, and frameshift mutations (10). Missense mutations are point mutations that result in a single amino acid change within the protein; nonsense mutations generate a stop codon and can truncate the protein. Insertion and deletion mutations cause in-frame or frameshift mutations, the latter of which change the grouping of nucleotide bases into codons. Splice site mutations may alter splicing of messenger ribonucleic acid. In our recent cohort of type 1 LQTS (11), a missense mutation accounted for 81% of all the mutations, and the type of mutation (missense vs. nonmissense) was not an independent risk factor. On the other hand, nonmissense mutations such as frameshift and nonsense mutations have been reported to be more frequently identified in the type 2 LQTS patients (11,12).

Moreover, topology of mutations (α-helical domain, β-sheet domain, and other uncategorized location) has been recently reported to relate to the function of mutated channel in the type 2 LQTS patients (8).

We hypothesized that the distinct location, coding type, and topology of the channel mutation would have important influence on the phenotypic manifestations and clinical course of patients with type 2 LQTS. To test this hypothesis, we investigated the clinical aspects of 858 subjects having a spectrum of *KCNH2* mutations categorized by the distinct location, coding type, and topology of the channel mutations.

Abbreviations and Acronyms

ECG = electrocardiogram

I_{Kr} = rapid component of the delayed rectifier repolarizing current

LQTS = long QT syndrome

NMD = nonsense-mediated decay

QTc = corrected QT

Methods

Study population. The study population of 858 subjects was derived from 213 proband-identified families with genetically confirmed *KCNH2* mutations. The proband in each family had corrected QT (QTc) prolongation not due to a known cause. The subjects were drawn from the U.S. portion of the International LQTS (Rochester) Registry (n = 456), the Netherlands' (Amsterdam) LQTS Registry (n = 214), the Japanese (National Cardiovascular Center) LQTS Registry (n = 95), and the Mayo Clinic LQTS Registry (n = 93). All subjects or their guardians provided informed consent for the genetic and clinical studies. Not included in the study population were 58 subjects with evidence of 2 or more LQTS mutations and an additional 18 who had polymorphisms (p.R176W or p.R1047L) that the authors felt might reduce I_{Kr} current. A total of 201 of the 456 patients enrolled from the U.S. portion of the International LQTS Registry and 61 of the 95 patients from the Japanese LQTS Registry were reported in our prior reports (9,12).

Phenotype characterization. Routine clinical and electrocardiographic parameters were acquired at the time of enrollment in each of the registries. Follow-up was censored at age 41 years to minimize the influence of coronary disease on cardiac events. Measured parameters on the first recorded ECG included QT and R-R intervals in milliseconds, with QT corrected for heart rate by Bazett's formula. The QTc interval was expressed in its continuous form and categorized into 4 levels: <460, 460 to 499, 500 to 530, and >530 ms. The QTc interval was categorized into 3 levels: <500, 500 to 530, and >530 ms for the end point of lethal cardiac events (aborted cardiac arrest or LQTS-related sudden cardiac death), because there were few lethal cardiac events in the lowest QTc group (<460 ms). Clinical data were collected on prospectively designed forms with information on demographic characteristics, personal and family medical history, electrocardiographic findings, therapy, and end points during long-term follow-up. Data common to all 4 LQTS registries involving genetically identified patients with type 2 LQTS genotype were electronically merged into a common database for this study.

Genotype characterization. The *KCNH2* mutations were identified using standard genetic tests performed in molecular-genetic laboratories in the participating academic centers. From the Rochester registry, 60 subjects died of sudden cardiac death at a young age and were not genotyped. These 60 subjects were assumed to have the same

KCNH2 mutation as other affected close members of their respective family.

Genetic alterations of the amino acid sequence were characterized by location in the channel protein, by the type of mutation (missense, splice site, in-frame insertions/deletions, nonsense [stop codon], and frameshift), and by the topology of mutation (α-helical domain, β-sheet domain, and other uncategorized location) (Fig. 1). The transmembrane region of the *KCNH2* encoded channel was defined as the coding sequence involving amino acid residues from 398 through 657 (S5-loop-S6 region: 552 to 657), with the N-terminus region defined before residue 398, and the C-terminus region after residue 657 (Fig. 1) (13,14).

We evaluated the risk associated with 4 main prespecified regions: 1) N-terminus; 2) transmembrane "nonpore" region (S1–S4); 3) transmembrane "pore" region (S5-loop-S6); and 4) C-terminus. We also evaluated the risk associated with distinct types of mutation and topology of mutation.

Statistical analysis. Differences in the univariate characteristics by specific groupings were evaluated by standard statistical methods. The primary end point was time to syncope, aborted cardiac arrest, or sudden death, whichever occurred first. The cumulative probability of a first cardiac event was assessed by the Kaplan-Meier method, with significance testing by the log-rank statistic. The Cox proportional-hazards survivorship model was used to evaluate the independent contribution of clinical and genetic factors to the first occurrence of time-dependent cardiac events from birth through age 40 years (15). The Cox regression models, stratified by decade of birth year and allowing for time-dependent covariates, were fit to estimate the adjusted hazard ratio (HR) of each factor as a predictor of first cardiac events. We observed that sex was not proportional as a function of age, with crossover in risk at age 13 on univariate Kaplan-Meier analysis. To fulfill the assumption of proportional hazards for sex over the entire age range, a time-dependent covariate for sex (via an interaction with time) was incorporated, allowing for different hazard ratios by sex before and after age 13 years.

Since almost all subjects were first- and second-degree relatives of probands, the effect of potential lack of independence between subjects was evaluated by refitting the Cox model using the robust sandwich estimator for family membership (16). All significant predictors of risk maintained significance using this robust measure of variance.

Patients who did not have an ECG for QTc measurement were identified in the Cox models as "QTc missing."

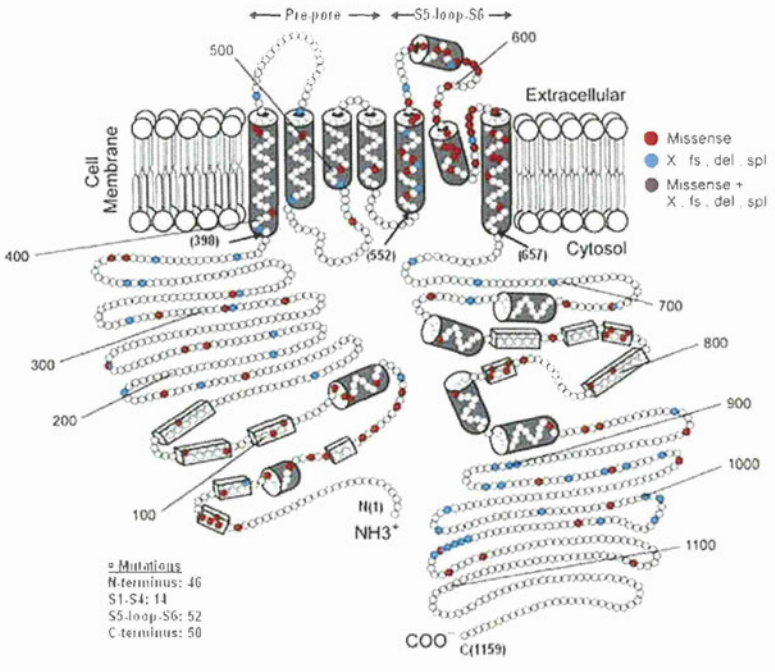

Figure 1 **Location of Different Mutations in KCNH2 Potassium Channel**

Diagramatic location of 162 different mutations in the KCNH2 potassium channel involving 858 subjects. The α subunit involves the N-terminus ($NH3^+$), 6 membrane-spanning segments, and the C-terminus portion (COO^-). The **numbers in parentheses** refer to the position of the amino acid beginning at the N-term position (1), the beginning of the transmembrane nonpore S1 to S4 sequence (398), the beginning of the transmembrane S5-loop-S6 sequence (552), the end of the transmembrane S6 sequence (657), and at the C-term end position (1,159). The **open circles** represent individual amino acids, the **red circles** indicate the missense mutations, and the **blue circles** indicate nonmissense mutations. The **cylinders** represent putative α-helical segments, and the **bars** represent putative β-sheets.

Pre-specified covariate interactions between mutation location, type, and α-helical domains were evaluated. Only the mutation location–missense interaction was significant. To test the impact of the interaction between the 4 different mutation locations and missense mutation type, 3 interaction terms were added to the Cox proportional hazards regression model. A 3 degree of freedom likelihood-ratio test was performed to determine their statistical significance. The influence of time-dependent β-blocker therapy (the age at which β-blocker therapy was initiated) on outcome was determined by adding this variable to the final Cox model containing the various covariates.

Results

Total study population. The continuum of *KCNH2* mutations and their respective number of subjects by location, type, and topology of mutation and contributing registry are presented in the Online Table, and the location, type, and topology of the mutations are diagrammatically presented in Figure 1. A total of 162 different *KCNH2* mutations were identified in 858 subjects. The mutations were predominantly found in 3 regions: the N-terminus (28.4%, n = 46), the C-terminus (30.9%, n = 50), and the transmembrane domain (40.7%, n = 66). Of the 66 mutations within the transmembrane domain, 78.8% (n = 52) were located within the S5-loop-S6 region. Missense (single amino acid substitutions) accounted for 61.7% (n = 100) of all the mutations, splice site for 1.9% (n = 3), in-frame insertions/deletions for 0.6% (n = 1), nonsense for 10.5% (n = 17), and frameshift for 25.3% (n = 41). Sixty-six mutations (40.7%) were located in the α-helical domain, 17 (10.5%) in the β-sheet domain, and 79 (48.8%) in other uncategorized locations.

The phenotypic characteristics of patients enrolled in each of the 4 registries and by location, type, and topology of mutation are presented in Table 1. The age was younger in the Mayo Clinic registry than in the other 3 registries. The QTc interval was longer and the cardiac events were more frequent in the U.S. and Japanese registries than in the other 2 registries. A pacemaker was more frequently implanted in the U.S. registry, and a defibrillator in the Mayo Clinic registry. LQTS-related death was more frequent in the U.S. registry than in the other 3 registries; that seems mainly because the U.S. registry included the largest proportion of patients missing ECG data and was the longest-standing registry, in which 44 of the 92 deaths occurred before 1980. It is not surprising that the death rate in subjects missing ECG data (i.e., QTc) was very high.

Location, type, and topology of mutation on clinical outcome. As to the location of mutation, the QTc interval was longer and cardiac events were more frequent in patients with mutations in the transmembrane pore locations (S5-loop-S6) than in patients with mutations in transmembrane nonpore (S1 to S4), N-terminus, or C-terminus locations. As to the type of mutation, the QTc interval was longer in patients with missense mutations than in patients with either frameshift/nonsense or other mutations. Sudden death was also more frequent among patients with missense mutations. As to the topology of mutation, the QTc interval was longer and cardiac events were more frequent among patients with mutations located in the α-helical domain than among patients with mutations in either the β-sheet domain or other uncategorized location.

The cumulative probabilities of first cardiac event by type, location, and topology of mutation are presented in Figures 2A, 2B, and 2C, respectively. No significant difference in event rates was observed among types of mutation (p = 0.68) (Fig. 2A), although missense mutations were more associated with longer QTc interval and increased risk for sudden death compared with other types of mutations. Conversely, significantly higher event rates were found among subjects with transmembrane pore mutations than among subjects with mutations in transmembrane nonpore, N-terminus, or C-terminus regions, with a gradual increase in event rates occurring during ages 5 to 40 years (Fig. 2B). Significantly higher event rates were also observed among subjects with mutations located in the α-helical domains than among subjects with mutations in either the β-sheet domains or other locations (Fig. 2C).

The findings from the Cox regression analysis by location and by topology of *KCNH2* mutations for first cardiac events and those for aborted cardiac arrest or LQTS-related sudden cardiac death are presented in Table 2. The clinical risk factors associated with first cardiac events involved males before age 13 years (HR: 1.54 vs. females), females after age 13 years (HR: 3.29 vs. males), and longer QTc intervals (HR: 3.33, QTc >530 ms [n = 112] vs. QTc <460 ms [n = 239]; HR: 2.09, QTc 500 to 530 ms [n = 146] vs. QTc <460 ms; HR: 1.56, QTc 460 to 499 ms [n = 251] vs. QTc <460 ms). Mutations located in the transmembrane pore region made significant and independent contributions to the risk model, with C-terminus region as reference (HR: 1.56). Mutations located in the α-helical domains made significant contributions to the risk model with the β-sheet domains as reference (HR: 1.74). A mutation in the α-helical domain located in the transmembrane pore region would have a risk equal to the multiplicative product of the 2 hazard ratios, namely, 1.56 × 1.74 = 2.71. On the other hand, a mutation in the α-helical domain located in the nonpore transmembrane S1 to S4 region would have a risk of 0.61 × 1.74 = 1.06, and this value was very similar to 1. Time-dependent β-blocker use was associated with a significant 63% reduction in the risk of first cardiac events (p < 0.001). The clinical risk factors associated with lethal cardiac events showed similar tendency to those with cardiac events, and involved females after age 13 years (HR: 2.38 vs. males) and longer QTc intervals (HR: 4.97, QTc >530 ms vs. QTc <500 ms; HR: 2.57, QTc 500 to 530 ms vs. QTc <500

Table 1 Phenotypic Characteristics by Source of Subjects, Location of Mutation, Type of Mutation, and Topology of Mutation

Characteristics	Source of Subjects				Location of Mutation				Type of Mutation			Topology of Mutation		
	Rochester	the Netherlands	Japan	Mayo	Transmembrane (S1–S4)	Transmembrane (S5-Loop-S6)	N-Terminus	C-Terminus	Missense	Frameshift/ Nonsense	Others	α-Helices	β-Sheet	Neither
Unique mutations					14	52	46	50	100	58	4	66	17	79
Patients	456	214	95	93	44	259	243	312	555	261	42	319	141	398
Female	57	59	66	57	57	59	56	60	60	56	55	57	55	61
ECG at enrollment														
Age*†‡, yrs	25 ± 20	33 ± 21	30 ± 18	22 ± 16	28 ± 16	24 ± 19	32 ± 21	26 ± 19	28 ± 20	27 ± 19	26 ± 22	25 ± 19	31 ± 22	28 ± 19
QTc*†‡§, s	0.49 ± 0.06	0.47 ± 0.05	0.49 ± 0.05	0.47 ± 0.05	0.48 ± 0.05	0.50 ± 0.06	0.47 ± 0.06	0.48 ± 0.05	0.49 ± 0.06	0.47 ± 0.05	0.47 ± 0.06	0.49 ± 0.05	0.48 ± 0.05	0.48 ± 0.06
QTp*†, s	0.34 ± 0.07	0.33 ± 0.05	0.38 ± 0.06	0.34 ± 0.06	0.37 ± 0.07	0.36 ± 0.07	0.34 ± 0.06	0.34 ± 0.07	0.35 ± 0.07	0.34 ± 0.06	0.34 ± 0.08	0.35 ± 0.07	0.33 ± 0.07	0.34 ± 0.06
Therapy														
β-blockers	51	45	45	60	48	53	45	51	49	51	50	51	48	49
Pacemaker*	6.8	0.5	1.1	0	2.3	6.6	2.5	2.9	4.5	2.7	2.4	5.6	2.8	2.8
Sympathectomy	2	0.9	0	1.1	2.3	1.5	0	2.2	1.6	0.8	2.4	1.6	2.8	0.8
Defibrillator*	14	4.7	6.3	25	18	14	8.2	12	11	13	17	12	9.9	13
First cardiac event*†‡‖	50	34	52	31	34	58	40	38	45	44	29	54	30	41
Syncope*†‡	42	31	52	28	32	49	36	34	39	39	29	45	26	38
Aborted cardiac arrest	0.7	1.9	0	3.2	2.3	1.2	1.2	1	1.3	1.1	0	1.6	0.7	1
Death*†‡	7.7	0.5	0	0	0	7.7	2.9	2.9	5.0	3.1	0	7.2	2.8	2.3
Ever cardiac event														
Syncope*†‡	42	31	55	28	32	49	36	34	39	39	29	45	26	38
Aborted cardiac arrest*	4.6	7.5	16	7.5	11	6.9	6.2	6.7	6.1	8.4	7.1	7.8	4.3	7
Death*†‡§	18	3.3	0	2.2	4.5	17	11	6.7	14	5.7	7.1	16	8.5	7.8

Values are n, %, or mean ± SD. Percentages ≥10 are rounded to a whole number. The 858 subjects in this table include 60 subjects from the Rochester-based registry who died suddenly at a young age, were from families with known *KCNH2* mutation, and were assumed to have the family mutation. *p < 0.01 for the comparison of characteristics among the 4 sources of subjects. †p < 0.01 for the comparison of characteristics among the 4 locations of the mutations. ‡p < 0.01 for the comparison of characteristics among the 3 major topologies of mutations. §p < 0.01 for the comparison of characteristics among the 3 major types of mutations. ‖First cardiac event was syncope, aborted cardiac arrest, or sudden death, whichever occurred first.

ECG = electrocardiogram; QTc = corrected QT; QTp = QT peak interval.

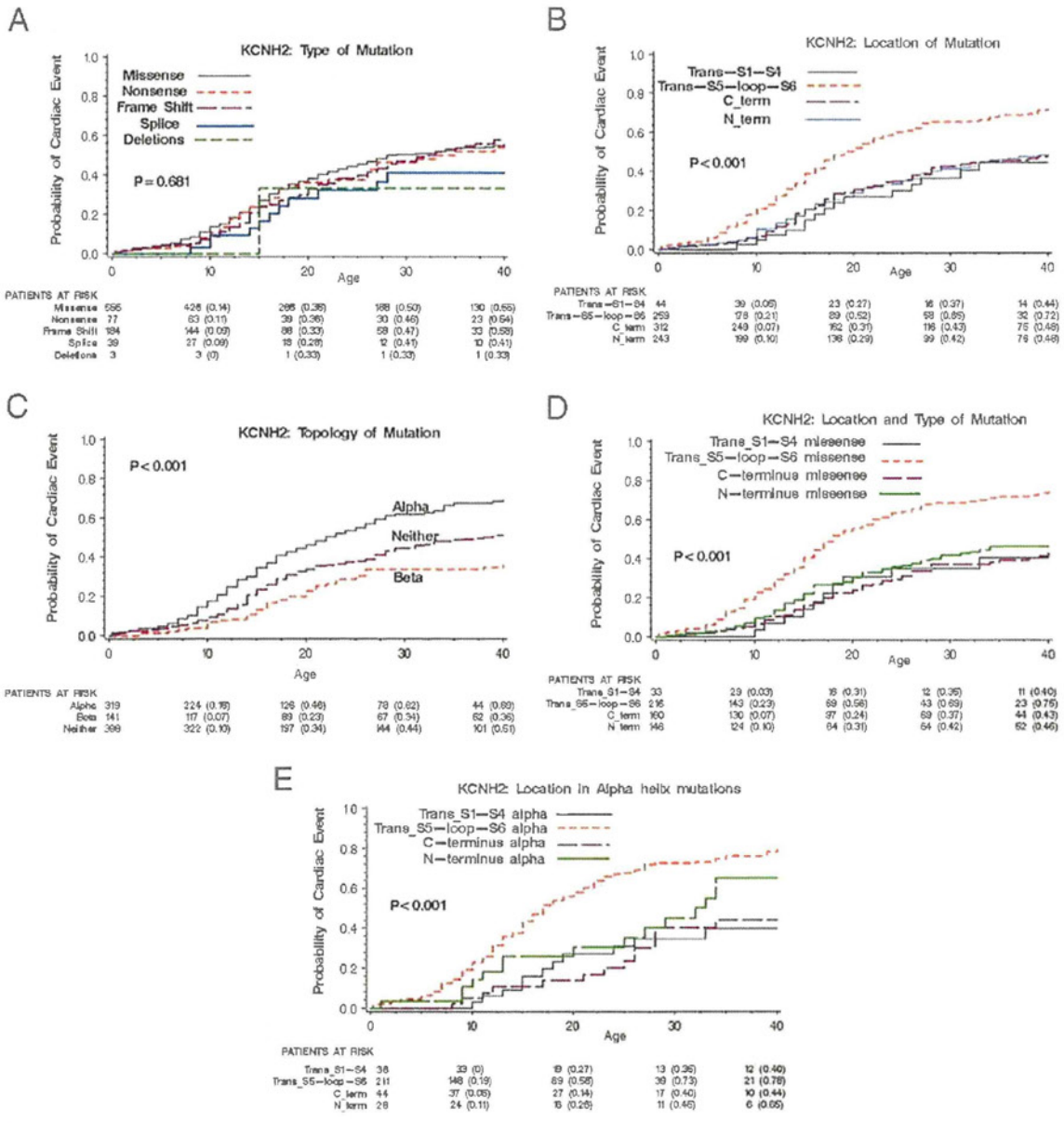

Figure 2 **Kaplan-Meier Estimates of Cumulative Probability of First Cardiac Event**

Kaplan-Meier estimate of the cumulative probability of a first cardiac event by **(A)** type, **(B)** location, and **(C)** topology of the mutation for all 858 subjects with genetically confirmed *KCNH2* mutations. Kaplan-Meier estimate of the cumulative probability of a first cardiac event for **(D)** missense mutations within different locations and for **(E)** mutations located in the α-helical domains within different locations. The **numbers in parentheses** reflect the cumulative event rate at that point in time.

ms). History of prior syncope was a significant risk for lethal cardiac events (HR: 3.42). Time-dependent β-blocker use showed a reduction in the risk of lethal cardiac events by 26%, but this did not reach statistical significance.

Combination of location and type of mutation on clinical outcome. The inter-relation between location, type, and topology of mutation is presented in Table 3. Among 52 mutations within the transmembrane pore region, 46 mutations (88.5%) were missense mutations, and only 6 mutations (11.5%) were frameshift/nonsense mutations. Conversely, frameshift/nonsense mutations were more frequently located in the C-terminus region (31 of 50 mutations, 62.0%); 17 mutations (34.0%) were missense mutation, and the remaining 2 mutations (4.0%) were from any other type (splice mutation). Because transmembrane pore mutations are more risky than

Table 2 Cox Regression With Multiple Predictor Variables Including Location of Mutations for First Cardiac Event and Aborted Cardiac Arrest/Long QT Syndrome Death

Variable	Hazard Ratio	95% Confidence Interval	p Value
First cardiac event			
Enrolling sites with the Netherlands as reference			
Rochester	1.38	1.03–1.85	0.030
Japan	1.10	0.74–1.63	0.644
Mayo	0.94	0.60–1.47	0.786
Sex/age			
Males/females age <13 yrs	1.54	1.08–2.20	0.018
Females/males age 13 to 40 yrs	3.29	2.36–4.60	<0.001
QTc categories with QTc <460 ms as reference, ms			
QTc ≥530	3.33	2.30–4.83	<0.001
QTc 500 to 530	2.09	1.45–3.02	<0.001
QTc 460 to 499	1.56	1.11–2.21	0.011
QTc missing*	3.33	2.25–4.92	<0.001
C-terminus region as reference			
Transmembrane S5-loop-S6 region	1.56	1.14–2.14	0.006
Transmembrane S1–S4 region	0.61	0.34–1.09	0.095
N-terminus region	1.22	0.92–1.62	0.173
Subunit topology with β-sheets as reference			
α-helical domains	1.74	1.15–2.63	0.009
Uncategorized locations	1.33	0.93–1.90	0.115
Time-dependent β-blocker use	0.37	0.22–0.63	<0.001
Aborted cardiac arrest/long QT syndrome death			
Enrolling sites with the Netherlands as reference			
Rochester	1.38	0.79–2.41	0.257
Japan	1.87	0.89–3.94	0.099
Mayo	1.37	0.53–3.52	0.520
Sex/age			
Males/females age <13 yrs	1.55	0.52–4.64	0.433
Females/males age 13 to 40 yrs	2.38	1.50–3.79	<0.001
QTc categories with QTc <500 ms as reference, ms			
QTc ≥530	4.97	2.72–9.07	<0.001
QTc 500–530	2.57	1.39–4.76	0.003
QTc missing*	25.58	14.46–45.26	<0.001
History of prior syncope	3.42	2.25–5.20	<0.001
C-terminus region as reference			
Transmembrane S5-loop-S6 region	1.00	0.56–1.80	0.993
Transmembrane S1–S4 region	1.00	0.39–2.61	0.994
N-terminus region	1.33	0.80–2.22	0.271
Subunit topology with β-sheets as reference			
α-helical domains	1.47	0.72–2.98	0.269
Uncategorized locations	1.12	0.60–2.10	0.658
Time-dependent β-blocker use	0.74	0.42–1.31	0.300

The Cox analysis involved 858 subjects with 259 transmembrane S5-loop-S6, 44 transmembrane S1 to S4, 243 N-terminus, and 312 C-terminus mutations. *The corrected QT (QTc) missing category involves 110 subjects, 69 of whom died suddenly at a young age without a prior electrocardiogram.

mutations in the transmembrane nonpore, C-terminus, or N-terminus regions (Fig. 2B), and there is no significant difference in event rates among the types of mutation (Fig. 2A), nonmissense mutations, mainly frameshift/nonsense mutations in the C-terminus region, may be an independent risk. Therefore, we further investigated the risk associated with a combination of location and type of mutation.

The cumulative probabilities of first cardiac event for missense mutations within different locations are presented in Figure 2D, and those for mutations located in the α-helical domains within different locations are presented in Figure 2E. Significantly higher event rates were found in subjects with missense mutations (Fig. 2D) and mutations in the α-helical domains (Fig. 2E) located in transmembrane pore region than in those located in any other regions. Among 261 patients with frameshift/nonsense mutations, the event rates were not different by location of mutations (data not shown).

Table 3 Mutation Group by Location, Type, and Topology

Type	Location: Transmembrane (S1–S4)	Transmembrane (S5-Loop-S6)	N-Terminus	C-Terminus	Total
Missense					
Topology					
α-helices	31 (12)	170 (63)	25 (9)	44 (16)	270 (100)
β-sheet	—	—	56 (43)	74 (57)	130 (100)
Neither	2 (1)	46 (30)	65 (42)	42 (27)	155 (100)
Total	33 (6)	216 (39)	146 (26)	160 (29)	555 (100)
Frameshift/nonsense					
Topology					
α-helices	5 (10)	41 (84)	3 (6)	—	49 (100)
β-sheet	—	—	4 (100)	—	4 (100)
Neither	6 (3)	2 (1)	56 (27)	144 (69)	208 (100)
Total	11 (4)	43 (17)	63 (24)	144 (55)	261 (100)
Others					
Topology					
α-helices	—	—	—	—	—
β-sheet	—	—	—	7 (100)	7 (100)
Neither	—	—	34 (97)	1 (3)	35 (100)
Total	—	—	34 (81)	8 (19)	42 (100)
Total					
Topology					
α-helices	36 (11)	211 (66)	28 (9)	44 (14)	319 (100)
β-sheet	—	—	60 (43)	81 (57)	141 (100)
Neither	8 (2)	48 (12)	155 (39)	187 (47)	398 (100)
Total	44 (5)	259 (30)	243 (28)	312 (36)	858 (100)

Values are n (%)

The Cox regression analysis by a combination of location and type of mutations for first cardiac events and that for aborted cardiac arrest or LQTS-related sudden cardiac death is presented in Table 4. For patients with missense mutations, the transmembrane pore (S5-loop-S6) and N-terminus regions were a significantly greater risk than the C-terminus region (HR: 2.87 and 1.86, respectively), but the transmembrane nonpore (S1 to S4) region was not (HR: 1.19). However, for nonmissense mutations, these other regions were no longer riskier than the C-terminus (HR: 1.13, 0.77, and 0.46, respectively). Likewise, subjects with nonmissense mutations, mainly frameshift/nonsense mutations, were at significantly higher risk than were subjects with missense mutations in the C-terminus region (HR: 2.00), but that was not the case in other regions. This mutation location-type interaction was significant ($p = 0.008$). However, a mutation topology-type analysis did not reveal a significant interaction ($p = 0.11$). Also, the mutation location-type interaction was not seen for the aborted cardiac arrest or LQTS-related sudden cardiac death end point reported in Table 4.

Among subjects with missense mutations, the transmembrane pore region was a significantly higher risk than were the transmembrane nonpore, N-terminus, or C-terminus regions (not shown HR: 2.42, 1.54, and 2.87, respectively). For subjects with nonmissense mutations, the transmembrane pore region was not a significantly higher risk than were the transmembrane nonpore, N-terminus, or C-terminus regions (HR: 2.47, 1.48, and 1.13, respectively). It is interesting to note that, while not significant, the effect sizes (HRs) of the pore risk stay relatively constant across mutation type except in the case of the C-terminus, further evidence of the location-type interaction.

Discussion

The major findings of the present study from 858 type 2 LQTS subjects with genetically confirmed *KCNH2* mutations derived from 4 LQTS registries are that: 1) there is a significant mutation type-location interaction; specifically, that the relative risk between C-terminus and the regions is different for missense versus nonmissense locations; 2) patients with missense mutations in the transmembrane pore region have significantly higher cardiac event rates than do patients with missense mutations in the N-terminus, transmembrane nonpore, or C-terminus regions; 3) patients with nonmissense mutations were at significantly higher risk than were patients with missense mutations in the C-terminus region; and 4) patients with mutations located in putative α-helical domains have significantly higher cardiac event rates than do patients with mutations in either the β-sheet domains or other uncategorized locations, and these higher event rates are independent of traditional clinical risk factors and of β-blocker therapy. Our data indicate that

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Table 4 Cox Regression With Multiple Predictor Variables Including Location and Type of Mutations and Their Interaction for First Cardiac Event and for Aborted Cardiac Arrest/Long QT Syndrome Death

	Hazard Ratio	95% Confidence Interval	p Value
First cardiac event			
1. Mutation location by type			
Transmembrane pore (S5-loop-S6)/C-terminus (reference)			
Missense mutations	2.87	2.03–4.07	<0.001
Nonmissense mutations	1.13	0.65–1.95	0.663
N-terminus/C-terminus (reference)			
Missense mutations	1.86	1.25–2.78	0.002
Nonmissense mutations	0.77	0.50–1.17	0.220
Transmembrane nonpore (S1–S4)/C-terminus (reference)			
Missense mutations	1.19	0.59–2.39	0.632
Nonmissense mutations	0.46	0.18–1.17	0.103
2. Mutation type by location			
Nonmissense/missense (reference)			
C-terminus location	2.00	1.33–3.00	0.001
Other locations (N-terminus, S1–S4, S5-loop-S6)			NS
3. Interaction between mutation location and type*	—	—	0.008
Aborted cardiac arrest/long QT syndrome death			
1. Mutation location by type			
Transmembrane pore (S5-loop-S6)/C-terminus (reference)			
Missense mutations	1.65	0.93–2.91	0.085
Nonmissense mutations	0.57	0.19–1.74	0.324
N-terminus/C-terminus (reference)			
Missense mutations	1.95	0.99–3.83	0.052
Nonmissense mutations	0.80	0.37–1.73	0.575
Transmembrane nonpore (S1–S4)/C-terminus (reference)			
Missense mutations	1.94	0.61–6.20	0.264
Nonmissense mutations	0.55	0.12–2.56	0.446
2. Mutation type by location			
Nonmissense/missense (reference)			
C-terminus location	1.75	0.85–3.61	0.131
Other locations (N-terminus, S1–S4, S5-loop-S6)			NS
3. Interaction between mutation location and type*	—	—	0.208

Note: Items 1, 2, and 3 identify risk factors from the same model. The model adjusted for enrolling site, sex, age, corrected QT, and time-dependent β-blockers as in Table 3. When family members who experienced long QT syndrome-related sudden cardiac death without being genotyped were omitted from the analyses, the hazard ratios, confidence intervals, and p values for location and type of mutation were similar to those values in the above table, but the significance for the interaction between mutation location and type was reduced from $p = 0.008$ to $p = 0.09$. *The interaction between mutation location and type measures whether the cardiac event risk for a location relative to the C-terminus varies significantly between missense and nonmissense mutations. The hazard ratio and confidence intervals are not provided for this interaction because the p value is an overall significance level for 3 interaction terms.

NS = not significant.

risk stratification and specific management or treatment by distinct location, coding type, and topology of the channel mutation in addition to classical risk factors such as QTc, sex, or history of prior syncope may be possible in patients with type 2 LQTS, although further studies are definitely required.

A total of 12 forms of congenital LQTS have been reported (2,4,17–20), and clinical studies for genotype-phenotype correlations have been rigorously investigated in the type 1, 2, and 3 LQTS, which constitute >90% of genotyped patients with LQTS (2,21–25). More recently, mutation-location specific differences in the severity of clinical phenotype have been investigated in each genotype (9,11,12,26,27). As to the type 1 LQTS, a large cohort of 600 patients with *KCNQ1* mutations has demonstrated that location and biophysical function of mutations were independent risk factors influencing the clinical course (11). However, the distribution of mutation location as well as the frequency of mutation type are reported to be different in each of 3 major genotypes (9,11,12,26,27). More recently, putative secondary structures of α-helices or β-sheet are reported to have an important role on the channel function in the type 2 LQTS (8). Therefore, a larger cohort of patients having a spectrum of *KCNH2* mutations is required to test the hypothesis that the location, coding type, and topology of mutations would influence the clinical course in the type 2 LQTS.

In contrast to our cohort of 600 type 1 LQTS patients in which the majority of mutations were found in the transmem-

brane region (66.2%) (11), in the present study, mutations in *KCNH2* were more evenly distributed in the N-terminus, the transmembrane domain, and the C-terminus. As to the type of mutation, missense mutations dominated (80.5%), and only 13% of the mutations were frameshift/nonsense mutations in our type 1 LQTS cohort (11). In contrast, missense mutations accounted for 61.7%, and frameshift/nonsense mutations were more frequently observed (35.8%) in this type 2 LQTS cohort. Interestingly, most of the mutations located in the transmembrane pore region were missense mutations (46 of 52, 88.5%) in the present study, a finding concordant with the previous type 2 LQTS cohort by Moss et al. (9) (13 of 14, 92.9%). This indicated that the severe phenotype in patients with mutations located in the transmembrane pore region was probably because missense mutations that are expected to cause dominant negative effects were predominant in this region. However, our type 2 LQTS patients with missense mutations located in the N-terminus, transmembrane nonpore, and C-terminus regions were at significantly less risk than were patients with missense mutations in the transmembrane pore region. These data suggest that location of mutation, in other words, the transmembrane pore region, itself was an independent risk in type 2 LQTS patients with *KCNH2* missense mutation.

Conversely, patients with nonmissense mutations, mainly frameshift/nonsense mutations, were at significantly higher risk than were patients with missense mutations in the C-terminus region, and the event rates in patients with frameshift/nonsense mutations were not different among the transmembrane pore, transmembrane nonpore, N-terminus, and C-terminus regions. Gong et al. (28) recently suggested that most frameshift/nonsense mutations would cause nonsense-mediated decay (NMD), thereby producing less messenger ribonucleic acid from the mutant alleles (28). This potentially would allow for the wild type allele to express more normal channels. Therefore, it is expected that the type 2 LQTS patients with frameshift/nonsense mutation causing NMD would have a mild phenotype. In contrast, the type 2 LQTS patients with frameshift/nonsense mutation without NMD would be expected to have a more severe phenotype because a truncated protein would be produced. Thus, the fact that some frameshift/nonsense mutations show NMD, whereas the other mutations do not, makes the clinical phenotype in the type 2 LQTS patients with frameshift/nonsense mutations more complicated, although this scenario is only a speculation. The present study confirmed the higher risk in patients with nonmissense mutations than in patients with missense mutations in the C-terminus region, suggesting that more careful follow-up is required for type 2 LQTS patients with nonmissense mutations in the C-terminus region.

With regard to the topology of mutation, Anderson et al. (8) recently reported that missense mutations located in a highly ordered structure as α-helices or β-sheet correlated with a class 2 trafficking-deficient phenotype in the type 2 LQTS patients. In the present cohort, mutations located in the α-helical domains were associated with a significantly higher risk compared with mutations in either the β-sheet domains or other uncategorized locations. It is possible that missense mutations in α-helices, where secondary protein structure is thought to be highly ordered, lead to altered secondary and tertiary channel protein structure and abnormal trafficking. This new analysis considering putative secondary structures of mutated channel would be a useful approach in stratifying the risk of cardiac events in patients with LQTS.

β-blockers have long been the first choice of therapy for patients with congenital LQTS (2,29). However, it has been shown in previous studies that the protection that β-blockers provide against cardiac events for type 2 and 3 LQTS patients is somewhat less effective than for type 1 LQTS patients (23,30). A variety of experimental data also support the genotype-specific efficacy of β-blockers for type 1 LQTS (31). In the present study, time-dependent β-blocker use significantly reduced the risk of first cardiac events by 63% ($p < 0.001$), confirming the efficacy of β-blockers as a first line of therapy in patients with type 2 LQTS as well as suggesting more prophylactic use of β-blockers, especially for high-risk patients with type 2 LQTS. However, β-blocker use was associated with less protection (29%) in the prevention of lethal cardiac events compared to first cardiac events (mostly syncope), indicating that additional treatment such as potassium supplement or an implantable cardioverter-defibrillator implantation may be considered in high-risk patients with type 2 LQTS. The patients who have aborted cardiac arrest/sudden death may have a more malignant pathophysiology that is more resistant to β-blockers than are syncopal episodes. We purposely included "ECG missing" in the Cox model so that the β-blocker effect is actually adjusted for subjects with "ECG missing" who probably did not receive β-blockers.

Study limitations. We did not evaluate the risk associated with distinct type of biophysical ion-channel dysfunction (dominant-negative or haplotype insufficient), because only a small percentage of the mutations present within our patient population have been studied extensively in identical cellular expression experiments. There were 60 patients who were not genotyped, and they had an increased risk for events mainly because their fatal events occurred at a young age before they were genotyped. When these patients were excluded from the analysis, the pattern of risk in the missense and nonmissense subgroups remains similar to that of the total population, but the significance of the effect is attenuated because of the reduced number of events.

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Key Words: arrhythmia ■ electrocardiography ■ long QT syndrome ■ genetics ■ syncope.

APPENDIX

For a table on the *KCNH2* mutations by location, coding type, and topology of mutation, and contributing registry, please see the online version of this article.

Long-Term Prognosis of Probands With Brugada-Pattern ST-Elevation in Leads V_1–V_3

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Background—The prognosis of patients with saddleback or noncoved type (non–type 1) ST-elevation in Brugada syndrome is unknown. The purpose of this study was to clarify the long-term prognosis of probands with non–type 1 ECG and those with coved (type 1) Brugada-pattern ECG.

Methods and Results—A total of 330 (123 symptomatic, 207 asymptomatic) probands with a coved or saddleback ST-elevation ≥1 mm in leads V_1–V_3 were divided into 2 ECG groups—type 1 (245 probands) and non–type 1 (85 probands)—and were prospectively followed for 48.7±15.0 months. The absence of type 1 ECG was confirmed by drug provocation test and multiple recordings. The ratio of individuals with a family history of sudden cardiac death (14%) was lower than previous studies. Clinical profiles and outcomes were not notably different between the 2 groups (annual arrhythmic event rate of probands with ventricular fibrillation; type 1: 10.2%, non–type 1: 10.6%, probands with syncope; type 1: 0.6%, non–type 1: 1.2%, and asymptomatic probands; type 1: 0.5%, non–type 1: 0%). Family history of sudden cardiac death at age <45 years and coexistence of inferolateral early repolarization with Brugada-pattern ECG were independent predictors of fatal arrhythmic events (hazard ratio, 3.28; 95% confidence interval, 1.42 to 7.60; $P=0.005$; hazard ratio, 2.66; 95% confidence interval, 1.06 to 6.71; $P=0.03$, respectively, by multivariate analysis), although spontaneous type 1 ECG and ventricular fibrillation inducibility by electrophysiological study were not reliable parameters.

Conclusions—The long-term prognosis of probands in non–type 1 group was similar to that of type 1 group. Family history of sudden cardiac death and the presence of early repolarization were predictors of poor outcome in this study, which included only probands with Brugada-pattern ST-elevation. (***Circ Arrhythmia Electrophysiol.* 2009;2:495-503.**)

Key Words: death, sudden ■ prognosis ■ follow-up studies ■ electrocardiography ■ Brugada syndrome

Brugada syndrome is a hereditary arrhythmogenic disease characterized by ST-elevation in the right precordial lead of standard ECGs and an increased risk of sudden cardiac death (SCD).[1] The prognosis for this condition and the management approaches have been reported in several multicenter studies of patients with the coved type 1 ECG. However, no prospective data have been reported in patients with saddleback type or noncoved Brugada-pattern ST-elevation before, because they were excluded from previous

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studies as atypical Brugada patients showing a benign clinical course. Besides, the data from previous studies are all conflicting with regard to the prognosis of the typical Bru-

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gada syndrome.[2-5] This may be caused by cohort studies that included a significant number of family members other than probands, in which the prognosis of pedigree members can be affected by the disease severity of probands. Furthermore, a selection bias can be present if the data are analyzed retrospectively. Therefore, we aimed to investigate the long-term prognosis of probands with noncoved type ST-elevation in leads V_1–V_3, prospectively, and compared it with that of probands with the type 1 ST-elevation.

Methods

Patient Population

A total of 330 individuals with spontaneous ST-elevation were registered consecutively in this study, namely, "a multicenter study for risk stratification and management in patients with Brugada syndrome." The study was conducted at 26 institutions across Japan beginning in July 2001. These individuals were prospectively followed up for more than 12 months to the end of March 2007. Subjects were enrolled in this study if they met the following inclusion criteria: (1) proband, (2) J-point (QRS-ST junction) amplitude of ≥0.1 mV (1 mm) with either coved or saddle back type ST-segment elevation in at least 2 of the 3 precordial leads (V_1–V_3) on resting standard 12-lead ECG, (3) normal findings on physical examination, and (4) no abnormality in either right or left ventricular morphology and/or function demonstrated by chest radiography and echocardiography. Patients with vasospastic angina and those with vasovagal syncope were excluded from this study. Patients were not administered antiarrhythmic drugs and did not have electrolyte abnormalities at the time of baseline ECG recording and other examinations.

Classification of Groups

We divided the 330 patients with Brugada-pattern ECG into 3 groups according to their symptoms: The ventricular fibrillation (VF) group consisted of 56 probands with aborted sudden death and/or documented VF, the syncope group consisted of 67 probands with syncope without documented arrhythmias that was not typical for vasovagal syncope, and the asymptomatic group consisted of 207 asymptomatic individuals whose ECGs were mainly detected by individual annual medical checkup or health screening in their place of employment.

We also divided these patients into 2 groups according to ECG morphology: The type 1 group consisted of 245 probands with a spontaneous type 1 ECG or those who developed type 1 ECG with a drug provocation test. The non–type 1 group consisted of the remaining 85 probands who never showed type 1 ST-elevation even with the drug provocation test (Figure 1) and during the follow-up on standard 12-lead ECGs.

Clinical Data, ECG, and Electrophysiological Testing

Clinical data including age at the enrollment, sex, family history of SCD, and the presence of atrial fibrillation were collected for all patients. The standard ECGs were recorded more than 5 times during the follow-up period in all patients. ECG recording on higher intercostals spaces (third and/or second) in leads V_1–V_3[6] was encouraged in patients who had cardiac events during the follow-up period.

A type 1 ECG was defined as a prominent coved ST-segment elevation displaying J-point wave amplitude or ST-segment elevation ≥2 mm or 0.2 mV.[7,8] ECG patterns with a prominent coved ST-elevation ≥2 mm followed by a positive or flat T wave were also included in type 1 group (Figure 2A through C). A non–type 1 ECG was defined as one of the following: type 2 ECG,[7] type 3 ECG,[7] and ECG displaying coved or saddleback ST-elevation with J-wave amplitude ≥1 mm and <2 mm (Figures 1 and 2D through 2G).

The presence of early repolarization in the inferolateral leads[9] was evaluated by baseline 12-lead ECGs at the time of enrollment to elucidate ECG findings associated with Brugada syndrome. Early repolarization was defined as an elevation of the J point in at least 2 leads. The amplitude of the J wave or J-point elevation had to be at least 1 mm above the baseline level, either as QRS slurring or notching in the inferior lead (II, III, and aVF), lateral (I, aVL, and V_4–V_6) lead, or both.[9]

ECGs were evaluated by 3 independent investigators (S.K., N.A., and W.S.) who were unaware of the patients' other clinical information. The ECG type or morphology was established by the evaluation in which at least 2 of the 3 observers were in agreement.

Sodium channel blocker pilsicainide (1 mg/kg body weight at a rate of 5 to 10 mg/min), disopyramide (1.5 mg/kg, 10 mg/min), flecainide (2 mg/kg, 10 mg/min), or procainamide (10 mg/kg, 100 mg/min) was administered intravenously in 270 (82%) patients (233, 15, 14, and 8, respectively) to test the conversion to typical coved ST-elevation.[8,10,11]

Baseline electrophysiological studies (EPS) were performed in 232 (70%) patients. A maximum of 3 ventricular extrastimuli were delivered from 2 right ventricular (RV) sites (RV apex and RV outflow tract) unless VF or polymorphic ventricular tachycardia (VT) (lasting ≥10 beats) that terminated spontaneously within 30 seconds, causing syncope, or requiring intervention to be terminated was elicited at a previous step. Premature beats were started in late diastole; coupling intervals were then reduced in 10-ms decrements until refractoriness was reached. Stimulation was performed at twice the diastolic threshold. Patients with inducible ventricular arrhythmias lasting less than 10 beats were classified as noninducible. The indices including age, sex distribution, a family history of SCD at

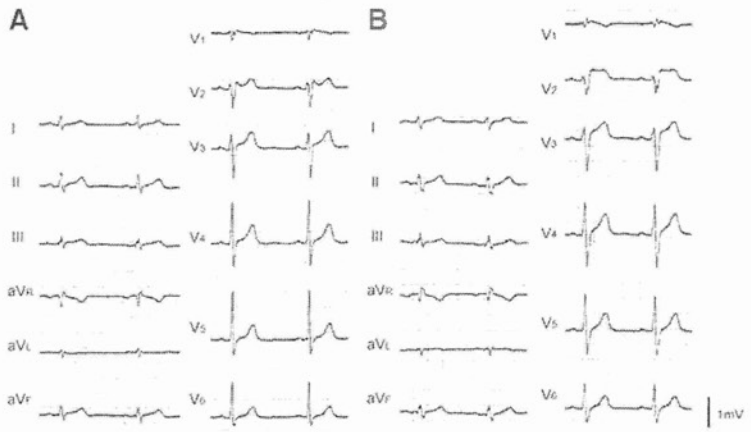

Figure 1. Presentation of 12-lead ECGs of a patient with non–type 1 ST-elevation. A, Baseline 12-lead ECG; B, 12-lead ECG after provocation by intravenous administration of 50 mg pilsicainide in the same patient. Saddleback-type ST-elevation in leads V_1 and V_2 was enhanced after pilsicainide but was not changed to type 1 ST-elevation. This 46-year-old male patient with a history of syncope but with no family history of SCD had inducible VF by electrophysiological study. He had spontaneous VF 11 months after enrollment.

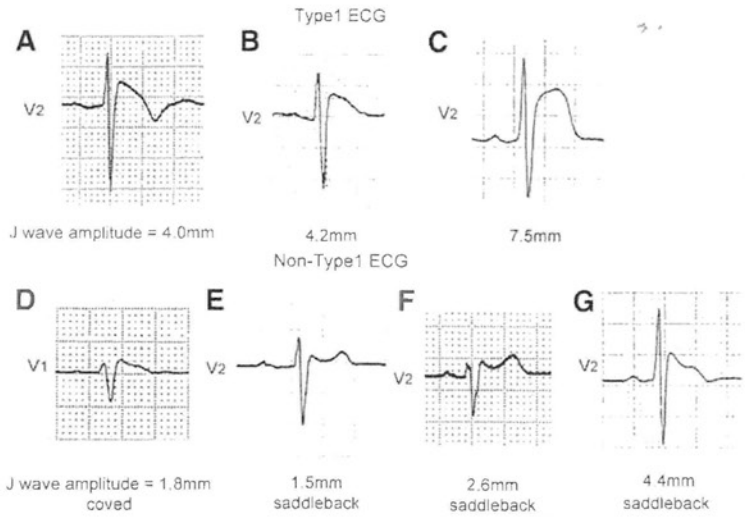

Figure 2. Presentation of type 1 and non–type 1 ECG. Coved-type ST-elevation with a J-wave amplitude ≥2 mm followed by a negative T wave (A) or a positive/flat T wave (B), and a coved ST-elevation followed by a smaller J wave than T wave (C) were defined as type 1 ECG. Coved (D) or saddleback-type ST-elevation (E) with a J-wave amplitude <2 mm, a saddleback ST-elevation with a J-wave amplitude ≥2 mm (F), and a saddleback ST-elevation displaying bigger J wave than T wave (G) were defined as non–type 1 ECG.

less than 45 years of age, and VF/polymorphic VT inducibility were compared with those reported in previously published studies[2,3,5] (Table 1). In addition to these parameters, the presence of atrial fibrillation, cardiac events at night, and inferolateral early repolarization were compared between type 1 and non–type 1 groups.

Patient treatment was based on clinical judgment of the participating hospital. Twenty-eight (8%) probands received antiarrhythmic drugs (quinidine sulfate ≤400 mg, bepridil ≤200 mg, disopyramide ≤300 mg, aprindine ≤30 mg, and amiodarone ≤200 mg/d) for prevention of atrial fibrillation or VF. Calcium antagonists were administered in 18 (5%) probands for hypertension. Quinidine and bepridil were administered only after a documentation of VF during follow-up. Among the 330 patients, 125 (38%) received an implantable cardioverter-defibrillator (ICD). During follow-up, patients were considered to have an arrhythmic event if sudden death occurred or VF was documented.

Statistical Analysis

Data are presented as mean±standard deviation. The Fisher exact test or the χ^2 test was used for categorical variables. One-way ANOVA was used for comparisons of continuous variables among the different groups. Survival curves were plotted by the Kaplan-Meier method and analyzed by the log-rank test. Cox proportional hazards models were used to analyze factors associated with the time to the first arrhythmic event during follow-up in all probands as well as in type 1, non–type 1, VF, and non-VF (syncope and asymptomatic) groups. Variables were included in the multivariate analysis with the use of a forward stepwise procedure with a criteria of $P<0.05$ for inclusion and $P>0.15$ for removal from the model. A probability value of $P<0.05$ was considered statistically significant.

This study was performed under the ethical code approved by the Health, Labor, and Welfare Ministry of Japan. Written informed consent was obtained from all individuals.

Results

Clinical Profiles of All Probands

The mean age of the 330 probands was 51.4±14.8 years (median, 53 years; range, 4 to 86 years). The majority (315; 95%) of probands were male. A low percentage (14%) of patients had a family history of SCD occurring before the age of 45 years. The induction rate of VF/polymorphic VT by EPS was higher (77/109: 72%, $P<0.005$) in symptomatic than asymptomatic probands (61/123: 50%) (Table 1).

Comparison of Clinical Characteristics Between Type 1 and Non–Type 1 Groups

Type 1 ECG was found in 245 probands (VF group: 45, 18%; syncope group: 46, 19%; and asymptomatic group: 154, 63%). Of these 245 probands, 173 (71%) showed type 1 ECG spontaneously and the remaining 72 (29%) showed characteristic type 1 morphology after class Ic or Ia antiarrhythmic drug administration. In 85 probands of the non–type 1 group (VF group: 11, 13%; syncope group: 21, 25%; and asymptomatic group: 53, 62%), non–type 1 ECG remained during the drug provocation test (type 2: 61,

Table 1. Comparison of Patient Characteristics Among 3 Large Registries

	Brugada et al[2]		Eckardt et al[5]		Kamakura et al	
	Sympt	Asympt	Sympt	Asympt	Sympt (VF, S)	Asympt
No.	144	190	89	123	123 (56, 67)	207
Age, y	41±16*	40±16	46±14	44±14	50.4±16.6	51.9±13.6
Men, %	83	71	76	68	96	95
FH of SCD, %	34	72	21	33	19 (25, 13)	11
VF/VT inducibility, %	73	33	63	39	71 (65, 75)	50

Values in parentheses are for the patients with aborted sudden death and an episode of syncope. Sympt indicates symptomatic; Asympt, asymptomatic; S, syncope; FH of SCD, prevalence of patients with a family history of sudden cardiac death at <45 years old; and VF/VT inducibility, induction rate of VF or polymorphic ventricular tachycardia by EPS.

*Age of patients with VF.

Table 2. Comparison of Clinical Profiles Between Probands With Type 1 ECG and Those With Non–Type 1 ECG

	Type 1 (n=245)			Non-Type 1 (n=85)			
	VF	Syncope	Asympt	VF	Syncope	Asympt	*P* Value
No.	45	46	154	11	21	53	0.33
Age, y	48.2±17.8	52.5±15.6	52.3±13.1	48.0±18.1	51.9±15.8	50.7±15.2	0.99
Men, n (%)	44 (98)	44 (96)	146 (95)	11 (100)	19 (90)	51 (96)	0.90
FH of SCD, n (%)	11 (24)	8 (17)	17 (11)	3 (27)	1 (5)	5 (9)	0.06
Event at night, n (%)	37/45 (82)	15/45 (33)		5/9 (56)	7/18 (39)		0.06
Inferolateral ER, n (%)	8 (18)	3 (7)	15 (10)	2 (18)	1 (5)	4 (8)	0.85
Prevalence of AF, n (%)	19 (42)	7 (15)	21 (14)	4 (36)	3 (14)	8 (15)	0.87
VF/VT inducibility, n (%)	27/41 (66)	31/40 (78)	52/91 (57)	7/11 (64)	12/17 (71)	9/32 (28)	0.04

n (%) indicates the number and the ratio of patients with each parameter; event at night, event developed at night (8 PM to 8 AM); inferolateral ER, inferolateral early repolarization; AF, atrial fibrillation; VF/VT inducibility, induction rate of VF or polymorphic ventricular tachycardia by EPS.

72%; coved with J-point amplitude <2 mm: 24, 28%) and the follow-up period. Most of the clinical parameters except for VF/VT inducibility, namely, age, sex distribution, the prevalence of atrial fibrillation, the presence of a family history of SCD, cardiac events at night (8 PM to 8 AM), and early repolarization, were of similar occurrence between type 1 and non–type 1 groups (Table 2). Only 8% (7/85) of probands in the non–type 1 group and 11% (26/245) of those in the type 1 group were associated with early repolarization in the inferolateral leads.

Follow-Up and Predictors of Outcome

The mean follow-up period for the entire study population was 48.7±14.9 months. Follow-up time was similar among VF (51.9±15.0 months), syncope (48.5±14.0 months), and asymptomatic (47.7±15.0 months) groups and between type 1 (48.6±15.2 months) and non–type 1 (48.9±14.2 months) groups. Twenty-four patients had fatal arrhythmic events during follow-up. The frequency of events in the type 1 group—15 of 45 (33%) in patients with VF, 1 of 46 (2%) in syncope patients, and 3 of 154 (2%) in asymptomatic patients— was similar to that in the non–type 1 group (4/11: 36%, 1/21: 5%, and 0/53: 0%, respectively, $P=0.22$; Figure 3). In 5 patients who had events in the non–type 1 group, 2 had shown a type 1 ST-elevation only in the higher (second or third) intercostal spaces—1 in a follow-up ECG and 1 after drug provocation test. The observed frequency of arrhythmic events was significantly highly in patients with early repolarization in the inferolateral leads (7/33; 21% versus 17/297; 6%, $P<0.005$), although there was no difference in risk between the 2 groups (type 1: 6/26; 23%, non–type 1: 1/7; 14%, $P=0.67$). One asymptomatic patient with type 1 ECG died suddenly 3 months after enrollment. Six patients died of nonarrhythmic causes; 3 died of cancer, 1 because of rupture of abdominal aortic aneurysm, 1 because of pneumonia, and cause of death for 1 patient was unknown. Seven percent of all patients who entered the study dropped out, the most frequent reason for drop-out was inability of follow-up due to patient's change of address.

Figure 4 shows the Kaplan–Meier analysis of arrhythmic events in probands with type 1 and non–type 1 ECG. Probands in the VF group had significantly worse prognosis than those in the syncope and asymptomatic groups. The

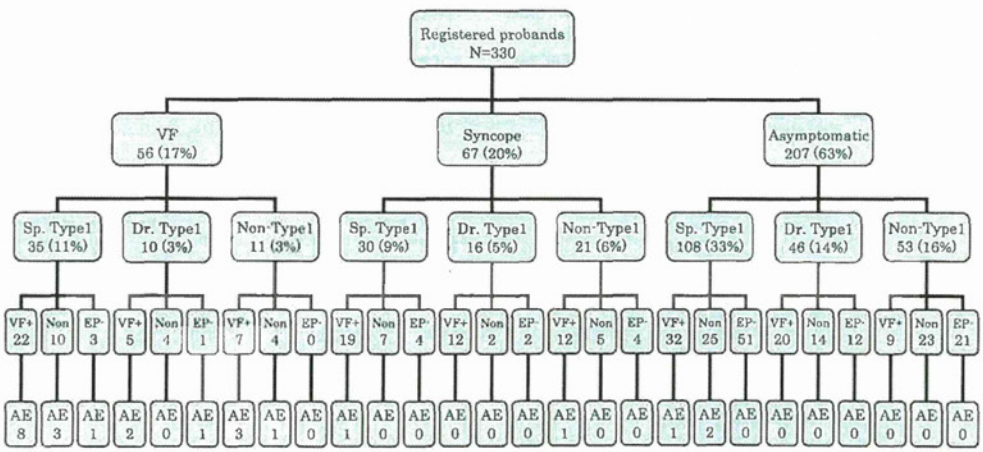

Figure 3. Flow chart of proband groups categorized according to symptom, ECG morphology, and VF/VT inducibility by electrophysiological study. Sp. Type 1 indicates spontaneous type 1 group; Dr. Type 1, drug-induced type 1 group; VF+, a group with inducible VF/VT; Non, a group with noninducible VF/VT; EP−, a group in which electrophysiological study was not performed; AE, fatal arrhythmic event during follow-up. The number indicates the number of probands in each category.

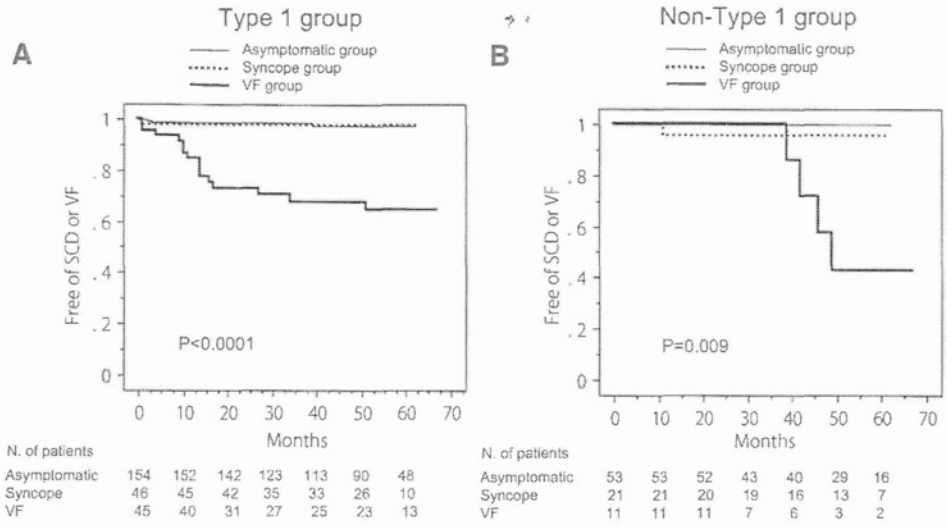

Figure 4. Kaplan–Meier analysis of arrhythmic events (SCD or documented VF) during follow-up depending on the clinical presentation (VF/aborted sudden death, syncope, or asymptomatic) in probands with type 1 ECG (A) and those with non–type 1 ECG (B). $P<0.0001$ represents overall comparison, and $P=0.009$ is for comparison between the VF group and the syncope group. There was no statistically significant difference ($P=0.95$) in the events-free survival of VF probands comparing type 1 and non–type 1 groups.

annual rate of arrhythmic events in probands with type 1 ECG was 10.2% in the VF group, 0.6% in the syncope group, and 0.5% in the asymptomatic group (Figure 4A). The cumulative rate of arrhythmic events in probands with non–type 1 ECG was similar to those with type 1 ECG. The annual arrhythmic event rate was 10.6%, 1.2%, and 0%, respectively (Figure 4B).

By univariate analysis, a family history of SCD was a predictor for arrhythmic events in the type 1 group (hazard ratio [HR], 5.1; 95% CI, 2.0 to 12.8; $P=0.0004$) and the non–type 1 group (HR, 12.3; 95% CI, 2.0 to 74.8; $P=0.006$). Coexistence of posterolateral early repolarization with precordial Brugada-pattern ECG was another predictor in the type 1 group (HR, 4.2; 95% CI, 1.6 to 11.2; $P=0.003$); however, other parameters were not reliable. Figure 5 shows the Kaplan–Meier curves of arrhythmic events in the type 1 group during follow-up, depending on the presence of a family history of SCD (Figure 5A), inferolateral early repolarization (Figure 5B), a spontaneous type 1 ST-elevation (Figure 5C), and inducibility of ventricular arrhythmias by EPS (Figure 5D). Multivariate analysis in all probands identified that the former 2 parameters were independent risk factors for arrhythmic events (a family history of SCD: HR, 3.28; 95% CI, 1.42 to 7.60; $P=0.005$; early repolarization: HR, 2.66; 95% CI, 1.06 to 6.71; $P=0.03$, Table 3) as well as a family history of SCD in analysis of probands without VF (syncope and asymptomatic groups) (HR, 12.5; 95% CI, 2.0 to 75.0; $P=0.005$).

Discussion

Main Findings

We present one of the largest series of consecutive patients with Brugada-pattern ECG. Importantly, in the present study only probands were included. Also, this study has the longest follow-up ever reported. The main finding is that probands who have a non–type 1 ECG, even after challenged with a sodium channel blocker, do not necessarily have a better prognosis than patients with spontaneous or drug-induced type 1 ECG. Patients presenting with aborted cardiac arrest had a grim prognosis and those presenting with syncope or no symptoms had an excellent prognosis irrespective of their ECG pattern (that is, type 1 versus non–type 1). Also, a family history of sudden death at age <45 years and coexistence of early repolarization in the inferolateral leads were predictors of poor outcome. In contrast, VF/VT inducibility during EPS was not a predictor of outcome.

Comparison With Previous Studies

In this study, the follow-up time was uniform among the 3 groups. The mean follow-up time for the asymptomatic individuals was the longest (47.7±15.0 months) compared with the studies by Brugada et al[2] (27±29 months), Priori et al[3] (34±44 months), and Eckardt et al[5] (33.7±52.2 months). The percentage of female patients (5%) and patients with a family history of SCD (14%) was significantly smaller than 2 of these previous reports (5% versus 24% to 28%[2,3,5]; $P<0.001$, and 14% versus 28% to 54%[2,3,5]; $P<0.001$), although the percentage (14%) of a family history of SCD was similar to that of probands (20%) that Priori et al[3] had reported. The values observed in the present study may reflect the true profile of the probands of Brugada syndrome in contrast to previous studies in which a significant number of family members were also enrolled.

Prognosis of Probands Presenting With Syncope and Without Symptoms

The prognosis of probands in the syncope and asymptomatic groups was very good, and the annual rate of arrhythmic events was ≤1.2%. In the syncope group, this rate is far less than reported in previous studies,[2–5] although the

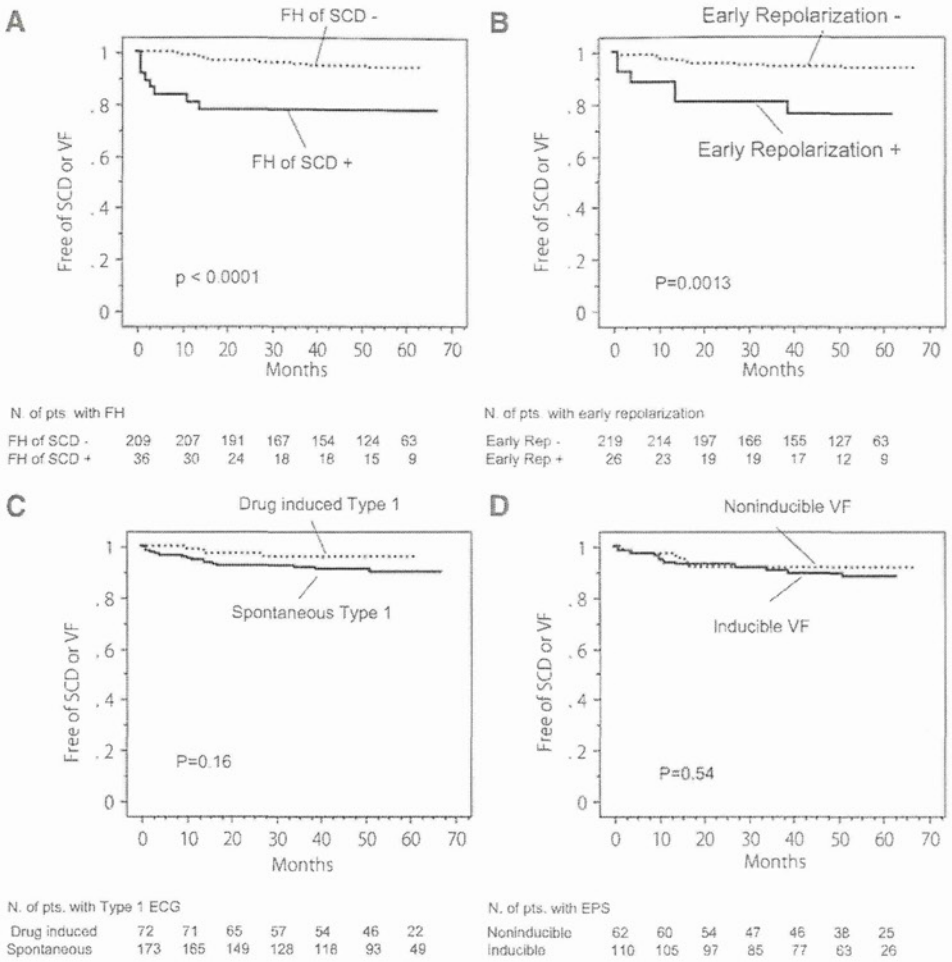

Figure 5. Kaplan–Meier analysis of fatal arrhythmic events during follow-up depending on a family history (FH) of SCD (FH of SCD− versus FH of SCD +) (A), inferolateral early repolarization (early repolarization− versus early repolarization+) (B), a spontaneous type 1 ST-elevation (drug-induced type 1 versus spontaneous type 1) (C), and inducibility of ventricular arrhythmias by EPS (noninducible VF versus inducible VF) (D).

rate in the asymptomatic group is similar to that in the Eckardt registry[5] and the rate of around 10% for the VF group is comparable to the rate reported in the Brugada registries.[2,8] The reason that the patients in the syncope group showed excellent prognosis is not entirely clear but may be related to the method of registry. Poor prognosis in prior studies is possibly related to the retrospective design of the studies consisting of probands and family members,[2,3,5] in which only severe syncope directly linked to VF tends to be categorized later as a syncope, despite difficulty to determine the cause of syncope at the onset. Even so, we cannot exclude the possibility that some patients with vasovagal syncope were inevitably included in the syncope group because not a few patients have undefined syncope and >30% of Brugada patients are reported to have both vasovagal syncope and the syncope due to ventricular arrhythmia.[12] Another reason for the good prognosis is the difference of genetic background. Brugada syndrome is known to be common in Asian people, which possibly relates to the higher prevalence of polymorphism of haplotype B, associated with the cardiac sodium channel.[13,14] The average prognosis of Asian patients with Brugada syndrome may be better than that of the white population, because individuals without a critical genetic defect are easily detected as a Brugada patient in a routine medical checkup. Further genetic studies are required to clarify the racial difference of outcome. Nevertheless, the patients in this study with an aborted sudden death showed worse prognosis than European people in the study by Eckardt et al[5] and had a similar outcome to those who underwent ICD implantation.[15]

Prognosis of Probands With Non–Type 1 ECG

The outcome of probands with non–type 1 ECG was similar to those with type 1 ECG and the rate of arrhythmic events in the VF group was considerably higher. Some of these patients had shown a coved (type 1) ST-elevation only in the higher (second or third) intercostal spaces during the drug provocation test or follow-up. Miyamoto et al[16] reported that men with a spontaneous type 1 ECG