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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.

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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-

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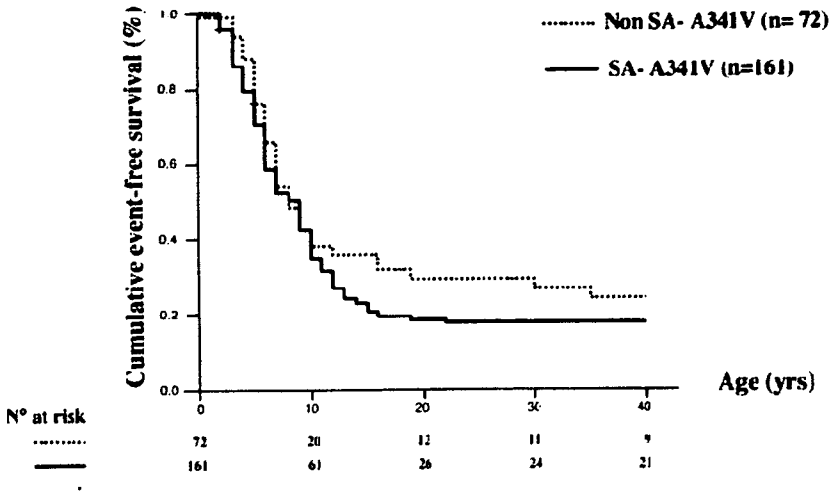

Figure 1. Unadjusted Kaplan-Meier estimate of the cumulative event-free survival in the non-SA and SA-A341V groups. Any cardiac event (syncope, CA, or LQTS-related SCD), whichever occurred first, was considered from birth through 40 years of age and before β-blocker therapy. Numbers at risk are indicated.

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

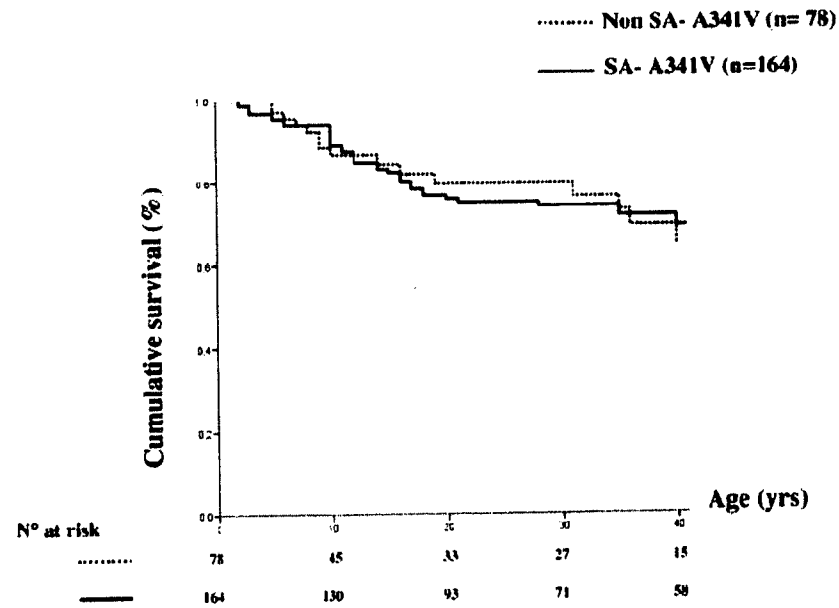

Figure 2. Unadjusted Kaplan-Meier estimate of the cumulative survival in the non-SA and SA-A341V groups. Only life-threatening cardiac events (CA or LQTS-related SCD) were considered from birth through 40 years of age and before β-blocker therapy. The SA group comprises 164 patients because of the lack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

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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

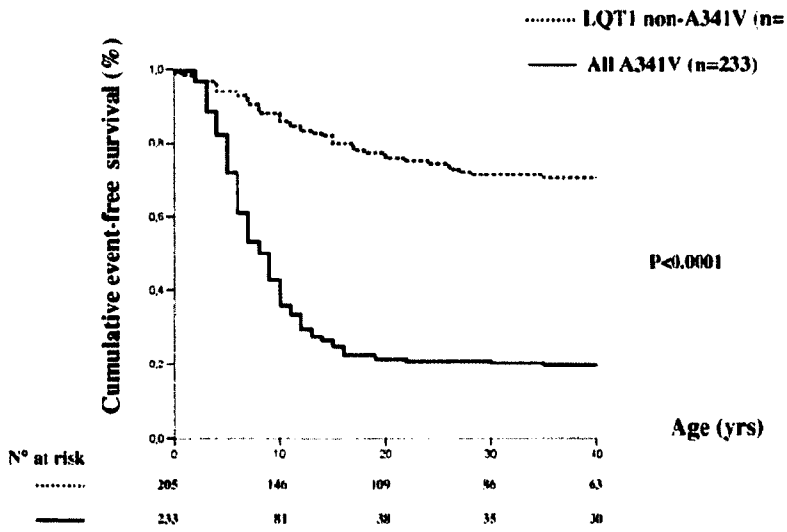

Figure 3. Unadjusted Kaplan-Meier estimate of the cumulative event-free survival (any first event) in the whole (non-SA+SA) A341V population plotted vs the LQT1 non-A341V group. Any cardiac event, whichever occurred first, was considered from birth through 40 years of age and before β-blocker therapy.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

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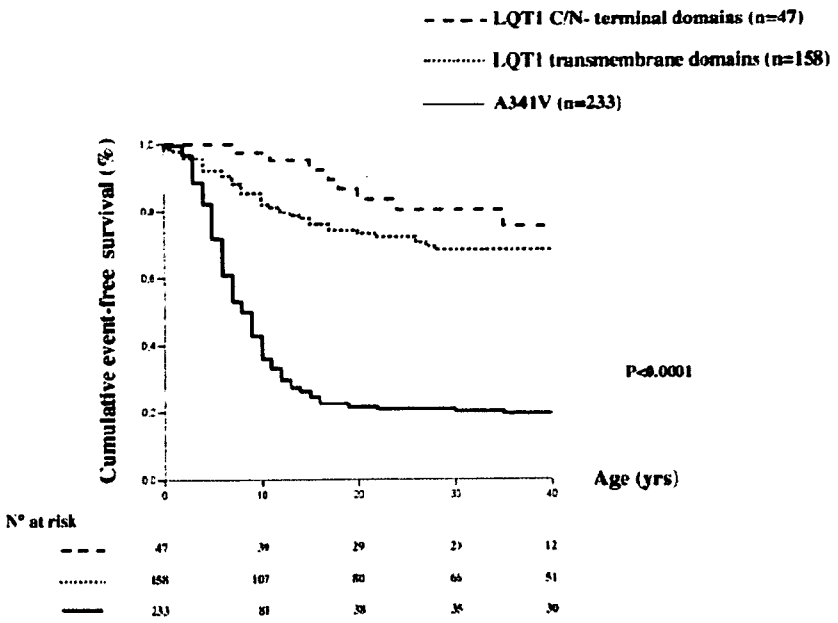

Figure 4. Unadjusted Kaplan-Meier estimate of the cumulative event-free survival (any first event) in the entire A341V and in the LQT1 non-A341V groups according to specific mutation site. Any cardiac event, whichever occurred first, was considered from birth through 40 years of age and before β-blocker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

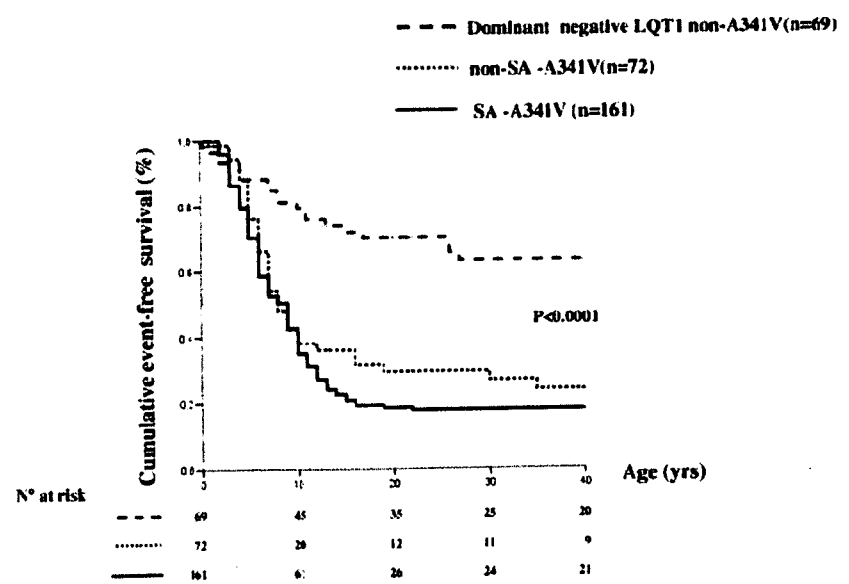

Figure 5. Unadjusted Kaplan-Meier estimate of the cumulative event-free survival (any first event) only in patients with LQT1 secondary to dominant-negative *KCNQ1* mutations; the 2 A341V groups are plotted vs the LQT1 non-A341V group. Any cardiac event, whichever occurred first, was considered from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

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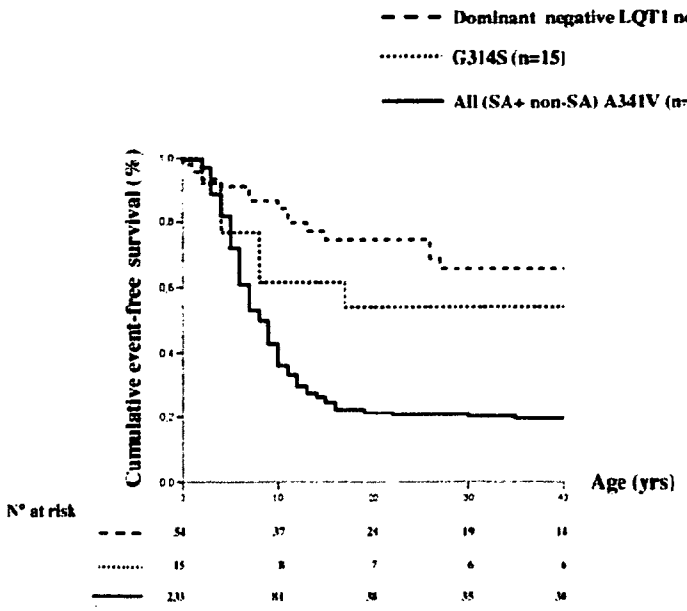

Figure 6. Unadjusted Kaplan-Meier estimate of the cumulative event-free survival (any first event) among patients with a mild (A341V) and strong (G314S) dominant-negative mutation. The entire A341V population (mild dominant-negative effect) is compared with a G314S population (strong dominant-negative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

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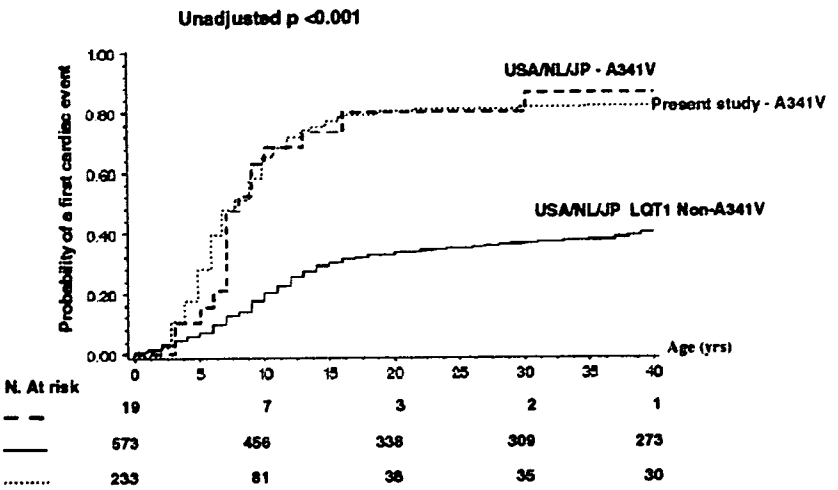

Figure 7. Unadjusted Kaplan-Meier estimate of the cumulative probability of a cardiac event (syncope, CA, or LQTS-related SCD, whichever occurred first) in the LQT1 population from the US-Netherlands-Japan collaborative study.[8] Carriers of A341V mutation are compared with all the other LQT1 non-A341V 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

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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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Circ J 2008; **72:** 88–93

Electrophysiologic Study-Guided Amiodarone for Sustained Ventricular Tachyarrhythmias Associated With Structural Heart Diseases

Takeshi Aiba, MD; Kenichiro Yamagata, MD; Wataru Shimizu, MD; Atsushi Taguchi, MD; Kazuhiro Satomi, MD; Takashi Noda, MD; Hideo Okamura, MD; Kazuhiro Suyama, MD; Naohiko Aihara, MD; Shiro Kamakura, MD; Takashi Kurita, MD

Background Although an electrophysiologic study (EPS) and Holter-monitoring are often helpful in evaluating the efficacy of antiarrhythmic drugs in patients with ventricular tachyarrhythmias (ventricular tachycardia/fibrillation (VT/VF)), the efficacy of EPS- or Holter-guided oral amiodarone therapy in Japanese patients is still unclear.

Methods and Results EPS was performed 1 month after starting amiodarone, and Holter-monitoring was recorded before and 1 month after amiodarone in 188 patients with sustained VT/VF because of structural heart diseases. In spite of the judgment of EPS (n=89) or Holter (n=75), all patients continued amiodarone. Patients were followed up to 3 years and the primary endpoint was VT/VF recurrence and secondary endpoint was death by all cause. Kaplan-Meier estimated the risk of VT/VF recurrence was significantly smaller with EPS-guided amiodarone ($p<0.01$) but not with Holter-guided amiodarone. Multivariate Cox hazard analysis revealed that EPS-guided amiodarone was an independent factor suppressing the recurrence of VT/VF ($p<0.05$, 95% confidence interval=0.15 to 0.96). In the subgroup analysis, EPS-guided amiodarone was effective in patients with relatively well-preserved left ventricular ejection fraction (LVEF ≥0.30) but not in patients with lower LVEF (LVEF <0.30).

Conclusion EPS-guided amiodarone was useful for preventing recurrence of VT/VF in patients with a relatively well-preserved LVEF, but not always beneficial in patients with a lower LVEF. (*Circ J* 2008; **72:** 88–93)

Key Words: Amiodarone; Electrophysiologic study; Holter monitoring; Ventricular fibrillation; Ventricular tachycardia

Ventricular tachyarrhythmias are critically important in the prognosis of patients with structural heart diseases. Amiodarone is one of the most advocated antiarrhythmic drugs available for preventing the recurrence of ventricular tachycardia (VT), ventricular fibrillation (VF), thereby reducing total mortality in patients with VT/VF![1–4] Although an electrophysiologic study (EPS) and Holter monitoring are performed to evaluate the efficacy of antiarrhythmic drugs, oral amiodarone is often prescribed empirically because the antiarrhythmic effect as guided by EPS or Holter monitoring is controversial![5–9] Recent clinical trials have shown that an implantable cardioverter defibrillator (ICD) is clearly superior to amiodarone for preventing sudden arrhythmic death![10–13] but cannot prevent the recurrence of VT/VF and sometimes gives an intolerable shock to the patient. Therefore, it is still important to clarify how to optimize amiodarone and/or ICD therapies in patients with sustained VT/VF and structural heart diseases![14,15]

On the other hand, patients with a lower left ventricular ejection fraction (LVEF) derive significantly more benefit from ICD therapy than those with a better preserved LVEF![16–18] Moreover, a recent randomized study reported that amiodarone had no favorable effect on survival but that ICD therapy reduced overall mortality by 23% in patients with congestive heart failure and LVEF <35%![19] Therefore, a cardiac function parameter, such as LVEF, is important in determining the prognosis of patients with sustained VT/VF. The goals of this study were: (1) to evaluate whether or not EPS- or Holter monitoring-guided therapy can stratify the risk of VT/VF recurrence after oral amiodarone, and (2) to investigate the extent to which specific patients subgroups benefit differently from amiodarone therapy.

Methods

Patients

This study retrospectively analyzed 400 patients who had been treated with oral amiodarone at the National Cardiovascular Center (Suita, Japan) from 1990 to 2004. All patients had a history of symptomatic sustained VT/VF because of structural heart diseases. We excluded 212 patients with a LVEF >0.50, treated with amiodarone for non-sustained VT or atrial arrhythmias, or who had undergone radiofrequency catheter ablation or surgical procedures for VT/VF. Therefore, this study registered 188 patients (mean age, 60±12 years; 149 males), which included 77 patients with previous myocardial infarction, 61 with dilated cardio-

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Table 1 Patients' Characteristics

	Overall	EPS-post amiodarone		EPS (−)
		VT (−)	VT (+)	
n	188	27	62	99
Age (years)	60±12	59±9	58±11	61±14
Sex (male, %)	149 (79)	22 (81)	48 (77)	80 (81)
LVEF (%)	30±12	30±11	34±11	28±12*
Structural heart disease (%)				
Old MI	77 (41)	14 (52)	24 (39)	39 (39)
DCM	61 (33)	7 (26)	18 (29)	36 (36)
HCM	8 (4)	0 (0)	4 (6)	4 (4)
ARVC	16 (9)	1 (4)	6 (10)	9 (9)
Sarcoidosis	11 (6)	2 (7)	6 (10)	3 (3)
Valvular heart disease	12 (6)	1 (4)	3 (5)	8 (8)
Other	3 (1)	2 (7)	1 (1)	0 (0)
Presenting arrhythmias (%)				
Sustained VT	150 (80)	23 (85)	56 (91)	70 (71)
VF	26 (14)	4 (15)	2 (3)	21 (21)
Sustained VT and VF	12 (6)	0 (0)	4 (6)	8 (8)
VF total (%)	38 (20)	4 (15)	6 (9)	29 (29)*
ICD (%)	81 (43)	7 (26)	40 (65)**	34 (34)
Medication (%)				
ACEI	103 (55)	18 (67)	30 (48)	55 (55)
β-blocker	102 (55)	12 (44)	34 (55)	56 (57)
Digitalis	60 (32)	9 (33)	13 (21)	38 (38)

EPS, electrophysiological study; VT (−), VT or VF is not induced by EPS; VT (+), VT or VF is induced by EPS; LVEF, left ventricular ejection fraction; MI, myocardial infarction; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; VT, ventricular tachycardia; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator; ACEI, angiotensin converting enzyme inhibitors.
**p<0.05 vs EPS-VT (+) group; ** p<0.05 vs EPS-VT (−) and EPS (−) group.*

myopathy, 16 with arrhythmogenic right ventricular cardiomyopathy, 8 with hypertrophic cardiomyopathy, and 11 with cardiac sarcoidosis. The mean LVEF of these patients was 30±12% (Table 1).

EPS and Holter Monitoring

After written informed consent was given, EPS was performed in the fasting, nonsedated state before (pre) and 1 month after (post) starting oral amiodarone. All other antiarrhythmic drugs were discontinued. The protocols of the programmed ventricular stimuli have been described in detail previously[4] In brief, up to 3 premature extrastimuli after an 8-beat stimulus drive were delivered from the right ventricular apex and outflow tract using a quadripolar-electrode catheter, and incremental ventricular stimulation with a constant cycle length. The stimulation protocol was terminated when sustained VT or VF was induced. The efficacy of amiodarone was determined by whether or not a run of VT >15 beats could be induced during EPS after starting amiodarone. Thus, we were not concerned about the inducibility of VT/VF before amiodarone therapy.

Twenty-four hours Holter electrocardiogram was recorded on magnetic tape before drug therapy, and repeated 1 month after administration of amiodarone and analyzed by computer to determine the frequency of arrhythmias. The efficacy of amiodarone by Holter recording was assessed by the criteria of the ESVEM trial[20] First, patients with total premature ventricular contractions (PVC) less than 300/day before amiodarone were excluded from the Holter judgment as an "undetermined" group. Therefore, patients with total PVCs more than 300/day before amiodarone and 70% reduction in the PVC count, 80% reduction in the PVC pair count, 90% reduction in the VT count, and absence of any runs of VT >15 beats were defined as "effective", but patients with no response to these criteria were defined as "ineffective".

Table 2 EPS and Holter Judgments

	EPS post amiodarone		EPS-post (−)
	VT (−)	VT (+)	
EPS pre amiodarone			
VT (−) (n=2)	1	0	1
VT (+) (n=37)	3	16	18
EPS-pre (−) (n=149)	23	46	80
Total (n=188)	27	62	99
Holter criteria			
Effective (n=37)	7	9	21
Ineffective (n=38)	7	10	21
Undetermined (n=113)	13	43	57

EPS-pre (−), EPS before amiodarone is not performed; EPS-post (−), EPS after amiodarone is not performed. Other abbreviations see in Table 1.

Follow-up After Amiodarone

Whether or not they had EPS or Holter monitoring, all patients continued treatment with amiodarone, the loading dose of which was 300 or 400 mg/day for 2 weeks followed by a maintenance dose of 150 or 200 mg/day. However, amiodarone was discontinued when critical side effects developed or it was obviously ineffective. All patients were followed up to 36 months and the primary endpoint was recurrence of VT/VF and the secondary endpoint was death from all causes. Implantation of an ICD was recommended in patients who were considered to be "ineffective" with amiodarone or had a history of syncope because of VT/VF.

Statistical Analysis

The continuous variables are expressed as mean±SD and were compared by an unpaired t-test when appropriate. Cumulative event rates were calculated by the Kaplan-

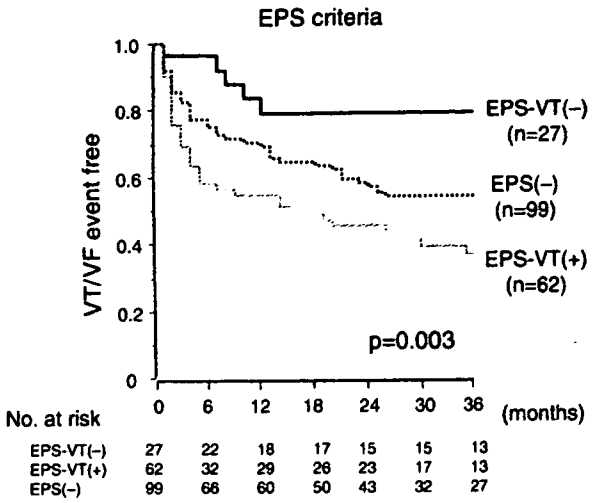

Fig 1. Cumulative risk of recurrent ventricular tachycardia/fibrillation (VT/VF) after amiodarone therapy in patients judged by electrophysiological study (EPS) criteria. EPS stratified the risk of VT/VF recurrence after amiodarone. EPS-VT(+), patients with inducible VT/VF by EPS after amiodarone; EPS-VT(−), patients with no inducible VT/VF by EPS after amiodarone; EPS(−), patients without EPS after amiodarone.

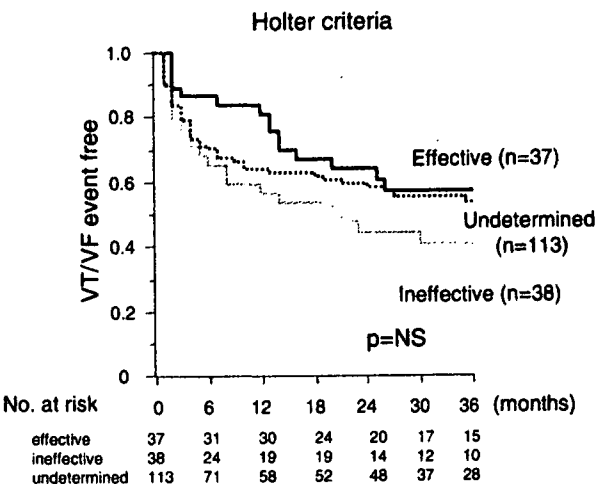

Fig 2. Cumulative risk of recurrent ventricular tachycardia/fibrillation (VT/VF) after amiodarone therapy in patients judged by Holter-monitoring criteria. Holter-monitoring could not stratify the risk of VT/VF recurrence after amiodarone. Effective, patients judged amiodarone effective by Holter; Ineffective, patients judged amiodarone ineffective by Holter; Undetermined, patients excluded from the Holter judgment.

Table 3 Cox Hazard Regression Analysis of VT/VF Recurrence

	OR (95%CI)	*p value*
Age	*1.26 (0.80–1.99)*	*0.33*
Sex (male)	*0.93 (0.54–1.60)*	*0.78*
Basal disease (Old MI)	*0.75 (0.45–1.25)*	*0.27*
LVEF <30%	*1.47 (0.94–2.32)*	*0.09*
EPS post amiodarone		
VT (+)	*1.71 (1.07–2.75)*	*0.02*
VT (−)	*0.34 (0.15–0.96)*	*0.04*
Holter judgment		
Ineffective	*1.47 (0.87–2.50)*	*0.15*
Effective	*0.77 (0.42–1.43)*	*0.42*

Abbreviations as in Tables 1,2.

Meier method. The significance of the difference between treatment groups was assessed with the log-rank test. Cox regression analysis was performed on the patients' baseline characteristics to investigate and compare the influence of different variables. Statistical significance was established as $p<0.05$.

Results

EPS and Holter Monitoring

Table 2 summarizes the results of EPS and Holter monitoring. The EPS before amiodarone was performed in 39 patients, and induced VT/VF in 37 (95%). The EPS after amiodarone was performed in 89 patients, and could not induce VT/VF in 27 (30%) patients (EPS-VT(−) group), but still induced VT/VF in 62 (70%) patients (EPS-VT(+) group). The remaining 99 patients taking amiodarone without judgment by EPS were defined as EPS(−) group.

Holter monitoring before and after amiodarone treatment was recorded in 139 patients; however, 64 patients had less PVCs than the Holter evaluation before amiodarone (300/day). Therefore, the remaining 75 patients were judged as amiodarone effective (n=37) or ineffective (n=38) by Holter monitoring.

Follow-up

During the follow-up period of 23±13 (range 1–36) months, 82 (44%) patients had recurrence of VT. Moreover, 28 (20%) patients died during follow-up because of heart failure (n=8), sudden unexpected death (n=8), pneumonia (n=2), and unknown causes (n=10). Side-effects of amiodarone occurred in 39 (21%) patients, including hypothyroidism (n=20), proarrhythmia (n=5), pneumonia (n=11), leukocytopenia (n=1), and liver dysfunction (n=2). Amiodarone was discontinued in 13 (8%) patients because of serious side-effects.

Fig 1 illustrates the follow-up results of patients under the EPS criteria. Among those assigned to the EPS-VT(+) group, the rate of VT/VF recurrence was 45.6% and 63.9% at 1 and 3 years, respectively. Conversely, in the EPS-VT(−) group it was 21.3% and 21.3%, and for the EPS(−) group 31.0% and 46.6% at 1 and 3 year's follow-up, respectively. Therefore, the VT/VF recurrence risk after amiodarone was significantly lower in the order of EPS-VT(−), EPS(−), and EPS-VT(+) groups ($p<0.003$). Table 1 summarizes the clinical characteristics in the 3 groups. Age, sex, basal disease, and medication, except antiarrhythmic drugs, did not differ between them, although LVEF was lower in the EPS(−) group than in the EPS-VT(+) group (28±12% vs 34±11%; $p=0.01$), and VF incidence before amiodarone was higher in the EPS(−) group than in the EPS-VT(+) group (29% vs 9%; $p=0.01$). ICDs were consequently implanted in many of the EPS-VT(+) group compared with the EPS-VT(−) and EPS(−) groups (65% vs 26%, 34%, respectively; $p<0.05$).

Fig 2 illustrates the follow-up results under the Holter criteria. In the patients assigned to the effective group, the VT/VF recurrence rates were 19.1% and 42.8% (1 and 3 years, respectively), whereas in the ineffective group, they were 43.4% and 59.6% (1 and 3 years, respectively) (p=NS). Therefore, Holter monitoring cannot stratify the risk of VT/VF recurrence after amiodarone.

Table 3 shows the results of multivariate Cox hazard regression analysis for the recurrence of VT/VF after amiodarone. The clinical factors, age, gender, basal disease

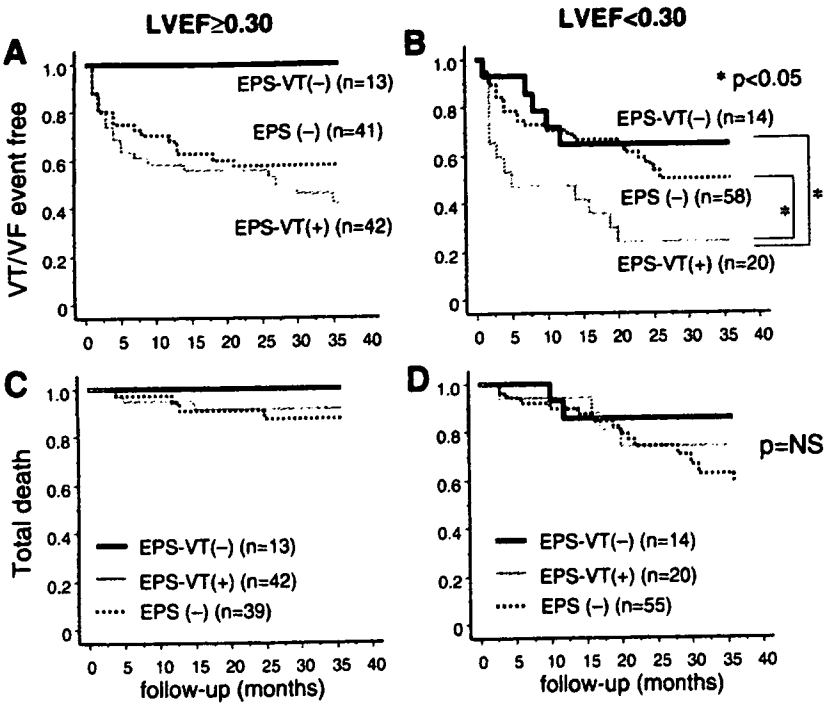

Fig 3. Cumulative risk of recurrent ventricular tachycardia/fibrillation (VT/VF) and total death after amiodarone therapy in different range of left ventricular ejection fraction (LVEF). Electrophysiological study (EPS) judgment could classify the risk of recurrent VT/VF and mortality after amiodarone in patients with LVEF ≥30% (A and C, respectively) but not in those with LVEF <30% (B and D, respectively). EPS-VT(+), patients with inducible VT/VF by EPS after amiodarone; EPS-VT(−), patients with no inducible VT/VF by EPS after amiodarone; EPS(−), patients without EPS after amiodarone.

(myocardial infarction) and Holter judgments were not related to VT/VF recurrence. The independent clinical factors for VT/VF recurrence were inducibility of VT/VF by EPS after amiodarone (odds ratio (OR) 1.71, 95% confidence interval (CI) 1.07–2.75, p=0.02). Lower LVEF (<30%) increased the risk of VT/VF recurrence but not significantly (OR 1.47, 95%CI 0.94–2.32, p=0.09).

EPS-Guided AmiodaroneTherapy and LVEF

Because of the possibility of lower LVEF increasing risk of VT/VF recurrence after amiodarone, we evaluated the EPS-guided amiodarone therapy in subgroups. Therefore, among the patients with relatively preserved LVEF (≥30%) (n=94), there was no VT/VF recurrence in the EPS-VT(−) group, whereas the rates of VT/VF recurrence for the EPS-VT(+) group were 42.1% and 58.5%, and those for the EPS(−) group were 32.3% and 42.7% (at 1 and 3 years, respectively) (Fig 3A). Thus, the risk of VT/VF recurrence was significantly lower in the EPS-VT(−) group compared with the EPS-VT(+) and EPS(−) groups. In contrast, among patients with lower LVEF (<30%) (n=91), the rates of VT/VF recurrence for the EPS-VT(+) group were significantly higher (58.6% and 76.4% at 1 and 3 years, respectively) than those for the EPS-VT(−) (35.7% and 35.7%) and EPS(−) group (30.0% and 51.0%, respectively) (p<0.05), whereas there was no significant difference in the recurrence rate between the EPS-VT(−) and the EPS(−) groups (Fig 3B). Furthermore, in patients with LVEF ≥30%, no patients died in the EPS-VT(−) group, whereas 3 of 42 patients in the EPS-VT(+) group and 4 of 39 patients in the EPS(−) group died during follow-up (Fig 3C). However, in patients with LVEF<30%, 2 of 14 patients in the EPS-VT(−), 4 of 20 patients in the EPS-VT(+) and 15 of 55 patients in the EPS(−) group died during follow-up (p=NS) (Fig 3D).

Table 4 shows the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for recurrence of VT/VF for Holter, EPS pre-post and EPS-post amiodarone therapy. The EPS judgment showed lower sensitivity but significantly higher specificity for recurrence of VT/VF, especially in patients with LVEF ≥30%.

Table 4 Predictors of Arrhythmic Events

	SNS	*SPC*	*PPV*	*NPV*	*ACC*
Holter-judgment (n=75)	55	59	58	56	57
EPS pre-post amiodarone (n=19)	69	100	100	38	74
EPS post amiodarone (n=89)	59	81	88	46	66
LVEF ≥30% (n=55)	52	100	100	35	62
LVEF <30% (n=34)	70	64	74	60	68

SNS, sensitivity; SPC, specificity; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy. Other abbreviations as in Table 1.

ICD and LVEF

We further analyzed the relationship between ICD and LVEF in patients treated with amiodarone. As shown in Fig 4A, the mortality of patients treated with amiodarone plus ICD did not differ between patients with higher (≥30%) and lower (<30%) LVEF. However, among patients with no ICD (amiodarone only) (Fig 4B), patients with LVEF ≥30% had a similar mortality to those with ICD, but patients with LVEF<30% had a significant worse mortality than the patients with higher LVEF (p=0.01). Therefore, patients with moderate to severe LV dysfunction achieved the greatest benefit from ICD therapy.

Discussions

Major Findings

This study retrospectively demonstrated the long-term effect of EPS-guided oral amiodarone therapy in Japanese patients with a history of life-threatening ventricular tachyarrhythmias because of structural heart diseases. EPS-guided amiodarone could reduce the recurrence of VT, especially in patients with relatively preserved (≥30%)

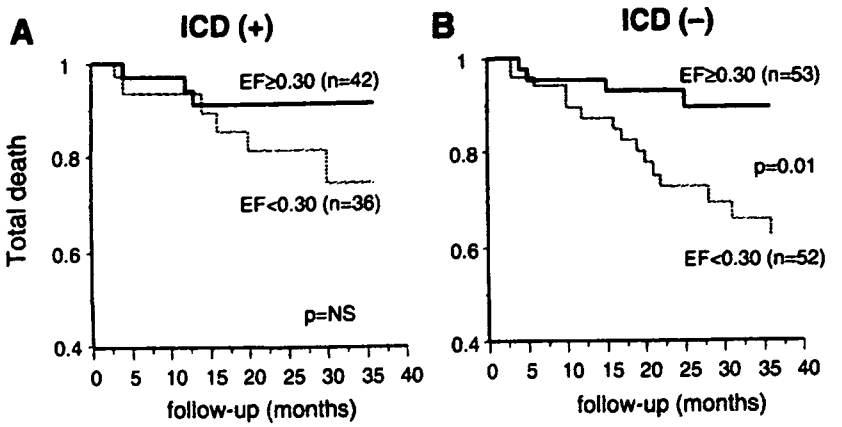

Fig 4. Cumulative risk of total death after amiodarone therapy in patients with implantable cardioverter defibrillator (ICD) (ICD(+)) and without ICD (ICD(−)). Higher (≥30%) and lower (<30%) left ventricular (LV) ejection fraction (EF) have similar risk for mortality in ICD(+) patients (A), but higher LVEF has significantly smaller risk of mortality than lower LVEF in ICD(−) patients (B).

LVEF, but was not always beneficial in patients with lower (<30%) LVEF. Therefore, amiodarone-treated patients with lower LVEF but not an implanted ICD remain at higher risk of sudden death.

EPS or Holter-Guided Amiodarone

Previous studies showed that EP-guided amiodarone therapy was useful for predicting recurrence of VT in patients at high risk for sudden cardiac death[5,7,8,21] McGovern et al reported that the sensitivity, specificity and accuracy of EP testing for recurrent VT was 58%, 91% and 67%, respectively[22] Those data coincide with our results showing that EPS-guided therapy has low sensitivity (59%), but high specificity (81%), for recurrence of VT after amiodarone. Moreover, this low sensitivity and high specificity of EP testing is more prominent in patients with LVEF ≥30% (52% and 100%, respectively) (Table 4). In this study, there were a small number of patients available for checking inducibility of VT before amiodarone, but the results of EPS-guided amiodarone are similar to those previously reported. Thus, it is not necessary to perform an EPS before starting amiodarone, and patients with LVEF ≥30% and non-inducible VT according to he EPS after amiodarone may remain free from recurrence of VT.

The ESVEM study showed that there was no significant difference between EPS and Holter monitoring in the probability of arrhythmic events occurring after antiarrhythmic drugs[20] However, that study mainly examined the effectiveness of class I antiarrhythmic drugs, not amiodarone. The efficacy of amiodarone by Holter monitoring is also controversial. Veltri et al reported that Holter monitoring could predict the long-term efficacy of amiodarone[6] Nasir et al showed that amiodarone strongly suppressed PVCs but this suppression did not predict clinical outcome[23] Our finding that a Holter judgment could not predict the recurrence of VT after amiodarone may have resulted because (1) there was a smaller number of patients undergoing Holter monitoring before and after amiodarone, (2) twenty-four hours recording cannot detect the number of PVCs or VT precisely, and (3) the apparent number of PVCs might have no relation to the trigger of critical VT or VF. In this study EPS was clearly superior to Holter monitoring for evaluating amiodarone efficacy, but EPS is invasive and is not always performed in all patients.

Amiodarone, ICD and LVEF

Zhu et al suggested that EPS testing during amiodarone therapy was useful for predicting arrhythmia recurrence in patients without new or worsening congestive heart failure[7] Other previous reports suggest that patients with lower LVEF (<35%) have a higher incidence of sudden cardiac death after amiodarone![6–18] Those results are consisted with our subgroup analysis showing that EPS-guided amiodarone therapy is beneficial for patients with LVEF ≥30% but not <30%. Therefore, it is suggested that ICD is indicated in patients with lower LVEF (≤30–35%) and a history of syncope or sustained VT/VF![7,24,25] On the other hand, patients with a relatively preserved LVEF (≥35%) do not always have better survival by ICD compared with amiodarone![6]

In this study, EPS-guided amiodarone responders with a LVEF ≥30% were considered to be lower risk for sudden cardiac death, whereas patients judged as amiodarone non-responders or with LVEF <30% remain high risk for sudden death. Although our data could not compare between amiodarone and ICD therapy in high-risk patients, amiodarone-treated patients with lower LVEF, but not an implanted ICD, remain at higher risk of sudden death (Fig 4B) and should be considered for additional ICD therapy, as previously reported[24]

In patients with congestive heart failure and LVEF <35%, a recent randomized study reported that amiodarone has no favorable effect on survival compared with placebo, but that ICD therapy reduced overall mortality by 23%![19] Although ICD reduces mortality compared with antiarrhythmic drugs, it is estimated that up to 50% of patients with an ICD ultimately need antiarrhythmic drug therapy to suppress frequent episodes of VT or supraventricular tachyarrhythmias, and that amiodarone is the most commonly used drug for this purpose in Japanese patients![5] Recently, Connolly et al reported that amiodarone plus β-blocker was effective for preventing ICD shocks, but increased the risk of drug-related adverse effect[26] Therefore, further studies in the Japanese patient population are necessary to evaluate whether or not amiodarone can improve a patient's clinical outcome by reducing the amount of ICD shocks![4]

Study Limitations

First, the study was not a prospective evaluation of EPS- or Holter-guided amiodarone treatment, so the direct efficacy of EPS or Holter-guided amiodarone in preventing the recurrence of VT/VF was not demonstrated; rather, an excellent prognosis for patients treated with EPS-guided amiodarone, especially in patients with a well-preserved LVEF, was demonstrated. Second, this study compared follow-up results between patients judged as amiodarone responder or non-responder by EPS, but did not compare

amiodarone responders with control patients. Therefore, it might overestimate the effectiveness of EPS-guided amiodarone therapy for suppression of recurrent VT/VF. Third, this study contained a small number of patients, and a multicenter trial with a large number of patients will be necessary to demonstrate the effect of amiodarone and ICD therapy more accurately in Japanese patients![14,15] Fourth, this study focused on the risk of recurrent (secondary) VT/VF, not on primary prevention. It is still controversial whether amiodarone and/or ICD are indicated in patients with nonsustained VT and lower LVEF for primary prevention of sudden death.

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