epilepsy imitators such as syncope due to arrhythmias by monitoring the electrocardiograms during the seizures. Computed tomography (CT) or magnetic resonance imaging (MRI) was performed in patients with epilepsy or syncope to determine the presence and extent of hypoxic ischemic encephalopathy, brain hemorrhages, and cerebral infarctions. For the 3 previously reported cases, the data concerning the neurological findings were obtained from their reports.

GENETIC ANALYSIS. The protocol for the genetic analysis was approved by the Institutional Ethics Committee and performed under its guidelines (M24-031-4). The genomic DNA was isolated from whole blood using a DNA analyzer (QIAGEN GmbH, Hilden, Germany) (19). Genetic screening for *KCNQ1*, *KCNH2*, and *SCN5A* (and if necessary *KCNE1*, *KCNE2*, and *KCNJ2*) mutations was performed by direct sequencing (ABI 3730 DNA Analyzer, Life Technologies, Carlsbad, California). The cDNA sequence numbering was based on the GenBank reference sequence.

STATISTICAL ANALYSIS. Statistical analysis was not performed to compare the clinical findings between perinatal LQTS and nonperinatal LQS, because of the small number population (n = 24) including 4 sibling pairs.

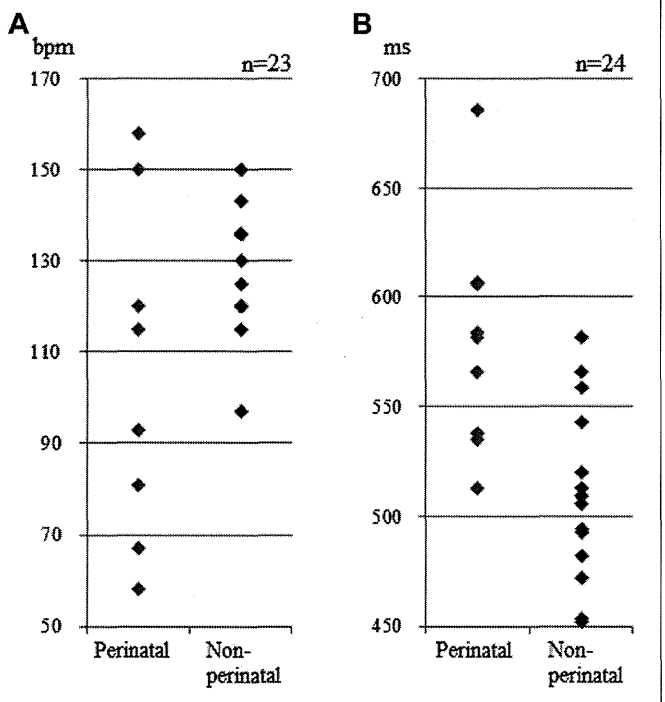
RESULTS

CLINICAL CHARACTERISTICS. The clinical characteristics are shown in **Table 1.** Patients #1 to #6 were perinatal LQTS patients from our institution, and 22 to 24 were previously reported perinatal LQTS patients with neurological seizures. Three of the 9 perinatal LQTS cases had TdP in utero as documented by magnetocardiography. One patient was delivered in our hospital because of maternal LQTS and the other 5 were transferred from other institutions or consulted because of frequent premature ventricular contractions, nonsustained ventricular tachycardia, or fatal arrhythmias. All 15 nonperinatal LQTS patients (Patients #7 to #21) were examined because of maternal or paternal LQTS but presented without symptoms. Thirteen patients in total were transplacentally administered antiarrhythmic agents, 2 for fetal TdP (Patient #5 and #6) and 11 for maternal LQTS.

The heart rate and QTc at the initial presentation were compared between 9 perinatal and 15 nonperinatal LQTS patients in **Figure 1.** The heart rate was 58 to 158 (median 104) beats/min and 97 to 150 (median 130) beats/min, and the QTc was 513 to 686 (median 582) ms and 452 to 582 (median 509) ms in perinatal and nonperinatal LQTS, respectively. The ECGs from our 6 perinatal LQTS patients are shown in **Figure 2.**

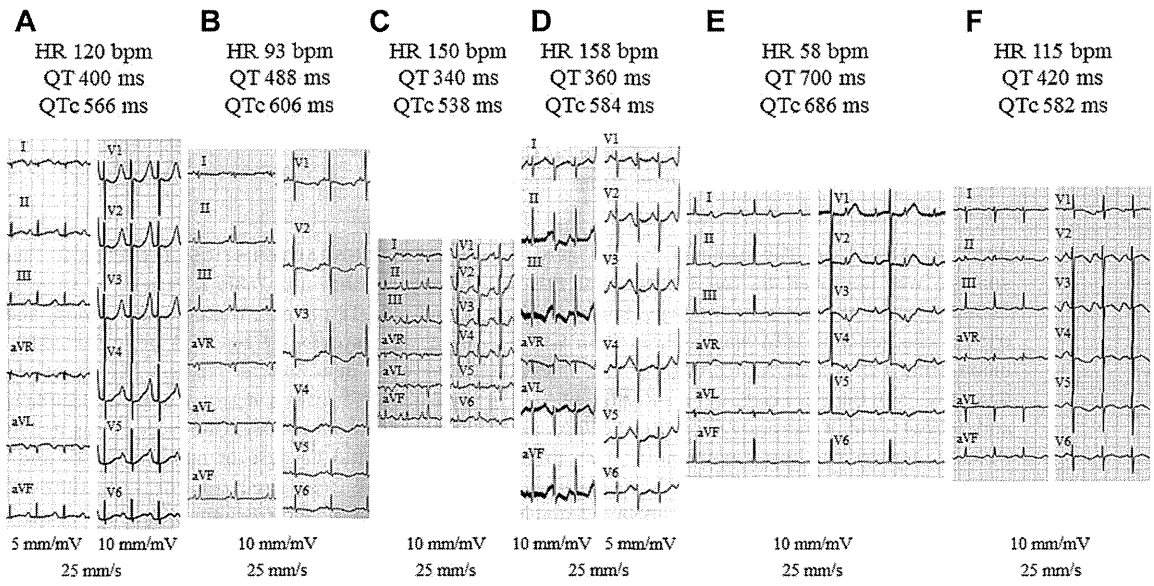
CLINICAL COURSE OF INFANTILE LQTS. Twenty-two patients were alive at the last follow-up and 2 patients with perinatal LQTS (Patients #4 and #23) died suddenly due to arrhythmias (**Table 2**). All 9 perinatal LQTS cases have been taking antiarrhythmic agents since their perinatal periods. Conventional pacemaker devices were implanted during the neonatal period in 5 patients (Patients #2, #5, #6, #22, and #24) and 4 were later upgraded to an implantable cardioverter-defibrillator. Patient #3 was implanted with an implantable cardioverter-defibrillator at 0.9 years old. Despite treatment, syncope or life-threatening arrhythmias still occurred after the neonatal period in 7 patients. In the nonperinatal LQTS group, 1 unmedicated patient (Patient #8) had syncope at 13.5 years of age.

FIGURE 1 Electrocardiography Findings at the Initial Presentation



The heart rate **(A)** and corrected QT interval **(B)** are compared between perinatal long QT syndrome (LQTS) and nonperinatal LQTS cases. Thirteen patients were administered antiarrhythmic agents transplacentally at the initial presentation (**Table 1**). Perinatal LQTS cases are represented by **pink** and LQTS cases without perinatal arrhythmias by **blue**.

FIGURE 2 Electrocardiograms From Perinatal LQTS Patients



(A to F) Representative electrocardiograms from Patients #1 to #6, respectively. HR = hazard ratio; LQTS = long QT syndrome; QTc = corrected QT.

COMPARISON OF THE CLINICAL FINDINGS AND KIDS BETWEEN PERINATAL LQTS AND NONPERINATAL LQTS IN 21 INFANTILE LQTS PATIENTS FROM OUR INSTITUTION. Among our 21 infantile LQTS patients, the age at the last follow-up was 1.0 to 16.8 (median 8.1) years in the 6 perinatal LQTS and 1.0 to 16.6 (median 3.8) years in the 15 nonperinatal LQTS patients. During the follow-up, syncope or life-threatening arrhythmias occurred in 5 perinatal LQTS patients (83%) and 1 nonperinatal LQTS patient (7%). Further, 5 perinatal LQTS patients (83%) were diagnosed with epilepsy and 4 (67%) with developmental disorders, while neither disorder was observed in the nonperinatal LQTS group. Among the perinatal LQTS patients, Patients #2, #3, #5, and #6 had all symptoms, such as syncope or life-threatening arrhythmias, epilepsy, and developmental disorders, while Patient #1 had no symptoms during the follow-up (**Figure 3**). There were no family members with epilepsy or developmental disorders.

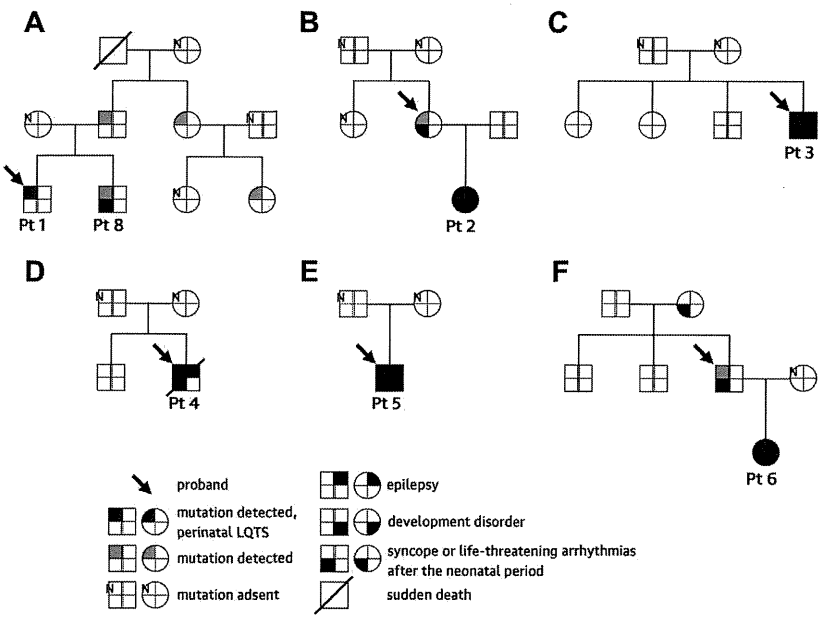
A type B KIDS was performed in 4 patients, type C in 5 patients, and type T in 5 patients (**Table 2**). The total and 9 subscales were compared between perinatal LQTS patients with epilepsy and nonperinatal LQTS cases in **Figure 4**. The total DQ was 17 to 72 (median 67) in 5 epileptic perinatal LQTS, while it was 73 to 129 (median 100) in 9 nonperinatal LQTS.

NEUROLOGICAL FINDINGS. No patients in either group had symptoms of cerebral palsy except for 2 previously reported cases without any information about it (Patients #23 and #24). The neurological findings of 8 perinatal LQTS patients with neurological disorders are shown in **Table 3**. The age at the onset of the epileptic seizures ranged from 2 days to 2.5 years of age and 5 had developmental disorders (**Table 3**). Epileptic seizures occurred under mexiletine or lidocaine in 7 patients, excluding Patient #22. Five patients had interictal EEG abnormalities (**Figure 5**), while 2 had none (Patients #2 and #24) and the remaining 1 had no data. Six patients had unremarkable findings on cerebral imaging (CT in 3 rather than MRI due to device implantations), while there were no data for 2 previously reported cases.

GENETIC CHARACTERISTICS. The LQT genotype was either LQT2 or LQT3 in all perinatal LQTS patients. In the nonperinatal LQTS patients, the genotype was more variable, either LQT1, 2, 3, or 7 (**Table 1**). Among 9 perinatal LQTS cases, 7 were probands. Five had a de novo mutation and 4 had inherited mutations.

The locations of the gene mutations in 8 perinatal LQTS patients with neurological disorders are shown in **Figure 6**. The *KCNH2* mutation in Patients #2, #6, and #24 (T613M, T623I) was previously reported without functional assays (20,21), and the S624R in

FIGURE 3 Pedigrees of LQTS Patients With Perinatal Arrhythmias



(A to F) Pedigrees of Patients #1 to #6, respectively. LQTS = long QT syndrome; Pt = patient.

Patient #5 was a novel mutation. The other 4 *SCN5A* mutations (P1332L, R1623Q, G1631D, M1766L) in the perinatal LQTS patients were previously reported with detailed functional assays (12,15,22,23). In the 6 perinatal LQTS cases with epileptic seizures, the mutations were located in the transmembrane loop of *KCNH2* (T613M, T623I, S 624R) and the D4/S4 segment of *SCN5A* (R1623Q, G1631D).

DISCUSSION

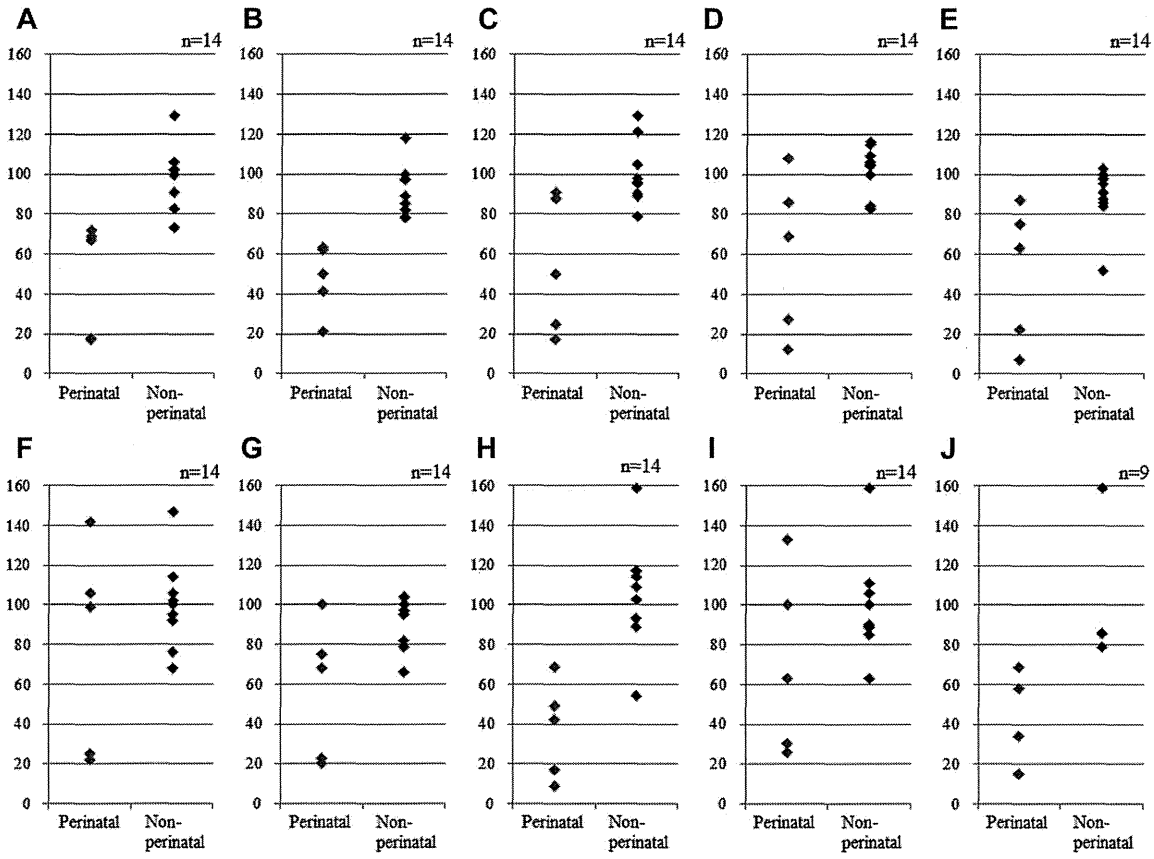
We showed a high incidence of comorbid epilepsy and/or developmental disorders in perinatal LQTS patients, while neither disorder was observed in the nonperinatal LQTS patients. In addition, the total DQ was 17 to 72 (median 67) in 5 epileptic perinatal LQTS. In the 8 perinatal LQTS patients with neurological disorders including 3 previously reported cases, epileptic seizures occurred between 2 days and 2.5 years of age and 5 had developmental disorders. We found no evidence of hypoxic ischemic brain injury in any of these patients. The mutations in patients with neurological comorbidities were in loci previously linked to LQTS with a severe cardiac phenotype. These findings indicate the possibility that neurological disorders are observed in perinatal LQTS as a neurological phenotype associated with the most severe cardiac phenotype of LQTS, life-threatening arrhythmias, during the perinatal period.

CLINICAL CHARACTERISTICS AND CLINICAL COURSE IN PERINATAL AND INFANTILE LQTS. Life-threatening cardiac events are rare during infancy in LQTS patients. Of 3,323 LQTS patients in an international registry, sudden cardiac death occurred in only 20 (0.6%), aborted cardiac arrest in 16 (0.4%), and syncope in 34 (1%) during the first year of life (1). However, these patients are known to be at a very high risk of aborted cardiac arrest or sudden death in the years to come, especially those with LQTS plus TdP or 2:1 AVB during the perinatal period (1-5).

In the present study, during the follow-up, more arrhythmic events were observed in the perinatal LQTS patients despite more intensive treatment. Notably, perinatal LQTS had a high incidence of epilepsy (83%) and developmental disorders (67%), while neither disorder was observed in the nonperinatal LQTS patients. Moreover, the total DQ by KIDS was revealed to be low, 17 to 72 (median 67), in 5 epileptic perinatal LQTS.

Previous relatively large-scale studies on perinatal LQTS did not report the rates of epilepsy and/or

FIGURE 4 Development Quotient for the Total and Each Subscale of the KIDS Battery for Perinatal LQTS and Nonperinatal LQTS Patients



Development quotient for the total **(A)**, physical motor **(B)**, manipulation **(C)**, language reception **(D)**, language expression **(E)**, concept **(F)**, socialization with other children **(G)**, socialization with adults **(H)**, training **(I)**, and feeding **(J)** were compared between perinatal long QT syndrome (LQTS) patients with epilepsy **(pink)** and nonperinatal LQTS cases **(blue)**. KIDS = Kinder Infant Development Scale.

developmental disorders (1,3,4,6), possibly because of the brief follow-up data in patients with rare phenotypes associated with early mortality. In addition, these reports were mostly retrospective analyses from registry data or questionnaire surveys rather than prospective studies with clinical monitoring.

NEUROLOGICAL FINDINGS. While the channelopathy could lead directly to neurological dysfunction, an alternative possibility is that the neurological disorder in perinatal LQTS arises secondary to hypoxic ischemic injury from perinatal arrhythmias. However, the clinical manifestations of the patients in the present study differed from that of the patients with intrapartum hypoxic ischemia. The main symptom of the patients with intrapartum hypoxic ischemia is cerebral palsy, and learning difficulties in these patients generally occur in conjunction with CP associated with severe motor disability and extensive brain damage observed by cerebral imaging (24). In this study, none of perinatal LQTS patients with neurological disorders had cerebral palsy and or any remarkable findings in the cerebral imaging. MRI is the most sensitive and specific imaging modality for examining infants with hypoxic-ischemic brain injuries (25). Also, cerebral CT can reveal the atrophic changes of the brain in the chronic phase of hypoxic-ischemic encephalopathy, but it is hard to detect small brain damage (25). In the present study, at least 3 patients were confirmed to have no findings of hypoxic ischemic brain injury by MRI, and another

TABLE 2 Clinical Findings During Follow-Up in LQTS Patients Under 1 Year of Age

Patient #	Genotype	Age at the Last Follow-Up	Syncope or Life-Threatening Arrhythmias After the Neonatal Period	Age at the Time of Syncope or Life-Threatening Arrhythmias After the Neonatal Period	AADs at the Last Follow-Up	PMI	Epileptic Seizure	Development Disorder	KIDS Type	Age at KIDS (yrs)	Total DQ
1	LQT3	16.8 yrs	-		BB, Mex	-	-	-	N/A		
2	LQT2	8.9 yrs	TdP	6.6 yrs	BB, Mex, Ver	ICD (VVI)	+	+	T	7.5	18
3	LQT3	8.3 yrs	TdP, ACA	2, 4, 11 months, 1.9, 2.0, 4.2, 4.8, 5.4, 7.6 yrs	BB, Mex, Ver	ICD (DDD)	+	+	T	6.7	17
4	LQT3	8.0 yrs	SCD	8.0 years	BB, Mex	-	+	-	T	6.6	72
5	LQT2	2.5 yrs	TdP	48 days	BB, Mex	ICD (DDD)	+	+	T	1.3	69
6	LQT2	1.0 yrs	VT	4 months	BB, Mex	PM (VVI)	+	+	T	1.0	67
7	LQT1	16.6 yrs	-		BB	-	-	-	N/A		
8	LQT3	15.1 yrs	syncope	13.5 yrs	BB, Mex, Ver	-	-	-	N/A		
9	LQT1	7.8 yrs	-		BB	-	-	-	C	6.6	73
10	LQT2	7.1 yrs	-		BB	-	-	-	C	5.8	106
11	LQT1	6.3 yrs	-		BB	-	-	-	C	4.9	102
12	LQT2	6.2 yrs	-		-	-	-	-	C	4.9	102
13	N/A	5.6 yrs	-		-	-	-	-	C	4.4	100
14	LQT7	3.8 yrs	-		-	-	-	-	N/A		
15	LQT1	3.4 yrs	-		-	-	-	-	B	2.9	91
16	LQT7	2.5 yrs	-		-	-	-	-	N/A		
17	LQT2	3.7 yrs	-		-	-	-	-	B	2.4	83
18	LQT1	2.7 yrs	-		-	-	-	-	B	1.4	129
19	LQT1	1.6 yrs	-		-	-	-	-	B	1.6	100
20	LQT2	1.0 yrs	-		-	-	-	-	N/A		
21	LQT1	1.0 yrs	-		-	-	-	-	N/A		
22*	LQT3	5 yrs	VT	45 days, 1.5 yrs	BB	ICD	+	+	N/A		
23*	LQT3	1.3 yrs	SCD	1.3 yrs	BB, Mex	-	+	N/A	N/A		
24*	LQT2	11 days	N/A		BB, Mex	ICD (DDD)	+	N/A	N/A		

*Patients #22, #23, and #24 were previously reported cases (11-13).

AAD = antiarrhythmic drug; ACA = aborted cardiac arrest; DQ = development quotients; ICD = implantable cardioverter-defibrillator; KIDS = Kinder Infant Development Scale; PMI = pacemaker implantation; PM = conventional pacemaker; SCD = sudden cardiac death; VF = ventricular fibrillation; other abbreviations as in **Table 1**.

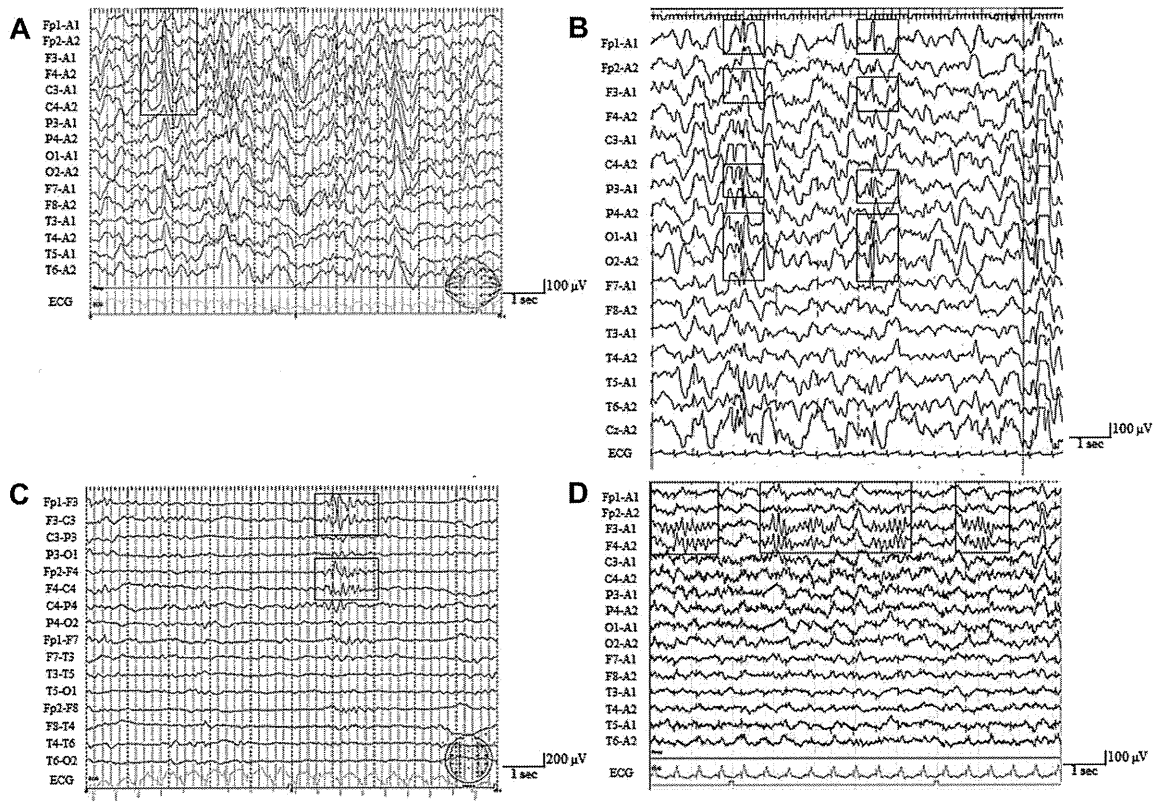
TABLE 3 Neurological Findings in 8 Perinatal LQTS Patients With Neurological Comorbidities

Patient #	LQT Type	Cerebral Palsy	Epileptic Seizure	Developmental Disorder	Age at the Onset of Epileptic Seizures	Antiepileptic Drugs at the Last Follow-Up	Age at the Time of the EEG	EEG Localization	Age at the Time of the Cerebral Imaging	Cerebral Images
2	LQT2	-	+	+	1.6 yrs	Clonazedpam, Gabapentin	2.0, 3.6, 4.6 yrs	No apparent paroxysmal discharge	6.6 yrs	CT; unremarkable
3	LQT3	-	+	+	0.4 yrs	Topiramate	1.7 yrs	Bilateral frontal	0.7 yrs	MRI; unremarkable
4	LQT3	-	+	-	2.5 yrs	Levetiracetam	4.4 yrs	Left occipital	4.5 yrs	MRI; unremarkable
5	LQT2	-	+	+	54 days	Zonisamide	54 days	Bilateral frontal	0.1, 0.3 yrs	CT; unremarkable
6	LQT2	-	+	+	0.7 yrs	None	0.7 yrs	Bilateral frontal	0.6, 0.7 yrs	CT; unremarkable
22*	LQT3	-	+	+	4 days	Valproic acid, Clobazam	5 days	Centrotemporal	5 days	MRI; unremarkable
23*	LQT3	N/A	+	N/A	2 days	Phenobarbital	N/A	N/A	N/A	N/A
24*	LQT2	N/A	+	N/A	7 days	None	7 days	No apparent paroxysmal discharge	N/A	N/A

*Patients #22, #23 and #24 were previously reported cases (11-13).

CT = computed tomography; EEG = electroencephalogram; LQTS = long QT syndrome; MRI = magnetic resonance imaging; N/A = not available.

FIGURE 5 Electroencephalograms From Perinatal LQTS Patients



(A to D) Representative electroencephalograms (EEGs) from Patients #3 (6.7 years of age), #4 (4.4 years of age), #5 (0.1 years of age), and #6 (0.7 years of age), respectively. The **red boxes** indicate focal abnormal EEG changes. The EEG leads are as follows: FP, most frontal leads; F, frontal; T, temporal; C, central; P, parietal; O, occipital; and A, ear. Leads with uneven numbers are EEG registrations from the left side and even numbers from the right side. LQTS = long QT syndrome.

3 did not exhibit any atrophic changes of the brain observed on CT. These finding support our hypothesis that neurological disorders in perinatal LQTS are manifested as a neurological phenotype. Nevertheless, still we could not completely deny the possibility that these were caused by a hypoxic ischemic brain injury, because childhood survivors of perinatal hypoxic ischemia was reported to be at risk for cognitive deficits even in the absence of functional motor disorders (24).

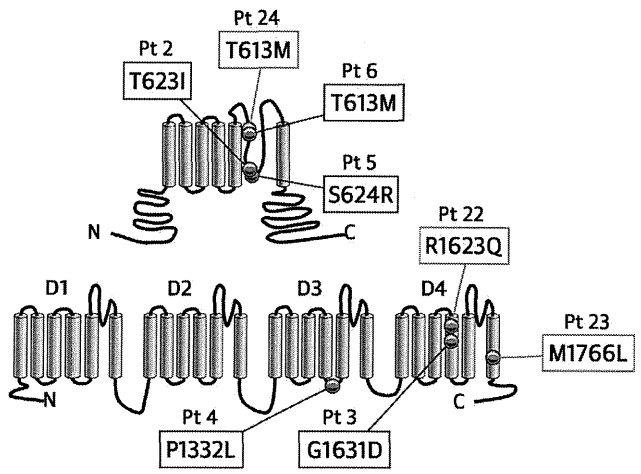
Another possibility is additional mutations at epilepsy susceptibility loci (26). While genetic testing for known epilepsy-associated mutations was not performed, in our 5 patients no family members had any neurological symptoms, and Patient #21 was reported to have no mutations of epilepsy susceptibility genes (11).

GENOTYPE-NEUROLOGICAL PHENOTYPE CORRELATION. LQTS patients with arrhythmias during the perinatal period have predominantly LQT2 or LQT3 (3). Indeed, all 9 perinatal LQTS patients in the present study had LQT2 or LQT3, 8 of which exhibited neurological comorbidities.

A clinical association between LQTS and epilepsy was recently reported in older LQTS patients. EEG abnormalities were found in 71% of individuals with LQT1 or LQT2 (8). Further, the seizure incidence was significantly higher in LQT2 than LQT1 or LQT3 patients (9). In a large cohort of Australian cases of sudden unexpected death in epilepsy, genetic analyses revealed 6 nonsynonymous variants in *KCNH2* and *SCN5A* among 68 patients (10).

KCNH2 and *SCN5A* are expressed not only in the heart, but also in brain. A correlation between

FIGURE 6 Locations of the Gene Mutations in 8 Perinatal LQTS Patients With Neurological Comorbidities



The **upper and lower figures** show the predicted topology of the Kv11.1 cardiac potassium channel α-subunit and the Nav1.5 cardiac sodium channel α-subunit, respectively. The **pink solid circles** indicate the mutations in patients with perinatal long QT syndrome (LQTS) with epilepsy and/or developmental disorders from our institution. The **blue solid circle** indicates the mutation in a previously reported case of perinatal LQTS and neurological seizures.

mutations in these genes and neurological phenotypes has been proposed but there have been no molecular investigations. LQT2 is caused by loss-of-function mutations in *KCNH2*, encoding the α-subunit of the Kv11.1 potassium channel that conducts the I_{Kr} current (27). Expression of *KCNH2* transcripts have been detected within hippocampal astrocytes, cerebellar Purkinje cells, and vestibular nucleus neurons (28). These I_{Kr} currents are important for spatial buffering of extracellular potassium ions by astrocytes during high neuronal activity. Kv11.1 mutations could affect the potassium ion buffering properties of astrocytes, leading to epilepsy (9,28). Alternatively, LQT3 is caused by mutations in the Nav1.5 sodium channel α-subunit gene *SCN5A*, which increase the persistent inward sodium current (27). *SCN5A* expression has been detected in the rat limbic forebrain (29). Persistent depolarization by abnormally prolonged sodium currents in limbic cortex neurons due to *SCA5A* mutations would elicit epileptiform bursting, synchronous network activation, and seizures (11,29).

Among 7 mutations in 8 perinatal LQTS patients with neurological disorders, T613M in KCNH2, and R1623Q and G1631D in SCN5A were reported as mutations in life-threatening perinatal LQTS (4,15,20,23). Further, in 6 of 8 patients, the mutations were located in the transmembrane loop of *KCNH2* (T613M, T623I, S 624R) and the D4/S4 segment (R1623Q, G1631D) of *SCN5A*. Mutations in the transmembrane loop of *KCNH2* are correlated with a severe LQTS cardiac phenotype (30), and mutations in the SCN5A D4/S4 segment, a component of the voltage-sensor important for activation and inactivation, are correlated with severe perinatal LQTS (15). Another 1 of the remaining 2 mutations, the P1332L mutation in the D3/S4-S5 linker, was also correlated with a severe cardiac phenotype, but with a good response to mexiletine (22). Based on these findings, we speculated that the channelopathy associated with the most severe cardiac phenotype also conferred susceptibility to a "neurological phenotype," such as epilepsy and/or developmental disorders.

STUDY LIMITATIONS. There were several limitations to this study. First, the static analysis was not available because of the small sample size. Second, 5 perinatal LQTS patients with comorbid neurological disorders were not examined by MRI because of device implantations. Even when the findings of the present study are supported our hypothesis, still the possibility that the neurological disorders were the result of a perfusion injury due to hemodynamically compromising arrhythmias could not be completely excluded. Third, functional assays were not available for the 3 KCNH2 mutations. Fourth, the EEG and KIDS were performed at various ages. Finally, we did not test for mutations in epilepsy susceptibility genes. Nevertheless, these findings strongly suggest that certain mutations associated with severe LQTS (with life-threatening cardiac arrhythmias in the perinatal period) may also enhance the susceptibility to neurological disorders, such as epilepsy and/or developmental disorders.

CONCLUSIONS

In this study of LQTS patients diagnosed in infancy, 8 with perinatal arrhythmias, including 3 previously reported cases, exhibited a comorbid neurological phenotype. We found no evidence of hypoxic ischemic brain injury in any of these patients. In addition, the total DQ scores on the KIDS was revealed to be low, 17 to 72 (median 67), in 5 epileptic perinatal LQTS. The mutations in the perinatal LQTS with epilepsy cases were located in ion channel gene loci associated with a severe cardiac phenotype. Although we could not completely deny the possibility that the neurological disorders were the result

of a brain perfusion injury, our findings suggested that channel dysfunction leading to a most severe cardiac phenotype may also confer susceptibility to a neurological phenotype. Further study is needed to define the etiology of the neurodevelopmental anomalies in perinatal LQTS.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Current therapies have resulted in relatively favorable life prognoses in perinatal LQTS. Based on our findings that they have a high comorbidity of neurological disorders, the improvement of their developmental prognoses should be considered as the next step of the medical treatment.

TRANSLATIONAL OUTLOOK: Further larger prospective studies with a more detailed neurological evaluation are needed to define the etiology of comorbid neurological disorders in perinatal LQTS.

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KEY WORDS developmental disorder, epilepsy, perinatal LQTS

Sudden Cardiac Death Compendium

Circulation Research **Compendium on Sudden Cardiac Death**

The Spectrum of Epidemiology Underlying Sudden Cardiac Death
Sudden Cardiac Death Risk Stratification
Genetics of Sudden Cardiac Death
Mechanisms of Sudden Cardiac Death: Oxidants and Metabolism
Role of Sodium and Calcium Dysregulation in Tachyarrhythmias in Sudden Cardiac Death
Ion Channel Macromolecular Complexes in Cardiomyocytes: Roles in Sudden Cardiac Death
Finding the Rhythm of Sudden Cardiac Death: New Opportunities Using Induced Pluripotent Stem Cell–Derived Cardiomyocytes
Cardiac Innervation and Sudden Cardiac Death
Clinical Management and Prevention of Sudden Cardiac Death
Cardiac Arrest: Resuscitation and Reperfusion

Gordon Tomaselli, Editor

The Spectrum of Epidemiology Underlying Sudden Cardiac Death

Meiso Hayashi, Wataru Shimizu, Christine M. Albert

Abstract: **Sudden cardiac death (SCD) from cardiac arrest is a major international public health problem accounting for an estimated 15%–20% of all deaths. Although resuscitation rates are generally improving throughout the world, the majority of individuals who experience a sudden cardiac arrest will not survive. SCD most often develops in older adults with acquired structural heart disease, but it also rarely occurs in the young, where it is more commonly because of inherited disorders. Coronary heart disease is known to be the most common pathology underlying SCD, followed by cardiomyopathies, inherited arrhythmia syndromes, and valvular heart disease. During the past 3 decades, declines in SCD rates have not been as steep as for other causes of coronary heart disease deaths, and there is a growing fraction of SCDs not due to coronary heart disease and ventricular arrhythmias, particularly among certain subsets of the population. The growing heterogeneity of the pathologies and mechanisms underlying SCD present major challenges for SCD prevention, which are magnified further by a frequent lack of recognition of the underlying cardiac condition before death. Multifaceted preventative approaches, which address risk factors in seemingly low-risk and known high-risk populations, will be required to decrease the burden of SCD. In this Compendium, we review the wide-ranging spectrum of epidemiology underlying SCD within both the general population and in high-risk subsets with established cardiac disease placing an emphasis on recent global trends, remaining uncertainties, and potential targeted preventive strategies. (*Circ Res*. 2015;116:1887-1906. DOI: 10.1161/CIRCRESAHA.116.304521.)**

Key Words: cardiomyopathies ■ coronary disease ■ death, sudden, cardiac ■ epidemiology

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Nonstandard Abbreviations and Acronyms	
AF	atrial fibrillation
ARVC	arrhythmogenic right ventricular cardiomyopathy
BrS	Brugada syndrome
CHD	coronary heart disease
EMS	emergency medical service
ERP	early repolarization ECG pattern
HCM	hypertrophic cardiomyopathy
HF	heart failure
ICD	implantable cardioverter defibrillator
LQTS	long-QT syndrome
LVEF	left ventricular ejection fraction
MI	myocardial infarction
NIDCM	non–ischemic dilated cardiomyopathy
OHCA	out of hospital cardiac arrests
PEA	pulseless electrical activity
SCA	sudden cardiac arrest
SCD	sudden cardiac death
VF	ventricular fibrillation
VT	ventricular tachycardia

Sudden Cardiac Death/Sudden Cardiac Arrest: Background, Mechanisms, and Risks

Sudden cardiac death (SCD)/sudden cardiac arrest (SCA) refers to an unexpected death or arrest from a cardiovascular cause that occurs rapidly outside of the hospital or in the emergency room.[1,2] The presumption based on epidemiologic studies of SCD and SCA survivors is that such rapid deaths are often because of lethal ventricular arrhythmias in the setting of underlying coronary heart disease (CHD).[3–5] Despite major advances in treatment and prevention of CHD and implantable cardioverter defibrillators (ICDs) for SCD prevention in high-risk patients, SCD remains a major public health problem estimated to account for 15%–20% of all deaths.[6,7] Reported declines in SCD rates[8] have not been as steep as for other causes of CHD death,[9–12] and the reasons for this disparity are not well understood. There may be a growing fraction of SCDs where the underlying cause is not CHD or ventricular arrhythmias, particularly among certain subsets of the population. In addition, SCD preventive strategies are lacking in low-risk individuals without established heart disease that comprise the largest proportion of SCDs.[5,13,14] To further reduce the incidence of SCD, preventive strategies need to be tailored to diverse populations at varying levels of risk. In this Compendium, we review the broad spectrum of epidemiology underlying SCD, from common to rare forms, with an emphasis on preventive strategies, recent trends, and unanswered questions.

SCA Incidence: Estimates and Definitions

Estimates on the annual incidence of SCA and SCD vary widely depending on data sources for case ascertainment, definitions used, and methods used for extrapolation of rates.[15,16] These difficulties in extrapolating SCA and SCD rates are likely magnified further when comparing SCD rates across countries where emergency medical service (EMS) protocols, autopsy rates, and national recording systems vary. The majority of global comparisons (Figure 1) are based on rates of EMS-attended out of hospital cardiac arrests (OHCA), which seem to be much lower in Asia (52.5 per 100 000 person-years) as compared with Europe (86.4 per 100 000 person-years), North America (98.1 per 100 000 person-years), and Australia (111.9 per 100 000 person-years). There also seem to be regional variations within geographic regions.[17] For instance, among 10 regions in North America, rates of EMS attended cardiac arrest range from 159 per 100 000 person-years in Dallas, TX, to 71.8 per 100 000 person-years in Ottawa, ON.

However, the above estimates are crude approximations which at the same time both over- and under-estimate SCA rates. First, EMS is not in attendance for a significant fraction of SCAs, and the proportion of EMS-attended deaths is known to vary significantly across countries. Second, a significant fraction of EMS-attended OHCAs are not unexpected nor do they occur in a short time frame from the onset of symptoms. Death certificates are also known to overestimate SCD rates for similar reasons.[18] To obtain a more precise estimate of SCD/SCA, expert panels have advocated for the establishment of precise and uniform definitions of SCD/SCA and to integrate multiple source methods for case ascertainment.[2,15] Standardized definitions of SCD/SCA have been

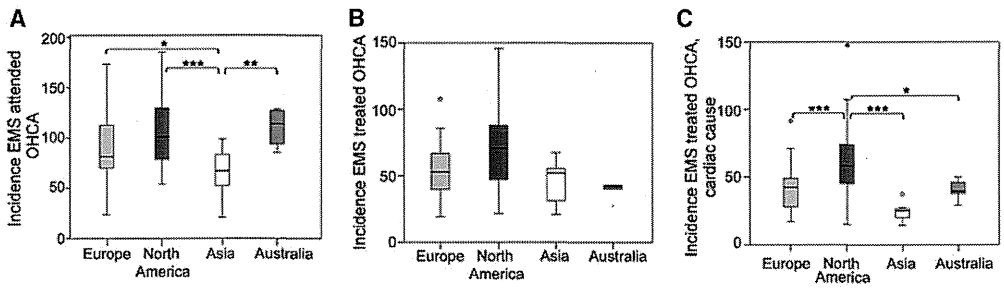

Figure 1. Incidence rates of emergency medical service (EMS)–attended out of hospital cardiac arrests (OHCA; A), EMS-treated OHCA (B), and EMS-treated OHCA of presumed cardiac cause (C). Incidence is per 100 000 person-years. Compared with Europe, North America, and Australia, EMS-attended OHCA was lower in Asia, and EMS-treated OHCA of presumed cardiac cause was higher in North America than in other regions. *P<0.05; **P<0.01; and ***P<0.001. Adapted from Berdowski et al[17] with permission of the publisher.

proposed, which generally define SCD as an unexpected death without obvious extra-cardiac cause that occurs in association with a witnessed rapid collapse or within 1 hour of the onset of symptoms.[1,2,19] There are no national surveillance mechanisms to record such characteristics of deaths; and therefore, approximations are based on extrapolations from population-based studies. In prospective studies using standardized definitions and multiple sources of surveillance for case ascertainment in the United States,[18] Netherlands,[20] Ireland,[21] and China,[22] SCD rates range from 40 to 100 per 100 000 in the general population,[2] with rates being lowest in China.[22] In individuals aged <35 years, SCD is rare with an incidence of 1 to 3 per 100 000 per year in recent reports.[23–25]

Even when a strict definition and multiple sources of ascertainment are used, other noncardiac conditions that evolve rapidly such as acute cerebral hemorrhage, aortic rupture, and pulmonary embolism cannot be excluded without a carefully performed autopsy. Autopsy rates are generally low and vary widely across countries with rates as low as 10% of all deaths within the United States[26] compared with 23.8% in Finland,[27] and the protocols for the performance of autopsies in the cases of suspected SCD vary widely as well, even within regions of countries. These differences in autopsy rates and protocols likely contribute to some of the geographical differences in the incidence and causes of SCD.

SCA Trends in Survival and Underlying Rhythm

Several major advances in cardiopulmonary resuscitation (CPR)[28] and postresuscitation care have resulted in improved resuscitation rates from OHCA. In a recent report from the Cardiac Arrest Registry to Enhance Survival, a prospective clinical registry of 70 000 OHCA survivors in the United States, survival rates to hospital discharge increased from 5.7% in 2005 to 8.3% in 2012.[29] In Denmark, even greater increases in 30-day survival (3.5%–10.8%) were observed from 2001 to 2010.[30] Both inhospital and prehospital survival rates contribute to these improved outcomes post OHCA. However, even with these improvements, absolute survival rates remain in the ≤10% range.

Although survival rates are higher for OHCA where ventricular fibrillation (VF) is the initial rhythm (21%), the proportion of cases where VF is found at the time of EMS arrival has been declining during the past 3 decades,[31,32] with a resultant increase in cases where pulseless electrical activity (PEA) and asystole are the initial rhythm.[33] This is an unsettling trend because resuscitation rates are much lower for these rhythms, and we currently have no known strategies for prevention of these deaths.[33] Part of this changing pattern seems to be explained by a concomitant increase in the proportion of arrests occurring in the home,[4,20,34] where the arrest is less likely to be witnessed. However, even when the arrest is witnessed by a bystander or an automated external defibrillator is applied, VF or pulseless ventricular tachycardia (VT) is less likely to be encountered as the initial rhythm in arrests occurring in the home versus public.[4] Proposed explanations for the proportional decline in VF as compared with other rhythms include an overall decrease in the prevalence of CHD and an increased use of β-blockers and ICDs in high-risk patients.[27,29] At the same time, the population is aging, and advances in medical treatments have resulted in an increased prevalence of end-stage cardiovascular disease as well as other severe comorbidities. These older, sicker patients may be more likely to have arrests in the home setting and to have acute precipitants leading to PEA (ie, respiratory, metabolic, and vascular)[33,35] and be less likely to sustain VF up to the point of EMS arrival.

Demographics of SCD Victims

The majority of SCDs occur in the adult population, with <1% occurring in individuals aged <35 years.[10] Among adults, the absolute rate of SCD increases markedly with age; however, the proportion of deaths that are sudden seems to be higher in younger age groups.[5,19,36] There are also recognized differences in SCD incidence by sex and race, which are largely unexplained. Women have a lower incidence of SCD and SCA than men,[37] even when one accounts for the prevalence of other predisposing conditions such as CHD, myocardial infarction (MI), and heart failure (HF).[13,38,39] Women who experience OHCA are on average older, more likely to present with PEA, and experience their arrest at home as compared with men.[40] These demographics may partially explain why the decline in SCD and OHCA rate has been less pronounced among women as opposed to men in recent years.[10,12,40] However, women, especially at younger ages,[41] seem to have a higher rate of successful resuscitation and survival from shockable rhythms,[40] possibly because of favorable effects of smaller body size and estrogen on success of defibrillation and postresuscitation hemodynamics.

With respect to race, black as opposed to white Americans have been documented to have higher rates of OHCA[42,43] and SCD,[44,45] as well as poorer rates of survival from cardiac arrest.[46] Similar to women, blacks of both sexes are more likely to have an unwitnessed arrest or PEA documented at the time of the arrest.[42,46,47] These unfavorable arrest characteristics do not entirely account for the poorer survival among blacks. Even when limited to OHCAs because of VF/VT, national rates of survival to hospital discharge have been documented to be 27% lower among black patients, and much, but not all, of this disparity seems to be explained by black patients receiving treatment at hospitals with worse outcomes.[48] Blacks may also be less likely to receive prehospital resuscitation efforts in the United States. In 1 recent large cohort study, patients with OHCA in low-income black neighborhoods were less likely to receive bystander-initiated CPR than those in high-income white neighborhoods.[49]

Data are even more limited for other racial and ethnic differences in SCD incidence. Despite having a higher prevalence of cardiac risk factors,[50] Hispanic Americans may have lower SCD rates than non-Hispanic populations based on limited data from death certificates[10,51] and coroner evaluations in the United States.[52] It also seems that the incidence of SCD may be lower among Asian populations in the United States based on death certificate data.[10] Estimates of SCD incidence in longitudinal population-based studies of SCD in China[22] and Japan[53] are consistently lower than those from studies performed in North America or other regions with predominantly

white populations. These racial differences in SCD/SCA incidence and survival are poorly understood, and further studies performed in large-scale population-based cohort studies of diverse ethnicity are needed to determine the origin of these disparities.

Underlying Pathophysiology of SCD

The epidemiology of SCD is directly related to the pathophysiology that underlies the event. Our knowledge on the predominant pathologies underlying SCD is primarily dependent on autopsy series and cardiac evaluations in cardiac arrest survivors, the detail nature of which may vary significantly among counties. Variation in the meticulous nature of histologic examinations across countries likely influences the reported proportions of pathologic causes of sudden death worldwide. Despite these limitations, it is generally accepted that CHD is the most common cardiac pathology underlying SCD (Figure 2) in adults aged >35 years, particularly among white men where it is responsible for ≈70%–75% of SCDs.[7,16,20,54] In women, the percentage of SCD and SCA because of CHD seems to be lower. In cardiac arrest survivor series[55] and SCD autopsy series,[54] CHD was found in 45%–50% of women versus 80%–90% of men.[54] The percentage of SCDs with underlying CHD also seems to be lower in blacks versus whites (47% versus 63%) and left ventricular hypertrophy is more common among older black than white SCD victims.[56] In Japan, CHD is thought to account for a much lower percentage of SCDs,[53] although the percentage because of CHD seems to be increasing over time.[57]

Beyond CHD, the causes of SCD are heterogeneous and include cardiomyopathies, valvular heart disease, myocarditis, hypertrophy, and primary electrical heart disease accounting for the remainder. (Figure 2).[7] On average, a significant cardiac abnormality is not found after clinical evaluation or on autopsy in 5% of SCA cases.[55,58] This percentage seems to be higher in women, where structurally normal hearts are more commonly encountered.[54,55,59] In Asians, the primary ion channelopathies are estimated to be responsible for 10% of SCDs.[60] In young adults and children aged <35 years, CHD accounts for a much smaller proportion of deaths, with hypertrophic cardiomyopathy (HCM), coronary artery anomalies, myocarditis, arrhythmogenic right ventricular cardiomyopathy (ARVC), and primary ion channelopathies accounting for significant proportions.[61]

The presumed mechanism underlying an abrupt, unheralded death in these conditions is electrical instability leading to a lethal arrhythmia triggered by ischemia or other arrhythmogenic stimuli resulting in acute hemodynamic collapse. This hypothesis is difficult to prove as most deaths are not monitored, and those that are monitored comprise a highly selected population. Studies in epidemiologic cohorts of men[3] and women[5] from the 1970s to 1990s suggest that 88% to 91% of deaths that occur within 1 hour of symptom onset are arrhythmic in nature. Because VF degenerates to asystole during the course of several minutes, the majority of SCD victims demonstrate asystole or PEA when first examined by rescue teams.[47] In cases of SCD where there has been a relatively short delay between collapse and the initial determination of rhythm, the proportion of cases with documented ventricular

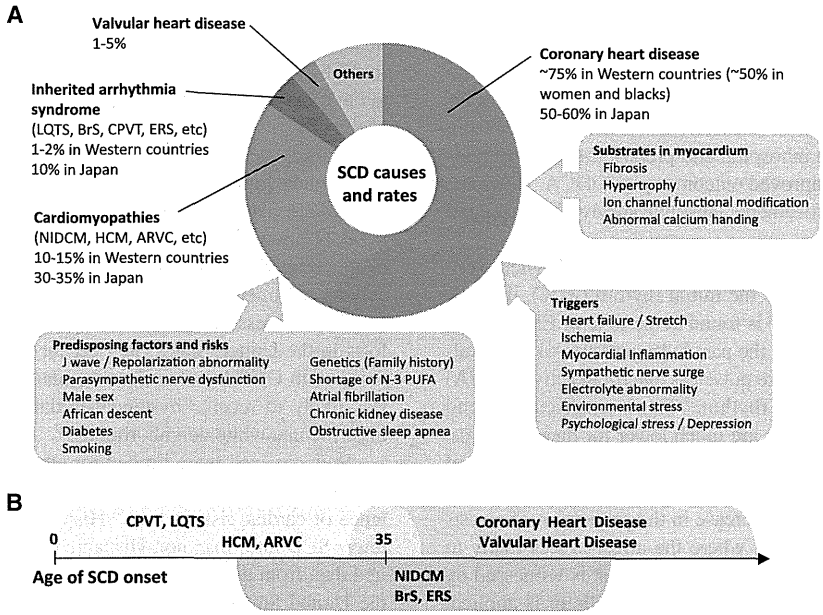

Figure 2. Causes of sudden cardiac death (SCD) and rates (A) and age of SCD onset in each disease (B). A, Coronary heart disease is the leading cause of SCD, but the rates of baseline heart disease differ between Western countries and Japan. **B**, SCDs occur in elderly populations in coronary heart disease and valvular heart disease, whereas most SCDs in catecholaminergic polymorphic ventricular tachycardia (CPVT) and long-QT syndrome (LQTS) develop at age <35 years. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; ERS, early repolarization syndrome; HCM, hypertrophic cardiomyopathy; NIDCM, non–ischemic dilated cardiomyopathy; and PUFA, polyunsaturated fatty acids.

tachyarrhythmias increases to 75% to 80%.[4,62,63] However, as mentioned previously, VF is less often and PEA is more commonly encountered in recent OHCA series.[31] Therefore, a proportion of SCD is likely because of abrupt hemodynamic collapse in the absence of preceding fatal arrhythmia, and this proportion may be growing in the population.

Risk Factors and Predisposing Conditions for SCD in the General Population

The presence of overt structural and primary electrical heart disease is associated with major elevations in SCD risk, and separate risk stratification schema exist for the majority of these disorders, which will be discussed in later sections. However, the majority of SCDs occur among individuals without clinically recognized heart disease.[5,13,14] Approximately 44%–52% of men and 59%–69% of women who experience SCD will not have had cardiovascular disease diagnosed before the event, and therefore SCD is the first manifestation of heart disease.[5,13,14] Although the absolute incidence among individuals without apparent heart disease is low, the majority of SCD events take place in this segment of the population. For this segment of the population, current efforts directed at preventing SCD primarily comprised risk factor and lifestyle modification.

CHD Risk Factors

As described above, CHD underlies a significant proportion of SCD, thus risk factors for CHD are associated with SCD risk in the population. Hypertension, diabetes mellitus, hypercholesterolemia, obesity, and smoking have all been associated with elevated risks of SCD among men and women in prospective cohort studies.[5,13,44,64,65] Diabetes mellitus is a particularly strong risk factor for SCD,[64,66] even in higher risk populations.[67,68] Hypertension and resultant left ventricular hypertrophy seem to be particularly important markers of SCD risk in blacks,[45,56] in whom the prevalence of these conditions is greater.[69] Smoking confers marked elevations in SCD risk, especially among women.[5] Importantly, smoking cessation is associated with a prompt reduction in the elevated risk for SCDs[70–72] (Figure 3), particularly among individuals who have not yet developed overt CHD.[72] Serum cholesterol seems to be more strongly related to SCD at younger ages,[5,38] and a recent meta-analysis of randomized trials suggests that cholesterol lowering with statins may confer modest benefits on SCD incidence.[73]

Family History of SCD

Several studies have demonstrated a familial predisposition to SCD and VF.[64,74–76] Three separate case–control studies have demonstrate that a history of SCD among a first-degree relative is an independent risk factor for VF[75,77] or SCD[76] in the setting of an acute MI. In the Paris Prospective Study,[64] parental history of SCD was an independent risk factor for occurrence of SCD (relative risk, 1.80; 95% confidence interval, 1.11–2.88), but was not associated with fatal MI. Conversely, a parental history of fatal MI had no effect on SCD risk. These data in aggregate suggest that genetic or unknown environmental factors responsible for the familial aggregation of SCD or ischemic VF may predispose to fatal arrhythmia as a discrete trait and manifestation of CHD. The consistent associations implicating a family history of arrhythmic death as an independent risk factor for SCD in the general population has led to several studies focused on identifying common genetic variants that predispose to ventricular arrhythmias and SCD in the population.[78,79]

Diet

Dietary intake and blood-based measures of selected nutrients have been specifically associated with SCD in epidemiologic studies. In observational studies, consuming fish ≈1 to 2×/wk has been associated with significant 42%–50% reductions in SCD risk, with minimal impact of risk of non–fatal MI.[80–82] These inverse associations with SCD were more extreme when marine n-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) were estimated as a proportion of fatty acids from the diet[83] or measured directly in blood.[80,84] These

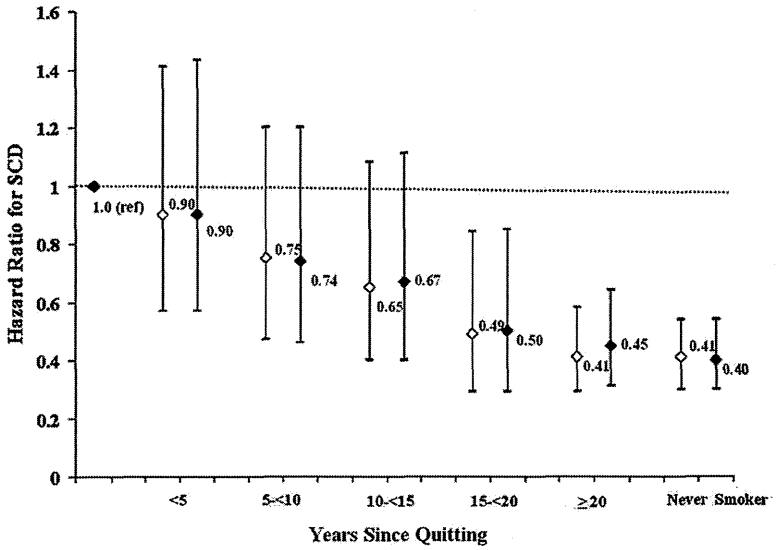

Figure 3. Reduction in sudden cardiac death (SCD) risk associated with smoking cessation among US middle-aged women. The reference category is current smokers. White diamond, Age-adjusted hazard ratio (HR). Black diamond, Multivariable-adjusted HR. *P* value for trend <0.0001 in age and multivariable-adjusted models. Adapted from Sandhu et al[72] with permission of the publisher. Copyright © 2012, Wolters Kluwer Health. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

data in relatively healthy observational cohorts are supportive of experimental data suggesting that n-3 fatty acids may have a selective effect on susceptibility to arrhythmias.[85] However, randomized trial data in post-MI populations have not been consistently supportive of this hypothesis.[86–88]

Magnesium intake has also been related to SCD rates. In the Nurses' Health Study, the relative risk of SCD was significantly lower among women in the highest quartile of dietary magnesium intake. The inverse association was stronger for plasma magnesium, where each 0.25 mg/dL (1 SD) increment in plasma magnesium was associated with a 41% reduced risk of SCD.[89] A similar inverse association between serum magnesium and SCD was also found in the Atherosclerosis Risk in Communities study.[90] Finally, there are likely additive and interactive effects of these and other nutrients on SCD incidence.[91] Recent data suggest that a Mediterranean-style diet pattern, consisting of higher intake of vegetables, fruits, nuts, whole grains, fish, and low intake of red/processed meat, may also lower SCD risk among women.[92,93]

Alcohol Intake

The relationship between alcohol intake and SCD is complex. Prospective US cohort studies comprised of individuals consuming small-to-moderate amounts of alcohol[94–96] have found U-shaped associations between recent alcohol intake and SCD with reduced risks at levels of ½ to 1 drink/d and no reduction at ≥2 drinks/d. Heavy levels of alcohol consumption (>6 drinks/d) have also been associated with increased risk for SCD in other populations.[97] In contrast, alcohol intake has an inverse linear association with non–fatal MI.[98] Recently, consuming >1 drink/d was found to be associated with 2-fold elevations in the risk of experiencing VF during acute ST-segment–elevation MI.[77] These data in aggregate suggest that the favorable effects of alcohol on atherosclerosis and thrombosis may be offset by potential proarrhythmic effects at higher levels of intake.

Atrial fibrillation, Renal Disease, and OSA

Recent data have highlighted the potential link between atrial fibrillation (AF) and SCD. In patients with established AF treated with anticoagulation, SCD accounts for >20% of all deaths.[99] In recent population-based cohort and case–control studies, patients with AF have on average a 2.5-fold increased risk of SCD[100] or VF[77,101] as compared with those without AF. The mechanism underlying this elevation in SCD risk is not completely understood, but it does not seem to be entirely dependent on coexisting cardiovascular disease or explained by the use of antiarrhythmic drugs[101]; however, in a population-based study, much of the excess SCD risk associated with AF could be accounted for by coexisting HF.[102]

Patients with severe chronic kidney disease (CKD) are also at higher risk for SCD, with annualized SCD rates approaching 5.5% in patients undergoing dialysis.[103] There are also recent data to suggest that individuals with more moderate levels of CKD have a higher risk for SCD as compared with people with normal kidney function.[68,104] Presumably, some of this could be because of electrolyte shifts and significant degrees of left ventricular hypertrophy observed in these patients. Recent data also suggest that obstructive sleep apnea[105] and seizure disorders[106] may be contributors to SCD risk in the population. Whether treatment for the above disorders will attenuate the elevated SCD risk is unknown and requires further exploration.

Triggers of SCD

Diurnal/Seasonal Variation

SCD tends to occur more frequently at certain times of the day, week, and year. SCD incidence peaks from 6:00 AM to noon[107,108] and is highest on Monday and lowest during the weekend.[109,110] These morning and Monday peaks in SCD rates seem to be blunted by β-blockers,[111] suggesting that adrenergic triggers may underlie part of these circadian variations. There also seems to be seasonal variability in SCD incidence, with the highest and lowest rates observed in the winter and summer months, respectively, in both hemispheres.[110,112] These relationships observed in the general population may differ in patients with underlying heart diseases. In patients with ARVC and Brugada syndrome (BrS), ventricular arrhythmias tend to peak in the summer months.[113,114] These findings suggest that the onset of SCD may be associated with endogenous rhythms and external factors such as activity levels, psychological exposures, sunlight, temperature, and other climatic conditions.[112,115]

Physical Activity

Most studies,[65,116–119] but not all,[120,121] have found protective associations between regular physical activity and SCD or cardiac arrest, particularly for moderate levels of exertion.[65,68,117–119] It is also well recognized that SCD occurs with a higher than average frequency during or shortly after vigorous exertion. The proportion of exertion-related SCDs varies widely from 3% to 13%[116,119,121–123] depending on the population surveyed. Case–control and case-crossover analyses have demonstrated that vigorous exertion can trigger cardiac arrest[116] and SCD,[119,121] and this risk seems to be greater in men versus women.[119,121] Habitual exercise lowers this transient excess risk of SCD; however for men, the risk remains significantly elevated even among those who exercise most frequently.[119,121]

Despite these risks, the absolute risk of exertion-related SCD is low. Recent population-based estimates on the frequency of exercise-related OHCA and SCD range from 2.1 per 100 000 person-years in the Netherlands[122] to 0.46 per 100 000 person-years in France.[123] The majority of these exertion-related SCD events took place in adults aged >35 years (Figure 4), and the incidence was 15- to 20-fold higher in men than in women.[122] Even among athletes participating in the same sporting activity, rates of exertion-related SCD remain significantly higher among men.[124]

Psychosocial Determinants

Depression, anxiety, and psychological stress have all been linked to SCD and OHCA risk in diverse populations. Anxiety, particularly phobic anxiety, has been directly associated with SCD, but not nonfatal MI risk, in men[125] and women.[126] Depression[127,128] and other major psychiatric disorders, in particular schizophrenia,[129] have been associated with higher rates of SCD as well. Potential proarrhythmic properties of

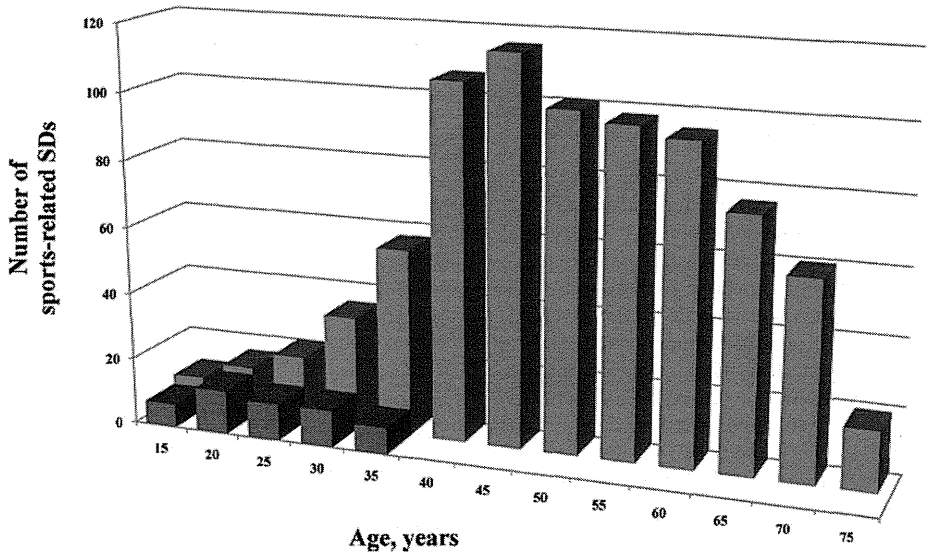

Figure 4. Age distribution of sports-related sudden deaths (SDs) in France. Deaths in the overall population (back) vs young competitive athletes (front). Among the 820 reported sports-related SDs, only 50 cases (6%) occurred in young competitive athletes. Adapted from Marijon et al[123] with permission of the publisher. Copyright © 2011, Wolters Kluwer Health. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

antipsychotic or antidepressant medications[130,131] could underlie part of this apparent excess SCD risk observed in patients with psychiatric disorders. In addition to the chronic effects of psychosocial stress, acute mental stress may act as a trigger for SCD.

Acute increases in the incidence of SCD have been documented in populations experiencing disasters such as earthquakes or wars.[132–135] On the day of the Northridge earthquake, there was a sharp increase in the number of SCDs related to CHD, which was followed by an unusually low incidence of CHD deaths in the week after the earthquake. In contrast, in the recent Japan earthquake and tsunami, where multiple aftershocks occurred and the level of devastation was high in comparison, the incidence of SCD[135] and OHCA[134] was increased for up to 4 weeks after the event, particularly among the elderly, and was significantly associated with level of seismic activity.[135] These disasters demonstrate how severe emotional stress may precipitate cardiac events in vulnerable and predisposed populations.

Air Pollution

Several studies have examined the impact of short-term air pollution exposures (most often fine particulate matter ($PM_{2.5}$), carbon monoxide, or oxides of nitrogen), and risk of OHCA.[136] In studies based in metropolitan areas of Europe,[137,138] United States,[139,140] and Australia,[141] elevated risks of OHCA have been temporally associated with increased levels of particulate matter. However, other studies from Washington State, United States,[142] and Copenhagen, Denmark,[143] did not find consistent associations. Long-term exposures to air pollution have been associated with increased mortality from CHD[144,145] and exposure to roadway pollutants may elevate SCD risk.[146]

SCD in the Patient Populations With Structural Heart Disease

Coronary Heart Disease

CHD underlies a significant proportion of SCD, especially in Western countries, and overt CHD is associated with marked increases in SCD risk.[147] In the Framingham Study, pre-existing CHD was associated with 2.8- to 5.3-fold increases in SCD risk,[13] and women and men have a 4- to 10-fold higher risk of SCD, respectively, after experiencing an MI.[5,38] The absolute rate of SCD seems to be highest in the first 30 days after MI and decreases gradually with time,[148,149] although the proportion of patients who die from non-SCD is greater in the first 18 months.[150] The incidence of SCD after MI has declined in parallel with CHD mortality over time,[149] with rates as low as 1%/y in patients receiving optimal medical therapy and revascularization.[150] However, rates remain high in certain subsets of post-MI patients.

There are 3 general settings where SCD occurs in patients with CHD: (1) during or after acute MI, (2) provoked by coronary ischemia without MI, and (3) in the presence of myocardial structural alterations (fibrosis, scar, left ventricular dilatation) secondary to prior MI or chronic ischemia. Only 19% and 38% of cardiac arrest survivors develop a new Q-wave MI and enzymatic evidence of MI, respectively.[62] The prevalence of acute coronary thrombus or active coronary lesion in autopsy series of SCD varies depending on autopsy protocol and histological techniques, ranging from 19% to 74%.[151–153] With respect to the type of active lesion found at autopsy, approximately two-third of coronary thrombi are organizing, and late stage lesions or coronary erosions are more commonly encountered in women.[154] In most series,[152,155,156] stable plaques and chronic changes alone are found in ≈50%

of SCD victims with CHD on autopsy. From these data, it seems that plaque rupture with or without associated thrombosis and MI is present in some, but not all, patients with CHD at the time of SCD.

The potential underlying mechanism precipitating SCD also differs depending on the setting in which it occurs and the chronicity of disease. The 2 most common mechanisms are thought to be polymorphic VT/VF precipitated by acute ischemia and infarction and monomorphic VT degenerating to VF arising from a reentrant circuit within or surrounding a myocardial scar. In addition to these primary arrhythmic causes, a significant proportion of SCDs in the post-MI population seem to be because of nonarrhythmic causes such as myocardial rupture and extensive reinfarction, and this percentage seems to be highest within the first month after MI.[157] In patients with end-stage ischemic cardiomyopathy, other modes of death such as acute pump failure and respiratory arrest resulting in PEA, or primary bradyarrhythmias comprise a significant proportion of SCD as well.[158]

Risk Factors for SCD in Patients With Established CHD

Left ventricular systolic dysfunction and severity of HF symptoms are currently the strongest predictors of SCD risk among patients with prior MI and ischemic cardiomyopathy.[158–160] After MI, mortality risk increases gradually until the left ventricular ejection fraction (LVEF) declines to 40%, and then exponentially increases as LVEF decreases further.[161] SCD rates reach 10% during a median follow-up of ≈2 years among patients with LVEF <30% and CHF in clinical trials.[148,162] Based on randomized clinical trials performed in populations with low LVEFs and CHF,[162–164] ICD therapy is recommended for patients with ischemic dilated cardiomyopathy, prior MI, New York Heart Association class II and III HF, and LVEF ≤35%.[165] In contrast, ICD therapy does not reduce mortality in the early post-MI period (within 40 days),[166,167] possibly because of a predominance of nonarrhythmic causes of death during this time window.[157]

Stratifying SCD risk based solely on LVEF and degree of systolic HF has 2 major well-recognized limitations. First, LVEF and New York Heart Association class are both strongly associated with other modes of cardiovascular death,[148,168] and patients with the greatest functional impairment secondary to systolic HF and lowest LVEF are more likely to die from HF as opposed to SCD.[158] The inability of these clinical markers to discriminate SCD risk from other competing causes of death has important clinical implications. In a recent prospective study series of 1100 patients with systolic dysfunction,[169] patients with CHD who received primary prevention ICDs on the basis of LVEF and CHF were more likely to die than to experience an appropriate ICD therapy from their device. Second, the majority of patients who experience a SCA or SCD do not seem to have LV systolic dysfunction and clinical HF preceding death.[7,19] In a prospective registry of cardiac arrests in the Netherlands, only 26% of SCAs with heart disease had HF before death, and only 19% of patients had an LVEF ≤30%.[14] In a more contemporary cohort in Multnomah County, Oregon, one-third of SCAs who had an echocardiogram before death had an LVEF<35%.[170]

In addition to LVEF and CHF, other potential markers of increased SCD risk in patients with CHD include sustained VT induced at electrophysiology study, left ventricular scar size and heterogeneity on cardiac magnetic resonance, T-wave alternans, markers of autonomic function such as baroreflex sensitivity and impaired heart rate turbulence, and conventional ECG measures such as left bundle branch block, QRS duration, left ventricular hypertrophy, and QT interval.[161,171–173] To date, only inducible sustained VT at electrophysiology study has been proven in a randomized clinical trial to identify individuals at a higher risk of SCA versus non-SCA.[171] However, the sensitivity of this test in isolation is inadequate to guide ICD therapy, especially in patients with LVEF <30%.[161,171] Recently, sustained VT at electrophysiology study was also found to be effective at stratifying arrhythmic death risk among patients with LVEF <35% in the early post-MI period.[174]

Risk Factors for SCD in Patients With Preserved LVEF

Although the incidence of SCD is lower in patients with HF with preserved LVEF as compared with those with reduced LVEF, the ratio of SCD to progressive HF deaths is higher, with SCD comprising 11% to 28% of all deaths.[175–177] Relatively little is known about SCD risk prediction in patients with CHD with preserved LVEFs. Prior history of MI, HF, and history of diabetes mellitus are consistent risk factors for SCD in this population.[178,179] Other potential clinical risk factors identified in these populations include male sex, AF, physical inactivity, left bundle branch block on ECG, NT-proBNP (N-terminal pro-B type natriuretic peptide) levels, and severity of coronary artery disease.[68,178,179]

Cardiomyopathies

Next to CHD, non–ischemic cardiomyopathies are the second most frequent cause of SCD in the United States and European countries, which account for ≈10% to 15% (Figure 2).[7,10,18] Furthermore, the prevalence of cardiomyopathies in young autopsied SCD victims aged ≤35 years is higher and is reported to be 15% to 30%.[24,25,180,181] However, non–ischemic cardiomyopathies are more frequently observed as a cause of SCD in Japan (≈30%–35% of SCD victims).[182] The 3 major causally distinct cardiomyopathies are non–ischemic dilated cardiomyopathy (NIDCM), HCM, and ARVC.

Non–Ischemic Dilated Cardiomyopathy

NIDCM has an estimated prevalence of 1:2500[183] and is defined by the presence of LV dilatation and LV systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment.[184] Causes of NIDCM include gene mutations, myocarditis caused by viral, bacterial, fungal, or parasitic infections, toxicity because of alcohol, chemotherapeutic agents, metals, and autoimmune and systemic disorders. However, the majority of cases remain unexplained despite a thorough evaluation. Inherited NIDCM is reported to occur in ≤40% of cases, mostly in an autosomal dominant fashion.[185] To date, mutations in >40 genes have been reported, in which *TTN, MYH7, TNNT2,* and *LMNA* are the most frequently identified, encoding titin, myosin heavy chain, cardiac troponin T (all in sarcomere), and lamin A/C (in nuclear envelope), respectively.[185]

Prior episodes of sustained VT, history of syncope, reduced LVEF, HF, and family history of SCD are the primary

risk factors used to identify patients at a sufficiently high enough SCD risk to warrant ICD therapy.[186] Two primary prevention randomized trials of ICD therapy[187,188] included NIDCM patients with LVEF of ≤35% and HF symptoms (New York Heart Association I–III) and demonstrated significant reductions in the SCD rate in patients with NIDCM (hazard ratio of 0.20[188] and 0.34[189]) and reductions in total mortality when combined in meta-analysis.[189] However, as in patients with ischemic cardiomyopathy, LVEF has a low sensitivity and specificity for predicting SCD and more specific markers are needed.[190] Recently, midwall fibrosis detected by late gadolinium enhancement cardiac magnetic resonance was demonstrated to improve SCD risk prediction beyond LVEF in a large study of patients with NIDCM.[191]

Hypertrophic Cardiomyopathy

HCM, defined by increased LV wall thickness not solely explained by abnormal loading conditions, is considered the most common inherited cardiac disease with an estimated prevalence of 1:500 in the general population.[192] In adult patients, the clinical diagnosis of HCM is made by cardiac imaging showing a left ventricular wall thickness of ≥15 mm in ≥1 segments. HCM can be present with lesser degrees of the wall thickening (13–14 mm), but other features of HCM, such as a family history, noncardiac symptoms and signs, ECG abnormalities, and abnormalities on multimodality cardiac imaging, are required to support the diagnosis.[193] To date, >1500 mutations in >11 genes encoding components of the sarcomere or adjacent Z-disc have been identified, with the most common encoding β-myosin heavy chain and myosin binding protein C.[192,193]

The annual incidence of cardiovascular death in HCM is ≈0.5% to 2% in contemporary series, and SCD from a lethal ventricular arrhythmia remains one of the common modes of death.[192,193] SCD is more likely to occur in young patients (<30 years) and is uncommon in older patients (>60 years).[192] Established risk factors for SCD in patients with HCM include a history of unexplained syncope, family history of SCD, a maximal left ventricular wall thickness of ≥30 mm, repetitive non–sustained VT, and abnormal blood pressure response to exercise.[192] According to the American College of Cardiology Foundation and American Heart Association guidelines, the presence of ≥1 of these risk factors can be used to select patients for primary prevention ICD placement.[194] The most recent European Society of Cardiology guidelines[193] recommend the use of a prediction model, which incorporates absolute risk and individual effect sizes of the above and other SCD risk factors (Figure 5)[195] at 1- to 2-year intervals. Implantation of an ICD is recommended in patients with an estimated 5-year SCD risk of ≥6% and a life expectancy of >1 year (class IIa).

Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC is a genetically determined heart muscle disorder characterized by fibrofatty replacement of the right ventricular myocardium.[196] As the disease progresses, the left ventricle may also become involved. The estimated prevalence of ARVC is 1: 2000 to 5000,[197] and ≤60% of the patients have a mutation with an autosomal dominant trait and incomplete penetrance.[198] Among ≈15 genes have been reported to cause

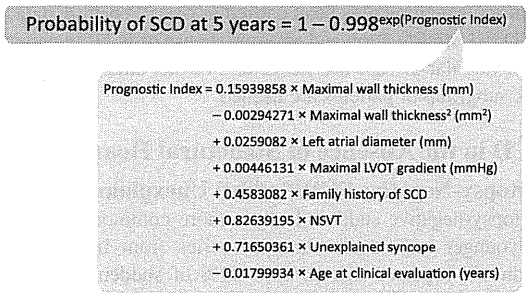

Figure 5. Sudden cardiac death (SCD) risk prediction model for patients with hypertrophic cardiomyopathy. A web-based risk calculator is provided on the website of European Society of Cardiology (http://www.doc2do.com/hcm/webHCM.html). LVOT indicates left ventricular outflow tract; and NSVT, non–sustained ventricular tachycardia. Adapted from O'Mahony et al[195] and Elliott et al[193] with permission of the publisher. Copyrights © 2014, Oxford University Press. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

ARVC, mutations in genes encoding components of cardiac desmosomes (plakophilin 2, desmoglein 2, and desmoplakin) are most frequently identified.[198] The 2010 Task Force diagnostic criteria for ARVC[196] consist of major and minor findings in 6 different categories: (1) structural alterations, (2) tissue characterization, (3) repolarization abnormalities, (4) depolarization abnormalities, (5) arrhythmias, and (6) family history including genetic testing.

SCD is a common cause of death in patients with ARVC especially in those in the fourth decade of life or younger, and it may be the first arrhythmic event in up to 50% of cases.[199,200] Several observational studies[201–204] showed that the annual rate of death or VF in patients treated by ICDs was 1.5% to 4%, and predictors of appropriate ICD therapy include a history of a cardiac arrest or VT with hemodynamic compromise, younger age, LV involvement, unexplained syncope, presence of non–sustained VT, and inducibility during electrophysiology study.[201,204] Current American College of Cardiology Foundation/ American Heart Association/Heart Rhythm Society guidelines[186] recommend the prophylactic use of an ICD in those who have ≥1 risk factors for SCD (class IIa).

Valvular Heart Disease

Valvular heart disease is reported to be the cause of death in 1% to 5% of the SCD victims (Figure 2).[10,18,205] Even after surgical procedures, SCD occurs in 15% to 30% of patients, accounting for 0.2% to 0.9%/y and is most commonly triggered by ventricular arrhythmias.[206] Patients with aortic stenosis are at the highest risk of SCD after valve replacement, particularly within 2 years.[206] Before valve replacement, asymptomatic patients with severe AS have annual SCD rates of 1%–3 %,[207,208] and recent observational data suggest that this risk may be lowered by early surgery.[209] The role of mitral valve prolapse in SCD is controversial. The majority of mitral valve prolapse is thought to be benign, but there are certain characteristics such as leaflet thickness, redundancy, and increased LV diameter that seem to be associated with higher risk,[210] and recent data suggest that women with bileaflet prolapse and complex

ventricular ectopy may be at particular risk.[211] Overall, data on SCD risk stratification and appropriate use of ICDs in patients with valvular disease are scarce and further studies in this at-risk subgroup of patients are needed.

SCD in the Absence of Structural Heart Disease

Autopsy-Negative SCD/Sudden Unexplained Death

Autopsy-negative sudden death is more commonly reported in younger individuals. Autopsy series from Ireland[24] and Sydney[181] reported that 27% to 29% of sudden arrhythmic deaths in individuals aged <35 years had no demonstrable structural heart disease on autopsy. In a Danish nationwide study of SCD,[23] this proportion was even higher (43%). However, when detailed histologic examinations are performed, the percentage of autopsy-negative SCD is much lower. In a prospective study of 273 consecutive SCD cases aged 1 to 35 years in Italy,[180] detailed histologic examination identified concealed pathologic substrates, such as focal myocarditis, regional ARVC, and conduction system abnormalities in 60 of 76 cases without macroscopic evidence for structural heart disease. After histologic exam, only 16 (6%) had no detectable abnormalities. Although discordances in the frequency of the autopsy-negative SCDs could be because of differences in regional genetic background, it is likely that the frequency of autopsy-negative cases would decrease if more detailed histologic examinations were carried out in all SCD victims.

Among patients with autopsy negative SCD, ≈50% will have inherited arrhythmic syndromes,[212,213] such as, long-QT syndrome (LQTS), BrS, catecholaminergic polymorphic VT, and early repolarization syndrome. Even when structural abnormalities of uncertain significance are found, inherited arrhythmic syndromes seem to underlie a significant fraction of SCDs.[214] Taken together, these finding suggest that substantial numbers of SCD may be attributable to inherited arrhythmic syndromes in the young. Performing molecular autopsies in cases with autopsy-negative SCD and cascade screening of families is important to establish the cause of death and to identify relatives potentially at high SCD risk. In cases of sudden unexplained death, where a diagnosis is not made either by antemortem or postmortem analysis, genetic testing of family members reveals a possible disease-causing mutation in 31% of families, and inherited arrhythmic syndromes comprise 30% of these mutations.[215]

Inherited Arrhythmic Disorders and Their Epidemiology

Long-QT Syndrome

Congenital LQTS is a hereditary disorder, characterized by delayed myocardial repolarization resulting in prolongation of the QT interval on 12-lead ECG and predisposition to torsade de pointes, which can result in SCD.[216,217] Approximately 75% of patients with LQTS and 95% of genotype-positive LQTS will have a mutation in genes encoding the slow component (*KCNQ1*, LQT1) and the rapid component (*KCNH2*, LQT2) of the delayed rectifier potassium current and the cardiac sodium channel (*SCN5A*, LQT3).[218,219] Conversely, it is estimated that 25% to 35% of genetically affected patients have a normal or borderline QTc at rest,[219,220] requiring exercise or a catecholamine infusion to disclose the masked QT interval.[217,220,221] To directly estimate the prevalence of LQTS, Schwartz et al[222] performed 12-lead ECGs in 43 080 white infants. Prolonged QTc intervals of 451 to 460, 461 to 470, and >470 ms were observed in 177 (0.41%), 28 (0.06%), and 31 (0.07%) infants, respectively. Of these, 17 of 43 080 infants were found to be affected by LQTS on the basis of genetic testing and further clinical evaluation, indicating a prevalence among whites of 1:2534. Extrapolating these results to the nongenotyped infants, the authors estimated the prevalence of LQTS was closer to 1:2000.[222]

The estimated incidence of cardiac arrest or SCD before the age of 40 years in untreated patients is estimated to be 0.30%/y, 0.60%/y, and 0.56%/y in LQT1, LQT2, and LQT3, respectively.[219] Most arrhythmic events developed during exercise or emotional stress in LQT1, at rest or with sudden noises in LQT2, and at rest or during sleep in LQT3.[223] Other risk factors for arrhythmic events in LQTS include prior history of syncope, significant QTc prolongation,[219,224] and location and number of mutations.[219,224–227] β-Blockers remain the mainstay of therapy for the majority of these patients, and ICDs are generally reserved for patients who have experienced a cardiac arrest.[228]

Brugada Syndrome

BrS was first described in 1992[229] and is thought to underlie, to a certain extent, the mystery of unexpected nocturnal death, which is colloquially called Pokkuri in Japan, Lai Tai in Thailand, and Bangungut in the Philippines.[230] BrS is a primary electrical disorder affecting middle-aged men with their first arrhythmic event typically developing during sleep at a mean age of 40 years.[231] The clinical phenotype is 8 to 10× more prevalent in men than in women, which is attributable, at least in part, to the higher testosterone level in men.[232] Twelve-lead ECGs at rest are characterized by a coved type ST-segment and J point elevation of ≥2 mm (0.2 mV) followed by a negative T wave in the right precordial leads (V1-3), which is referred to as a type 1 Brugada ECG.[231]

In the 2013 Heart Rhythm Society/European Heart Rhythm Association/ Asia Pacific Heart Rhythm Society expert consensus statement,[228] BrS is diagnosed when a type 1 ST-segment elevation is observed either spontaneously or after the administration of a sodium channel blocking agent in at least 1 right precordial lead (V1 and V2), which is placed in a standard or a superior position; in which case, documentation of VT/VF, clinical symptoms, or a family history is no longer necessary. Table 1 displays the reported prevalence of a type 1 Brugada ECG across population-based studies. The prevalence of the type 1 ECG pattern in adults is greatest in Japan,[233,234] the Philippines,[235] and among Japanese-Americans in North America[236] (0.15%–0.27% [1:350–700]). Rates in Europe[237–239] (0%–0.017% [<1:5000]) and North America[240,241] (0.005%–0.1% [1:1000–20 000]) seem to be lower. These estimates of BrS do not account for temporal variability of the ECG morphology[233] or patients who exhibit type 1 ECG only in the superior lead positions or after drug-provocation.[228]

Table 1. Prevalence of a Type 1 Brugada ECG* in the Population Studies

Country	Authors	Year Published	Individuals Screened, n	Male Sex, %	Mean Age or Range of Age, y	Type 1 ECG, n (%)
Europe						
Finland	Junttila et al[264]	2004	2479	100	18–30	0
Greece	Letsas et al[237]	2007	11488	58	15–98	2 (0.017)
Italy	Gallagher et al[238]	2008	12012	91	30±9	2 (0.017)
Germany	Sinner et al[265]	2009	4149	49	51±14	0
Denmark	Pecini et al[239]	2010	18974	45†	52±12*	0
North America						
Canada	Lee et al[241]	2005	3983	100	31	4 (0.100)
United States (Japanese–American)	Ito et al[236]	2006	8006	100	45–68	12 (0.150)
United States	Patel et al[240]	2009	162590	65	Not described	8 (0.005)
Asia						
Japan	Sakabe et al[233]	2003	3339	79	>18	5 (0.150)‡
Japan	Yamakawa et al[266]	2004	20387	51	10	1 (0.005)
Japan	Oe et al[267]	2005	21944	51	7	1 (0.005)
Japan	Tsuji et al[234]	2008	13904	27	58±10	37 (0.266)
Philippines	Gervacio-Domingo et al[235]	2008	3907	Not described	≥20	7 (0.179)
Taiwan	Juang et al	2011	20562	39	49±21	1 (0.005)
Korea	Uhm et al	2011	10867	100	21±5	0

*Studies including patients with a coved type ECG and J point amplitude ≥0.1 mV were excluded.

†In the first examination.

‡Those with a continuous type 1 ECG.

The primary risk factors for SCD in type 1 BrS are prior history of syncope or aborted SCD. In recently published multicenter registry studies,[242–244] the incidence of the cardiac events (SCD, VF, and appropriate ICD shocks) in type I BrS ranged from 7.7% to 10.2%/y, 0.6%–3.0%/y, and 0.5%–0.8%/y in those with a history of aborted SCD because of VF, syncopal episodes, and no symptoms, respectively.

Catecholaminergic Polymorphic VT

Catecholaminergic polymorphic VT is a familial arrhythmogenic disorder characterized by polymorphic ventricular tachyarrhythmias or bidirectional VT induced by physical or emotional stress.[245] The patients show no detectable cardiac morphological abnormalities, and the ECG is normal except for a lower heart rate at rest.[245,246] The affected patients usually develop arrhythmic events (syncope, aborted cardiac arrest, or SCD) during adrenergic activity in the first or second decade of life,[245,247–249] and the clinical course is considered to be highly malignant. Without proper treatment such as β-blockers, flecainide, and ICDs,[245–251] mortality reaches >30% by the age of 30 years[250] and the estimated 8-year fatal or aborted SCA event rate after the diagnosis is 13%.[247] The population prevalence of catecholaminergic polymorphic VT is difficult to estimate because it cannot be detected on resting 12-lead ECG, but is projected to be ≈1:10000.[228]

Early Repolarization Syndrome

An early repolarization ECG pattern (ERP), which consists of a J wave elevation ≥0.1 mV, either notched or slurred, accompanied by an ST-segment elevation, has long been considered to be a benign finding and unrelated to serious cardiac events.[252,253] This notion has recently been challenged by studies demonstrating that an ERP in the inferior and lateral leads is more commonly found in patients with idiopathic VF as compared with controls,[254,255] raising the possibility that the ERP may be a marker of an arrhythmogenic substrate. Considering these data, a recent expert consensus panel defined ERP as the presence of J point elevation ≥0.1 mV in ≥2 contiguous inferior and lateral leads, and early repolarization syndrome is diagnosed in the presence of ERP in a patient resuscitated from otherwise unexplained VF/polymorphic VT or autopsy negative SCD victim with a previous ECG demonstrating ERP.[228]

The question of whether an ERP on resting ECG confers an increased risk of SCD in the general population has been examined in several population-based studies,[253,256–261] which are summarized in Table 2. The definition of ERP varies widely between these studies. In some studies, ERP had to be present in the inferior and lateral leads,[256,257,260] but others considered J point ST elevations in all body surface leads to be ERP.[253,258,259,261] Prevalence estimates in these studies range from 1% to 24% and 0.6% to 6.4% for J point elevation of ≥0.1 and 0.2 mV, respectively. Notwithstanding these differences in methodology, ERP is reported to be more prevalent in younger age groups, men, or individuals of African descent.[258,259,262] The majority of European studies[256,257] and Japanese studies[260,261]

Table 2. Prevalence of Early Repolarization ECGs and Their Prognosis in the Population Studies

Country	Authors	Year Published	Position of ERP	Individuals Screened, n	Male Sex, %	Mean Age at Baseline, y	J Point Elevation, n (%)		Mean Follow-Up Period, y	RR of Death According to the ERP	
							≥0.1 mV	≥0.2 mV		Cardiac	Sudden or Arrhythymic
Europe											
Finland	Tikkanen et al[256]	2009	Inf or lat	10864	52	44±8	630 (5.8)	67 (0.6)	30±11	1.28* in inf 1.34* in lat	1.43* in inf 0.75 in lat
Germany	Sinner et al[257]	2010	Inf or lat	6213	49	52±10	812 (13.1)	Not described	19	3.44*	Not described
France	Rollin et al[268]	2012	Inf or lat	1161	52	50±9	159 (13.7)	74 (6.4)	14±2	5.28* in inf 6.27* in lat†	Not described
North America											
United States	Klatsky et al[253]	2003	All	73088	44	37±13	670 (0.9)	494 (0.7)	14	0.8†	Not described
United States	Uberoi et al[269]	2011	Inf or lat	29281	87	55±15	664 (2.3)	0	8±4	1.73 in inf 0.83 in lat†	Not described
United States	Olson et al[258]	2011	All	15141	44	54±6	1866 (12.3)	Not described	17±4	Not described	1.23 in all 2.03* in whites
United States	Ilkhanoff et al[259]	2014	All	5039	46	25	1249 (20.9)‡	Not described	23	0.96†	Not described
Asia											
Japan	Haruta et al[260]	2011	Inf or lat	5976	44	Not described	1429 (23.9)	Not described	24±15	0.75*	1.83*
Japan	Hisamatsu et al[261]	2013	All§	7630	41	52	264 (3.5)	Not described	15	2.54*	Not described

ERP indicates early repolarization pattern; Inf, inferior leads; Lat, lateral leads; and RR, relative risk.

*Statistically significant.

†For the cardiovascular death.

‡At baseline.

§≥0.2 mV in anterior leads.

found significant associations between the ERP and cardiac or sudden arrhythmic death, whereas studies conducted in the United States generally did not.[253,258,259] One US study suggested that the association between ERP and SCD may be limited to women and white individuals.[258] These results suggest that there may be an ethnic, racial, and sex differences in the relationship between the ERP and SCD.

It is important to note that the calculated relative risks for sudden arrhythmic death associated with a J point elevation of 0.1 mV are modest (Table 2) and the absolute risk of arrhythmic death in asymptomatic individuals with the ERP on ECG is extremely low.[255] Three-fold elevations in sudden/arrhythmic death have been observed when ERP is more strictly defined as a J point elevation of >0.2 mV associated with horizontal/descending ST segment limited to the inferior leads.[256,263] However, this pattern was only noted in 0.3% of the population.[263]

Conclusions

SCD is a major public health problem all over the world, and although resuscitation rates are improving, the majority of individuals who experience SCA will not survive, and often the underlying cardiac condition is not recognized before death. Behind these tragic events, there are various causes, risks, and predisposing conditions, which differ in the prevalence according to region, age, ethnicity, race, and sex. As such, a multifaceted approach, which addresses risk factors both in high- and low-risk populations, will be required to decrease the burden of SCD. Population-wide approaches as well as improved identification of high-risk individuals who will benefit from ICDs will be crucial to prevent SCD events and improve patient outcomes. Although substantial progress has been made in this field, further studies addressing SCD prevention across the whole spectrum of disorders, from CHD in the general population to the rarer inherited disorders, are warranted to address many remaining uncertainties on the multitude of factors, which underlie susceptibility to SCD.

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Disclosures

None.