Patients with inherited arrhythmia syndromes, such as long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia, and their latent forms, are at risk for fatal arrhythmias. These diseases are typically associated with genetic mutations that perturb cardiac ionic currents. The analysis of cardiac events by genotype-phenotype correlation studies has revealed that fatal arrhythmias in some genotypes are triggered by physical or emotional stress, and those in the others are more likely to occur during sleep or at rest. Thus, the risk stratification and management of affected patients differ strikingly according to the genetic variant of the inherited arrhythmia syndrome. Risk stratification may be further refined by considering the precipitating factors, such as drugs, bradycardia, electrolyte disturbances, fever, and cardiac memory. Moreover, an increasing number of studies imply that the susceptibility of fatal arrhythmias in patients with acute coronary syndrome or takotsubo cardiomyopathy is at least partly ascribed to the genetic variants causing inherited arrhythmia syndromes.

In this article, we review the recent advances in the understanding of the molecular genetics and genotype-phenotype correlations in inherited arrhythmia syndromes and consider the triggers and precipitating factors for fatal arrhythmias in these disorders. Further studies to explore the triggers and precipitating factors specific to the genotypes and diseases are needed for better clinical management. (Circ J 2015; 79: 1185–1192)

Key Words: Fatal arrhythmias; Genes; Mutations; Precipitating factors; Triggers

Since the identification of the genes for long QT syndrome (LQTS) manifesting as syncope and sudden cardiac death (SCD), an increasing number of new genes associated with a new group of syndrome, called the inherited arrhythmia syndromes, have been discovered. Those include LQTS, Brugada syndrome (BrS), early repolarization syndrome (ERS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) etc. and the term “channelopathies” defines the inherited arrhythmia syndromes caused by mutations of the genes encoding cardiac ion channel proteins or their modifiers that regulate cardiac ion channels.

Patients with an inherited arrhythmia syndrome are at variable risk for SCD and need to be managed according to risk stratification that includes the genotype of the disease. Current pharmacological treatments are not always successful in preventing cardiac events and an implanteable cardioverter defibrillator (ICD) is the only option for high-risk patients; therefore, risk stratification is a critical step in clinical management. In particular, the identification of triggers and precipitating factors for fatal arrhythmias is effective for predicting cardiac events and reducing the risk for SCD.

This review will focus on the genetic basis and the triggers or precipitating factors for fatal arrhythmias in inherited arrhythmia syndromes, including their latent forms. Recent studies point to an important role for genetic variants of ion channels in patients with acute coronary syndrome (ACS) or takotsubo cardiomyopathy accompanying fatal arrhythmias.

Inherited Arrhythmia Syndromes

LQTS
LQTS is a genetically heterogeneous disorder characterized by QT interval prolongation on ECG and polymorphic VT, torsades de pointes (TdP), leading to syncope and SCD. Since the discovery of 3 causative genes (KCNQ1 for LQT1; KCNH2 for LQT2; SCN5A for LQT3) in 1995 and 1996,1,3 to date at least 13 genes for LQTS have been identified (Table 1).4-6 Most of them encode cardiac ion channels or their modifiers. The first 3 LQTS (LQT1–3) account for approximately 75% of clinically definite LQTS, and the other genes account for only 5% of cases.

KCNQ1 and KCNH2 encode the α-subunit of the slow component (hs) and rapid components (hk), respectively, of the delayed rectifier potassium currents.7,8 SCN5A encodes the α-subunit of the cardiac voltage-gated sodium channels (sodium currents: Ina). A decrease of the outward currents (hks) or an increase of the inward currents (Ina) in ventricular myocytes causes a delay of repolarization, thus leading to prolongation of the QT interval on ECG (Figure 1). TdP is thought to be triggered by ventricular action potential (AP) phase 2
early afterdepolarization under conditions of a prolonged QT interval.\(^4\) Because the \(I_s\) activates very slowly on depolarization and is increased by sympathetic activation, its net repolarizing current can accumulate at higher heart rates, thus contributing to QT adaptation during tachycardia. Loss-of-function of the \(I_s\) by \(KCNQ1\) mutations can theoretically cause QT prolongation, especially during tachycardia. Indeed, cardiac events in LQT1 mostly occur during physical exertion or emotional stress, typically during swimming (Table 2).\(^9\) The \(I_s\) rapidly activates but is suppressed by strong depolarization because of its inward rectification property.\(^8\) Emotional stress and sudden auditory stimuli are major triggers for cardiac events in LQT2 (Table 2).\(^9,10\) Moreover, female patients with LQT2 have an increased risk of cardiac events during the postpartum period.\(^11\) In contrast to LQT1 and LQT2, cardiac events in LQT3 patients mainly occur during sleep or at rest (Table 2).\(^8\) In this manner, the triggers for fatal arrhythmias in LQTS differ strikingly among the genotypes.

\(\beta\)-blocker therapy (propranolol or nadolol but not metoprolol) is extremely effective for patients with LQT1,\(^12,13\) and also partly effective in patients with LQT2,\(^15\) but efficacy is controversial in patients with LQT3.\(^16\) Mexiletine, which blocks persistent \(I_{Na}\), can shorten the QT interval and may be effective in LQT3.\(^15\) The appropriate guidance to avoid specific triggers for fatal arrhythmias should be given to genotyped LQTS patients.

### Table 1. Responsible Genes and Their Altered Functions in Inherited Arrhythmia Syndromes

<table>
<thead>
<tr>
<th>LQTS</th>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>Kv7.1</td>
<td>↓ (I_s)</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNH2</td>
<td>Kv11.1</td>
<td>↓ (I_Na)</td>
</tr>
<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>Nav1.5</td>
<td>↑ (I_Na)</td>
</tr>
<tr>
<td>LQT4</td>
<td>ANKB</td>
<td>Ankyrin</td>
<td>↑ Na/K, ATPase</td>
</tr>
<tr>
<td>LQT5</td>
<td>KCNE1</td>
<td>MinK</td>
<td>↓ (I_Ka)</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE2</td>
<td>MiRP1</td>
<td>↓ (I_Ks)</td>
</tr>
<tr>
<td>LQT7</td>
<td>KCNJ2</td>
<td>Kir2.1</td>
<td>↓ (I_K1)</td>
</tr>
<tr>
<td>LQT8</td>
<td>CACNA1C</td>
<td>Cav1.2</td>
<td>↑ (I_Ca)</td>
</tr>
<tr>
<td>LQT9</td>
<td>CAV3</td>
<td>Caveolin-3</td>
<td>↑ (I_Na)</td>
</tr>
<tr>
<td>LQT10</td>
<td>SCN4B</td>
<td>Nav64</td>
<td>↑ (I_Na)</td>
</tr>
<tr>
<td>LQT11</td>
<td>AKAP9</td>
<td>Yotiao</td>
<td>↓ (I_Ks)</td>
</tr>
<tr>
<td>LQT12</td>
<td>SNTA1</td>
<td>Syntrophin-(\alpha1)</td>
<td>↑ (I_Na)</td>
</tr>
</tbody>
</table>
| LQT13 | KCNJ5 | Kir3.4 | ↑ \(I_Ka\)
| LQT | CALM1 | Calmodulin | ↓ Ca\(^{2+}\) binding to proteins |
| LQT | CALM2 | Calmodulin | ↓ Ca\(^{2+}\) binding to proteins |

| BrS | SCN5A | Nav1.5 | ↓ \(I_Na\) |
| BrS2 | GPD1-L | GPD1-L | ↓ \(I_Na\) |
| BrS3 | CACNA1C | Cav1.2 | ↓ \(I_Ca\) |
| BrS4 | CACNB2b | Cav\(\beta2\) | ↓ \(I_Ca\) |
| BrS5 | SCN1B | Nav\(\beta1\) | ↓ \(I_Na\) |
| BrS6 | KCNE3 | MiRP2 | ↑ \(I_Ks\) |
| BrS7 | SCN3B | Nav\(\beta3\) | ↓ \(I_Na\) |
| BrS8 | KCNJ8 | Kir\(\beta\) | ↑ \(I_Ka\)
| BrS9 | CACNA2D1 | Cavo\(\beta2\) | ↓ \(I_Ca\) |
| BrS10 | KCND3 | Kv4.3 | ↑ \(I_Ks\) |
| BrS11 | MOG1 | MOG1 | ↓ \(I_Na\) |
| BrS12 | ABCC9 | SUR2A | ↑ \(I_{Na}\)

| ERS | KCNJ8 | Kir\(\beta\) | ↑ \(I_Ka\)
| ERS2 | CACNA1C | Cav1.2 | ↓ \(I_Ca\) |
| ERS3 | CACNB2b | Cav\(\beta2\) | ↓ \(I_Ca\) |
| ERS4 | CACNA2D1 | Cavo\(\beta2\) | ↓ \(I_Ca\) |
| ERS5 | ABCC9 | SUR2A | ↑ \(I_{Na}\)
| ERS6 | SCN5A | Nav1.5 | ↓ \(I_Na\) |

| CPVT | RYR2 | Ryanodine receptor | ↑ \(Ca^{2+}\) release from SR |
| CPVT2 | CASQ2 | Calsequestrin-2 | ↑ \(Ca^{2+}\) release from SR |
| CPVT3 | KCNJ2 | Kir2.1 | ↓ \(I_K1\) |
| CPVT4 | TRDN | Triadine | |
| CPVT5 | CALM1 | Calmodulin | ↓ \(Ca^{2+}\) binding to proteins |
| CPVT6 | CALM2 | Calmodulin | ↓ \(Ca^{2+}\) binding to proteins |

Modified with permission from Mizusawa Y, et al\(^h\) and Antzelevitch C.\(^h\) BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ERS, early repolarization syndrome; LQTS, long QT syndrome; SR, sarcoplasmic reticulum.
patients. In LQT1, excessive physical stress, especially swimming, should be avoided. In LQT2, the use of items that cause sudden noises such as alarm clocks and ringing telephones should be avoided. LQT3 patients who experience aborted cardiac arrest or are resistant to optimal medical therapy are indicated for ICD. Left cardiac sympathetic denervation (LCSD) is another therapeutic option for patients at high risk.\textsuperscript{16}

**BrS**

BrS is a hereditary disorder characterized by ST segment elevations in the right precordial ECG leads, associated with a high incidence of syncope or SCD because of fatal arrhythmias, which mostly affects adult males.\textsuperscript{4,17}

The transient outward potassium current ($I_{to}$), which is abundant in the right ventricular epicardium compared with the endomyocardium, has been postulated to contribute to the pathogenesis of BrS. The presence of a prominent $I_{to}$-mediated AP notch in the right ventricular epicardium but not endomyocardium causes a transmural voltage gradient manifested as a J-point elevation on the right precordial ECG.\textsuperscript{18} An additional decrease of the inward currents ($I_{Na}$, $I_{Ca}$: Ca currents) or increase of the outward currents ($I_{to}$ and $I_{KATP}$, ATP-sensitive potassium channels) during the early phase of the AP can theoretically lead to an increased transmural voltage gradient, manifesting as the Brugada ECG pattern and phase 2 reentry.\textsuperscript{18}

Since the first identification of a causative SCN5A mutation in 1998,\textsuperscript{19} BrS has been linked to mutations in genes that perturb cardiac ionic currents contributing to the early phase of the AP (Table 1).\textsuperscript{4,5,20,21} Mutations in SCN5A that cause loss-of-function of the $I_{Na}$ have accounted for the major form of BrS in approximately 20% of cases, and other gene mutations account for approximately 10%; thus, approximately 70% of BrS cases remain to be genetically elucidated.

In contrast to LQTS, the knowledge about the genotype-phenotype correlation in BrS is limited. Cardiac events in BrS patients mostly occur during sleep or at rest (Table 2).\textsuperscript{22} ICD is the only available treatment for preventing SCD. Isoproterenol infusion, which increases the $I_{Na}$ and suppresses the $I_{to}$ by insufficient recovery from inactivation with increasing heart rate, is useful for suppressing the electrical storm of ventricular fibrillation (VF).\textsuperscript{23} Quinidine and bepridil, which have an inhibitory effect on $I_{Na}$, and cilostazol, a phosphodiesterase III inhibitor that increases $I_{Ca}$ through elevation of cAMP, have been shown to be effective to some extent as adjunctive therapy in cases of frequent ICD shocks (Table 2).\textsuperscript{23–25}

**ERS**

The ER or J wave is characterized by ≥0.1 mV J-point elevation in 2 contiguous inferior and/or lateral ECG leads. The prevalence of ER in the general population is highly variable and ranges from 1% to 13%.\textsuperscript{26} An ER pattern was long thought to be a benign ECG manifestation. However, Haissaguerre et al demonstrated an association between ER and idiopathic VF in 2008,\textsuperscript{27} and the combination is now defined as ERS.\textsuperscript{28}

As with BrS, a higher epicardial $I_{Na}$ relative to the endocardium, as well as other ionic currents contributing to the early phase of the AP, have been implicated as important mediators of ER. ERS shares similar ECG characteristics, clinical characteristics and risk factors with BrS.\textsuperscript{29} Most patients with ERS experience arrhythmic events during sleep or at rest (Table 2).\textsuperscript{16} Of note, the genetic basis for ERS overlaps that for BrS (Table 1).\textsuperscript{30} The presence of ER on ECG is associated with electrical storm in patients with BrS.\textsuperscript{29} Akin to BrS, VF can be suppressed to some extent by quinidine, bepridil, cilostazol, and isoproterenol infusion or with pacing at increasingly rapid rates (Table 2).\textsuperscript{29,30}

**CPVT**

CPVT is a hereditary disorder characterized by adrenergic-induced bidirectional and polymorphic VT without structural heart diseases, leading to syncope and SCD.\textsuperscript{31,32}

**RYR2** (encoding the cardiac ryanodine receptor), **CAQS2** (encoding cardiac calsequestrin), **KCNJ2** (encoding $I_{K}$: inward rectifying potassium currents), **TRDN** (encoding the junctional protein triadine) have been identified as causative genes for CPVT (Table 1).\textsuperscript{3,5,32} Recently, mutations in 2 (CALM1 and CALM2) of 3 genes (CALM1–3) encoding identical peptide sequences for the essential Ca$^{2+}$-signaling protein calmodulin were reported to be associated with malignant forms of LQTS, CPVT and idiopathic VF.\textsuperscript{34,35}

In CPVT, cytosolic Ca$^{2+}$ overload in ventricular myocytes or Purkinje cells generates inward currents thorough the Na$^{+}$/Ca$^{2+}$ exchanger, leading to membrane depolarization called delayed afterdepolarization (DAD). If Ca$^{2+}$ overload under adrenergic conditions is sufficient to bring DAD to a threshold, it induces full AP, manifesting as ventricular ectopies on ECG.\textsuperscript{32} Exercise or catecholamine infusion can easily induce an arrhythmic burden in patients with CPVT.\textsuperscript{31,36} Therefore, exercise should be limited in affected patients. $\beta$-blocker therapy can reduce the arrhythmia burden and death, so is the first choice for CPVT, but is not completely effective.\textsuperscript{31} Patients with CPVT resistant to $\beta$-blocker therapy should be considered for flecainide (Table 2).\textsuperscript{37} Combined therapy with LCSD can be also considered. ICD should be the last intervention because the device can potentially have proarrhythmic effects because discharges could prove disastrous by evoking a self-induced vicious circle.\textsuperscript{32}

### Table 2. Typical Triggers for Fatal Arrhythmias and Appropriate Medical Therapy in Inherited Arrhythmia Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Typical trigger</th>
<th>Medical therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>Exercise, swimming</td>
<td>$\beta$-blockers</td>
</tr>
<tr>
<td>LQT2</td>
<td>Emotion, auditory stimuli, postpartum period</td>
<td>$\beta$-blockers, potassium supplement</td>
</tr>
<tr>
<td>LQT3</td>
<td>Sleep, rest</td>
<td>($\beta$-blockers), mexiletine</td>
</tr>
<tr>
<td>BrS</td>
<td>Sleep, rest, fever</td>
<td>Isoproterenol infusion, quinidine, bepridil, cilostazol</td>
</tr>
<tr>
<td>ERS</td>
<td>Sleep, rest</td>
<td>Isoproterenol infusion, quinidine, bepridil, cilostazol</td>
</tr>
<tr>
<td>CPVT</td>
<td>Exercise</td>
<td>$\beta$-blockers, flecainide</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
Precipitating Factors for Fatal Arrhythmias

Several factors are known to be precipitators for cardiac events in patients with inherited arrhythmia syndromes or their latent forms (Table 3). Combinations of precipitating factors can increase the risk of fatal arrhythmias. Gene-specific or mutation site-specific precipitating factors may also be present.

Drugs

Not only QT-prolonging antiarrhythmic drugs, such as quinidine and sotalol, but also other non-antiarrhythmic drugs, such as antihistamines, antibiotics and antipsychotics, exhibit marked QT prolongation and development of TdP (drug-induced LQTS (dLQTS)).

Between 5% and 30% of patients with complete atrioventricular (AV) block (AVB) develop TdP. Patients with AVB-induced TdP display an abnormally prolonged QT interval at slower heart rates than do those without TdP, though, in general, the slower the heart rate, the longer repolarization.

Bradyarrhythmias

Between 5% and 30% of patients with complete atrioventricular block (AVB) develop TdP. Patients with AVB-induced TdP display an abnormally prolonged QT interval at slower heart rates than do those without TdP, though, in general, the slower the heart rate, the longer repolarization.

Electrolyte Disturbances

Electrolyte disturbances such as hypokalemia, hypocalcemia and hypomagnesemia, especially hypokalemia, are major precipitating factors for TdP.

In the case of dLQTS, QT-prolonging drugs and those interfering with their metabolism must be promptly discontinued. Intravenous magnesium sulfate is the initial therapy of choice regardless of serum level. Serum potassium, which paradoxically increases the $I_{Kr}$, should be maintained in the high-normal range. Because drug-induced TdP is pause-dependent, as with other acquired LQTS, temporal cardiac pacing is highly effective in preventing recurrence of TdP. If temporal cardiac pacing is not available or while preparing for it, isoproterenol infusion should be considered to increase heart rate.

On the other hand, many drugs, including antiarrhythmic drugs, psychotropic drugs, and anesthetic drugs, have been reported to induce the Brugada ECG and/or fatal arrhythmias in patients with BrS (refer to www.brugadadrugs.org). Patients with BrS should be advised not to use these drugs or to use them only under controlled conditions.

<table>
<thead>
<tr>
<th>Precipitating factor</th>
<th>Phase</th>
<th>Fatal arrhythmia</th>
<th>Phenotype</th>
<th>Responsible gene and mutation/variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>TdP</td>
<td>LQTS</td>
<td>LQTS-causing genes (≤40%)</td>
<td></td>
</tr>
<tr>
<td>Bradyarrhythmias</td>
<td>TdP</td>
<td>LQTS</td>
<td>LQTS-causing genes (17–28%); common in KCNH2 but rare in KCNQ1</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>TdP</td>
<td>LQTS</td>
<td>LQTS-causing genes</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>TdP</td>
<td>LQTS</td>
<td>KCNH2 (5S-pore region)</td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>Subacute</td>
<td>Electrical storm</td>
<td>SCN5A G400A</td>
<td></td>
</tr>
<tr>
<td>Takotsubo cardiomyopathy</td>
<td>Acute</td>
<td>VT</td>
<td>KCNH2 V115-A121dup</td>
<td></td>
</tr>
<tr>
<td>Cardiac memory</td>
<td>TdP</td>
<td>LQTS</td>
<td>KCNH2</td>
<td></td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; TdP, torsades de pointes; VF, ventricular fibrillation. Other abbreviations as in Table 1.
Precipitating Factors for Fatal Arrhythmias

Fever has been reported as a precipitating factor for fatal arrhythmias in both BrS and LQTS (Table 3). In some BrS patients, fever unmasks the Brugada ECG and also triggers fatal arrhythmias. We also recently identified a G584S mutation in KCNH2, which has been previously identified in patients with mild phenotype, in a female patient with dLQTS who developed TdP during fever. Of note, these mutations converge at the S5-Pore region in KCNH2 (Figure 3), a region that has been postulated to be related to voltage-dependent inactivation of KCNH2 channels. Functional analysis has demonstrated that wild-type (WT) KCNH2 increased current amplitudes when temperature is elevated, but mutants (A558P, F640V) did not much increase current amplitudes compared with the WT, possibly because of its faster inactivation rate at elevated temperature, which suggested that the failure of an increase of $I_{Kr}$ might be the cause of QT prolongation and TdP during fever. These findings make us aware of the importance of reducing body temperature by timely use of antipyretics.

**Figure 2.** Fever-induced coved-type ST elevations and frequent premature ventricular contractions in a patient with Brugada syndrome. 12-lead ECG recorded at (A) normal body temperature (36.2°C) and (B) in a febrile state (38.5°C).

**Figure 3.** Location of KCNH2 mutations associated with fever-induced long QT syndrome in a predicted topology of KCNH2. Red filled circles indicate the mutation sites.
ACS
ACS is often accompanied by the development of fatal arrhythmias during its acute phase. Despite successful resuscitation from aborted SCD, fatal arrhythmias sometimes occur incessantly, the so-called electrical storm. A novel SCN5A G400A mutation has been identified in a patient who experienced electrical storm during the acute phase of myocardial infarction (MI) (Table 3).64 Myocardial ischemia and subsequent reperfusion result in increased production of reactive oxygen species (ROS), which induced a wide range of modifications to cellular lipids, nucleic acids and proteins, and the cardiac sodium channel is 1 of the proteins that can be modified by ROS.65 Besides reduction of I_Ks by SCN5A mutation, further reduction of the I_Ks in the setting of ACS may cause pronounced slowed conduction and prolonged refractoriness in the ventricular myocardium, leading to the formation of a substrate for reentry. Therefore, indigenous I_Ks reduction may contribute to electrical storm during the acute phase of ACS.

On the other hand, a rare form of fatal arrhythmia, which is associated with excessive QT prolongation and has the characteristics of pause-dependent TdP (ACS-TdP), was reported to occur during the subacute phase of ACS (3–11 days after presentation) in 8 (1.8%) of 434 patients.66 Crotti et al reported that 2 (15%) of 13 Caucasian patients with ACS-TdP were found to carry LQTS mutations (KCNH2 R744X, SCN5A E446K) (Table 3).67 Additionally, 9 (62%) of the remaining 11 patients carried the KCN2H2 K897T variant, which is commonly present in an allele frequency of 35% in Caucasians but is rare in Asians. We have previously reported a patient with ACS-TdP, in whom we identified a KCNQ1 G643S variant.68 Carriers of the variant are at higher risk for fatal arrhythmias in the presence of appropriate precipitating factors such as bradycardia and hypokalemia, and the variant shows mild reduction of the KCNQ1/KCNEL (I_Ks) channels,71 although the allele frequency of the variant in Asians is approximately 6–10%.72 A rat experimental model of MI showed that downregulation of potassium channel gene expression (ERG, KCNE1, KCNQ1) and the potassium currents (I_Ks, I_Kr) occurs in surviving myocytes from the infarct zone 2 days after MI.73 This suggests that major repolarizing currents (ie, I_Ks and I_Kr) may be reduced in the actual setting of the subacute phase of ACS in humans. Therefore, it is conceivable that patients with genetic variants, such as KCNQ1 G643S and KCN2H2 K897T, would be at higher risk of TdP in the presence of additional reduction of repolarizing currents during the subacute phase of ACS.

Takotsubo Cardiomyopathy
Takotsubo cardiomyopathy is characterized by transient ventricular dysfunction in the absence of coronary artery disease and accompanied by repolarization abnormalities, including T-wave inversions and QT prolongation. It is commonly triggered by severe emotional or physical stress.74 The exact underlying mechanisms of the disease remain unclear; however, it is believed that ventricular dysfunction and subsequent repolarization abnormalities result from catecholamine-mediated myocardial toxicity.

Madias et al reported that 8 (8.6%) of 93 total patients with takotsubo cardiomyopathy developed TdP or VF.75 The QT interval became pronouncedly prolonged over the 24–48 h after presentation, and most cases of TdP or VF occurred during the subacute phase of the disease. The initiation pattern of TdP exhibits characteristics of pause-dependent LQTS. A novel duplication mutation (V115-A121dup) in the Per-Arnt-Sim domain of KCNH2 has been identified in a patient with takotsubo cardiomyopathy who experienced excessive QT prolongation and syncope (Table 3).76 suggesting that patients with LQTS have a higher risk of TdP when experiencing takotsubo cardiomyopathy.

Cardiac Memory
Cardiac memory is characterized by an altered T wave (marked inversion of T-wave polarity with QT prolongation) on the surface ECG during normal ventricular activation following altered electrical activation such as left bundle branch block, ventricular preexcitation and right ventricular pacing.77 Although cardiac memory is usually considered benign, cessation of long-lasting ventricular pacing has induced T-wave polarity changes with marked QT prolongation after a normal ventricular activation pattern, followed by TdP in a LQT2 patient (Table 3).78 Therefore, apart from patients with pause-dependent TdP, unnecessary ventricular pacing should be avoided in LQTS patients. Conversely, in LQTS patients with ventricular pacing, the appearance of occasional spontaneous normal rhythm should be inhibited.

Besides those mentioned, other factors such as congestive heart failure, nervous system injury, starvation, female sex etc are also known as precipitating factors for fatal arrhythmias.79

Conclusions
In this review, we have highlighted the triggers and precipitating factors for fatal arrhythmias in patients with inherited arrhythmia syndromes, including their latent forms, in which clinical phenotypes become manifest under specific conditions (drugs, bradycardia, electrolyte disturbances, fever, ACS, takotsubo cardiomyopathy, and cardiac memory). At present, risk stratification is based on clinical phenotype, including episodes of syncope, findings of the surface ECG and electrophysiological study, and family history for SCD, and the yield of genetic testing is not sufficient to determine the risk for future events. Further studies to unmask the potential triggers and precipitating factors for fatal cardiac events in patients carrying genetic variants associated with inherited arrhythmia syndromes is urgently required to improve the risk stratification process.

Acknowledgments
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Disclosures
None.

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