WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)
Robert W. Hickey

Date Submitted for review: January 5, 2010

Clinical question.
Following unsuccessful attempts at resuscitation in previously healthy children and young adults (<50 yo) with cardiac arrest (P), does consideration of a channelopathy as the etiology of the arrest (I), as compared with standard management (C), improve outcome (appropriate diagnosis and management, identification of at risk family members)

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<th>Is this question addressing an intervention/therapy, prognosis or diagnosis?</th>
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<td>State if this is a proposed new topic or revision of existing worksheet:</td>
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Conflict of interest specific to this question
Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?
No

Search strategy (including electronic databases searched).

- State inclusion and exclusion criteria
   Included studies of children and young adults with sudden death without an etiology
   Last searched in July of 2009

- PubMed: Arrhythmia, Cardiac/*genetic/mortality: 206 hits
- PubMed: sudden death AND channelopathy: 91 hits
- EM Base: Disease search of sudden death (exploded terms) and limited to humans from 1995 on: 308 hits
- EM Base: Disease search of sudden death (exploded terms) AND channelopathy from 1995 on: 441 hits
- Cochrane library for “sudden death”: 27 reviews, none relevant
- Hand searching of citations from review articles
- I have an extensive personal file on this topic: I have ongoing Pubmed (Cubby, MyNCBI) searches on a variety of resuscitation topics including “cardiac arrest” and I have been collecting articles on channelopathies for over 10 years. This file was hand searched.

Number of articles/sources meeting criteria for further review:
129 articles added to End Note library.
18 citations in COS statement
A total of 62 citations in Worksheet

NOTE: search strategy was run again on Dec 24, 2009. There were several new reviews, case reports, and descriptions of new mutations—these are not added to the worksheet. There is a new article by Petko analyzing the outcome of children with LQTS identified by family screening (nonproband)—amongst 84 such patients, 13 had implantable defibrillators placed with 4 delivering appropriate shocks. This study is placed in the evidence grid and worksheet (under section 5: Will a diagnosis of channelopathy...) but is not included in the COS. Also, there is a new article by Johnson describing a link between a gene responsible for LXTS type 2 and epilepsy that is included in the worksheet within the miscellaneous section.
# Summary of evidence

## Evidence Supporting Clinical Question

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<td>Arnestad 2007&lt;sup&gt;P/S&lt;/sup&gt;</td>
<td>Doolan 2004&lt;sup&gt;Au&lt;/sup&gt; Puranik 2005&lt;sup&gt;Au&lt;/sup&gt; Ong 2006&lt;sup&gt;Au&lt;/sup&gt; Behr 2003&lt;sup&gt;F&lt;/sup&gt; Behr 2008&lt;sup&gt;F&lt;/sup&gt; Tan 2005&lt;sup&gt;F&lt;/sup&gt; [Petko, 2008, 1756-8]&lt;sup&gt;F&lt;/sup&gt;</td>
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**Level of evidence**

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint

- **Au**=Autopsy
- **P**=Proband not SIDS
- **P/S**=Proband SIDS
- **F**=Family

**Note:** Most studies were technically of good quality within the limitations of the population studied and the genes that were targeted. For the purpose of this review, quality of evidence was influenced by sample size, number of genes screened and potential for referral bias.
### Evidence Neutral to Clinical question

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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
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E = Other endpoint

*Italicics* = Animal studies

### Evidence Opposing Clinical Question

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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint

*Italicics* = Animal studies
Background: Sudden unexpected death (SUD) is a lethal event that occurs in an apparently healthy person without warning or obvious cause. Causes of sudden death can be categorized as: (adopted from Ellison [Ellison, 2005, 37-44]): 1) Structural-functional: hypertrophic cardiomyopathy (HCM), coronary artery anomalies, cardiomyopathies, myocarditis, endocarditis, left ventricular outflow obstruction, atherosclerotic disease, congenital heart disease, 2) Electrical: Long QT syndrome (LQTS), short QT syndrome, WPW, Brugada syndrome, congenital heart block, catecholaminergic ventricular tachycardia (CVT), arrhythmogenic right ventricular cardiomyopathy (ARVC), and 3) Other: Pulmonary hypertension, drugs, commotio cordis. An Australian study of sudden cardiac death in people <35 yo found: congenital heart disease 7%, myocarditis 12%, HCM 15%, coronary artery disease 24%, unexplained (probable arrhythmogenic) 31% and other 11% [Doolan, 2004, 110-2].

Sudden death is defined as a witnessed natural unexpected death occurring within 1 h after onset of symptoms in a previously healthy person, or an unwitnessed natural unexpected death of a person observed to be well 24 h prior to being found dead. Sudden unexpected death best describes the scenario in the hospital (typically ED) setting when the patient is pronounced dead without an obvious etiology. Sudden unexplained death best describes the patient with a normal autopsy following sudden unexpected death. The acronym SAD refers to sudden adult death (compared to sudden infant death [SID]) in some literature. But later literature refers to SAD as sudden arrhythmic death to acknowledge the likely-etioloogy (dysrhythmia) of death in patients with a negative autopsy and to acknowledge that it occurs in children and adults. A prospective study of coroners in the UK identified the annual number of deaths from SAD at 1.34/100,000 population with 18% of cases having a family history of other premature deaths. They estimated that this is equivalent to 500 deaths per year in the UK and 2,500 deaths per year in the US [Behr, 2007, 601-5]. Ellison estimates that there are approximately 500 cases of unexplained SAD among children and adolescents in the US per year [Ellison, 2005, 37-44]. The underlying causes of inherited arrhythmic deaths in SAD include a variety of mutations in ion channel genes causing “channelopathies.” The incidence of the most common channelopathy, LQTS, is approximately 1 in 5,000 people.

Making the diagnosis of an arrhythmic death can be challenging. With the exception of HCM and ARVC (a problem primarily of the desmosome that can cause fibro-fatty deposits and conduction problems) the autopsy is normal. Some patients present with a preceding history of “cardiac syncope” or a family history of unexplained deaths, drownings or accidents. But for many patients, death is the presenting symptom. In specialized cardio-genetic centers the diagnosis can be established post-mortem using the “molecular autopsy” to identify mutations in ion channels and by screening surviving family members for channelopathy genotypes and phenotypes. Shepard states, “The majority of genetic heart diseases show autosomal dominant inheritance and marked clinical heterogeneity. This means the probability of other family members being affected is high, but the variability in presenting phenotypes can often make a diagnosis very difficult.” [Shephard, 2009, 145-55].

This worksheet focuses on the importance of making the diagnosis of an arrhythmic death following an unsuccessful resuscitation attempt. Specifically: Following unsuccessful attempts at resuscitation in previously healthy children and young adults (<35 yo) with cardiac arrest (P), does consideration of a channelopathy as the etiology of the arrest (I), as compared with standard management (C), improve outcome (appropriate diagnosis and management, identification of at risk family members).

Evidence Evaluation:

To address this issue, several related questions need to be answered. Specifically, 1) what is the incidence of autopsy-negative sudden death cases (the population that will contain patients with channelopathies), 2) what is the incidence of diagnosable channelopathies within the population of autopsy-negative sudden death cases, 3) what clinical and laboratory approach will identify channelopathies in the deceased patient and surviving family members, 4) will a diagnosis of a channelopathy in the proband identify others at risk for sudden death, and 5) will a diagnosis of channelopathy in a deceased patient result in life-saving treatment of at-risk surviving family members? Related important questions are: a) what is the cost of a “molecular autopsy” b) do clinicians obtain important historic information following an unsuccessful resuscitation that will identify families that are at particularly high-risk for channelopathy (history of syncope, unexpected deaths from drowning and vehicle crashes, etc), and c) what is the psychosocial value of providing a “diagnosis” for grieving family members? The evidence relevant to these questions is reviewed below.

1) What is the incidence of autopsy-negative sudden death cases (the population that will contain patients with channelopathies)?

- In 2005 Puranik et al reported on the autopsies of non-traumatic sudden death in pts 5-35 yo [Puranik, 2005, 1277-82]. They concluded that 29% had “no or minimal structural heart disease” and thus likely had arrhythmic deaths. Of note, other cases of sudden death were reported in 4.5% of these families.
• Doolan et al reviewed 2986 autopsies in patients <35 yo. There were 193 cases of sudden death. Of these, the autopsy was negative in 60 (31%)--the authors infer that this 31% died of arrhythmogenic disorders [Doolan, 2004, 110-2].
• Eckart et al examined 126 nontraumatic sudden death in military recruits during basic training [Eckart, 2004, 829-34]. Autopsy was negative in 35%.
• In an editorial, Behr notes that sudden deaths account for approximately 10% of all deaths in pts 1-22 yo and 50% of these are “autopsy negative” [Behr, 2003, 1457-9].
• Up to 80% of autopsies in young children with unexpected death in children 1 week-18 mo, the age for SIDS, have negative autopsies [Cote, 1999, 437-43].
• Ong et al described autopsy results from a prospective cohort of cardiac arrests (from the OPALS study) occurring in children < 19 yo. Amongst patients with “natural death” (excludes accident, suicide, homicide) there were 78/208 (37.5%) normal autopsies. When SIDS was excluded the rate of normal autopsies decreased to 15/158 (9.5%) [Ong, 2006, 335-42].

2) What is the incidence of diagnosable channelopathies within the population of autopsy-negative sudden death cases?

This literature is subject to several biases. Many studies come from centers with an interest in channelopathies and have a referral bias because cases are more likely to be referred to them if someone suspects a channelopathy (thus inflating the number of positive findings). Also, many studies looked for only selected mutations and the number of identified mutations has increased over time (thus deflating the number of true channelopathies in earlier studies and those examining only selected mutations). There are currently 12 genes associated with LQTS, 7 with Brugada syndrome, 7 with ARVC, and 2 with CVPT. Further, identification of a mutation in a “channel gene” does not necessarily mean the phenotype will be associated with disease.

• Schwartz performed routine electrocardiograms on the third or fourth day of life in 34,442 infants and found that prolongation of the QT interval was associated with SIDS. [Schwartz, 1998, 1709-14]
• Arnestad demonstrated that 19 of 201 (9.5%) cases diagnosed as SIDS carry “functionally significant genetic variants in LQTS genes.” [Arnestad, 2007, 361-7]
• Ackerman performed postmortem molecular analysis looking for mutations in SCN5A in 93 SIDS patients. They found a mutation in 2 (2%). [Ackerman, 2001, 2264-9]
• Plant found a SCN5A mutation in 5% of African Americans with SIDS [Plant, 2006, 430-5].
• Otagiri found mutations of channel ion genes in 10% of a Japanese population with SIDS [Otagiri, 2008, 482-7].
• Conk found a functional mutation in a supporting protein associated with the sodium channel in 6% of black infants with SIDS [Cronk, 2007, 161-6].
• Millat found mutations of channel ion genes in 8.8% of a French population with SIDS [Millat, 2009, 502-9].
• Tester reviewed the literature of SIDS and channelopathies and concluded that 3-5% of SIDS cases are “proven” channelopathies and a more “realistic” estimate is 5-10% (based upon the presumption that not all channelopathies are yet identified and screening tests are imperfect) [Tester, 2005, 388-96].
• Lunetta screened drowned victims for selected LQTS-associated mutations and found 1 in 165 consecutive patients [Lunetta, 2003, 115-7].
• Tester surveyed for RyR2 mutations in SUD cases referred to his facility and found mutations in 7/49 (14%) [Tester, 2004, 1380-4].
• Chugh looked for selected, known channelopathy mutations in archived, paraffin-embedded myocardial tissue (not ideal for tissue sampling) and found mutations in 2/12 (16%) pts with SUD [Chugh, 2004, 1625-9].
• Tester found 10 LQTS-associated mutations among 49 cases of SUD referred to the Mayo Clinic’s Sudden Death Genomics Laboratory (note: there is a potential for referral bias) [Tester, 2007, 240-6].
• Albert found channel gene mutations in 10% of women with SADS [Albert, 2008, 16-23].

3) What clinical and laboratory approach will identify channelopathies in the deceased patient and surviving family members?

Studies examining survivors for inherited causes of cardiac death have included a variety of methods including: detailed history and physical exams, ECGs, echocardiograms, and molecular screens. The choice of tests and interpretation of results should be performed by a knowledgeable cardiologist. Some centers have established multidisciplinary cardiogenetic centers to facilitate an individualized, focused evaluation and genetic counseling as appropriate.

Other relevant literature:

• Behr has published an algorithm for diagnostic work up of families with SADS [Behr, 2008, 1670-80]
• ECG parameters for LQTS. [Allan, 2001, 178-82]
- Postema describes a method for accurate measurement of QT interval [Postema, 2008, 1015-8].
- It is important to calculate the QT interval because computer-generated readings are inaccurate. [Miller, 2001, 8-12] Even so, QT intervals may not permit accurate diagnosis. [Vincent, 1992, 846-52]
- EDTA-preserved blood or frozen tissue is better than paraffin embedded tissue for molecular diagnosis. Lymphocytes from spleen are best. [Carturan, 2008, 391-7]

4) Will a diagnosis of a channelopathy in the proband identify others at risk for sudden death?
- Behr examined families of Sudden Arrhythmic Death Syndrome (criteria: white, aged 4-64 yo, no cardiac history, seen alive in the 12 h before death, normal autopsy—including heart, negative toxicology screen) [Behr, 2003, 1457-9]. Seven of 32 families (22%) were diagnosed with an inherited cardiac disease: four with long QT syndrome; one with non-structural cardiac electrophysiological disease; one with myotonic dystrophy; and one with hypertrophic cardiomyopathy. One family had a death occur in a sibling during the interval between identifying the proband and interviewing the family.
- Behr later published a report with more extensive testing of families with SADS and found 53% of families have evidence of inherited heart disease and 30% had a history of additional unexplained premature deaths [Behr, 2008, 1670-80]. The reference describes the yield of individual tests and provides a nice algorithm for diagnostic work up of families.
- Tan investigated 43 families with a sudden unexplained death (SUD) at < 40 yo [Tan, 2005, 207-13]. They found an inherited arrhythmogenic disease in 12 (28%) of the families. Work up included ECG and echo with selected molecular genetic analysis. They identified 151 presymptomatic disease carriers (8.9 per family). There is some selection bias (15 families were referred to the author’s center—the remainder were seen primarily at the author’s center).
- In Tester’s study (referenced above) [Tester, 2007, 240-6], 7 of 10 families with LQTS-associated mutations identified on autopsy returned to the clinic for additional evaluation of first and second-degree relatives: 23 additional genotype-positive family members were identified.
- Hofman examined the first and second degree relatives of 25 families referred to their cardiogenetics department (referral bias) after sudden cardiac death of a child (1-18 yo) with ECG, exercise testing, echocardiography and DNA analysis. They established an inherited channelopathy in 11 (44%) families. [Hofman, 2007, e967-73]
- Baruteau reviews the literature and makes an argument for ECG screening of relatives of children with SIDS [Baruteau, 2009, 771-7].
- Additional case reports: [Todd, 2005, 540-3]

5) Will a diagnosis of channelopathy in a deceased patient result in life-saving treatment of at-risk surviving family members?

Because channelopathies are inherited (mostly autosomal dominant) other family members with the genotype are likely to be identified (as shown in #4 above). However, the phenotype is highly variable with some family members demonstrating a history of worrisome symptoms and others completely asymptomatic into old age. Furthermore, a “mutation” in an ion channel gene (especially a new mutation that has not been previously described in sudden death) may not confer a physiologic effect. Thus, it is not possible to answer this broadly stated question and generate an overall “number needed to screen to save one life”. Nonetheless, there are clearly documented cases of multiple deaths occurring in families with inherited channelopathies. The risk of death or aborted death in patients with an identified channelopathy is real but dependent upon the type of channelopathy and other factors. [Goldenberg, 2008, 2184-91, Hayashi, 2009, 2426-34, Hobbs, 2006, 1249-54, Kaufman, 2008, 831-6] Importantly, Beta blockers, sympathetic denervation and ICDs are available therapies that have been shown to prevent death. Note: a study published in 2008 by Petko et al analyzed the outcome of children with LQTS identified by family screening (nonproband) amongst 84 such patients, 13 had implantable defibrillators placed with 4 delivering appropriate shocks [Petko, 2008, 1756-8]

Related important questions are:
  a) what is the cost of a “molecular autopsy”?  
- In a review by Tester in 2006, the cost of cardiac channel genetic testing is estimated at $5,400 for LQTS alone and it is noted that insurance does not cover this cost. [Tester, 2006, 166-72]. Targeted family-specific (gene-specific) confirmatory tests for surviving family members cost approximately $900/person [Tester, 2005, 675-7]. Several commercial tests are now available. Personal communication with these companies reveals that they will perform tests on specimens from live patients as well as post-mortem specimens. Payment can often be negotiated with the companies and, with somewhat variable success, with insurance companies. It is particularly difficult to obtain payment from insurance companies for post-mortem specimens (deceased patients are no longer “covered entities”).
- A cost-analysis of genetic testing for LQTS in symptomatic index cases (not at autopsy) revealed an estimated cost of $2,500 per year of life saved [Phillips, 2005, 1294-300]
b) do clinicians obtain important historic information following an unsuccessful resuscitation that will identify families that are particularly high-risk for channelopathy (history of syncope, unexpected deaths from drowning and vehicle crashes, etc)?

- This is a knowledge gap. But in my personal experience, these questions are often undocumented.

c) what is the value of providing a “diagnosis” for grieving family members?

A review of grieving in sudden death has been published. [Merlevede, 2004, 341-8, Parkes, 1998, 856-9] In addition to the issue of grieving, there are important issues related to lawsuits (blame on health care providers for unsuccessful resuscitations), genetic counseling, etc. Establishing a diagnosis is of obvious benefit for these “intangibles.”

Good Review Articles:

Miscellaneous:
A recent study documented that 13/31 patients with LQTS experienced diagnostic delay after presentation with syncope or seizure (median delay 2.4 yrs) and 10 of the patients (31%) underwent at least one EEG for suspected primary seizures prior to the diagnosis of LQTS (lengthening the delay in diagnosis to a median of 9.75 yrs for those misdiagnosed with epilepsy). [MacCormick, 2009, 26-32]

Another recently published study found a link between LQTS type 2 and epilepsy [Johnson, 2009, 224-31]. The gene responsible for LQTS2, the KCNH2 gene, was originally cloned from the hippocampus and encodes a potassium channel active in astrocytes.

Identification and prevention of sudden death prior to the event is beyond the scope of this worksheet. However, an excellent commentary on the subject including a standardized cardiovascular risk-assessment form has been published in Pediatrics [Campbell, 2006, 802-4]. Of note, a separate worksheet on the “warning signs” of sudden death is being performed by ILCOR.

NOTE: subsequent to the July 30, 2009 Webinar the decision was made to extend the population of interest from <35 yo to < 50 yo. The autopsy data is limited to < 35 yo but the published recommendation for asking about a history of unexpected death uses a cutoff of 50 yo. For ease of teaching we changed the COS and Treatment recommendation to the 50 yo cutoff which is consistent with the AAPs question for preparticipation sports physicals and is also consistent with Pediatric Sudden Cardiac Death Risk Assessment form published by Campbell and Stuart [Campbell, 2006, 802-4].
Citations:


LOE 3. Quality Fair. They only looked at only one gene so they may have under reported the true frequency of channelopathies in this population. They used in vitro transfection to confirm phenotypic changes in conduction properties of ion channels.


LOE 3. Quality Fair. Population based longitudinal cohort of nurses and health care providers. Screened 5 genes. A limitation is that more lethal mutations would not have survived to study entry. They used in vitro transfection to confirm phenotypic changes in conduction properties of ion channels.


LOE 3. Quality Good. Norwegian study (more likely to capture patients in their health care system and provide population-based frequencies). I corresponded with the authors about the possibility of referral bias and they responded that they believe they are referred almost all of the cases in their catchment area and deny the possibility of significant referral bias. Screened 7 genes. They used in vitro transfection to confirm phenotypic changes in conduction properties of ion channels.


LOE 4. Quality Good. Prospectively identified patient population. There is a particularly tragic example where a 19 yo brother died during sleep in the interval between the proband's death and the formal assessment of the family.


LOE 4 Quality Good. Prospectively identified patient population. This is a follow up study to this groups previous study using a new population with an enhanced exam by expert cardiac pathologists and mutation analysis when feasible. They show a nice algorithm of their evaluation protocol for victims and family members.


LOE 4. Quality Poor. Very small sample size. Screened 5 genes. Archived, paraffin-embedded tissue (decreases yield). They used in vitro transfection to confirm phenotypic changes in conduction properties of ion channels.


LOE 3. Quality Poor. Screened only a single gene. This gene does not produce a channel pore protein but rather an pore-associated protein that affects the function of the channel (opening up a whole new area of inquiry). They claim the samples are "population based." Of interest, CAV protein mutations are also associated with molecular dystrophies and myopathies. They used in vitro transfection to confirm phenotypic changes in conduction properties of ion channels.


LOE 4. Quality: Good. Chart review. 425 cases of sudden unexpected death (excluding SIDS). 232 had a non-cardiac diagnosis on autopsy. 193 were diagnosed as sudden cardiac deaths. Cardiac deaths included coronary artery disease, HCM, myocarditis, congenital heart disease and "unascertained, probable primary arrhythmia". A total of 60 of the 425 cases of sudden unexpected death (14%) had a completely normal autopsy and were categorized as "unascertained, probable primary arrhythmia." Not clear if this is a tertiary care facility with associated referral bias.


LOE 4. Quality Fair. Chart review. Highly selective patient population (mostly healthy, young males) in a unique, stressful environment (basic training). 44/126 (35%) recruits with non-traumatic death had a normal autopsy.


LOE 4. Quality Fair. Referral bias (families were referred to their cardiogenetics department).


LOE 3 Quality Fair. Identified 474 cardiac arrests in children below 19 yo as part of OPALS study. 439 had matching autopsy records. Excellent population based study for pediatrics.


LOE 3 Quality Poor. Only screened one gene in an African American population. Not clear if population based or a referral population. Of interest, there was increased homozygous alleles (5%) in the SIDS population with a 1% frequency in a control population. Also of interest, transfected cells had nl ion channel properties at nl PH but abnormal function with acidosis (respiratory acidosis may be a trigger for SIDS).


LOE4. Quality Good. Chart review. Not clear if this is a referral center with associated referral bias. 16% of patients (70/427) with sudden non-traumatic death 5-35 yo had a normal autopsy. However, it could be argued that some of these non-traumatic sudden deaths were not "unexpected": they include some pts with asthma, diabetes, epilepsy, and sepsis as an etiology of sudden death (WHO defines sudden death as occurring within 24 h of symptom onset). If you exclude the patients with diabetes, epilepsy, and sepsis the prevalence of negative autopsies in those with truly unexpected death is 70/321 (21%).


LOE 4 Quality Good. Population from the Netherlands. I wrote to the corresponding author asking him about the potential for referral bias. He responded that referral bias was unlikely and he thought the majority of eligible cases were referred to their center (I believe that this is more likely in the Netherlands than in the US).


LOE4 Quality Poor. Likely referral bias. Small sample size. Screened one gene (associated with CPVT).


LOE 3 Quality Poor. Screened only 1 gene (associated with CPVT). Not clear if population based or referral population. Of interest, transfected cells had worse channel function when exposed to phosphorylated PKA or elevated intracellular Ca concentration (both, presumably associated with catecholamine surge). The authors speculate on a cause for catecholamine surge during sleep in infants with SIDS. Taken together, all of the SIDS studies by this group show: 1-2% CPVT, 5-10% LQTS and "older" SIDS victims (6mo-12mo) had a frequency of LQTS or CPVT in approximately 1/3rd


