Epidemiology and clinical aspects of sudden cardiac death in the young
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Are individuals within families with truly unexplained premature sudden death at risk during long-term follow-up?

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Submitted
ABSTRACT

Introduction
Sudden unexplained death (SUD) in young individuals often results from inherited cardiac disease. Accordingly, comprehensive cardiologic and molecular-genetic examination in surviving first-degree relatives unmasks such disease in ~35% of families. It is unknown whether individuals from diagnosis-negative families (in which such investigations revealed no such disease) are at risk of developing manifest disease or cardiac events during follow-up.

Methods
We retrieved vital status of surviving first-degree relatives from 84 families who presented to our cardiogenetics department in 1996-2009 because of SUD of ≥1 relative aged 1 to 50 years, in whom no diagnosis could be made. Moreover, we contacted relatives who previously visited our center for detailed information on themselves and their relatives.

Results
We obtained detailed follow-up (median duration of 6.6 years; interquartile range, 4.7-9.6) in 340 of 417 first-degree relatives (81.5%) from 77 of 83 diagnosis-negative families (87.2%). Vital status, available in 405 relatives, showed that 20 (4.9%) relatives died during follow-up, including one natural death under the age of 50. This 10-year-old girl belonged to a family with multiple previous cases of (aborted) SUD, in which another child was successfully resuscitated during follow-up. Two-hundred and thirty-four of 340 first-degree relatives (68.8%) underwent cardiologic examination. Of these, 76 (32.5%) were reevaluated. Inherited cardiac disease was diagnosed in three families (3.6%).

Conclusions
In first-degree relatives of young SUD victims with no manifest abnormalities during initial examination, the risk of developing manifest inherited cardiac disease or cardiac events during follow-up is low. This does not apply to families with a clear idiopathic inherited arrhythmia syndrome.
INTRODUCTION
Sudden death in apparently healthy young individuals is often caused by inherited cardiac diseases. Consequently, the risk of cardiovascular disease and ventricular arrhythmias is higher in relatives of young sudden cardiac death victims, in particular relatives under the age of 35, than in the general population. In approximately 18% (range, 6%–35%) of young sudden death cases, autopsy does not reveal the cause of death, and in many countries autopsy is not routinely performed in all of these fatalities. Sudden unexplained death (SUD) is diagnosed in both cases. Comprehensive cardiologic and molecular-genetic evaluation of first-degree relatives of young SUD victims is indicated. This evaluation unmasks an inherited cardiac disease, potentially explaining the fatal event, in approximately 35% of the families, enabling timely prophylactic treatment. Relatives from SUD victims in whom the initial comprehensive cardiologic and genetic examination does not lead to a familiar diagnosis are usually advised to undergo cardiologic reexamination on a regular basis, as inherited cardiac diseases may manifest during follow-up. Whether cardiologic examination during follow-up unmasks previously undiagnosed inherited conditions and whether these relatives are at risk for SUD has, to our knowledge, not been studied. Indeed, if relatives of an SUD victim are carrier of an undiagnosed inherited cardiac disease, potentially fatal cardiac events could occur during follow-up. To address these issues, we carried out an observational follow-up study among first-degree relatives of young SUD victims, in whom the initial cardiologic and genetic examination did not lead to a diagnosis.

METHODS
Setting
Details on our multidisciplinary cardiogenetics outpatient clinic at the Academic Medical Center, Amsterdam, the Netherlands (teaching hospital), and our SUD registry comprising families who underwent cardiologic and genetic examination after the SUD of a relative aged 1 to 50 years (the proband), have been described in detail. SUD was defined as out-of-hospital natural death in a previously healthy individual whose family had no known inherited cardiac disease, in whom death occurred within one hour after the start of complaints or within 24 hours of the victim being seen alive and well, and in whom autopsy was not performed or initially did not explain the death. In our cardiogenetics clinic, relatives of SUD victims are counseled by both a cardiologist and a clinical geneticist or genetic counselor, who collect detailed information on the SUD proband (including circumstances of SUD) and the family. This is followed by tailored cardiologic examination and targeted molecular genetic testing. When these investigations are completed, the relatives receive a letter that summarizes the complete evaluation that was performed in their family. When a diagnosis is made, appropriate follow-up is arranged. When no diagnosis is made (diagnosis-negative family), most relatives are advised to undergo repeated cardiologic evaluation, in particular when they develop possible cardiac symptoms. This advice is individualized and based on the level of suspicion of an inherited cardiac disease and age. For example, children are usually advised to undergo yearly cardiologic evaluation, whereas adults are advised to undergo evaluation every three to five years.
Study population

This analysis comprised all surviving first-degree relatives (parent, sibling, or child) from diagnosis-negative families of a SUD victim aged 1 to 50 years, of whom ≥1 first-degree relative presented to our cardiogenetics clinic between 1996 and mid 2009.14

Follow-up

First, all first-degree relatives who had not visited our center recently were contacted by using a standardized questionnaire to obtain detailed information on themselves and their family. Second, we contacted at least one first-degree relative per family by phone for additional questioning. Cardiologic reevaluation, newly diagnosed (inherited) cardiac disease and the occurrence of cardiac events (aborted cardiac arrest or sudden death) as well as death due to other causes at any age in the family were questioned. In relatives who had visited our center and consented, additional information was obtained from the relative’s general practitioner, cardiologist, or hospital records, when necessary. All the relatives who were examined within a year after the family came to our attention were considered to be part of the initial examination. The yield of cardiologic evaluation during follow-up included the yield of cardiologic evaluation in all relatives who were evaluated for the first time ≥1 year after the family came to our attention and the yield of reevaluation in relatives who were part of the initial examination.

Information on vital status of first-degree relatives in whom no detailed information could be collected was obtained from the Dutch national population registry and was verified until January 1, 2013. This national population registry does not contain information on the cause of death. Follow-up durations were counted from the date when the first relative of that family presented to our center to the date when information on a relative was obtained or the relative’s death.

Statistical analysis

Continuous data are presented as median (interquartile range) and categorical variables as number (percentage). Descriptive statistics were used for analysis.

RESULTS

Study population

Ten of the 93 SUD families who were classified diagnosis-negative SUD after the first cardiologic examination14 were excluded from the present analysis: five families because only second-degree relatives were examined, three who were double-counted because it was found after initial analysis that they were related to each other, and two because no follow-up information, including vital status, was available in any relative. Hence, we included the first-degree relatives of 83 SUD victims. Nineteen probands (22.9%) were aged <21 years, and autopsy was performed in 40 (48.2%) (Table 1). At time of their SUD, the 83 SUD victims had 417 living first-degree relatives. Complete detailed follow-up information was available in 63 families (75.9%), comprising 308 first-degree relatives. In 20 families (24.1%) follow-up was incomplete, with detailed follow-up information in 34 relatives, vital status only in 61, and no follow-up information in 12. The median follow-up period was 6.6 years (interquartile range, 4.7-9.6).
Overall, vital status was retrieved in 405 of 417 relatives (97.1%; median of 4 per family; range, 1-13) from all 83 families. Their median age was 41.5 years (interquartile range, 26-55) when their family first came to our attention, 267 relatives were below the age of 50, and 177 (44.1%) were male. During follow-up, 20 (4.9%) relatives died, including two under the age of 50 (0.7% of this age-group). One girl died suddenly at the age of ten while watching television (II:5 in Figure 1; see text below), although the cardiologic evaluation that was performed three months earlier was unremarkable. A female relative from another family committed suicide at the age of 44. Of the 18 deceased individuals over the age of 50, eight died from a definite non-cardiac cause, while the cause of death was unknown in 10 relatives.

In addition, four sudden death events among non-first-degree related relatives were reported in four families: one 48-year old uncle of a SUD proband died suddenly from an unknown cause while gardening; one 41-year old aunt of a SUD proband died presumably from a ruptured abdominal aortic aneurysm; and a second cousin of a SUD proband died suddenly and unexpectedly in his early forties. Finally, the aunt of a SUD proband died suddenly at the age of 44 while vacuum cleaning. Autopsy revealed arrhythmogenic cardiomyopathy. Molecular-genetic testing of all genes linked to arrhythmogenic cardiomyopathy (PKP2, DSP, DSC2, DSG2, JUP, TMEM43 and PLN) was negative.

Nonfatal cardiac events
Detailed follow-up information was available in 340 relatives (81.5%; median of 4 per family; range, 0-13) from 77 families. These relatives had a median age of 41 years (interquartile range, 27-54) when their family first came to our attention, including 230 below the age of 50, and 157 (46.2%) were male. During follow-up, one more definite cardiac event occurred: a younger sister of the 10-year old girl that died suddenly, was successfully resuscitated (II:6 in Figure 1) and received an appropriate implantable cardioverter-defibrillator (ICD) shock after an episode of ventricular fibrillation one year later. The girls originated from a Moroccan family with an extremely malignant family history in one generation including multiple cases of (aborted) idiopathic ventricular
fibrillation (IVF; ventricular fibrillation of unknown etiology) and SUD (Figure 1). This family came to our attention in 2001 after the aborted cardiac arrest of a 16-year old boy (II:3). His family history included SUD of his sister at the age of 9 (II:4). Consanguinity was denied. Comprehensive cardiologic examination in the 16-year old boy, the parents and the other children did not reveal any abnormalities. Very recently, the causal genetic substrate, a mutation in the gene encoding calmodulin 1 (\textit{CALM1}), was identified in all affected individuals (unpublished data).

Cardiologic reevaluation and inherited cardiac disease

Of the 340 relatives with detailed follow-up information, 223 were evaluated once following the SUD event in their family. In addition, the information of 11 relatives who underwent cardiologic examination for other reasons could also be used. Thus, 234 of 340 first-degree relatives (68.8%) were part of the initial evaluation. Of these, 76 (32.5%) were reevaluated as recommended after the negative initial examination (N=66) or for another reason (N=10).

In three families (3.6%) an inherited cardiac disease was identified during follow-up. In the first family, a brother of the 39-year-old male SUD victim was diagnosed with Brugada syndrome. No autopsy had been performed in the proband. Only the daughter of the SUD victim had previously been examined, and results of all tests, including ajmaline challenge, were unremarkable. The individual in whom Brugada syndrome was diagnosed, was cardiologically evaluated for the first time during follow-up.

The second family underwent evaluation because of the SUD of 42-year-old man in whom no autopsy was performed. Initial cardiologic examination revealed a slightly dilated aorta in the proband’s brother. During follow-up, minimal aorta dilatation was identified in two other brothers. In all three brothers and their mother a missense mutation in the \textit{TGFBR1} gene was identified. Because none of the relatives showed signs of Marfan syndrome or Loeys-Dietz syndrome, the final diagnosis was familial thoracic aortic aneurysms/dissections.

In a third family, three first-degree relatives who were aged 37-53 years experienced myocardial infarction during 10.5 years of follow-up. In addition, one relative underwent coronary artery bypass graft surgery. All affected relatives were diabetic and had hyperhomocysteinemia, possibly related to folate deficiency. Two of these relatives were part of the initial evaluation.

Figure 1. Family tree of a family with multiple cases of SUD and IVF. SUD indicates sudden unexplained death; IVF, idiopathic ventricular fibrillation.
in their family. At that time, premature atherosclerosis was already suspected based on the family history, but an inherited dyslipidemia or definite coronary artery disease could not be identified in the evaluated relatives. Finally, one first-degree relatives got an ICD implanted in his fifties, but information on the indication is lacking.

**DISCUSSION**

This study demonstrates that first-degree relatives from young SUD victims in whom the initial cardiologic and genetic evaluation did not lead to a diagnosis, have a favorable prognosis. In this large cohort of diagnosis-negative SUD families the cardiac event rate during follow-up was low. Importantly, all events that were definitely related to the SUD of the proband occurred in one family with an extremely malignant history of IVF and SUD. During follow-up, inherited cardiac disease manifested in three families (3.6%). In these families, the first relative in whom the diagnosis was made showed discrete, non-diagnostic abnormalities at the initial evaluation, or had not been examined before.

**Follow-up of patients and families with IVF or SUD**

IVF or SUD may ultimately be explained through a manifested phenotype during long-term follow-up. However, follow-up data of relatives of young victims of IVF or SUD are scarce. In a study on the role of provocative testing with procainamide and epinephrine in IVF, Krahn and coworkers included 47 unaffected first- and second-degree relatives of IVF and SUD victims. Second-degree were only included when evidence suggested that more than one relative was affected. During 4.8±3.8 years of follow-up no events occurred, suggesting a favorable prognosis. Indeed, in the present large cohort of first-degree relatives from diagnosis-negative SUD families, outcomes after a median period of over six years were favorable. Clearly the presence of undiagnosed inherited cardiac disease in SUD families, including conditions that remain to be discovered, can never completely be excluded. However, based on the present data relatives may be reassured that the odds of such a scenario are low. Importantly, cardiac events or detection of previously undiagnosed inherited cardiac disease during follow-up were not observed in relatives who did not show any abnormalities when first evaluated.

**Clinical implications**

Cardiac events or newly diagnosed inherited cardiac disease were only observed in siblings from a family with multiple cases of IVF and SUD, relatives with subtle abnormalities at the initial cardiologic examination, or relatives who did not undergo cardiologic examination when members from their family first presented to our cardiogenetics department. Thus, following relatives with a malignant family history or the presence of subtle abnormalities at the initial examination as well as stressing the importance of (at least) a single evaluation for all first-degree relatives of a young SUD victim, especially in the presence of possible cardiac symptoms, seems pertinent. Based on the favorable outcomes of the large population of adults from diagnosis-negative SUD families in this study, it is conceivable that in these relatives a completely unremarkable first
evaluation is sufficient to exclude the presence of an inherited cardiac disease. Thus, intensity of repeated cardiologic examination during follow-up may be diminished. However, in children from diagnosis-negative SUD families manifestations of a particular inherited cardiac disease may develop with increasing age, so we still consider repeated cardiologic follow-up safe and indicated in these children.

These recommendations are further supported by recent observations in a nationwide study from Denmark in which the incidence of cardiovascular disease in relatives of young sudden cardiac death victims was compared with that in the general population. The risks of both cardiovascular disease and ventricular arrhythmia among first- and second-degree of young autopsy-negative SUD victims was increased among those younger than 35 years, but similar to the general population in relatives of all ages.

**Study limitations**

First, detailed follow-up information could not be collected in all relatives. To compensate for this lack of data, we obtained information on vital status in almost all of these relatives, so only the risk of non-fatal cardiac events or developing inherited cardiac disease may be underestimated.

Second, only a minority of relatives underwent cardiologic reevaluation, most probably because they or their cardiologists felt reassured after the unremarkable results of their first evaluation. Thus, inherited cardiac disease may have remained undiagnosed in families that were only evaluated once. Yet, the relatives that underwent reevaluation may well be those in whom cardiologic reevaluation was strongly recommended because of the family history and/or discrete abnormalities at the initial examination, making the odds of diagnosing inherited cardiac disease during follow-up higher in these reevaluated relatives than in other individuals.

**CONCLUSION**

In first-degree relatives of young SUD victims with no manifest abnormalities during initial cardiologic examination, the risk of developing manifest inherited cardiac disease or potentially fatal cardiac events during follow-up is low. In adult relatives with a completely unremarkable first evaluation, repeated cardiologic examination during follow-up may not be necessary. This does not apply to children, adults with subtle abnormalities at the first examination and families with a clear idiopathic inherited arrhythmia syndrome leading to multiple cases of IVF and SUD.
REFERENCES