Epidemiology and clinical aspects of sudden cardiac death in the young
van der Werf, C.

Citation for published version (APA):
van der Werf, C. (2013). Epidemiology and clinical aspects of sudden cardiac death in the young

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Sudden death in the young: what do we know about it and how to prevent?

Christian van der Werf, Irene M. van Langen, and Arthur A.M. Wilde

Amsterdam, the Netherlands

Circ Arrhythm Electrophysiol 2010;3:96-104
INTRODUCTION

Sudden death (SD) of children and adults ages 1 to 40 years has received increasing attention over the past decades. In this report, we provide an overview of this problem, consider several mass screening strategies to prevent these events, and critically appraise these strategies in light of the well-known Wilson and Jungner criteria (Table 1). Finally, we present an alternative approach: optimal assessment of first-degree relatives of newly diagnosed patients with an inherited cardiac disease and young SD victims to identify those relatives at risk of sudden cardiac death (SCD).

THE PROBLEM

Definitions

SD or its synonyms are generally defined as natural, unexpected death within 1 hour of the onset of symptoms. Four temporal elements should be considered in the use of this definition, that is, prodromes, onset of the terminal event, cardiac arrest, and biological death. The 1-hour definition refers to the period between onset of the terminal event, that is, acute changes in cardiovascular status, and cardiac arrest. Nonspecific prodromal symptoms, for example, chest pain, palpitations, or dyspnea, can be present during the days or weeks before a cardiac arrest. The biological legal death can occur days or weeks after the cardiac arrest, as patients can survive with irreversible brain damage and life support. In addition, when death occurs unwitnessed within 24 hours of being seen alive and functioning normally, this is also termed SD. In this report, the 1-hour definition is applied unless otherwise indicated.

Depending on the underlying cause, SD can be divided into SCD, defined as SD from a cardiac cause, and SD due to noncardiac causes, for example, intracranial hemorrhage, epilepsy, pulmonary embolism, or asthma. This subdivision is clinically relevant because cardiac causes are inherited in a significant proportion, whereas noncardiac causes usually are not. Death in absence of a diagnosis despite autopsy is generally termed sudden unexplained death (SUD) or autopsy-negative SUD. In countries where autopsy is not mandatory in the case of SD at a young age, cases in which no autopsy is performed are considered to be SUD. SD remaining unexplained after thorough postmortem investigation in infants under 1 year of age is termed sudden infant death syndrome (SIDS) and is considered a different entity in terms of etiology.

Epidemiology

The incidence of SD in the general population ages 20 to 75 years is 1 in 1000 individuals, which accounts for 18.5% of all deaths. In the 1- to 40-year age group, the incidence is approximately 1.3 to 8.5 per 100,000 person-years. The vast majority of cases are considered to be SCD. In individuals under 35 years of age, the incidence is highest in the 0- to 5-year age group. In adults, incidence increases with age in both sexes but is substantially less in women than in men at all ages. Approximately 80% of SD events take place at home, and around half of them are witnessed. The incidence of SD in young competitive athletes currently is approximately 0.4 to 0.6 per 100,000 person-years.
Etiology

Atherosclerotic coronary artery disease (CAD) accounts for the large majority of cases of SD in individuals over 40 years of age, mainly men. In younger victims, a variety of causes have been identified in several series. Below we summarize the causes of SD as assessed by autopsy and by cardiological and genetic assessment of the victim’s first-degree relatives.

Clinicopathologically assessed series

In clinicopathological studies in young SD victims from the general population, structural cardiac disease is found (and assumed to explain SD) in approximately 69% (Table 2 and Figure 1). In approximately 18%, autopsy does not reveal any structural cardiac disease, making this SUD. The application of a 24-hour time frame between the onset of complaints and the event or any other than the usual definition of SD reduces the proportion of cardiac causes (Table 2 and Figure 1). Within the 1- to 40-year age group, the proportion of SCD, noncardiac SD, and SUD probably differs by age. Because the incidence of premature CAD gradually increases with age, the proportion of other cardiac causes of SD is presumably higher in the lower age groups.5

Primary arrhythmia syndromes probably dominate in pediatric SD victims, whereas the cardiomyopathies typically manifest during young adulthood. The most frequent structural cardiac diseases in pooled clinicopathological series in the general population are premature CAD (31.3%; 95% CI, 29.4% to 33.4%), myocarditis (9.1%; 95% CI, 8.0% to 10.3%), left ventricular hypertrophy (LVH; 7.7%; 95% CI, 6.5% to 9.1%), and hypertrophic cardiomyopathy (HCM; 7.5%; 95% CI, 6.5 to 8.8%) (Table 2 and Figure 2). LVH is either idiopathic but not fulfilling the diagnostic criteria for HCM, or secondary to known hypertension. We emphasize that not all diagnoses explain SCD with certainty; for example, myxoid degeneration of the mitral valve with prolapse without atrial dilatation or LVH and with intact chordae is considered to be an uncertain diagnosis of SCD. Various clinicopathologically established causes of SD in competitive athletes and military recruits - both groups can be regarded to represent extremes in the population by their unique lifestyle - are reported in different proportions as

---

Table 1. Wilson and Jungner criteria for assessment of screening.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>The condition should be an important health problem.</td>
</tr>
<tr>
<td>2.</td>
<td>There should be an accepted treatment for patients with recognized disease.</td>
</tr>
<tr>
<td>3.</td>
<td>Facilities for diagnosis and treatment should be available.</td>
</tr>
<tr>
<td>4.</td>
<td>There should be a recognizable latent or early symptomatic stage.</td>
</tr>
<tr>
<td>5.</td>
<td>There should be a suitable test or examination.</td>
</tr>
<tr>
<td>6.</td>
<td>The test should be acceptable to the population.</td>
</tr>
<tr>
<td>7.</td>
<td>The natural history of the condition, including development from latent to declared disease, should be adequately understood.</td>
</tr>
<tr>
<td>8.</td>
<td>There should be an agreed policy on whom to treat as patients.</td>
</tr>
<tr>
<td>9.</td>
<td>The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.</td>
</tr>
<tr>
<td>10.</td>
<td>Case-finding should be a continuing process, and not a ‘once and for all’ project.</td>
</tr>
</tbody>
</table>

From reference 1.
compared with the general population (see Supplemental Table). The proportion of HCM and coronary artery anomalies appears to be systematically higher in these subgroups compared with the general population (2% to 49% vs. 7.5%; 95% CI, 6.5% to 8.8%; and 7% to 19% versus 2.4%; 95% CI, 1.8% to 3.1%, respectively), although in none of the studies were these populations directly compared. Moreover, SD among men is overrepresented in these populations.

The inherited causes of SCD can be divided into three groups: (1) the cardiomyopathies, in particular HCM and arrhythmogenic right ventricular dysplasia cardiomyopathy (ARVD/C), which are principally inherited diseases, and dilated cardiomyopathy (DCM), which can be inherited; (2) premature CAD, which can result from inherited dyslipidemia (e.g., familial hypercholesterolemia [FH]) or combined cardiovascular risk factors; and (3) the primary arrhythmia syndromes, for example, catecholaminergic polymorphic ventricular tachycardia (CPVT), long-QT syndrome (LQTS), and Brugada syndrome (BrS), which become more likely in autopsy-negative cases. Most often, inheritance is autosomal dominant.

Several studies on the yield of molecular autopsy, that is, nontargeted screening of the genes associated with primary arrhythmia syndromes, in cases of autopsy-negative SUD have been

![Figure 1. Distribution of causes of SD ≤40 years in the general population in clinicopathological series published between 1990 and mid 2009 using various definitions of SD (N=486 and N=1342).](image-url)
Table 2. Clinicopathological series on SD ≤40 years published between 1990 and mid 2009.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of SD</th>
<th>Hours from onset of complaints</th>
<th>Study period</th>
<th>Age, y</th>
<th>Study population</th>
<th>N</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke 21</td>
<td>SCD/SUD</td>
<td>&lt;24</td>
<td>1981-1988</td>
<td>14-40</td>
<td>general</td>
<td>690</td>
<td>United States</td>
</tr>
<tr>
<td>Corrado 27</td>
<td>SCD/NCSD/SUD</td>
<td>&lt;1</td>
<td>1979-1999</td>
<td>12-35</td>
<td>general/athletes</td>
<td>245/51*</td>
<td>Italy</td>
</tr>
<tr>
<td>Doolan 39</td>
<td>SCD/NCSD/SUD</td>
<td>&lt;24</td>
<td>1994-2002</td>
<td>&lt;35</td>
<td>general</td>
<td>425†</td>
<td>Australia</td>
</tr>
<tr>
<td>Eckart 8</td>
<td>SCD/NCSD/SUD</td>
<td>&lt;1</td>
<td>1977-2001</td>
<td>17-35</td>
<td>military</td>
<td>126</td>
<td>United States</td>
</tr>
<tr>
<td>Fabre 23</td>
<td>SCD/SUD</td>
<td>ND</td>
<td>1994-2003</td>
<td>15-35</td>
<td>general</td>
<td>223</td>
<td>United States</td>
</tr>
<tr>
<td>Gioia 18</td>
<td>SCD/NCSD/SUD</td>
<td>&lt;6</td>
<td>2001-2005</td>
<td>1-40</td>
<td>general</td>
<td>155</td>
<td>Italy</td>
</tr>
<tr>
<td>Maron 31</td>
<td>SCD/NCSD/SUD</td>
<td>ND</td>
<td>1985-2000</td>
<td>&lt;35</td>
<td>athletes</td>
<td>1041‡</td>
<td>United States</td>
</tr>
<tr>
<td>Morris 46</td>
<td>SCD/NCSD/SUD</td>
<td>&lt;1</td>
<td>2005</td>
<td>&lt;35</td>
<td>general</td>
<td>62§</td>
<td>Ireland</td>
</tr>
<tr>
<td>De Noronha 27</td>
<td>SCD/SUD</td>
<td>&lt;12</td>
<td>1996-2008</td>
<td>&lt;35</td>
<td>athletes</td>
<td>89</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Puranik 49</td>
<td>SCD/NCSD/SUD</td>
<td>&lt;24</td>
<td>1995-2004</td>
<td>5-35</td>
<td>general</td>
<td>427</td>
<td>Australia</td>
</tr>
<tr>
<td>Quigley 22</td>
<td>SCD/SUD</td>
<td>&lt;6</td>
<td>1993-2002</td>
<td>&lt;35</td>
<td>general</td>
<td>72</td>
<td>Ireland</td>
</tr>
<tr>
<td>Shen 9</td>
<td>SCD/NCSD/SUD</td>
<td>&lt;1</td>
<td>1960-1989</td>
<td>20-40</td>
<td>general</td>
<td>54</td>
<td>United States</td>
</tr>
<tr>
<td>Steinberger 25</td>
<td>SCD/SUD</td>
<td>&lt;24</td>
<td>1967-1992</td>
<td>1-21</td>
<td>general</td>
<td>50</td>
<td>United States</td>
</tr>
<tr>
<td>Van Camp 26</td>
<td>SCD/NCSD/SUD</td>
<td>&lt;1</td>
<td>1983-1993</td>
<td>13-24</td>
<td>athletes</td>
<td>105§</td>
<td>United States</td>
</tr>
<tr>
<td>Wren 7</td>
<td>SCD/NCSD/SUD</td>
<td>ND##</td>
<td>1985-1994</td>
<td>1-20</td>
<td>general</td>
<td>128</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>

We selected all clinicopathological studies including SD victims aged 1 to 40 years and published between 1990 and mid 2009. Only studies which extensively described the causes of SD/SCD were included, e.g. a specified type of cardiomyopathy instead of “cardiomyopathy” as the final diagnosis. SD indicates sudden death; SCD, sudden cardiac death; SUD, sudden unexplained death; NCSD, noncardiac sudden death; ND, not described. *Number of SCD/SUD cases in athletes, pulmonary thromboembolism (N=1) excluded; †181 SD victims aged <1 years excluded; ‡Number of SCD/SUD cases, sickle cell trait (N=5) and stroke (N=3) excluded; §Number of SCD/SUD cases, 16 SD victims aged <1 years excluded; ¶Number of SCD/SUD cases, ruptured cerebellar arteriovenous malformation (N=1) and subarachnoid hemorrhage (N=1) excluded; #SD out of hospital, on arrival at hospital or in the emergency department.
published. In a series consisting of 49 victims of autopsy-negative SUD ages 1 to 43 years, genetic testing of the LQTS- and CPVT-associated genes provided a putative pathogenic basis for SUD in 34.7% of cases (CPVT, 14.3% and LQTS, 20.4%). By contrast, in another study, genetic analysis of only two LQTS-associated genes in 59 autopsy-negative SUD victims age <35 years did not reveal any disease-causing mutations. In a third series of 17 autopsy-negative SUD cases ages 12 to 42 years, mutational screening was performed in two LQTS-associated genes, and one mutation was found. Also, the CPVT-associated ryanodine receptor 2 gene (RyrR2) was examined, and this revealed three mutations; thus, a putative pathogenic mutation was found in 23.5% of cases. Finally, three of 19 autopsy-negative SUD victims (15.8%), who were 16 to 68 years of age, were found to be carriers of an RyrR2 mutation.

Yield of cardiological and genetic assessment of relatives in SUD

In the case of SUD, inherited primary arrhythmia syndromes play an important role. This was demonstrated among others in our study in 43 families referred because of ≥1 case of SUD at <40 years of age, including 21 victims in which no autopsy had been performed. Cardiological
and genetic examination in the surviving relatives revealed an inherited cardiac disease and probable cause of death in 40%. CPVT was the most frequently diagnosed disease (12%), followed by LQTS (9%) and BrS (5%). Behr and coworkers published two studies on the results of cardiological and genetic assessment in relatives of SUD victims ages 4 to 64 years with no abnormalities found at autopsy and negative toxicology results. In the first series, an inherited cardiac disease was established in seven of 32 families (22%). In a subsequent series of 57 families, more extensive cardiological examination was performed and the yield increased to 53%. (Probable) LQTS was the most frequent diagnosis (28%), followed by BrS and ARVD/C (both 9%). In a study in surviving relatives of 25 young SUD victims (ages 1 to 18 years) cause of death was diagnosed in 56%, with LQTS (28%) and CPVT (12%) as the most frequent diagnoses.

**SCREENING STRATEGIES TO PREVENT SD**

In the last decennia several mass screening programs in the general population and in athletes, aimed at reducing the number of young SCD victims, have been conducted. These screening strategies, in particular those in athletes, have extensively been debated.

**Mass screening strategies**

**Studies to date**

**Population screening**

Population screening for cardiac disease to prevent SCD has been performed in young Japanese adolescents ages 12 to 15 years since 1973. All subjects are examined by history-taking and a resting 12-lead ECG, and subjects with abnormalities at first-line screening are additionally cardiologically examined. Nine of 37 807 screened students (0.024%) who were followed for six years were classified as high-risk subjects for SCD, including five with HCM. In six years, three subjects died suddenly, including two students with no clues of an increased risk for SCD. An estimated cost of $8800 per year of life saved by the screening program was calculated.

In a Taiwanese study, 25 816 school children ages six to seven, nine to ten, and 12 to 13 years were screened. The first stage of the screening program consisted of history-taking, ECG, and phonocardiography. Approximately 3% of the total study population was referred for additional examinations. Eventually, cardiac disease was newly diagnosed in 178 children (0.7% of the total study population), including 26 potentially lethal conditions (0.1%).

**Preparticipation screening of athletes**

One often proposed measure to prevent SCD in the young is preparticipation cardiological screening of competitive athletes, since a fatal arrhythmia may be triggered by exercise in those with occult cardiac disorders. Athletes have an estimated 2.8 times higher risk of SCD compared with nonathletes. The incidence of SCD in young competitive athletes substantially declined in the Veneto region of Italy since a mandatory nationwide systematic screening was introduced in 1982. Adolescents and young adults ages 12 to 35 years who participate in an organized sports program that requires regular training and competition are screened by history-taking,
physical examination, and ECG. Echocardiography was performed in 3016 (8.9%) of 33,735 athletes because of an abnormality in first-line screening, yielding 22 cases of HCM (0.07% of those screened) and 133 cases of valvular disease (0.4%). Finally, 621 athletes (1.8%) were disqualified from competitive sports because of cardiovascular disease. The annual incidence of SD in screened athletes ages 12 to 35 years in the Veneto region of Italy decreased by 89% comparing 2003 to 2004 to the prescreening period (1979 to 1981), whereas no change occurred among unscreened nonathletes of the same age.

In the United Kingdom, elite athletes between 14 and 35 years were screened between 1996 and 2006. The screening comprised history-taking, physical examination, ECG, and echocardiography. This extensive strategy had a poor yield, as many thousands of athletes needed to be screened to identify one case of HCM, among others as a consequence of an extremely low prevalence of HCM in these elite athletes. Resting ECG exclusively proved to be useful in identifying possible pathological LVH and electric disorders that are considered a cause of SCD.

In the 1990s, 5,615 US high school athletes were once-only screened by history-taking, physical examination, and ECG, which revealed an abnormality in 582 subjects (10%). Eventually, 22 athletes (0.4%) were disqualified. No cases of HCM or other frequent causes of SCD were detected. In the same period, one athlete with normal screening results was successfully resuscitated. In a cost-effectiveness analysis, the costs of ECG per year of life saved was lowest ($44,000) when compared with specific cardiovascular history and physical examination ($84,000) and with echocardiography ($200,000).

In 2004 the International Olympic Committee recommended the implementation of a screening protocol for young competitive athletes, consisting of family and personal history-taking, physical examination, and ECG, complemented by additional cardiological examinations in the case of any abnormality, that is, the Lausanne protocol. This screening should take place every two years in athletes until 35 years. The American Heart Association did not concur with this recommendation; it emphasized the program’s low specificity and the considerable resources necessary but did not advise against noninvasive volunteer-based athlete screening programs on a smaller scale.

Critical appraisal in light of the Wilson and Jungner criteria

Important health problem

The impact of the SD of a previously healthy young individual on its environment and the community clearly is enormous. From an epidemiological point of view, SD at young age is a problem in which many productive life-years can be saved. However, although a high incidence does not necessarily imply a health problem to be important, it is a usual requirement. Thus, are these tragic events important enough to perform mass screening in tens of thousands of individuals to prevent one?

Availability of an accepted treatment

Nowadays, in most (inherited) cardiac diseases, preventive measures in terms of lifestyle modification, drug therapy, and device implants and consensus on the use of these measures are available.
**Availability of facilities for diagnosis and treatment**

The availability of facilities for diagnosis and treatment differ per country. The largest problem is probably the availability of physicians who are sufficiently competent to assess the ECGs and detect the rare, sometimes subtle, but important abnormalities. Achieving an adequate accuracy of a mass screening program requires specially trained physicians for ECG interpretation. In Italy, this is available in terms of specifically trained sports physicians, but in other countries physicians would have to be trained for this purpose.

**Presence of recognizable latent or early symptomatic stage**

A recognizable latent stage is present in all (inherited) cardiac diseases that can cause SCD. In inherited cardiac diseases, this stage consists of mutation carrier-ship. Over years, the phenotype usually develops gradually, but only a minority of disease carriers have cardiac symptoms such as syncope, palpitations, and chest pain. However, when these symptoms are present, they should be carefully evaluated.

**Availability of a suitable test**

ECG in addition to history-taking and physical examination is the most frequently advised and most cost-effective screening tool. However, ECG comprises significant false-positive rates, specifically in athletes. False-positive ECGs are an innocent consequence of an “athlete’s heart,” and distinct ECG abnormalities, such as T-wave inversions, increased R- and S-wave voltages suggestive of LVH and conduction abnormalities, are reported in 4% to 14% of athletes at different levels. On the other hand, the false-negative rates of ECG are concerning. Athletes with CAD, coronary artery anomalies, CPVT, or a (yet) incomplete penetrance of LQTS or ARVD/C are not identified. Extensive cardiological examination might be needed to recognize these conditions. The addition of exercise testing or echocardiography increases the yield of screening but is less cost-effective.

**Acceptability of tests**

The burden associated with the most applied screening tests, that is, ECG in addition to personal and family history-taking and physical examination, is considered acceptable. However, although the psychological impact has never been studied, it seems reasonable to assume that the thousands of individuals with a false-positive result will be anxious until additional examinations have been performed. Also, the fact that most previously described screening programs are mandatory undermines the individual’s autonomy. In athletes, the freedom to continue sports practice with the acceptance of the risk of SCD is reduced.

**Understanding of natural history**

The criterion on understanding of natural history is difficult to assess, as it is a spectrum of diseases that may cause SCD in the young. Overall, the risk of SCD in individuals affected with an inherited cardiac disease is ill defined but considered to be low in absolute numbers, that is, approximately 1% per year in HCM.
Policy on whom to treat as patients

When additional examinations are performed because of abnormalities at first-line screening, the separate diagnostic criteria and the associated treatment for each (cardiac) disease become relevant. In general, these can distinguish affected individuals from healthy ones, although borderline subjects can present, for example, cases of borderline ARVC, or discriminating an “athlete’s heart” from a cardiomyopathy.

Cost-effectiveness

Only few data are available on the costs per year of life saved as a result of the mass screening programs. The results differ enormously, from $8800 per year of life in Japan\(^40\) to $44 000 in the United States\(^46\) and an unspecified amount below $50 000 in Italy.\(^49\) More data are needed to conclude if this criterion can be met.

Continuous process

Implementing a screening program to prevent SD in the young will probably imply a continuous screening program in the population as well as in one individual. However, within individuals, the optimal screening interval has not been determined, although an interval of two years (starting from the age of 12 to 14) has been recommended in Europe.

Further remarks

Apart from the Wilson and Jungner criteria, it should be noted that there is a lack of irrefutable evidence of efficacy of preparticipation screening of athletes on the incidence of SD. The decline in annual incidence of SD in screened athletes in the Veneto region of Italy must be interpreted with caution, as this study was not a controlled comparison of screening versus nonscreening in athletes.\(^57\) It appears that the major decline in SD among the Italian athletes occurred from 1982 to 1985, as the mortality rate between Veneto and the US state of Minnesota (where preparticipation screening of athletes does not involve ECG) was similar between 1993 and 2004.\(^58\) Moreover, it is possible that (part of) the decline in incidence of SD in Italy was caused by the improved survival of witnessed cardiac arrests in the last decades.\(^38\) Finally, the Italian results cannot simply be translated to other countries because of differences in incidences and prevalences of causes of SD.

Overall, the results of mass screening programs have not been convincing, in particular because of the considerable false-positive and false-negative rates. In addition, some of the Wilson and Jungner are not met, especially the criteria on availability and acceptability of a suitable test, on availability of facilities to actually execute the mass screening program and perform additional examinations in those individuals with abnormalities and on cost-effectiveness. Therefore, in our opinion, a recommendation to initiate mass screening programs for the prevention of SCD at this stage is premature. In countries where mass screening is performed, subsequent assessment of relatives of individuals in whom an inherited cardiac disease is identified through the screening program could improve the efficacy and cost-effectiveness of these screening programs. This potential additional benefit of mass screening programs is often neglected in literature.
Alternative approach
As SD at <40 years of age is a result of inherited cardiac disease in a significant number of cases, an alternative approach is to optimize the cardiological and genetic assessment in relatives of a newly diagnosed patient with an inherited cardiac disease, or of a young SD victim.\textsuperscript{59,60} This approach appears to be a promising alternative because of the autosomal inheritance pattern of most inherited cardiac diseases, implying that first-degree relatives have a 50% a priori likelihood of being affected. The presented alternative approach could also be relevant in SIDS, because 5\% to 10\% of cases is thought to be attributable to primary arrhythmia syndromes, although a part of those cases may be due to sporadic mutations in the cardiac ion channel genes.\textsuperscript{61–63}

The first step in this approach is the performance of autopsy after the death of a young individual. Second, it consists of comprehensive cardiological and genetic examination in first-degree relatives of the deceased (when autopsy reveals an inherited cardiac disease, does not reveal any abnormalities, or was not performed).

Autopsy
Autopsy is able to reveal the cause of death in more than 80\% of cases. In the case of SCD caused by an inherited cardiac disease or SUD, surviving first-degree relatives of the SD victim are advised to have cardiological and genetic examination. If a noninherited cardiac disease at autopsy is identified, relatives can be reassured accordingly. Ideally, autopsy in these victims is performed according to the new guidelines of the Association for European Cardiovascular Pathology, yielding adequate assessment of the major causes of noncardiac and cardiac SD, and including a protocol for heart examination and histological sampling.\textsuperscript{29} These guidelines also provide a detailed description of storage of material for toxicological and molecular investigation.

Cardiological and genetic assessment of first-degree relatives
Comprehensive cardiological and genetic assessment of first-degree relatives is ideally performed by a multidisciplinary team including cardiologists, clinical geneticists, genetic counselors, and psychosocial workers.\textsuperscript{59} The assessment starts with genetic counseling before testing, which emphasizes the advantages (for example, the possible measures to prevent SCD when an inherited cardiac disease is diagnosed) and disadvantages (for example, difficulties in getting life insurance). Subsequently, detailed medical information on the proband and the attending first-degree relatives is obtained, as well as a family history including a three-generation pedigree, and a baseline ECG is made. Further steps depend on the information collected.

When autopsy of a SD victim reveals a certain inherited cardiac disease, first-degree relatives are examined with a focus on that specific disease.\textsuperscript{64} When a pathogenic mutation is identified in the SD victim, the first-degree relatives can be predictively systematically tested for carriership, also known as cascade screening. Next, mutation-carrying relatives are referred for cardiological examination. When no disease-associated mutation is detected within the family, assessment consists of cardiological examination only. Alternatively, when no diagnosis in an SD victim has been made at that time, further steps consist of the revision of autopsy in a specialized center and cardiological examination of the
first-degree relatives, which in general includes an exercise testing and echocardiography. Complementary cardiological examinations are performed by indication (Figure 3). With current techniques, targeted genetic assessment is performed.  When history and cardiological examination yield a suspicion of a specific disease or phenotype, targeted genetic analysis of the associated candidate gene(s) is performed in material obtained from the deceased individual at the time of postmortem examination or in those relatives with clinical abnormalities. Recently, genotyping was shown to be most cost-effective in patients with conclusive diagnosis of LQTS and CPVT and in patients with a type 1 BrS ECG with atrioventricular conduction delay.  Nontargeted genetic testing of healthy relatives of young SD victims was highly ineffective and expensive.

There are several barriers that may hamper the implementation of molecular autopsy in routine health care.  First, it is essential that high-quality DNA is acquired at autopsy to allow postmortem genetic testing in case of SUD. Unfortunately, this is currently only performed in the minority of cases, particularly in countries where autopsy is not mandatory. Second, at present, insurance companies usually do not reimburse molecular autopsy of a deceased individual, regardless of the consequences for the living relatives. Apart from the important advantage of the possibility of cascade screening within a family, the identification of a putative pathogenic mutation has two additional advantages in the setting of some specific conditions. First, it can be a tool for risk stratification, for example, in DCM, as patients with DCM due to lamin A/C mutations have a poorer survival as compared with noncarrier DCM patients. Second, the genotype can guide the therapeutic approach, as most clearly demonstrated in LQTS. Indeed, β-blocker therapy is highly effective in LQT1 and less so in patients with LQT2 or LQT3.

Critical appraisal

As our recommended approach concerns a comprehensive strategy to identify those relatives at risk of SCD within a family with known or presumed inherited cardiac disease, the population screening criteria of Wilson and Jungner cannot be applied well. However, several comments can be made. First, survival benefit as a result of this approach has never been demonstrated. However, with such a high a priori likelihood of relatives being affected with an inherited cardiac disease, relatively many more individuals at risk of SCD are identified as compared with mass screening programs. For most single inherited cardiac diseases, a survival benefit of (often asymptomatic) treated patients compared with undiagnosed and/or untreated patients has been demonstrated, for example, in CPVT and in LQTS. Second, the psychological, social, and financial consequences of autopsy and assessment of relatives have rarely been studied. The proportion of eligible relatives of an index patient who attend a clinical geneticist and/or cardiologist varies considerably: 57% within a mean follow-up of two years in families with potentially primary arrhythmia syndromes or cardiomyopathies, or 39% within one year in HCM families, when relatives are informed by an other relative by means of a family letter. Cascade screening in FH has been demonstrated to be cost-effective ($4479 per life year gained). As far as we are aware, cardiological and genetic assessment of relatives of young victims of SCD and SUD is performed in the minority of cases, probably because of a lack of knowledge.
Figure 3. Algorithm for cardiological and genetic examination in relatives of SUD victims. This algorithm contains the most utilized diagnostic tools, but is not exhaustive. SUD indicates sudden unexplained death; LQTS, long QT syndrome; BrS, Brugada syndrome; SQTS, short QT syndrome; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; FH, familial hypercholesterolemia; CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; RCM, restrictive cardiomyopathy; CM, cardiomyopathy. *Including revision of autopsy by cardiac pathologists, if possible; †Consider adrenaline provocation; ‡Class I drugs (ajmaline or flecainide); §Advice to monitor traditional cardiovascular risk factors (e.g. hypertension, diabetes mellitus, hypercholesterolemia, overweight); ||Advice repetition of cardiological examination in 3-5 years; #When not performed yet, consider examinations in one or more of the other pathways; **Consider cardiac MRI to exclude ARVD/C.
on inherited cardiac diseases among potential referring physicians and a lack of specialized cardiogenetic departments. Because the development of nationwide programs that implement this approach could have many advantages compared with other strategies, the evaluation of all its important aspects (i.e., survival benefit, costeffectiveness, and psychological impact) should have high priority, for example, by means of a mandatory national registry of young SD victims.

CONCLUSIONS

SD of a young individual is a rare but shocking event. Approximately 70% of SD is caused by structural cardiac disease, the majority containing a hereditary component. In the case of SUD, detailed cardiological and genetic examination in the surviving relatives nowadays reveals an inherited cardiac disease in approximately 40% of cases. Mass screening programs to prevent SCD in the general population and screening of high-risk groups, for example, athletes, remain controversial. An alternative approach that avoids the disadvantages associated with mass or high-risk screening is directed toward first-degree relatives of SD victims. These are screened through effective targeted cardiological and genetic examination, preceded by complete diagnostics in the SD victim by means of accurate autopsy and DNA storage. Such an approach is irrefutably effective in principle, in relatives of living newly diagnosed patients. Whether or not that approach is also effective and costeffective in practice must be evaluated in future studies. Nationwide evaluation of this approach should be given high priority, as it could have a larger impact on the prevention of SCD than the currently applied mass screening approaches.

ACKNOWLEDGEMENTS

We thank Y.M. Pinto, MD, PhD, and E. Birnie, PhD, for their valuable comments on this manuscript.
REFERENCES


38. Viskin S, Antagonist: routine screening of all athletes prior to participation in competitive sports should be mandatory to prevent sudden cardiac death. Heart Rhythm 2007;4:525-8.


### Table S1. Distribution of causes of SCD ≤40 years across different study populations in clinicopathological series published between 1990 to mid 2009.

<table>
<thead>
<tr>
<th></th>
<th>Maron 1</th>
<th>Van Camp 2</th>
<th>Eckart 3</th>
<th>De Noronha 4</th>
<th>Corrado 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>4</td>
<td>7</td>
<td>12</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>LVH</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>HCM</td>
<td>24</td>
<td>49</td>
<td>7</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>DCM</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>4</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>ARVD/C</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Anomalous CA</td>
<td>11</td>
<td>15</td>
<td>19</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Unknown</td>
<td>38</td>
<td>7</td>
<td>41</td>
<td>29</td>
<td>4</td>
</tr>
</tbody>
</table>

Values are represented as percentage of total SCD/SUD.

CAD indicates coronary artery disease; LVH, left ventricular hypertrophy; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; anomalous CA, anomalous coronary artery.

### References