Sudden cardiac death among the young in Sweden 1992-1999

From epidemiology to support of the bereaved

Aase Wisten
Department of Public Health and Clinical Medicine
Umeå University, Umeå, Sweden and
Department of Internal Medicine, Sunderby Hospital,
SE-971 80 Luleå, Sweden

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To
Åke
Ola and Eilif
Anne and Max

Remember, we all stumble,
everyone of us.
That’s why it’s a comfort to go
hand in hand

Emily Kimbrough
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVC</td>
<td>arrhythmogenic right ventricular cardiomyopathy</td>
</tr>
<tr>
<td>ASD</td>
<td>atrial septal defect</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>COD</td>
<td>cause of death</td>
</tr>
<tr>
<td>DCM</td>
<td>dilated cardiomyopathy</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>HCM</td>
<td>hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>ICD</td>
<td>implantable cardioverter defibrillator</td>
</tr>
<tr>
<td>LQTS</td>
<td>long QT syndrome</td>
</tr>
<tr>
<td>NBFM</td>
<td>National Board of Forensic Medicine</td>
</tr>
<tr>
<td>SCD</td>
<td>sudden cardiac death</td>
</tr>
<tr>
<td>SD</td>
<td>sudden death</td>
</tr>
<tr>
<td>SIDS</td>
<td>sudden infant death syndrome</td>
</tr>
<tr>
<td>SNH</td>
<td>structurally normal heart</td>
</tr>
<tr>
<td>SQTS</td>
<td>short QT syndrome</td>
</tr>
<tr>
<td>VSD</td>
<td>ventricular septal defect</td>
</tr>
<tr>
<td>WPW</td>
<td>Wolff-Parkinson-White</td>
</tr>
</tbody>
</table>
ABSTRACT

Sudden cardiac death (SCD) in a young person is a rare but tragic event, and the potential of prevention is unknown. The aim of this thesis is to contribute to the prevention by analysing SCD in the young in Sweden during the period 1992-1999. Data of SCD in the young based on a national registry is not previously reported. The approach is broad, covering the spectrum from epidemiology to supportive needs of families confronted with SCD. The survey methods comprised analyses of national registries, questionnaires, personal interviews, forensic-, police-, medical- and military conscription records.

The SCD group selected from the database of the National Board of Forensic Medicine consisted of 181 persons, 15 to 35 years old, who had suffered an SCD during 1992-1999 in Sweden, 132 men (73 %) and 49 women (27 %). The mean incidence was 0.93 per 100,000 per year. The trend showed no decrease during the surveyed years, 1992-1999. The most common diagnoses were the structurally normal heart (21 %), coronary artery disease (18 %), and dilated cardiomyopathy (12 %). In a study group of 162 individuals (19 cases of aortic aneurysm, 17 men and two women, were excluded), ECGs, symptoms and lifestyle factors were analysed and related to the autopsy findings.

ECGs were available in 66 individuals (59 men and seven women) and 50 % of these were pathological. The most frequent aberrations were repolarisation abnormalities and in half of the cases with more than one ECG a development in a pathological direction was seen. In four out of ten seeking medical advice because of symptoms an ECG was taken and three of these were pathological. Possibly cardiac-related symptoms such as syncope, chest pain or palpitations were common, but also non-specific symptoms such as fatigue after an influenza-like illness. It was not possible to link a certain sign or symptom to a specific diagnosis. In 26 (16 %) there was a family history of SCD.

Physical activity and body mass index (BMI) in men were the same as in a control group, whilst women had a higher BMI and a lower level of physical activity than the controls. In coronary artery disease deaths there were a high percentage of smokers and BMI was higher than in the controls in both sexes. Competing athletes more often died during physical activity than non-athletes, but were not overrepresented in the SCD group. The majority of the athletes who died during physical activity had an underlying structural cardiac disease. Death during sleep was the most common mode of death in subjects with structurally normal heart.

A lack of supportive structures in the handling of bereaved relatives were disclosed in the interviews. Most participants felt that they had been left mainly to themselves to find information and support. A common reflection from the bereaved was that there is a need of the same supportive routines in cases of a single death as in accidents where there are several casualties. The bereaved had a need of getting an explanation and a need of supportive structures. The cognitive dimension of understanding and the emotional dimension of being understood were found to be significant for the complex processes of mourning and recreating one's life as a bereaved.

In summary, SCD was uncommon in the young, but the incidence was not decreasing during the study period. The most common autopsy findings were the structurally normal heart and
coronary artery disease. Symptoms preceding SCD were common but often misinterpreted. The SCD group was very similar to the normal population with regard to life style factors. In certain cardiac disorders physical activity seemed to trigger sudden death, whilst in others death during sleep was the most common mode of death. There is no single test which predicts if a person is at risk of SCD. A further cardiac evaluation in cases with pathological ECGs, and in cases with a positive family history or serious unexplained symptoms such as syncope, might permit the early identification of persons at risk of SCD. ECG is an underused tool in the investigation of symptoms, and a database with old ECGs available for comparison could be useful in the prevention of SCD. There is a need of better care of the bereaved, and based on our findings we propose the introduction of a supportive program.

Key words: Epidemiology, symptoms, sudden cardiac death, young, prevention, Sweden, electrocardiogram, forensic diagnosis, athletic activities, risk factors, family, bereavement.
SAMMANFATTNING PÅ SVENSKA (SUMMARY IN SWEDISH)


Den här studien syftar till att bidra till förebyggandet av dessa dödsfall genom att undersöka plötslig hjärtdöd ur ett brett perspektiv: hur många som drabbas, de bakomliggande sjukdomstillstånden, eventuella symptom före dödsfallet och livsstilsfaktorer i gruppen. Då en del av dessa dödsfall trots ökade kunskaper kommer att inträffa även i framtiden undersöker den också hur anhöriga upplevde stödet och informationen i samband med dödsfallen.


I en del fall hittades sjukliga förändringar i hjärtat, t. ex. åderförkalkning i hjärtats kranskärl eller hjärtmuskelsjukdom med förtjockning av muskelväggarna i hjärtat och ibland av skiljeväggen. Den största gruppen, ca 20 %, utgjordes dock av individer som hade ett helt normalt hjärta utan synbara sjukliga förändringar. En förklaring till att hjärtat stannat i dessa fall var olika typer av elektriska störningar som uppstått trots att hjärtmuskeln ser helt frisk ut. Sådana störningar kan vara medfödda men kan även vara förvärvade, t.ex. efter en infektion. Sammantaget fanns det ett tiotal olika hjärtdiagnoser i gruppen som avlidit i plötslig hjärtdöd.

EKG:n fanns tillgängliga i mindre än hälften av fallen. Ungefär hälften av dessa EKG:n uppvisade vissa förändringar medan de övriga var helt normala. De flesta EKG:n gällde män och var vanligen tagna många år före dödsfallet i samband med mönstringen. När det fanns mer än ett EKG kunde i vissa fall en förändring av EKG-kurvan över tid ses, eventuellt tydande på en sjuklig process i hjärtat.


Den grupp som drabbades av plötslig hjärtdöd skilde sig inte från en kontrollgrupp av samma ålder när det gällde livsstilsfaktorer såsom t. ex. rökning, fysisk aktivitetsnivå och deltagande i idrottstävlingar. Kvinnorna hade en lägre fysisk aktivitetsnivå och hade även ett högre body mass index (vikten/längdenxlängden) än kontrollgruppen. Det fanns ingen överrepresentation av idrottare i gruppen, men de som tävlingsidrottrade avled oftare under fysisk
aktivitet. I gruppen med åderförkalkningssjukdom i hjärtat fanns många rökare och överviktig.
De anhöriga upplevde ofta en brist på stöd och information i samband med dödsfallet. Ett
bra bemötande, bra information och någon att vänta sig till med sina frågor var viktigt för
de anhöriga som intervjuades. Många efterfrågade någon form av krisgrupp av den typ som
förekommer när flera personer dör, t. ex. i samband med olyckor, och ansåg att rutinerna
borde förbättras vid den här typen av dödsfall. Baserat på dessa intervjuer har ett förslag till
strukturerat program vid plötsliga dödsfall tagits fram.

Sammantaget är plötslig hjärtdöd bland unga ovanligt, men antalet som drabbas minskar ej.
Fler män än kvinnor drabbas. Riskpatienten är svår att känna igen. Vid vissa hjärtsjukdomar
can det vara livsviktigt att minska på träning/tävlingsaktivitetet, medan andra inte har sam-
band med ökad risk för plötslig död vid fysisk aktivitet. Hjärtrelaterade symptom såsom
svinning, bröstsmärt, hjärtklappning, andfäddhet eller ospecifika symptom efter en infek-
tion var vanliga i den drabbade gruppen, liksom EKG-förändringar. En basal utredning med
EKG kan vara viktig vid misstänkt hjärtrelaterade symptom liksom en utredning av nära
släktingar till de som drabbas av plötslig hjärtdöd.
This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.


IV. Wisten A, Messner T. Young Swedish patients with sudden cardiac death have a lifestyle very similar to the general population. Scandinavian Cardiovascular Journal. 2005; 2005: 0-00.

V. Wisten A, Zingmark K. Understanding and being understood. Supportive needs of families confronted with sudden cardiac death. In manuscript.

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INTRODUCTION

According to the legend the Greek soldier Pheidippides suddenly died after having com-
pleted his run from Maraton to Athens in 490 B.C. to deliver the message of the victory over
the Persians (1). During the last decades several stories about famous athletes dying sud-
denly and unexpectedly during competitions have caused headlines in the newspapers. Most
non-violent, unexpected sudden deaths in the young population have cardiac causes, and the
potential for prevention is unknown. In young athletes suffering sudden cardiac death (SCD)
autopsy most often reveals structural cardiovascular lesions such as hypertrophic cardio-
myopathy (HCM) (2) or arrhythmogenic right ventricular cardiomyopathy (ARVC) (3).

In unselected population studies of SCD in children and young adults (1-35 years old) a di-
verse set of structural and non-structural cardiac diagnoses is found. Prevention is linked to
the recognition of symptoms, if any, and an accurate diagnosis. Coronary artery disease
(CAD) and different cardiomyopathies are the most common findings in the older patients in
this age group (3-5). Myocarditis and different congenital lesions are the most common di-
agnoses in the children (6).

Among SCD victims there is also a considerable subset with structurally normal heart
(SNH) (4, 7), possibly associated with a range of primary arrhythmogenic disorders. Re-
cently, groups of familial arrhythmogenic disorders such as Brugada syndrome, ARVC, long
QT syndrome (LQTS), and short QT syndrome (SQTS) have been recognized (8-12). In
these days there is a rapid development within the genetic field of arrhythmogenic cardiac
disorders.

The prevention of SCD is a challenge. Previous studies on symptoms and risk factors have
most often analysed the general population (all ages) where up to 80 % of the individuals
who suffer SCD have coronary heart disease (13). Systematic investigations in the younger
age group are difficult to perform because of low patient numbers, and the main focus has
been on athletic activity as a presumed risk factor for SCD (3, 14).

SCD in a young person is frustrating for the medical community, and to the families left
behind a devastating and shocking experience. These are “hearts too good to die” to cite the
American cardiac surgeon Claude Beck in his vision for cardiac resuscitation from 1956
(15).This thesis has a broad approach to the phenomenon of SCD covering the spectrum
from epidemiology to support of the bereaved.
BACKGROUND

Definition of SCD
The following definition of SCD is used both by the Task Force on Sudden Cardiac Death of the European Society of Cardiology (16), and these studies: SCD is natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms. Preexisting heart disease may or may not have known to be present, but the time and mode of death are unexpected. If the death is unwitnessed the definition is used for a person known to be alive and functioning normally 24 hours before being found dead (17).

Because many sudden unexpected deaths are unwitnessed [40 % in the Maastrich Sudden Death study (18)], it is often difficult to establish when the person was last seen and in good health.

In a report on SCD in the United States 1989-1998 by Zheng et al., (19) it was emphasized that the above definition is difficult to apply in public health surveillance, because the death certificate often does not include the time of onset. Instead SCD in this report was defined as a death from cardiac disease that occurred out-of-hospital or in an emergency department, or one in which the decedent was reported “dead on arrival” at a hospital. This alternate definition was presented by Gillum et al. and is considered useful for assessing population trends in SCD (20).

Mechanisms
Cardiac arrest can be due to mechanical factors, i.e., aortic rupture with cardiac tamponade. However, in most cases the mechanism is arrhythmia, commonly with the onset of ventricular tachycardia that progresses to ventricular fibrillation (21, 22). The onset and rapid development of such an arrhythmia is still a pathophysiological enigma. Complex interactions between structural abnormalities and functional alterations may lead to lethal tachyarrhythmia or severe bradyarrhythmia and asystole, as illustrated in a biological model by Myerburg et al. in 1989 (23) (Fig. 1).

However, with increasing knowledge of molecular genetics, the distinction between structural and functional abnormalities is no longer obvious. LQTS, SQTS or Brugada syndrome are structural diseases on a molecular level (ion-channel disease) which lead to functional alterations (ionic disturbances) (9-12). Another area with close relation between structure and function is acute inflammation. A link between inflammation and electrophysiological phenomena leading to arrhythmia has been established by Hoffman and Guo who showed that activation of neutrophils and eosinophils in canines produces early afterdepolarization and arrhythmia (24). In cases of sudden death (SD) in association with myocardial infarction the ventricular fibrillation leading to death is believed to be due to a metabolic crisis. This starts with an excess uptake of free fatty acids which eventually leads to an abnormal cytosolic calcium overload in hypoxic cells (25).
### Classification

In the 1995 WHO classification of cardiomyopathies, diseases of the myocardium associated with cardiac dysfunction were defined. ARVC was at that time acknowledged as a new separate entity and ischaemic, valvular and hypertensive disorders were regarded as specific cardiomyopathies (26). Thiene et al. have recently suggested a new classification system of cardiomyopathies on a genomic basis (27). Due to advances in molecular genetics it is now possible to describe cardiac structural abnormalities on a molecular level in some forms of dilated cardiomyopathy (DCM), ARVC and HCM (8, 28) as well as in non-structural heart diseases such as LQTS, SQTS and Brugada syndrome (10-12). Thiene et al. (27) thus propose a genomic classification including also non-structural diseases within the concept of cardiomyopathies:

- cytoskeletal cardiomyopathy (DCM and ARVC)
- sarcomeric cardiomyopathy (in HCM)
- ion-channel cardiomyopathy (“channelopathies”) (LQTS, SQTS and Brugada syndrome).

### Incidence of SCD

**The general population**

In western countries about two thirds of all natural sudden deaths in the general population are cardiac related (29, 30). Of all cardiac related deaths 50 % or more are classified as
SCD. In an analysis of mortality data from 1989 to 1998 in the United States, SCD increased in proportion to all cardiac deaths from 56 % to 64 %. The age-adjusted decline in SCD rates was 11.7 % in men and 5.8 % in women. During that period there was a 21 % increase in age-specific death rates for SCD among women aged 35 to 44 years (19). In the United States 460,000 died of SCD during 1999 (31) with CAD as the major cause.

The incidence of SCD in the general population is approximately 1/1,000 inhabitants per year (32, 33). In a register study from northern Sweden in persons aged 35-64 the incidence was 0.65/1,000 in men and 0.12/1,000 in women. The SCD incidence decreased significantly among men but not among women during the study period 1985-1999 (34).

The young population

SCD in the young population (in most studies ≤ 35 years old) is considerably more rare with incidence figures in the range of 0.4-4.3 /100,000 per year (Table 1) (3, 5, 35-40). In most studies all sudden deaths are included and the proportion classified as SCD ranges in the survey in Table 1 between 25 % in the age group 1-21 (37) and 93% in athletes with mean age 23 years old (3). Maron et al. showed that the incidence of SCD during competitive sports activities in Minnesota High School athletes was 0.5/100,000/year (41). A prospective study in the Veneto region in Italy showed a higher incidence of SCD in competing athletes (2.1/100,000/year) as compared with non-athletes (0.7/100,000/year) (3). In this region a prospective clinico-pathologic investigation of SD in the young (≤ 35 years old) has been performed since 1979 (42). This has been possible because of a pre-participation screening programme for competitive athletes including history, physical examination, 12-lead electrocardiogram, and limited exercise testing, as required by Italian law (43, 44). Other studies in Table 1 are all retrospective.

Cardiovascular diagnoses

The young SCD group is heterogenous with a large spectrum of diagnoses, both congenital and acquired (Table 2). In infants < 1 year of age coronary artery anomalies or other congenital lesions are common (45, 46). It is considered that a fraction of sudden infant death syndrome (SIDS) (infants 0-6 months) with an incidence of about 1/10,000/year, may also be due to unrecognised cardiac causes (47). In young ages (≤ 20 years) myocarditis is a common diagnosis (35, 37, 39), whilst CAD becomes the most common diagnosis in studies including also age groups above 20 (3-5). An exception is the athletic population ≤ 35 years in which HCM was found to be the most common diagnosis in the United States (2, 14) and ARVC in Italy (3). Dissecting aortic aneurysm is commonly included in the concept of SCD, pulmonary embolism is only included occasionally (3).
### Table 1. Sudden cardiac death in the young – incidence and major diagnoses in previous studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Age range years</th>
<th>Total SD no.</th>
<th>Total SCD no.</th>
<th>SCD incidence*</th>
<th>Major SCD diagnosis</th>
<th>Unknown cause of death no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Driscoll et al., USA 1950-1982 (35)</td>
<td>3-20</td>
<td>12</td>
<td>7</td>
<td>0.8</td>
<td>All different</td>
<td>5</td>
</tr>
<tr>
<td>Shen et al., USA 1960-1989¹ (36)</td>
<td>20-40</td>
<td>54</td>
<td>32</td>
<td>3.7</td>
<td>CAD</td>
<td>7</td>
</tr>
<tr>
<td>Neuspiel et al., USA 1972-1980 (37)</td>
<td>1-21</td>
<td>207</td>
<td>51</td>
<td>1.1</td>
<td>Myocarditis</td>
<td>29</td>
</tr>
<tr>
<td>Kennedy et al., USA 1981-1982 (38)</td>
<td>20-29</td>
<td>24</td>
<td>14</td>
<td>4.3</td>
<td>CAD</td>
<td>0</td>
</tr>
<tr>
<td>Molander, Sweden 1982 (39)</td>
<td>1-20</td>
<td>31</td>
<td>9</td>
<td>0.4</td>
<td>Myocarditis</td>
<td>4</td>
</tr>
<tr>
<td>Morentin, Spain 1991-1998 (5)</td>
<td>1-35</td>
<td>107</td>
<td>46</td>
<td>1.0</td>
<td>CAD</td>
<td>19</td>
</tr>
<tr>
<td>Corrado et al., Italy 1979-1999² (3)</td>
<td>12-35</td>
<td>245</td>
<td>208</td>
<td>0.7</td>
<td>CAD</td>
<td>17</td>
</tr>
<tr>
<td>Corrado et al., Italy 1979-1999³ (3)</td>
<td>12-35</td>
<td>55</td>
<td>51</td>
<td>2.1</td>
<td>ARVC</td>
<td>1</td>
</tr>
<tr>
<td>Drory et al., Israel 1976-1985 (40)</td>
<td>9-39</td>
<td>162</td>
<td>118</td>
<td>-</td>
<td>CAD</td>
<td>19</td>
</tr>
</tbody>
</table>

*Per 100,000 per year. Calculated from the incidence of sudden death given in the article.

¹Cocain abuse included
²Non-athletes
³Athletes

SD=sudden death, SCD=sudden cardiac death, CAD=coronary artery disease, ARVC=arrhythmogenic right ventricular cardiomyopathy

### Table 2. Cardiovascular autopsy findings with possible relation to death

- Atherosclerotic coronary artery disease
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Myocarditis
- Arrhythmogenic right ventricular cardiomyopathy
- Cardiomyopathies in various hereditary muscle dystrophy diseases
- Coronary artery anomalies
- Valvular disease
- Postoperative congenital cardiac disease
- Intramural tunneled coronary artery
- Disease of conduction system
- Congenital heart malformations (e.g. ventricular septal defect, atrial septal defect)
- Dissecting aortic aneurysm
- Pulmonary embolism
Structural findings

Coronary atherosclerosis
CAD in the young is associated with the major risk factors for atherosclerosis, such as smoking, hypertension and a high serum cholesterol level (13, 48). The risk of SCD in the young with CAD, however, is much higher than in older patients with similar manifestations of coronary heart disease (49, 50). The mechanisms behind SCD in the young are probably different from those in older patients. Plaque erosion has been identified as the most frequent type of plaque complication in young patients with SCD and has shown preference for women (51). Smooth muscle hyperplasia was typical for these plaques in the young with only scarce lipid cores and little inflammation in contrast to the large lipid cores often seen in older patients. In a recent study it was shown that in the majority of young adults with coronary thrombotic findings, occlusion had occurred at least days to weeks prior to the acute event (52). In athletes the lesions frequently occur at sites without previous high grade of stenosis, and the mechanism suggested is a rapid expansion of a formerly noncritical plaque (53). Such plaques would probably not have been found by screening procedures such as exercise stress testing (54).

Cardiomyopathies in the general population
In HCM a prevalence figure of 1-2/1,000 (55, 56) is reported, and a risk of SD of about 4 % to 6 % in children and adolescents, and 2 %-4 % in adults (57-59). In ARVC and DCM the prevalence is 1/1,000-1/10,000 (16), and 0.5/1,000 (60), respectively. These three cardiomyopathies, familial in 30-50 % (61-64), are genetically and clinically heterogeneous diseases. The symptoms develop gradually which makes the majority of patients asymptomatic or only mildly symptomatic (17).

HCM, described in 1958 by Teare (65), is characterized by ventricular hypertrophy in the absence of an obvious cause, and hyperdynamic ventricular function (66). A young person with syncope at diagnosis, severe dyspnoea and a family history of SCD could be at high risk of SCD (58). Recently non-sustained ventricular tachycardia was shown to be a useful marker of increased risk of SCD in patients with HCM (67).

ARVC, described in 1981 by Marcus et al. (68), is a myocardial disease with a regional or global fibro-fatty replacement of the right ventricular myocardium, sometimes with involvement of the left ventricle (26, 69). Although SCD in ARVC is a rare event, the reason for several SCDs in certain families is unknown (70). Typical clinical features reported in ARVC are syncope and palpitations (71, 72).

DCM is a syndrome of impaired systolic function characterized by left ventricular dilatation, many deaths being secondary to progressive pump failure, but a large proportion of patients die suddenly (73). Syncope in heart failure patients with DCM seems to be associated with a higher risk of SCD (74).

In myocarditis, considered an underestimated cause of SCD (75), a recent flu-like illness is common. The cardiac involvement may cause heart block or ventricular arrhythmias. Symptoms can vary from fatigue and precordial discomfort (17) to syncope and/or palpitations, and SCD may occur both in the active or healed phases of myocarditis (75).

Diagnostic difficulties
The autopsy may reveal cardiac abnormalities (Table 2), but the cause of death may still be uncertain. “Giving the cause of sudden death for purposes of death certification is an exer-
cise in probabilities rather than certainties” according to the British pathologist Davies (76). Findings like a myocardial bridge (intramural tunneled coronary artery), anomalies of the coronary vessels, minor inflammatory changes or mitral valve prolapse, may be coincidental findings and are difficult to judge. Evidence of clinical symptoms such as angina may strengthen the relation between the findings and the cause of death. Structural abnormalities may also be overlooked, e.g., atrioventricular accessory connections or minor abnormalities in the conduction system. Focal manifestations or early stages of HCM or ARVC are also easily missed at autopsy (76, 77).

Valvular and congenital disease
Aortic valve stenosis with a significant left ventricular hypertrophy is a well-known cause of SCD. Minor degrees of floppy mitral valve are common in the population and probably an uncommon cause of SCD (76). Congenital malformations such as atrial septal defect (ASD) or ventricular septal defect (VSD) are also uncommon causes of death. Some patients who have previously had cardiac surgery have been identified as being at increased risk of SCD. Up to 40 % of late deaths after the Mustard repair in simple transposition of the great arteries are sudden (78). A population based study of late postoperative SCD in surgically treated congenital diseases showed an average risk of 0.9 per 1,000 patient-years, a risk above average in subjects with transposition of the great arteries, aortic valve stenosis, tetralogy of Fallot or coarctation of the aorta (79).

Primary arrhythmia
Subjects with no cardiac abnormalities despite a careful cardiac examination might have a primary arrhythmogenic disorder. In previous studies this SNH group was most commonly referred to as a subset with “unknown” cause of death, but this group is now more often referred to as a presumed primary arrhythmogenic disorder. In studies concerning only athletes this group is small, 2 % in a study of young competitive athletes (14), but in the normal young population in several studies quite common (4, 5, 7, 80, 81).

In a review, from 1977 to 2001, of autopsies in military recruits aged 18 to 35 years in the United States, 35 % of the deaths remained unexplained after detailed medical investigation (4). In school children in Japan 62 % of the deaths were unexplained (80), and in an Australian population study from 1994 to 2002 in the age group <= 35 years, 31 % of the deaths were presumed due to primary arrhythmogenic disorders (7). Symptoms like syncope and/or palpitations are common in the SNH group, but these disorders may present with SD or aborted SD. It is estimated that survivors of SCD without obvious heart disease have a 30 % recurrence rate of ventricular fibrillation, syncope and cardiac arrest, and implantable cardioverter defibrillator (ICD) seems to be particularly useful in these patients (13, 82).

In cases with normal autopsy findings a saved ECG may reveal electrophysiological disturbances such as pre-excitation in Wolff-Parkinson-White (WPW) syndrome (83), LQTS and SQTS or Brugada syndrome (9, 84, 85). Another possibility is a chromosomal analysis of cardiac tissue that post mortem could disclose abnormalities associated with cardiac dysfunction (86). Cardiac conditions that may contribute to SD in the absence of visible structural changes are listed in Table 1 (9-12, 87).
Table 3. Primary arrhythmogenic causes of sudden cardiac death.

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long QT syndrome</td>
</tr>
<tr>
<td>Short QT syndrome</td>
</tr>
<tr>
<td>Brugada syndrome</td>
</tr>
<tr>
<td>Wolff-Parkinson-White syndrome</td>
</tr>
<tr>
<td>Acquired disease of AV node, sinus node or His-Purkinje system</td>
</tr>
<tr>
<td>Cathecholaminergic polymorphic tachycardia</td>
</tr>
<tr>
<td>Right ventricular outflow tract tachycardia</td>
</tr>
<tr>
<td>Coronary artery spasm</td>
</tr>
<tr>
<td>Undetected segmental forms of hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy</td>
</tr>
<tr>
<td>Intramural tunnelled coronary arteries</td>
</tr>
<tr>
<td>Congenital complete atrioventricular block</td>
</tr>
<tr>
<td>Atrioventricular node re-entrant tachycardia</td>
</tr>
</tbody>
</table>

**Comorbid conditions**

There are certain conditions that may cause SD in absence of cardiac disease. Acute and chronic alcohol ingestion may provoke supraventricular and ventricular arrhythmias (88), and drugs such as cocaine can directly affect electrical activity in the heart (89). Furthermore, there is a high SD mortality associated with fatty liver, in most cases alcoholrelated (90).

Use of antipsychotics has been recently shown in an epidemiological study to be associated with SCD, even at low doses (91). Severe obesity (92) and epilepsy (93) are also related to an increased risk of SD. Combining autopsy examination and clinical history, Chugh et al. found a possible explanation for the death in 8 of 14 cases of normal heart (2 cases each of arrhythmic drugs without overdose, seizure disorder, obesity, pre-excitation on ECG) (94).

**Detection and prevention**

*ECG as a diagnostic or screening tool*

The Bethesda conference No. 26 guidelines in the United States (1995; to be updated in 2005) offer recommendations for competitive athletes with established cardiovascular abnormalities but does not recommend a general pre-participation ECG screening of athletes (95). In contrast, a new European consensus document recommends the implementation of a common pre-participation European screening protocol for competitive athletes essentially based on 12-lead ECG (96). The background to the European recommendations is the 25-year Italian experience on screening of competitive athletes, and the authors mention the key role of ECG in detecting cardiomyopathies and channelopathies (Table 4).

During 1979-1996 a series of 33,735 athletes underwent pre-participation screening according to a report from Center for Sports Medicine of Padova, Italy. Of these, 621 athletes (1.8 %) were disqualified because of various cardiovascular abnormalities: rythm and conduction abnormalities (38.3 %), hypertension (27 %), valve diseases (21.4 %), and HCM (3.6 %) (96). The disqualification of athletes with HCM is believed in part to explain the low incidence of HCM as a cause of SD in Italy(44). However, the same pre-participation screening study showed that the identification of athletes with CAD was limited by the low sensitivity of both baseline and exercise ECG in detecting myocardial ischemia.
Table 4. ECG features of cardiac diseases detectable at pre-participation screening in young competitive athletes.

<table>
<thead>
<tr>
<th>Disease</th>
<th>QTc-interval</th>
<th>P wave</th>
<th>PR interval</th>
<th>QRS complex</th>
<th>ST interval</th>
<th>T wave</th>
<th>Arrhythmias˚</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Normal</td>
<td>(Left atrial enlargement)</td>
<td>Normal</td>
<td>Increased voltages in midleft precordial leads; abnormal Q waves in inferior and/or lateral leads; (LAD, LBBB); (delta wave)</td>
<td>Down-sloping (up-sloping)</td>
<td>Inverted in mid-left precordial leads; (giant and negative in the apical variant)</td>
<td></td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy/dysplasia</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Prolonged &gt; 110 ms in right precordial leads; epsilon waves in right precordial leads; reduced voltages ≤ 0,5 mV in frontal leads; (RBBB)</td>
<td>(Up-sloping in right precordial leads)</td>
<td>Inverted in right precordial leads</td>
<td>PVB with a LBBB pattern; (VT with a LBBB pattern)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>Normal</td>
<td>(Left atrial enlargement)</td>
<td>(Prolonged ≥ 0.21s)</td>
<td>LBBB</td>
<td>Down-sloping (up-sloping)</td>
<td>Normal</td>
<td>Inverted in inferior and/or lateral leads Bifid or biphasic in all leads</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
<td>Normal</td>
<td>PVB; (VT)</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>Normal</td>
<td>-</td>
<td>Prolonged &gt; 0.21 s</td>
<td>S1S2S3 pattern; (RBBB/LAD)</td>
<td>Up-sloping coved-type in right precordial leads</td>
<td>Inverted in right precordial leads</td>
<td>(Polymorphic VT); (atrial fibrillation) (sinus bradycardia)</td>
</tr>
<tr>
<td>Lenègre disease</td>
<td>Normal</td>
<td>Normal</td>
<td>Prolonged &gt; 0.21 s</td>
<td>RBBB; RBBB/LAD; LBBB</td>
<td>Normal</td>
<td>Secondary changes</td>
<td>(2nd or 3rd degree AV block)</td>
</tr>
<tr>
<td>Short QT syndrome</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Atrial fibrillation (polymorphic VT); Supraventricular tachycardia; (atrial fibrillation)</td>
</tr>
<tr>
<td>Pre-excitation syndrome (WPW)</td>
<td>Normal</td>
<td>Normal</td>
<td>Shortened &lt; 0.12 s</td>
<td>Delta wave</td>
<td>Secondary changes</td>
<td>Secondary changes</td>
<td></td>
</tr>
<tr>
<td>Coronary artery diseases*</td>
<td>(Prolonged)</td>
<td>Normal</td>
<td>Normal</td>
<td>(Abnormal Q waves)**</td>
<td>(Down- or up-sloping)</td>
<td>Inverted in ≥ 2 leads</td>
<td>PVB; (VT); (PVB); (torsade de pointes)</td>
</tr>
</tbody>
</table>

Less common or uncommon ECG findings are reported in brackets. QTc: QT interval corrected for heart rate by Bazett’s formula. LBBB: left bundle branch block. RBBB: right bundle branch block. LAD: left axis deviation of -30º or more. PVB: either single or coupled premature ventricular beats. VT: either non-sustained or sustained ventricular tachycardia. *Coronary artery disease: either premature coronary atherosclerosis or congenital coronary anomalies. ** Abnormal Q waves.
Other studies have also shown the benefits of ECG. A prospective screening of 5,615 high school athletes in the United States showed that ECG was a more sensitive tool for detection of cardiac disease than clinical investigation and family history (97). Among the arguments mentioned against screening were the low specificity, the possible decrease in life quality in the asymptomatic individual having an abnormal ECG, the unclear responsibility for organizing a screening, and the costs.

In Sweden there is no pre-participation screening of athletes, but the issue is discussed within the medical and sports communities. In fact, more than 95% of all 18-19 year old Swedish men underwent enlistment and had a pre-participation investigation including an ECG up to about 1995. The benefits of the screening for the individual have not been evaluated, but the frequency of ECG pathology in the normal, young male population in Sweden has been investigated based on enlistment data (98). Today, about 85% of Swedish young men undergo enlistment, and in about 40-45% an ECG is taken (Ingvar Ahlstrand, Pliktverket, personal communication).

Treatment options

Treatment of patients at risk of SCD is linked to an accurate diagnosis. The first challenge facing physicians involved with these patients is the recognition of potentially ominous symptoms. Thereafter the physician must initiate a cardiac evaluation. Both structural and non-structural disorders may be difficult to detect. ARVC, for example, may need an investigation with magnetic resonance imaging (99) for detection, and primary arrhythmias sometimes have transient abnormalities which are not seen in a single ECG (85, 100). A correct diagnosis is mandatory for risk assessment, choice of treatment, and suitable recommendations with respect to training activities.

There are treatment options such as immunosuppressive therapy with steroidal drugs which have proven effective in children with myocarditis (101), antiarrhythmic drugs such as beta blockers in, e.g., LQTS or HCM, pacemakers in individuals with atrial arrhythmias, ICD in patients at high risk of SCD in many cardiac diagnoses (16).

The Task Force on Sudden Cardiac Death of The European Society of Cardiology has provided evidence-based recommendations for the prediction and prevention of SCD in the general population (16). According to the authors, the recommendations are not intended to be “guidelines for treatment”. Interventions that are known to prevent SCD are identified and emphasized.

Out-of-hospital resuscitation

Many SCD victims are not identified as being at high risk before the event, and it is believed that better warning systems, education and widespread availability of automated defibrillation devices could increase the number of survivors of cardiac arrest (13). This view was emphasized already 50 years ago by Claude Beck, the first professor of cardiovascular surgery, who developed a technique for open heart resuscitation (15). In 1947 he performed the first successful resuscitation of a person by open heart massage, injection of procain hydrochloride, and two electrical shocks. A couple of years thereafter the method for closed-chest cardiac massage combined with defibrillation was introduced (102).

There is only a short time frame after cardiac arrest during which circulation has to be restored to prevent death or irreversible ischaemic brain damage (103). It is therefore essential that the cardiac arrest victim is identified as soon as possible, and it has been suggested that a public access to defibrillation equipment, could allow non physicians to defibrillate (104).
**Bereavement**

The death of a close family member is one of life’s greatest tragedies (105). When the death is sudden and unexpected, such as in cases of SCD, there is an increased risk of a complicated mourning process, compared to when death is expected (106). Studies from emergency departments show the lasting impact of the approach to the bereaved in the acute situation and the manner in which the tragedy is told (107, 108). About 50 percent of persons who contacted a regional bereavement support group within a year of bereavement, did so because of negative feelings surrounding the care given by the hospital staff at the time of the death (109).

The sudden unexpected death of a close family member gives rise to a traumatic crisis. When simplified, this crisis can be described as a process with four phases: shock, reaction, processing and new orientation (110). The care providers at the emergency ward or other acute care settings will be meeting the bereaved in the first phase of shock, and a therapeutic attitude, based on knowledge about acute crisis reactions, is crucial. The bereaved can react with anger, confusion, or paralysis, and should be offered support and company. Important information may not be assimilated.

The shock phase and the reactive phase constitute the acute phase of the crisis and lasts about 4-6 weeks. During this time a crisis intervention is valuable. The intervention aims at supporting the individual’s own resources of healing, and to support in the confrontation with the reality. Many bereaved seek help about a month after a crisis situation, but the need of therapeutic help can be hard to recognize for the care provider (110).

Sudden bereavement is a multidimensional process involving physical, psychological, and sociological domains (111). A recent French study emphasizes that the nature of bereavement as a human experience, must be known by the physicians. The process includes personal, familial, social and cultural components (112). A therapeutic/preventive approach to the bereaved is not common.

In many countries the professional responses to sudden unexpected death are focussed on the investigation of death. Previous studies of families suddenly bereaved of a young next-of-kin showed that general health problems, post-traumatic distress, and complicated grief reactions were common (113, 114). In a retrospective study in England of bereaved parents’ perceptions of care after the SD of their child (1 week to 12 years old), two thirds of the bereaved had turned to other bereaved parents. Most felt that community care was inadequate, leaving many feeling isolated.

The survivor organizations like SIDS societies probably have an important role in improving psychosocial support for their members. In some countries there are organizations which provide support to families affected by a sudden arrhythmogenic death in young adults and also work for the prevention of these deaths [the SADS (Sudden Arrhythmia Death Syndrome) foundations]. Probably because of low patient numbers there is no similar organization in Sweden, but local supportive groups for bereaved parents are sometimes available. Despite several studies on SD, especially in infancy and childhood (115), there is a lack of long term outcome data of supportive needs in bereaved confronted with SCD in young relatives.
AIMS OF THE STUDY

General aim

The young SCD group is heterogeneous, and the identification of the risk patient is a challenge for the medical community. Part of the difficulty is the relative infrequency of occurrence and the lack of clinical and pathological material and data. Data of SCD in the young based on a national registry is not previously reported. The general aim of this study is to contribute to the prevention of SCD by a broad analysis of young SCD victims in Sweden during the period 1992-1999. The general aim of the study includes care of the bereaved confronted with SCD.

Specific aims

1. To retrospectively study the incidence and pathogenesis of SCD cases among 15 to 35 year olds in Sweden during 1992-1999 selected from the database of the National Board of Forensic Medicine (NBFM), and to correlate the findings to age, gender and time.
2. To reanalyse any available ECG in the young SCD group and correlate the findings with the autopsy diagnosis in each individual.
3. To study preceding signs and symptoms, family history, and circumstances of death in relation to SCD diagnosis.
4. To analyse lifestyle factors such as physical activity, competitive activities, smoking, body mass index (BMI), etc. in the SCD group as compared with a control group of the same age.
5. To elucidate the provided support and supportive needs of bereaved confronted with SCD in a family member, both initially and in the long-term perspective (5-12 years post-loss).
METHODS

Paper I

Selection of the study group (See inside of cover)
Individuals 15 to 35 years old who had suffered an SCD in Sweden during the period 1992 through 1999 and undergone a medicolegal autopsy were included in the study. Since “SCD” was rarely used as an autopsy diagnosis, these cases were found by an exclusion of non-cardiac deaths and non-sudden deaths. The following selection procedure was used:

1. A search in the NBFM database excluded deaths from external causes such as trauma and intoxication, resulting in 871 natural deaths.

2. From these 871 cases 615 cases of non-cardiac death were excluded [drug abuse (n=184), epilepsy (n=102), cases with unnatural causes probably contributing to death (n=106), diabetes (n=61), infections (n=39), cerebral infarction (n=15), pulmonary embolism (n=14), bronchial asthma (n=14), cerebral haemorrhage (n=11), other (n=69)]. In addition, 52 cases were excluded because of decomposition, obviously not fulfilling the criteria of “sudden” deaths.

3. From the remaining group of 204 cases a further 23 were excluded because of the presence of other conditions that could have caused SD: alcohol level > 1 g/l and/or fatty liver (n=12), anorexia/bulimia (n=3), abuse of androgenic-anabolic steroids (n=1), medication with arrhythmogenic antipsychotic drugs (n=4), and non-sudden deaths (n=3).

4. Finally 181 cases remained to the study group. The medicolegal autopsy protocols were studied, but no re-evaluation of the diagnoses was performed.

Among the excluded cases the largest subgroup was drug abuse (184 subjects), some of them with bronchopneumonia as the terminal cause of death. In several cases the diagnosis was uncertain, but information in the NBFM database revealed co-morbid circumstances such as drug abuse, epilepsy or diabetes. Several diagnoses were included in the subgroup “other”: brain tumour, adrenocortical insufficiency, sarcoidosis, thyrotoxic crisis, acute gastrointestinal haemorrhages, pyelo- and glomerulonephritis, hydrocephalus, Down’s syndrome, and burn injuries among others.

Comparison with the National Cause of Death Registry (COD) of 1995
The NBFM database was compared with the COD Registry for the year 1995 in order to find the number of SCD cases not being investigated by medicolegal autopsy this year. The COD Registry contained 550 deaths in 15 to 35 year olds after exclusion of death from external causes. In the next step the following cases were excluded: non-cardiac and non-sudden diagnoses, cases that had died abroad, and cases already included in the study group (502 excluded). To adjudicate the remaining 48 cases, death certificates (n=48), clinical autopsy protocols (n=28), and medical records (n=11) were studied. This information lead to exclusion of a further 35 cases. Finally seven additional cases fulfilling the criteria of SCD were found in the COD Registry this year.

In papers I-IV information about each case in the study group was obtained from medicolegal autopsy records, police reports, military and medical records whenever available, and in
many cases also through interviews with family members. The methodology concerning the interviews is described in paper III. The medicolegal autopsy reports and the clinical data were independently reviewed by two persons.

The medicolegal autopsy
All medicolegal autopsies were performed by a limited number (about 20) of experienced medicolegal pathologists, according to “Principles and Procedures of Medicolegal Autopsy/Basis for National Guidelines”, issued by the NBFM (1994), and similar consensus documents. Amongst other, it is stated that both heart chambers should be examined, but there is no norm for the examination of the conduction system.

Paper II
In a subgroup of the original SCD group (162 individuals after exclusion of 19 cases with dissecting aortic aneurysm), twelve-lead ECGs were searched for in military conscription and medical records. At least one ECG was retrieved in 66/162, (41 %) of the individuals, 59 men and 7 women.

The ECGs were reanalysed by two independent reviewers and classified according to the Minnesota code criteria (116). The ECGs were classified as normal (I), probably normal (II), probably abnormal (III) or abnormal (IV). In this study, class I and II were considered normal, and class III and IV as pathological. The corrected QT time was calculated according to Bazett (117). Prolonged QT interval was defined as corrected QT time $> 0.46$ s. An ST segment elevation $\geq 2$ mm in V1-V4 or $\geq 1$ mm in any of the other leads fulfilled the criteria of ST segment elevation (116). Isolated ST elevation or isolated minor intraventricular block were considered probably normal findings. If more than one ECG had been recorded, the most abnormal was used for correlation with the autopsies. In addition, one individual with SQTS, not classified as pathological by the Minnesota code criteria, was found.

Papers III and IV
Information about the study group was obtained from interviews with relatives by a questionnaire and by a telephone interview. For each deceased an informant was identified, either by the police report, the medicolegal institute or the population registry. To those who accepted to participate a questionnaire was sent with questions concerning athletic activity, physical training, medication, family history, diseases, symptoms or complaints, food habits, use of stimulants. After the questionnaire was returned a semi-structured telephone interview was conducted.

Paper III
Symptoms of infection and/or fatigue were counted only if occurring within two months prior to death, other symptoms irrespective of when they occurred. If more than one symptom had been reported one of them was designated as the main symptom. If syncope/presyncope had occurred this was considered the main symptom. In other cases the symptom reported as the most serious/frequent was designated as the main symptom, and if no distinction was made the main symptom was in order of specificity: palpitations, chest pain, dyspnoea, fatigue/weakness, infectious disease.

Paper IV
An athlete was defined as an individual participating in an organized team sport or individual sport which requires regular training and competitions, according to a commonly used
definition (118). Physical activity in this study was defined as a regular training of a sports activity such as jogging or a team sport. Also individuals participating in recreational or leisure time physical activities were considered athletes if they participated in regular competitions. Thus, participation in competitions differentiated the athletes from the non-athletes.

The frequency of athletes in the study group was compared with the frequency of athletes of the same age group in the Swedish population (1999) as found in a report on athletic and competitive activity from the Swedish Sports Confederation (119). Other lifestyle factors were compared with a control group from the Swedish survey of living conditions (ages 16-34, in the years 1996-1997) (120). Both studies had been carried out on behalf on the Swedish National Board of Health and Welfare and were used as control populations in this study.

**Paper V**

In this study 27 parents and three siblings to 19 deceased individuals were interviewed. The deceased had suffered an SCD during the period 1992-1999 when they were 15-35 years old. The 30 participants were selected among the responders in a previous part of the study. The gender proportion in the interviewed group was approximately the same as the proportion in the total SCD group (70 % men). The participants were interviewed in their homes. A narrative approach was used in the interviews. The participants were asked about support and information provided and their perceived needs of support, from the tragic event up to the present situation. The tape recorded interviews were transcribed to text and then analysed using a method for qualitative content analysis (121, 122).

**Statistics**

The incidence of SCD for each year was calculated from the numbers of SCD in the NBFM database divided by the number of inhabitants in Sweden for each sex, age group and year, according to Statistics Sweden (123). Rank sum tests were used to test differences between groups, and Poisson regression to test SCD trends by calendar year and age (124). For comparison between groups the chi-square test was used. For comparison of BMI with the control group, one-sample t-test was used, and for comparison of categorical variables Fisher’s exact t test was used. In all analyses a p-value of less than 0.05 was considered significant. All statistical analyses were carried out with the statistical program Stata (125), the most recent version being used at each time of analysis.

**Ethical consideration**

The regional ethical committee approved the study and the interviewed family members had given their informed consent. Many of them expressed their appreciation of the study. One of the non-responders sent an annoyed letter and an apology letter was written in reply. The positive response from the majority of the families is in line with a recent study by Dyregrov (126) showing that parents confronted with SD of a child were positive to research participation and that no one regretted participation.
RESULTS

Paper I

Incidence
The mean incidence of SCD over the 8-year survey period was 1.3/100,000/year for men and 0.5/100,000/year for women. There was no statistically significant trend in the rates of SCD over time although the annual mortality rate per 100,000 of SCD varied between 0.87 and 1.83 for men and 0.25-0.76 for women. In both sexes there was a yearly increase with increasing age; for men with 4.0% yearly (95% confidence interval 1.1-6.8), and for women with 4.6% per year (95% confidence interval 0.1 to 9.4).

Comparison with the COD Registry
Data from 1995 showed 28 cases in the NBFM database and 35 cases in the COD Registry fulfilling the criteria of SCD, i.e., 80% of the SCD cases of 1995 were registered in the NBFM database. The seven “missing” cases included three with CAD, two with myocarditis, one with dissecting aortic aneurysm and one with DCM. The three subjects with CAD and the subject with DCM had ante mortem cardiac diagnoses. The incidence of SCD per 100,000 per year was 1.44 calculated from the COD Registry, as compared with 1.15 calculated from the NBFM database.

Cardiovascular diagnoses (Fig. 2)
The most common diagnoses were SNH (38 cases, 21%) and CAD (32 cases, 17.7%). Three cases of conduction disease (1.6%) had structurally normal myocardium, but were diagnosed ante mortem with LQTS and WPW syndrome. In the third subject an interruption of the left bundle in the conduction system was discovered at autopsy. In this case the clinical history revealed recurrent syncope starting after an infectious disease 4 months prior to death, and enlistment ECG showed a right bundle branch block. The cardiomyopathies varied in frequency from 6.6% in ARVC to 12.2% in DCM.

Figure 2. Diagnoses in 115 men and 47 women suffering a sudden cardiac death.
*Includes one with interruption of left bundle, **Includes 4 with congenital disease, ***Includes coronary anomalies and myocardial bridge
**Paper II**

In 66 study cases (59 men and 7 women) at least one ECG was retrieved. Those ECGs were pathological in 50 % of the cases with a mean time between recording and death of 4.4 years, compared to 5.5 years in non-pathological ECGs. The mean age at the time of death was 24 years for men and 26 years for women. Cardiac-related symptoms were seen in 76 % of the total group and a family history of a similar cardiac condition in 20 %. A family history of SCD was especially common in HCM (37 %), ARVC (38 %) and in DCM (44 %).

The proportion of pathological ECGs varied between the main diagnostic groups from 88 % in ARVC, 82 % in HCM, 50 % in myocarditis, 20 % in CAD to 11 % in DCM.

The most common ECG abnormalities were repolarisation disturbances such as T wave abnormalities (35 %) and ST segment changes (32 %). ST-T changes were especially common in ARVC but were observed in all diagnostic groups. T wave inversion was the most common T wave abnormality. One patient with SNH had an ante mortem diagnosed LQTS, but five other cases with prolonged QT interval were not clinically diagnosed.

Conduction abnormalities such as bundle branch or fascicular blocks were observed in 20 % of the study group. These changes were most common in HCM. Minor intraventricular conduction defects were seen in ten other cases. One individual with HCM was treated for a WPW syndrome, but five of six cases with preexcitation were not under clinical control.

In 48 cases (all men) an ECG recording was done in connection with enlistment. In three of these cases (6 %) the interpretation in this study differed from that made at the enlistment centres. In 20 cases with more than one ECG a progress in a pathological direction was seen in 11 (55 %) (Table 5).

**Paper III**

In 79 % (128/162) the probands completed the questionnaires. There was also information from police reports (156/162; 96 %) and from medical records (44/162; 27 %). Cardiac-related symptoms (syncope/presyncope, palpitations, chest pain, dyspnoea) were reported in 56 % (92/162) and unspecific symptoms such as post-influenza weakness in 22 % (35/162). Cardiac related symptoms were especially common in ARVC (83 %) and HCM (74 %), and occurred in the other diagnoses between 32 % in myocarditis and 59 % in CAD.

Syncope/presyncope (38/4) was the most common symptom in four of the six main diagnoses (Fig. 3). Syncope occurred during physical activity in 12/42 (29 %). Death was witnessed in 43 % of the subjects but in most a judgement of the circumstances and activity at death could be done. Death during daily activity was the most common in all diagnostic groups with the exception of ARVC (where death during physical activity was most common) and SNH (death during sleep was most common). Death during physical activity occurred in 41/162 (25 %) of the study group.
Table 5 Characteristics of 11 male sudden cardiac death victims with progress of ECG abnormalities.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age at ECG1</th>
<th>ECG comments</th>
<th>ECG class</th>
<th>Age at ECG2</th>
<th>ECG comments</th>
<th>ECG class</th>
<th>Age at death</th>
<th>Preceding symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal heart*</td>
<td>18</td>
<td>Minor intraventricular block</td>
<td>II</td>
<td>23</td>
<td>ST elevation, incomplete RBBB</td>
<td>III</td>
<td>24</td>
<td>Syncope at sleep, postinfectious fatigue</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>18</td>
<td>Normal</td>
<td>I</td>
<td>19</td>
<td>ST elevation, Q in AVL</td>
<td>III</td>
<td>20</td>
<td>Syncope, palpitations</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>19</td>
<td>ST elevation, right axis deviation, incomplete RBBB</td>
<td>III</td>
<td>31</td>
<td>T negativity, posterior Q, incomplete RBBB</td>
<td>IV</td>
<td>34</td>
<td>Palpitations, fatigue</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>25</td>
<td>ST depression, LAH</td>
<td>IV</td>
<td>31</td>
<td>Increasing QRS amplitudes</td>
<td>IV</td>
<td>32</td>
<td>Palpitations, presyncope</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>18</td>
<td>ST depression</td>
<td>II</td>
<td>19</td>
<td>Incomplete RBBB</td>
<td>III</td>
<td>21</td>
<td>Syncope, palpitations</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>18</td>
<td>Normal</td>
<td>I</td>
<td>31</td>
<td>AVI, T negativity</td>
<td>IV</td>
<td>32</td>
<td>Postinfectious fatigue</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>18</td>
<td>ST elevation, AVI</td>
<td>II</td>
<td>25</td>
<td>Atrial flutter</td>
<td>IV</td>
<td>27</td>
<td>Syncope, palpitations</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>18</td>
<td>Normal</td>
<td>I</td>
<td>21</td>
<td>Incomplete RBBB</td>
<td>IV</td>
<td>25</td>
<td>Presyncope</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>18</td>
<td>Normal</td>
<td>I</td>
<td>19</td>
<td>ST elevation</td>
<td>III</td>
<td>35</td>
<td>Syncope</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>18</td>
<td>VES, T negativity V2</td>
<td>III</td>
<td>20</td>
<td>T negativity V2-V3</td>
<td>IV</td>
<td>23</td>
<td>Syncope</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>5</td>
<td>LAH suspecta, left axis deviation</td>
<td>III</td>
<td>15</td>
<td>LAH, Increasing</td>
<td>IV</td>
<td>27</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

*Normal myocardium but interruption of left bundle
In all, 74/162 (46 %) had consulted a doctor because of symptoms and in 32 of these (43 %) an ECG had been taken. In 24 individuals the ECGs were pathological, and 23 of these had been referred for further evaluation. In seven of these cases a diagnosis had been set more than a year prior to death, in one case 2 months before death: HCM (n=3), LQTS (n=1), ARVC (n=1), DCM (n=1), W PW (n=1), myocardial infarction(n=1). All eight had been medically treated but none had received an ICD. Six other individuals had had congenital disease diagnosed in childhood, and four of these had been surgically treated (ASD, VSD, transposition of the great arteries, aortic stenosis). Heredity for SCD in a first degree relative (brother, sister, parent, child) was present in 16 %.

![Figure 3](image-url)

**Figure 3.** Main symptoms in sudden cardiac death, by diagnosis. ARVC= arrhythmogenic right ventricular cardiomyopathy, HCM= hypertrophic cardiomyopathy, DCM=dilated cardiomyopathy, CAD=coronary artery disease. Normal heart includes one with interruption of left bundle.

**Paper IV**

In 128 individuals information about lifestyle factors was collected from the interviews; in ten more subjects (nine cases of CAD and one case of DCM) relevant data were found in medicolegal or medical records. Thus, the study group for comparison with the control groups consisted of 138 subjects, 97 men and 41 women. BMI could be calculated in 141 individuals with data from the medicolegal autopsy protocols.

There were 32/138 (23 %) athletes in the SCD group, 28 men and 4 women. The deceased represented 14 different sports (11 European football, 6 floor ball, 2 running, 2 orienteering and one each of 11 different sports). Five were regarded as top athletes, having competed on a national level. Two of them had stopped competing because of symptoms such as syncope or palpitations (two cases of running). The other three had been advised to avoid strenuous training because of syncopal episodes (one case of ice-hockey and one case of orienteering) or postinfectious fatigue (one case of triathlon). The control group had 29 % athletes
(622/2131), i.e., a higher percentage than in the SCD group, but approximately the same percentage of athletes with a high training intensity (≥ 3 times/week).

The male SCD group was very similar to the normal population with respect to BMI (mean value 23.7 in both groups), medication and physical activity, but had more smokers (p=0.007) and fewer snuffers (p=0.002) than the controls. BMI was higher in men with CAD (27.0) than in the control group (23.7), p < 0.003. The CAD fraction of the SCD group had a high percentage of smokers (73 %).

The female SCD group had a higher BMI and a lower level of physical activity than the control group (SCD mean BMI 26.9 and control group 22.5, respectively). There was no difference with regard to competitive activity in the female group. There was no significant difference in smoking habits between SCD and control women.

Death during training was more common in athletes than in non-athletes (20/32; 63 % vs 18/106; 17 %, p<0.001). A majority of the athletes who died during physical activity had an underlying structural cardiac disease (17/20; 85 %).

**Paper V**

Four out of 30 participants witnessed the onset of SD in two of the deceased and started resuscitation that was continued by the ambulance or emergency staff. In six more of the SCD cases resuscitation attempts were performed at the emergency department and in one case at the primary health care centre. Ten of the deceased were found dead in their homes.

The loss of a young family member in SCD was described as a “forever life changing moment”. The loss was expressed in terms of “impossible to grasp” and “surreal”. The participants described the shock, anger, despair, bitterness, and grief they had perceived in relation to the tragic event. The majority had complaints about aspects of the handling in the acute situation.

Being present at the resuscitation attempt was important and appreciated, e.g., “I am so glad I was there all the time. I know that they did all they could, and even continued longer than they had to”. In contrast a mother who had to wait outside felt disappointed: “I saw a glimpse, but I was not allowed to enter. What difference would that have done? I understood anyhow.”

Many participants expressed the need of a distinct and clear death message with the use of evident words, e.g., “He didn’t say that he was dead, he said that there was nothing to do. He was absolutely worthless”. When the death occurred out-of-hospital, many of the participants (n=11) had no contact at all with the authorities. One of them said, “I expected a call from the hospital but it never came. I missed it so terribly”.

Most participants felt that they were left to themselves to find information and support. The tragic event forced the bereaved into a complex process of re-creating their lives, and that process was still ongoing five to 12 years after the bereavement. A lack of supportive structures in the handling of the bereaved was disclosed in the interviews. The participants told about being bereaved (initially, in the subacute phase and in a long-term perspective) and their stories revealed a striving for understanding and for being understood.
The cognitive dimension of understanding and the emotional dimension of being understood were significant for the complex processes of mourning and recreating one’s life as a bereaved (Fig. 4). Five general supportive aspects came out of the individual interviews, promoting the major needs of understanding and of being understood. Evidence, reconstruction and explanation were supportive aspects related to the need of understanding. Sensitivity from the personnel, friends etc., and structures such as cooperation between authorities and follow-up support were associated with the need of being understood.

Figure 4. Supportive needs of the bereaved.
DISCUSSION
This survey of young SCD cases in Sweden during 1992-1999 confirms the diversity of the group. The incidence was rather stable, about 1/100,000/year (73 % men) during the study period. More than ten diagnoses were found at autopsy. The most common autopsy findings were SNH (after strict exclusion of comorbid factors) and CAD. Abnormal ECGs and preceding symptoms were common. The symptoms varied from unspecific such as fatigue to more distinct such as recurrent syncope, and were often misinterpreted as being non-cardiac related. A family history was known in 16 % of the subjects, an infectious or idiopathic background in others. Life style factors were very similar to the normal population in men but the women suffering SCD were less physically active than the controls. The families left behind perceived a lack of routines for support and information. A number of supportive aspects of importance for meeting the relatives’ need of understanding and of being understood were identified.

The NBFM database
Since “SCD” was rarely used as an autopsy diagnosis, these cases were found by exclusion of all non-cardiac and all non-sudden deaths. To accomplish that requires information that was not easily available when the COD Registry was used. In this study the SCD cases were selected from the NBFM database.

The advantage of using the NBFM database is that it often contains a short information about the circumstances of death, e.g., “found in a toilet with syringes on the floor”. Such information can be of help in the selection procedure as abuse is involved in a significant number of SD in the young. Furthermore, the medicolegal files contain police records, medicolegal autopsy protocols and sometimes medical records which provide essential information. In contrast, the COD Registry only contains the coded diagnoses. Since 1991 in Sweden, only unnatural deaths or deaths which might be unnatural shall be reported to the police who decide about medicolegal autopsy. As cases of sudden unexpected death might be unnatural, especially when unwitnessed, medicolegal autopsy is often performed. In this study 57 % of the deaths had been witnessed but had been referred to medicolegal autopsy. The number of young SCD cases that is missed when using the NBFM database is unknown, but a control for 1995 found 20 % missing cases.

Strengths and weaknesses
The strength with this material is that it is based on data from the NBFM database covering the whole of Sweden, describing a considerable fraction of the deceased with regard to 
clinical history, symptoms, ECG and life style factors. Information came from a personal contact with relatives of 80 % of the study group, availability to medical records in 30 % of the cases and to medicolegal and police records in almost all cases. It is also a strength that the selection of the study cases is explained in some detail. The case selection procedure is commonly not described in similar studies on SCD in the young.

The largest weakness with this study is the underestimation of the SCD cohort, and that is a possible bias. Cases with a previously known heart disease should be a group less commonly referred to medicolegal autopsy. In 1995 four out of seven missing cases had a previously known cardiac affection. Witnessed sudden deaths with well-known symptoms, e.g., chest pain would also be less likely to be referred to medicolegal autopsy. This can lead to the situation in which cases of CAD are missed to a higher degree than other SCD diagnoses (in 1995 three out of seven missing cases had CAD). Also, in a few cases, sudden cardiac
deaths may falsely be classified as accidents if causing, e.g., a traffic accident. Another weakness is that there were few available ECGs, especially in the women. There is a bias selection introduced by the predominance of ECGs in men. Many of the ECGs in this study were obtained at enlistment several years prior to death. The normal ECGs were sometimes discarded, which contributes to the relatively high percentage of pathological ECGs. The time delay between ECG and SCD also means that signs of diseases acquired later in life such as myocarditis and CAD were missed. In addition early stages of the cardiomyopathies may not have developed a typical pattern. The bias involved in a retrospective investigation also applies to this study.

Cases with dissecting aortic aneurysm are often included in the SCD group, and this was also done in this study. These cases (n=19) were not further analysed in this context since they constitute a special subgroup with a primary mechanical mechanism as the cause of death in a majority of the cases, and not an electrical disturbance.

Other studies
The SCD incidence found in this study is comparable to those found in other studies (3, 5, 35-40) (paper I). It has not been possible to find another study that has systematically compared the ECG recordings with the findings at autopsy in cases of SCD (paper II). Symptoms have been found in similar studies to about the same extent (6), but not studied in such detail with regard to relation to diagnosis and visits to doctors (paper III). Athletes have been compared to non-athletes in a prospective study in Italy (3), but there is a lack of studies on other life style factors in the young SCD group (paper IV).

Gender differences
About one fourth (27 %) of the cases in this study were women, which is the same gender relation as seen in other studies (5) (papers I-IV). Among the athletes there was a larger difference, seven times more male athletes died from SCD than female athletes, which is of the same magnitude as reported previously (3, 127, 128). It has been proposed that male gender, in itself, is a risk factor for sports-related SD, because of the higher prevalence of cardiomyopathies (129, 130) and premature CAD in young men. It has also been thought that the gender difference in athletes are associated with a higher degree of training intensity and participation in competitions. Long-term athletic training leads to an increase in left ventricular mass, but in a large study of male athletes only 2.2 % had a significant increase in wall thickness and left ventricle (131). In a study of 600 female elite athletes this hypertrophic response to intensive training was not seen (132).

Camp et al. showed in a study of high school and college athletes in the USA that 98 % of all SCD cases in HCM were male (133). The present study also showed a male dominance in HCM and in dissecting aortic aneurysm (134). Both HCM and aortic dissection, the latter often associated with Marfan’s syndrome, are congenital diseases (135), and there is no obvious explanation for this gender difference. Apart from these diseases the pattern of SCD diagnoses were rather similar between men and women.

ECG was only retrieved in seven women and pathological in the same proportion as in men. The diagnoses corresponding to the pathological ECGs in women were: LQTS and VSD (ante mortem diagnosed), ARVC and myocardial bridge. In the two latter ECGs were taken because of syncope but not evaluated further.

Perhaps there is a different background to SCD in women. In this study the women had a lower level of physically activity and a higher BMI than the normal population whilst the
men were very similar to the controls. This might be an adaptation to a silent cardiac disease in the women. In the general population CAD has shown to be the most important predictor of cardiac arrest in women, whilst impaired left ventricular function is the most important predictor in men (136). One can also speculate if the figures are representative or if a higher percentage of men are referred to autopsy in cases of sudden unexpected death.

**ECG**

The study showed that 50 % of the ECGs were pathological (paperII). Although the bias described must be taken into consideration, 50 % is a high figure as compared with the normal population. Atterhög et al. (98) showed a prevalence of 2.5 % pathological ECGs in a population of 18-19-year-old Swedish men at conscription. T-wave abnormalities were the most common finding. Similar results were shown in a large study of flying personal in the US Air force by Hiss an Lamb: a prevalence of 1.5 % of T-wave abnormalities were found in a population of 16-19 year old men (137).

The high frequency of pathological ECGs in HCM (82 %) and ARVC (88 %) is in accordance with the literature (66, 138). The ECG abnormalities in HCM seen in this study were bundle branch blocks, ST-T changes, and pathological Q wave changes. Reported ECG changes in HCM most commonly affect the ST segment and T wave (66), but pathological Q waves and left atrial enlargement are also common findings (139).

In ARVC the typical ECG pattern is repolarization abnormalities with inverted T waves in the right precordial leads (138). Among the ARVC cases in this study all but one had T wave inversion and/or ST elevation, and in three cases there were also conduction defects. The disease often manifests in young adults with ventricular arrhythmias, most commonly with left bundle branch block (140).

Three cases of HCM and one case of ARVC were ante mortem diagnosed. Although all patients in this study with ARVC were cardially evaluated, ARVC was only diagnosed in one case where magnetic resonance imaging was also performed. This is reported to be the best technique for detection of ARVC (99). The Italian pre-participation screening of athletes 1979-1996 (44) also failed to detect ARVC, despite the fact that the ECGs in those athletes often showed inverted T waves in the right precordial leads and ventricular arrhythmias with a left bundle-branch block pattern. In addition, the athletes often had a history of syncopal episodes. The reason why those athletes were not noticed at the Italian screening was, according to the authors, that ARVC was at that time not recognized as a cause of SD during sports activity. In contrast, the screening program, based mainly on ECG, was efficient in detecting individuals with HCM (44).

It should be possible to detect a proportion of those with HCM or ARVC with an ECG taken as a routine at a certain age. However, it would still be difficult to predict who is at risk of SCD. Most of the study patients had a combination of ECG changes and cardiac related symptoms, and there was a family history in one third of the HCM cases and in one fourth of the ARVC cases. In contrast, DCM had a low percentage of pathological ECGs. The identification of these patients based on ECG findings is difficult. Syncope and family history might be predictors of SCD in DCM (63, 141). In this study one third of the DCM patients had syncope, but heredity of SCD was only known in 14 % (7/22). One case of DCM was ante mortem diagnosed.
In subjects with SNH one third of the cases had pathological ECGs with findings of conduction system disorders and repolarization defects. One case of LQTS and one case of WPW syndrome, were diagnosed several years prior to death. The remaining ECGs in subjects without structural autopsy findings were normal, but primary arrhythmogenic disorders such as LQTS (100) or Brugada syndrome (85) might be missed in a single ECG.

In the future also other electrophysiological syndromes might be discovered. Recently the SQTS was described (84), and this was recognized in one man with DCM in this study. His ECG was judged normal as this abnormality is not included in the Minnesota code criteria. His sister died one year after him. She belonged to the SNH group, but there was no ECG for comparison. The SQTS is characterized by familial SD, short refractory periods and inducible ventricular fibrillation (84).

In myocarditis, half of the ECGs were pathological with ST-T changes and conduction disturbances. In two more cases of myocarditis ECG had isolated minor intraventricular defects. Any evidence of conduction abnormality is associated with a more severe prognosis in patients with myocarditis (142, 143). The normal ECGs in myocarditis were taken years before death.

Only one pathological ECG was seen in this study in a patient with CAD. That was an old ECG showing preexcitation but the patient was not under clinical supervision. One of the study cases with CAD had done an exercise test because of chest pain and that was normal. It is known that there are difficulties with detecting signs of myocardial ischemia both in CAD and in coronary anomalies (44, 66).

In this study more than one ECG was present for 20 of the cases. In 11 of these the ECG had become more pathological in individuals with diagnoses such as myocarditis, DCM, HCM, and ARVC. Changes in ECG over time were also seen in a study of 16 young orienteers suffering an SCD in Sweden during 1979-1992. ECG in seven subjects showed ECG changes having developed after enlistment in five cases. T wave inversion was seen in three cases and ST-T changes in two cases (144).

Symptoms

The most common symptom in this study was syncope/presyncope that occurred in one third of the cases (paper III). Other SCD studies have also shown syncope being a common preceding symptom. This was reported in a study of young soldiers by Kramer et al., and in a study of children and adolescents by Driscoll and Edwards (35, 145). Drory et al. found chest pain being the most common symptom in subjects ≥ 20 years old and dizziness in those < 20 years old (40).

Syncope is a common symptom in the general young population and accounts for 3-5 % of emergency room visits (146, 147). Young patients with syncope are considered to be at low risk of cardiac disease, because more than 80 % of these have a vasovagal or psychogenic syncope, not associated with SD (148). However, the 1-year mortality risk of SD in patients with cardiac syncope ranges between 18 and 33 %, and it is important to perform a cardiac evaluation with an ECG as a first step (149).

Structural heart disease is a major risk factor of SCD in patients with syncope (71, 141, 150). This study partly confirmed that, as syncope was the most common symptom in the cardiomyopathies except in HCM, where palpitations was the most frequent symptom. Pos-
ibly the high frequency of palpitations in HCM, not previously reported as most common symptom in this disease, is an ominous sign preceding SCD. Non-sustained ventricular tachycardia is found a useful marker of increased risk of SCD in HCM (151). In the literature dyspnoea is reported in up to 90% of symptomatic patients with HCM (58), but chest pain, syncope and palpitations are also seen in these patients.

If syncope is associated with exercise a cardiac cause is considered more likely (149), but in this study only 30% of the cases were exercise-related. In one study case recurrent syncopal episodes always occurred during rest at night, starting about a month after a flu-like illness. Probably syncope in this case was caused by a total AV-block. ECG taken one year ante mortem showed right ventricular bundle branch block and ST-elevation. The autopsy showed a total interruption of the left fascicle. The symptoms in this patient were misinterpreted as suspected sleep apnoea. In myocarditis the symptoms often followed an influenza-like illness, syncope being most common but precordial discomfort or fatigue was sometimes the only symptom.

Chest pain was the second most common main symptom and not surprisingly the most common symptom in CAD. Half of the symptomatic CAD patients had been to a doctor because of chest pain, but only in two of seven had an ECG been taken.

Of all study cases seeking medical advice because of symptoms four out of ten (32 subjects) had an ECG taken. Symptoms were often misinterpreted as being non-cardiac related. Distinct symptoms such as syncope, chest pain or palpitations may arouse the suspicion of cardiac disease while febrile disease or fatigue will probably not. However, fatigue after an infection is sometimes the only sign of myocarditis, and this diagnosis may be revealed by an ECG, especially if there is an old ECG for comparison.

Also in persons seeking medical advice because of syncope, chest pain, palpitations or dyspnoea, the symptoms were often misinterpreted. There are different explanations for this: chest pain was sometimes interpreted as musculo-skeletal pain, palpitations as anxiety. The patients were often asymptomatic during the visit to the physician. Syncope was sometimes evaluated only for seizure or in one case referred to sleep apnoea investigation. It has been shown that syncope not uncommonly is misunderstood as seizure disorder in patients with LQTS (152) and evaluated with EEG. However, EEG has little value in investigation of unselected patients with syncope (153).

Is physical activity dangerous?
It is a topic of great interest whether physical activity is dangerous with respect to SCD or not (paper IV). This study shows that the SCD group was not more athletic than the controls but the athletes more often died during physical activity. In ARVC physical activity was the most common mode of death. There seems to be a triggering factor that can start the fatal mechanisms leading to SCD. In the general population it is known that hard exercise can trigger acute myocardial infarction and SCD (154), possibly by increasing platelet adhesiveness and aggregability. Physical activity or emotional stress can also be triggering factors in diseases such as HCM, ARVC, and long QT1 (155). On the other hand, in long QT3 (155), Brugada syndrome which is sometimes called “sudden unexpected nocturnal death syndrome” (156), and other conduction system disturbances, sleep or rest may be the most dangerous activity. In patients with Brugada syndrome it is believed that malignant ventricular arrhythmias occur at sleep because of an increased vagal activity and/or a decreased sympathetic drive (157). In this study death during sleep was the most common mode of death in
subjects with SNH, and in the total study group 70 % died during non exertional circumstances.

**Pre-participation screening**

For more than 25 years, a systematic pre-participation screening of athletes predominantly based on 12-lead ECG, clinical history and physical examination, has been in practice in Italy (96). Since 1971 Italian law has required that individuals annually undergo such a screening before entering competitive sports activities. The most common diagnosis in the athletic SCD group in the Veneto Region of Italy is ARVC (44). In contrast, several studies on athletes from the United States show that HCM is the predominant diagnosis (14, 41, 158). The low frequency of HCM in Italian athletes is considered to be due to the early detection of HCM at screening and recommendation to avoid training. ARVC seemed to be more difficult to detect and is also possibly endemic in the Veneto Region of Italy (62). Prospective studies in Italy have shown a 2.5 times higher incidence of SCD in athletes than in non-athletes (3), the incidence in athletes being 2.1/100,000/year and in non-athletes 0.7/100,000/year. In a study of Minnesota high school athletes by Maron et al. the incidence of SCD was estimated to be 0.5/100,000/year (41).

It may seem a little confusing that Italy with a pre-participation screening of competitive athletes for more than 30 years, has a higher mortality rate of athletes than the U. S. with no mandatory screening activity that includes an ECG. The incidence figures in the American studies may be considerably underestimated according to a recent review by Maron (158). In the study on Minnesota high school athletes the number of deaths and participants was based on an insurance programme mandatory for all student athletes (41). In some studies the cases are gathered from different sources by the National Center for Catastrophic Sports Injury Research, and the number of participants from sports associations (127). Another explanation recently proposed is the higher mean age in Italian athletes and the participation at a higher level of intensity as compared with US high school and college athletes (96). The higher frequency of SCD in athletes in Italy, as compared with that in USA, may also be due, in part, to the prospective study design.

The findings in this study, that the Swedish SCD group was not more athletic than the normal population, may not be contradictory to the Italian studies. The athletic group in Italy constitutes about 8 % (3) of the age group (12-35 years old) and is probably not comparable to the self reported athletic group of 29 % in our control group (15-35 years old).

In a recent European consensus document the implementation of a common pre-participation European screening protocol for competitive athletes essentially based on 12-lead ECG is suggested (96). The document refers to the 25-year Italian experience of pre-participation screening of athletes and emphasizes the key role of ECG in detecting cardiomyopathies and channelopathies. The results from this thesis confirm that ECG has a central role in the detection of cardiac diseases, but do not show an overrepresentation of competing athletes in the young SCD group. It is an interesting question how to limit the group to be screened, or whether the group should be limited at all. Many young people today participate in different recreational sports on a regular basis, often with a high level of training intensity. It is not evident that competitive physical activity increases the risk of a cardiovascular event more than non-competitive physical activities. Besides, a majority of the cases in this study died during sleep or normal daily activities.
Support of the bereaved

The British pathologist Davies commented on SCD in 1992: "Unexpected death in fit young people is distressing, but if the death is explicable the family may be able to begin the process of psychological adjustment" (159). The importance of getting an explanation is confirmed by this study, which also revealed that many bereaved confronted with SCD experienced a general lack of support (paper V). This is in accordance with other studies on SD in different age groups (115, 160).

The unique trait with this study is that it is part of a broad approach to SCD. The participants have, a couple of years ago, contributed to the medical dimension of SCD by answering questions about preceding signs and symptoms, and now, 5-12 years after the tragic event, give their thoughts about their supportive needs. A common reflection from the bereaved was that there is a need for the same supportive routines in cases with a single SD that are offered when there are accidents with several casualties. The supportive structure seemed to be especially weak when death occurred out-of-hospital, which probably is due to a lack of cooperation between the authorities involved (police, ambulance, medical community). Based on the findings in this study, a supportive program is proposed to be used in cases of sudden unexpected deaths. The process of mourning takes a life-time and a wise handling by the staff involved in the initial phase can be crucial for the outcome.
CONCLUSIONS

SCD in the young occurred in about 1/100,000/year and was almost three times more common in men than in women. The incidence did not decrease during the study period 1992 to 1999. The most common diagnoses were SNH and CAD (paper I).

Pathological 12-lead ECGs were common in SCD victims, in spite of being taken many years before death. An ECG could help identify prospective victims of SCD. The highest percentage of pathological ECGs was seen in the cardiomyopathies HCM and ARVC, and with ECGs taken at a certain age it seems possible to detect a proportion of individuals with these disorders. Study subjects with SNH might have had different arrhythmogenic disorders. The knowledge about ECG abnormalities in the female SCD group is very limited due the few ECGs in women. When reiterated the ECGs often developed in a pathological direction (only men) (paper II).

Symptoms preceding SCD such as syncope, chest pain or palpitations were common but often misinterpreted as being non-cardiac related. It was not possible to link a certain sign or symptom to a specific diagnosis. The patient seeking medical advice before suffering an SCD was characterized by one to three of the following: cardiac-related symptoms or non-specific symptoms often after an infectious disease, a pathological ECG, a family history of SCD. Non exertional syncope was more common than exertional syncope and should also be cardially evaluated (paper III).

The total SCD group was very similar to the normal population with regard to life style factors such as smoking, BMI, physical activity. There was no overrepresentation of athletes, but the athletes in the study group more often died during physical activity as compared to the non-athletes. In certain cardiac disorders physical activity seemed to trigger SCD, whilst in others death during sleep was the most common mode of death. Reduction of hard training and elimination of competitions, could be life-saving in athletes with cardiomyopathies. The SCD women had a higher BMI and a lower level of physical activity than the controls (paper IV).

There was a lack of supportive procedures for helping the bereaved, both initially and in the long run. The sudden and unexpected loss of a loved one affects the rest of one’s life. The needs of the bereaved had a cognitive dimension of understanding and an emotional dimension of being understood. Based on the interviews a supportive program is proposed (paper V).
IMPLICATIONS FOR PREVENTION

There is not a single test to predict who is at risk of SCD, but a correct diagnosis is crucial for risk assessment and a suitable treatment. In 4 out of 10 seeking medical advice an ECG had been taken and three of these were pathological. This implies that ECG is an underused tool in the investigation of symptoms, and an database with old ECGs available for comparison could be useful in the prevention of SCD. In one third of those who were thoroughly investigated a cardiac diagnosis could be settled ante mortem, suggesting that more diagnoses could be found in non-investigated patients. If the ECG is abnormal, the symptoms severe or there is a family history of SCD, the patient should be referred to further cardiological evaluation since drugs or an ICD could be an effective treatment to prevent SCD.

In this study a significant number had a non-structural heart disease, possibly with a genetic background. With the rapid progress of new genetic diagnostic methods, a molecular autopsy in the proband and clinical testing in the surviving family members may become a valuable complement for risk stratification of inherited cardiac diseases in the future.
PROPOSALS TO IMPROVE PREVENTION AND CARE

Increased awareness of preceding symptoms and the importance of ECG at health care stations and emergency departments could help to detect more young persons with suspected cardiac disease. National records for each patient with full coverage of all relevant health care information would make it easier for the physician to judge symptoms and to “get the whole picture”.

- Further development of diagnostic methods and improvement of risk assessment could give more of these patients a correct diagnosis and an optimal treatment.

- Increased cooperation between medicolegal or other autopsy authorities and clinical medicine could increase exchange of information in cases of SCD, as the knowledge within this area is difficult to assimilate due to the small number of patients.

- More large scale investigations of SCD in the young could assemble knowledge and improve diagnosis of these patients.

- In SCD cases a targeted molecular analysis of tissue in the proband and clinical testing in the surviving family members may become a valuable complement for diagnosis and risk stratification of inherited cardiac diseases in the future.

- Cooperation with enlistment services could help organize a large-scale ECG database, a database that could facilitate comparisons when needed.

- Increased education in the community and widespread defibrillation devices could increase the number of survivors of cardiac arrest.

- Introduction of a supportive program to be used in cases of sudden unexpected death, both in and out-of-hospital, could give a better support to those who are suddenly bereaved. Emergency room and ambulance personnel regularly attend cardiopulmonary resuscitation courses and regular education in a similar way about traumatic crisis reactions could improve care of suddenly bereaved.
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Erratalista.


Page 11. Line 5 reads “..in the young..”, should read “..in the athletic young..”

Page 12. Second paragraph, line six reads “..the time of onset.”, should read “..the time of onset of terminal event.”

Page 16. First paragraph, line 10 reads “.., occlusion had occurred..”, should read “.., thrombus formation had occurred..”. Line 11 reads “In athletes the lesions..”, should read “In sudden ischaemic deaths (in contrast to non-sudden) the lesions..”

Page 17. Last line reads “..in Table 1”, should read “..in Table 3”

Page 18. Table 3, title reads “Primary arrhythmogenic causes of sudden cardiac death”, should read “Primary arrhythmogenic or undetected causes of sudden cardiac death”

Page 20. Line four reads “..were the low..”, should read “..are the low..”

Page 22. First paragraph, last sentence reads “The general aim of this study includes care ..”, should read “The general aim of this study includes an analysis of care.”

Page 23. 2., line five reads “..decomposition, obviously not fulfilling the criteria of “sudden” deaths.”, should read “..decomposition, which made a proper investigation impossible. Many of the excluded non-cardiac deaths were also non-sudden deaths.”

Page 24. Paper II, last sentence should be moved to page 27, and should read “In addition, one individual with an uncorrected short QT time of 240 ms at enlistment, not classified as pathological by the Minnesota code criteria, was found.”

Page 26. Figure 2 abbreviations: DCM, dilated cardiomyopathy; CAD, coronary artery disease; HCM, hypertrophic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy

Page 28. Table 5, abbreviations: RBBB, right bundle branch block; SVES, supraventricular extrasystole; VES, ventricular extrasystole; AVI, first degree atrioventricular block; LAH, left anterior hemiblock

Page 29. First line reads “..be cause”, should read “..because”, line 5 reads “..W PW”, should read “..WPW”

Page 34. Paragraph two, line 5 reads “personal”, should read “personnel”, line 6 reads “Hiss an Lamb”, should read “Hiss and Lamb”

Page 37. Preparticipation screening line 10 reads “2.5 times”, should read “2.8 times”

Page 44. Reference 34 should read “..J Int Med 2003; 253: 320-328.”