Rationale and design of the CAREFUL study

The yield of CARdiogenetic scrEening in First degree relatives of sudden cardiac and UnexpLained death victims <45 years

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Background. **Sudden cardiac death (SCD) in the young (1-45 years) is a strong risk factor for the presence of inherited cardiac diseases in surviving first-degree relatives. Postmortem investigation of the victim and cardiogenetic evaluation of the first-degree relatives is indicated to detect inherited cardiac diseases and treat relatives at an early stage to prevent SCD. In the Netherlands, postmortem investigation is often not performed and relatives of SCD and sudden unexplained death (SUD) victims are rarely evaluated for inherited cardiac diseases.** ***Methods.*** **A prospective population-based follow-up study carried out in two intervention regions and two control regions. In the intervention regions a comprehensive intervention (stimulate autopsy and storage of victims DNA and the referral of first-degree relatives for cardiogenetic evaluation) is applied in a 'top down' and 'bottom up' mode. In each region, young sudden death victims are registered and for all cases performance of autopsy and evaluation of relatives in a cardiogenetics outpatient clinic will be determined.** ***Expected results.*** **The study will provide information on the incidence of sudden death in the young and the proportion of diagnosed**

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inherited cardiac diseases. Moreover, the additional value of the introduction of two different preventive strategies directed at early detection of inherited cardiac diseases in first-degree relatives to usual care will be evaluated. *Conclusion*. The CAREFUL study will help to set a new standard of care in the evaluation of young sudden death victims and their relatives to identify the presence of inherited cardiac diseases, in order to prevent sudden death. (Neth Heart J 2010;18:286-90.)

Keywords: Attitude to Death; Bereavement; Death; Family; Social Support; Genetic Counseling

Sudden cardiac death (SCD) and sudden unexplained death (SUD) before the age of 45 years are strong risk factors for the presence of inherited cardiac diseases in surviving first-degree relatives.[1-6] In Western countries the incidence of SCD in persons aged 1 to 40 years is estimated to be 0.9 to 1.6 per 100,000 person-years.[7] Hence, approximately 150 young individuals are annually a victim of SCD in the Netherlands.[7]

Inherited cardiac diseases can be subdivided into three main categories: cardiomyopathies, premature atherosclerosis, and primary arrhythmia syndromes (e.g. long-QT syndrome). In approximately half of SCD cases, cardiac arrest is the first manifestation of the underlying disease.[8]

As most inherited cardiac diseases show an autosomal dominant pattern of inheritance, first-degree relatives of SCD victims have 50% risk of being carrier of an inherited cardiac disease. In case of a SUD, i.e. when autopsy does not reveal the cause of death or is not performed, an inherited cardiac disease can be detected in 22 to 53% of families by cardiogenetic evaluation.[1-3,6] Early detection of inherited cardiac diseases in families offers opportunities to prevent SCD. These may include lifestyle modifications, pharmacological treatment and implantation of a pacemaker or implantable cardioverter defibrillator (ICD).

Postmortem investigation including autopsy and DNA storage is recommended after the sudden death of a young person, since detailed information on the victim's cause of death is relevant for surviving relatives.[9] When autopsy reveals a (possible) inherited cardiac disease or does not reveal any cause of death (in which case a primary arrhythmia syndrome should be suspected as the cause of death), prompt expert assessment of surviving relatives is recommended.[10] Storage of victims DNA enables molecular confirmation of a suspected disorder, when relatives attend a cardiogenetic clinic. Ideally, cardiogenetic evaluation of first-degree relatives should be performed soon after the victim's death at a multidisciplinary cardiogenetic outpatient clinic, currently located in each of eight univers-ity hospitals and in a few (satellite) the non-university hospitals in the Netherlands. First-degree relatives are genetically and cardiologically evaluated based on the results of investigations in the deceased or other symptomatic relatives.

Unfortunately, postmortem investigation of young sudden death victims is not always performed in the Netherlands. Emotional, financial and logistic factors may underlie this problem.[11] Confronting relatives with a request for autopsy might be difficult in the emotional turmoil following the sudden death of a young person. Besides, many physicians do not seem to be familiar with the procedure for requesting and arranging an autopsy. After a person is declared dead, the health insurance ceases immediately.[12] Costs for transport and autopsy are often not reimbursed for those who died out of hospital. In addition, it appears that insufficient attention is directed towards relatives, despite the considerable potential for prevention. As a result, potential inherited cardiac diseases will remain undetected.

The primary objective of the CAREFUL study (The yield of CARdiogenetic scrEening in First-degree relatives of sudden cardiac and UnexpLained death victims <45 years) is to identify an optimal strategy to increase the rate of postmortem investigation in young sudden death victims (1 to 45 years), and the rate of cardiogenetic evaluation of first-degree relatives. The secondary objective is to provide complete information on the incidence and causes of sudden death in the young and the presence of (treatable) inherited cardiac diseases in first-degree relatives.

We expect that the information obtained in this study will contribute to the development of a more general strategy, aiming at the prevention of SCD in the young in the Netherlands.

Design

The CAREFUL study is a prospective population-based follow-up study carried out in two intervention regions and two control regions in the Netherlands.

The regions of Amsterdam (Noord-Holland) and Utrecht (Midden-Nederland) will serve as intervention regions in which an intervention modality will be introduced to structure the usual care following a case of sudden death in a young individual. In the control regions of Leiden (Hollands Midden) and Groningen, the care following a case of sudden death will be observed without intervention. Together, these four regions comprise approximately 37% of the general Dutch population aged 1 to 45 years. Data collection was started on 1 June 2008 and will be continued for three years.

Table 1. Categories of causes of sudden death.

Category	Definition	Example
A. Definite SCD	Cardiac disease is established by post-mortem investigation	Hypertrophic cardiomyopathy established by autopsy
B. Probable SCD	Cardiac disease is the most likely cause of death	Sudden death during soccer game in a person with prior history of syncopal episodes and palpitations
C. Possible SCD	Both cardiac and non-cardiac diseases are possible causes of death	Unwitnessed death, no additional information on the circumstances of the victim's death. No family history of sudden death.
D. Non-cardiac SD	Non-cardiac disease is the most probable cause of death	Acute onset of severe haematemesis followed by collapse and sudden death
E. Probable non-natural SD	Non-natural cause of death is the most probable cause, but an underlying natural cause of death cannot be excluded	Car accident in which the underlying cause of the accident remains unexplained

SCD=sudden cardiac death; SD=sudden death.

Definitions

Sudden death is defined as unexpected death due to a natural cause of disease within 24 hours after the onset of symptoms. In addition, when unwitnessed death occurred within 24 hours after the person was last seen alive, this is also defined as sudden death. SCD is sudden death caused by any cardiac disease or aortic root disease (e.g. Marfan syndrome). SUD is defined as sudden death in which no cause of disease can be established based on clinical findings, postmortem studies or cardiogenetic evaluation of relatives.

Population

Two different study populations can be distinguished: the sudden death victims (index patients) and their first-degree relatives:

All victims of sudden death aged 1 to 45 years in the study regions will be included in the study when a natural cause of death is likely or cannot be excluded based on clinical findings and postmortem investigation, when performed. Also, non-natural deaths that are probably due to cardiac arrhythmias (e.g. sudden and unexplained drowning of an experienced swimmer) are initially included in the study. All other non-natural deaths will be excluded from the study (e.g. suicide).

All first-degree relatives of the SCD/SUD victims (parents, children and siblings) of the victims as described in sub (1) are eligible for study participation.

Usual care after SCD/SUD of a young person

In the Netherlands, when someone dies, physicians are legally obliged to inspect the corpse and complete a death certificate form. If a natural cause of death is suspected, a clinical autopsy can be requested if the victim's relatives grant permission. Often a general practitioner (GP) is responsible for requesting an autopsy, because most SCDs occur out of hospital.[13] To request a clinical autopsy, the nearest hospital with a pathology department can be contacted.

When a non-natural cause of death cannot be excluded, a coroner (who has to be a physician in the Netherlands) is contacted. If the possibility exists that the corpse could serve as evidence in a crime, the corpse can be confiscated by the public prosecutor. If the corpse is confiscated, a judicial autopsy can be performed by the Netherlands Forensic Institute (NFI), or the corpse is released and a clinical autopsy can be requested by the former treating physician.

Besides the request for autopsy, the GP also plays an important role in the referral of surviving first-degree relatives to a cardiogenetics clinic. However, the referral of relatives can be complicated when the victim's GP differs from the GP of the victim's first-degree relatives.

Registration of sudden death patients, autopsy rate and referral of first-degree relatives

Sudden death victims are registered by continuously reviewing the resuscitation records and the death declaration certificates on possible sudden death cases aged 1 to 45 years. Assessment of the probable cause of death and whether or not the victim is eligible for inclusion in the CAREFUL study will be performed by an expert panel consisting of a cardiologist, a pathologist, a clinical

geneticist and a GP. Based on the available information, the (possible/probable) cause of death is classified as one of five categories (table 1). The majority of pathology laboratories record autopsy data centrally in the PALGA (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief) database, a nationwide network and registry of autopsy, histopathology and cytopathology in the Netherlands.[14] The number of autopsies is estimated by extraction of data from the PALGA database and the Netherlands Forensic Institute databases.

All eight cardiogenetics departments in the Netherlands record relatives of young SCD/SUD victims that are referred to their clinics. When these relatives give informed consent, further data on the process and outcome of cardiogenetic evaluation is collected. Furthermore, six months after the victim's death, the GP will be contacted and interviewed through a structured questionnaire on the previous medical history of the patient, the (possible) request for autopsy and the (possible) referral of first-degree relatives to a cardiogenetics department or cardiologist.

Intervention

The intervention modality consists of two elements: (1) Stimulate autopsy and DNA storage in SUD/SUD victims aged 1 to 45 years, (2) Stimulate referral of first-degree relatives in an early stage to a cardiogenetics department by the GP.

The intervention is implemented in usual care in two different ways. In the Utrecht study region an 'optimal' intervention modality ('bottom-up' strategy) is introduced, which aims at educating and thereby changing the behaviour of the individual professional. During the first six months of the study period, the GPs and coroners are informed about the importance of autopsy and cardiogenetic evaluation of first-degree relatives by a letter and information meetings. In case of a sudden death in a young individual, the emergency medical services are instructed to leave an information letter for the professional who inspects the corpse and completes the death certificate form.

The second 'maximal' intervention modality ('top down' strategy) is implemented in the Amsterdam study region. A central 24/7 study telephone number and a dedicated website are available for the professionals involved in a case of sudden death in a young person. By contacting the telephone number and/or visiting the website, the professional is informed about the importance of autopsy and referral of first-degree relatives for cardiogenetic evaluation (if indicated). Moreover, the professional receives specific detailed information on how to execute both the autopsy request and the referral of relatives. The study telephone number is only promoted during the first six months of the study by a letter and information meetings. Both modalities will be compared in terms of autopsy rates, referral rates, and cost-effectiveness.

Baseline measurement

The increased awareness of inherited cardiac diseases as a possible cause of sudden death of a young person might result in an improvement of the usual care in both the control and intervention regions during the study period. To measure the effect of increased awareness in the separate intervention regions compared with the control regions, a baseline measurement is performed in all study regions over the two-year period preceding the CAREFUL study (June 2006 to May 2008). Based on this measurement, the change over time with respect to the performance of autopsy and the referral of first-degree relatives in the control regions and intervention regions can be monitored and a comparison among regions will be made.

Data analysis

The proportion of postmortem studies in young sudden death victims is the sum of autopsies as recorded in the PALGA and the NFI databases divided by the number of SCD/SUD victims. The proportion of first-degree relatives of young SCD/SUD victims that attend a cardiogenetics clinic within six months after the event is determined as the number of first-degree relatives that attend a cardiogenetic clinic divided by the total number of the victim's living first-degree relatives.

The primary outcomes are the proportion of postmortem studies in young SCD/SUD victims, and the proportion of first-degree relatives of young SCD/SUD victims attending a cardiogenetics department within six months after the event between the intervention regions and the control regions and between the two intervention regions. These proportions are compared using the χ^2 or Fisher's exact tests, or logistic regression models when statistical adjustment for potential confounder factors is deemed necessary. Similarly, the proportion of first-degree relatives who receive treatment or diagnostic follow-up because of an increased risk of sudden death identified after referral will be compared.

In addition, the incidence rate of SCD/SUD per 100,000 person-years is estimated as the total number of SCD/SUD divided by the number of person-years of the population at risk in the relevant age category in the study regions during the study period. Causes of death will be presented by overall percentages and specified by gender and age. In addition, sub-analyses will be performed for victims that are known to have died within one

hour after the onset of symptoms (instead of 24 hours) to allow comparisons with other studies (that use the one hour definition).

Summary

The aim of the CAREFUL study is to investigate and improve the care following a case of sudden death in young people by increasing the proportion of postmortem investigations in young sudden death victims and the proportion of cardiogenetically evaluated first-degree relatives. With this study, we will investigate the effectiveness of introducing a stimulation programme to increase the autopsy rate in SCD victims and the referral of their first-degree relatives. Also, information on incidence and causes of sudden death in the young will be generated. We anticipate that the results of this study will help to set a new standard of care in the evaluation of young SCD/SUD victims and their first-degree relatives to identify the presence of inherited cardiac diseases, and to prevent sudden cardiac death.

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