

Sudden Cardiac Death in the Young

National Incidence and figures 2005-2007

The Republic of Ireland

Sudden Cardiac Death in the Young Registry

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Table of Contents	Page
Summary of Figures and Tables	3
Contact Details for Registry	4
Executive Summary	5
Acknowledgements	7
Section I- Introduction	9
Section II- Methods	12
Section III- Results	15
III (a)- Ascertainment of cases	15
III (b)- Causes of confirmed SCD	17
III (c)- Incidence rates	19
III (d)- Specific results relating to common causes of SCD	19
III (e)- Activities at time of death	20
III (f)- Results of the comparison between CSO coding for the years 2006 and 2007	21
Discussion	23
National post mortem figures	24
Conclusion	28
Abbreviations	30
Glossary of terms	31
References	32

Summary of Figures and Tables

Figures

- Figure 1: Causes of ventricular fibrillation and sudden cardiac death in young people (figure reproduced with permission from The Report of the Taskforce on Sudden Cardiac Death, 2006¹).
- Figure 2: Flow chart of registry (SCDYR) case-selection process for the cases registered during the years 2005-2007 inclusive.
- Figure 3: Pie chart of the causes of SCD in Ireland, registered with the CSO for the years 2005 to 2007 inclusive, for persons aged between 15 and 34 years. Data based on persons with SCD as confirmed by SCDYR.
- Figure 4: Cause of sudden cardiac death for the years 2005 to 2007 inclusive, by year and frequency.
- Figure 5: Cause of sudden cardiac death by gender for the years 2005 to 2007 inclusive, for the ages 15-34 years.
- Figure 6: Circumstances of sudden cardiac death for the years 2005 to 2007 inclusive, for the ages 15-34 years.

Tables

- Table 1: Cardiac and non-cardiac cases, as identified by the SCDYR case ascertainment methodology, for the years 2005 to 2007 inclusive.
- Table 2: Demographic characteristics of confirmed cases of Sudden Cardiac Death in the Young, by year and using the SCDYR retrospective review strict ascertainment methodology.
- Table 3: Exertion-related cardiac deaths, and type of activity undertaken at time of SCD for the years 2005 to 2007 inclusive.
- Table 4: Variation in coding for SADS cases 2006: SCDYR SADS case coding versus CSO coded cases (based on death certificate information).
- Table 5: Variation in coding for SADS cases 2007: SCDYR SADS case coding versus CSO coded cases (based on death certificate information).

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Executive Summary

This is the first report of the Sudden Cardiac Death in the Young Registry. The Registry which was set up in 2009 will document the cause of sudden cardiac death in young people aged 15-35 years in Ireland through expert panel review and analysis of post-mortem reports. The current report deals with the years 2005-2007 inclusive. This data has been collected with the co-operation of the Central Statistic Office (CSO) and pathologists and coroners throughout the country without whose assistance it would not have been possible.

All deaths in this report were identified through the Central Statistics Office using a wide range of International Classification of Disease (ICD) codes under which a Sudden Cardiac Death (SCD) could potentially be coded. All post-mortem reports were supplied through the offices of the relevant coroner. Only deaths in which adequately detailed post-mortem reports were available have been included in the report. Two cardiologists and two pathologists reviewed all post-mortem reports.

Two hundred and ninety two cases of possible SCD in young people aged 15-35 years were identified through the CSO using death certificate information of which 86 post-mortem reports were unavailable leaving 206 cases. Of these, 87 were determined by the panel to be non-cardiac including deaths in the setting of prior epilepsy (n=22, 25.3%), deaths due to alcohol or drugs (n=19, 21.8%), PE (n=12, 13.8%), cancer (n=10, 11.5%) or suicide (n=13, 14.9%) leaving 119 SCDs between 15 and 35 years of age registered between Jan 1st 2005 and December 2007.

The incidence of SCD among those aged 15-35 years in the Republic of Ireland was 2.68 per 100,000 / yr. The incidence rates in this report may be an underestimation of the true figure due to missing or inadequate data resulting in case exclusions. The incidence is higher than in other similar European studies performed in Iceland and in Sweden. The reason for this is unclear and requires further investigation.

The commonest finding at autopsy in this cohort was a normal autopsy including toxicology screen. These cases were classified as deaths due to Sudden Arrhythmic Death Syndrome (SADS) and they accounted for 26% of cases. Coronary artery disease (20%), Hypertrophic Cardiomyopathy (14%) and Left Ventricular Hypertrophy without cardiomyopathy (10%) were the next commonest causes.

There was a significantly higher risk of SCD among males (4.11/100,000/yr) compared to females (1.19/100,000/yr). This male to female preponderance persisted despite the diagnosis. The ratio of male to female deaths was approximately 2:1 for SADS, 5:1 for HCM and for LVH and 7:1 for CAD.

Deaths attributed to SADS after panel review had been coded by the CSO under a variety of different codes. Only 20% of SADS cases had been coded correctly when compared to panel review. The degree of detail provided in post-mortem reports varied significantly. A national standard protocol for the performance of post-mortems in cases of SCD should be agreed and implemented similar to that in place for cases of SIDS.

Retention of tissue samples to allow for genetic testing was not employed in any cases as part of the post-mortem analysis. Tissue samples should be routinely retained in cases of SADS, for 'molecular autopsy' or analysis for genetic mutations responsible for the cardiac ion channelopathies, known to cause SADS (Long QT Syndrome, Brugada syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia).

The Registry plans to report on Sudden Cardiac Deaths in young people registered in the years 2008 and 2009 at the end of 2011 and will produce annual reports thereafter.

Acknowledgements

The Sudden Cardiac Death in the Young Registry has been two years in evolution from its original conception to the report published today. As with any major undertaking of this kind, it is only thanks to a large number of contributions from persons and organizations that we have been able to produce this retrospective analysis of sudden death in young persons in Ireland.

The Registry wishes to acknowledge the co-operation received and the dedication and enthusiasm of a number of sectors in bringing this report to fruition. A sincere thanks to the many people who helped us in our work. In particular;

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The SCDYR would also like to extend sincerest thanks to the pathologists and coroners throughout the State, whose co-operation has resulted in our ability to generate the data included in this report.

SECTION I

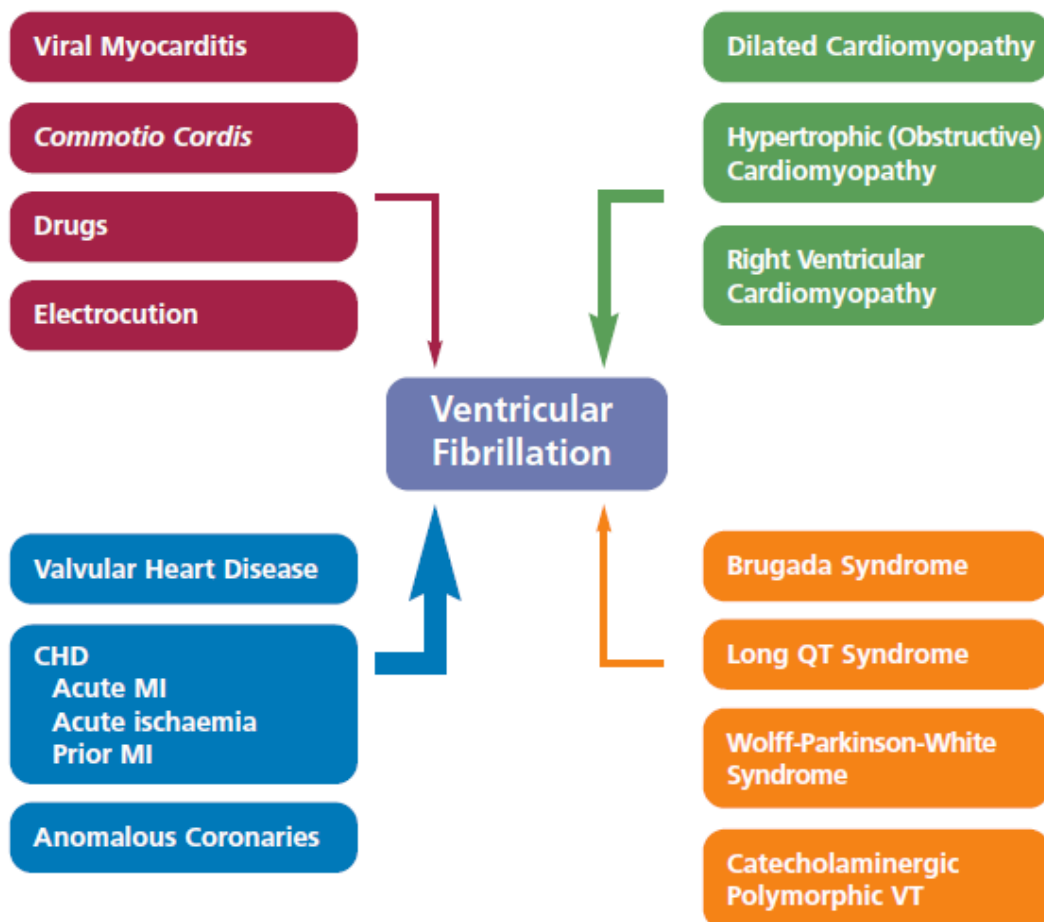
Introduction

Sudden Death due to cardiovascular disease (CVD) is one of the leading causes of death in Europe and the United States. The European Society of Cardiology estimate that the incidence of sudden death ranges from 36 to 128 deaths per 100,000 population per year, while in the United States the overall incidence is 1 to 2/1000 population per year. Over 60% of these cases relate to ischaemic heart disease.

The spectrum of causes of sudden death in the young (< 35yrs) are more diverse, with a significant proportion of these deaths occurring due to potentially hereditary conditions, which may manifest themselves in other family members in 25-50% of cases¹. With the emergence of understanding of molecular channelopathies, such as long QT or Brugada syndrome, and the improvement in genetic and phenotypic screening for certain types of cardiomyopathies, more is available in the way of screening for relatives of those affected by sudden cardiac death (SCD). The mechanisms of SCD include bradyarrhythmias, cardiogenic shock, and lethal tachyarrhythmias, of which ventricular fibrillation, is the commonest.

The common causes of ventricular fibrillation are listed in Figure 1.

Figure 1: Causes of ventricular fibrillation and sudden cardiac death in young people (figure reproduced with permission from The Report of the Taskforce on Sudden Cardiac Death, 2006²)



Worldwide, the overall incidence of SCD is estimated at 0.93/100,000 in Sweden from 1992-1999³ and 1.47/100,000 in Iceland. Behr et al estimate the incidence of Sudden Arrhythmic Death Syndrome or SADS in England, using prospective case reviews from 1997-1999, at 0.16 per 100,000 persons per year⁴. The incidence for 'unascertained cause of death' (ICD codes 798.1, 799.9, 427.8/9, 428.9 and 429.9) was higher at 1.34 per 100,000.

A population-based study in Minnesota/Olmsted County reported an incidence of 6.2 sudden deaths per 100,000 among 20-40yr olds over the period 1960-89, however it must be noted that deaths from drug-induced arrhythmia, eating disorders, cocaine, and alcohol were also included⁵. In Minnesota county athletes, the incidence was much lower amongst 14-18yr olds, at 0.46/100,000⁶. In a young athletic population in Italy rates of sudden cardiac death are estimated at 2.1/100,000⁷, compared with estimates of SCD due to HCM in athletes by Marron et al of 1:200,000 per year⁸.

This apparent variation in the incidence of SCD in the young highlights the need for country and/or region-specific estimations of the impact of these conditions. Knowledge of the true incidence of such a condition will assist health care planners to understand the potential impact of genetic testing facilities and national family screening services, and to examine any change in disease frequency over time.

Furthermore, such knowledge of the burden of SCD in a country will assist in improving awareness of this lethal condition for health care providers, coroners, and pathologists, as well as for the general population themselves.

Limited data are available describing the incidence of SCD in Ireland. The estimated national incidence of sudden cardiac death from a retrospective study of deaths registered in 2005, based on CSO death registration data, and National Census data was 3.18/100,000 for individuals aged 15-34 years old (5.59/100,000 for males and 0.78/100,000 for females)⁹.

Recently, however, the national focus has turned to the issue of SCD, including the tragedy of SCD in the young, and the National Taskforce on Sudden Cardiac Death was established. This group published their Taskforce document in 2006², and in it were contained recommendations to establish a means of ascertaining the incidence of SCD in Ireland.

Following the launch of the SCD Taskforce Report, an Implementation Group was set up by the HSE with multi-stakeholder involvement (Chair: Dr S. Jennings). This implementation group identified the importance of a governance group for an SCD register along with the need for inclusion of the many stakeholders.

Accurate mortality data is essential to monitor trends in SCD. The aim of surveillance of mortality is to systematically collect and review information on the epidemiology of SCD in Ireland. This would provide estimates of the incidence of SCD, and identify the causes and the demographic characteristics of those who died., The Sudden Cardiac Death in the Young Registry (SCDYR) was established in October 2008 with the aim of monitoring the incidence and causes of sudden death in persons aged less than 35 years of age. The Health Service Executive of Ireland, the Irish Heart Foundation, and an unrestricted educational grant from Medtronic Corporation, Ireland, initially funded the SCDYR.

In the first instance, the aims of the SCDYR were-

- To establish the number of deaths which were truly due to cardiac events, using a robust methodology, and to ascertain the cause of death where possible.
- To gather preliminary information on all sudden unexpected deaths in persons aged 15 to 34 years inclusive, from 2006 to 2007 inclusive.
- To review where possible the circumstances of the deaths.
- To integrate these findings with the previous findings from 2005, to create a large-scale retrospective review.
- To establish a reporting network throughout the country to identify cases of sudden cardiac death in the young, resulting in an annual report on the numbers of, and causes of, SCD in the young.
- To examine and make recommendations regarding the process and methodology of SCD reporting in Ireland.

SECTION II

Methods

This report details the findings of the SCDYR to date, and represents is a retrospective survey of all suspected sudden cardiac deaths occurring in young people between the ages 15-34years inclusive, registered by the CSO during the period 2005-2007. All suspected cardiac deaths registered by the CSO during the years 2005-2007 (January 1st to December 31st inclusive) were included for analysis. Data from 2005, which constituted a pilot study for the Registry, has been previously by Morris et al⁹. These potential sudden death records were classified according to source of notification, either individual hospital or coroner.

Any deaths not registered during this period were not included, Note must be made that this includes delayed death registration (in the case of coronial inquests even when death occurred during that period, for example), with data files often containing deaths that occurred outside the calendar year of 2005 to 2007 respectively.

Age

The SCDYR collects data on persons suffering a SCD between 15 yrs and 34 yrs inclusive.

Case definition

Subjects met our study criteria for death certificate-based SCD if they were classified under one or more specific ICD-9 or 10 codes by the CSO coding system, including if they died out-of-hospital, or in the emergency department.

ICD-9 codes used for 2005-2006 were

- (i) Diseases of the Circulatory System 390-459.7
- (ii) Other heart disease 420-423,
- (iii) Sudden death 798-799.

The equivalent ICD-10 codes used for 2007 data (CSO upgraded to ICD-10) were

- (i) Diseases of the Circulatory System I00-I99
- (ii) Ill-defined and unknown causes of mortality (including sudden cardiac death) R95-99.

Once the list of CSO-registered sudden deaths had been thus scrutinized to identify all deaths which may meet the inclusion criteria, the SCDYR requested the standard post mortem report, the toxicology report, and any specialist opinion reports which were available from the local coroner's office and/or hospital pathologist.

Once received, post mortem reports were reviewed by a panel of three cardiologists, with each person reviewing the case independently to classify the death as either cardiac or non-cardiac in nature. If the death was thought to be cardiac, the reviewer picked the most likely aetiology for the cause of death. In cases where there was any lack of agreement on the nature of the death, the post mortem report was referred for adjudication to two consultant pathologists, for consensus opinion.

In the context of this study, we used the most commonly accepted definition for SCD as our case-definition. Sudden cardiac death was defined as *sudden unexpected death either within one hour of symptom onset (event witnessed), or within 24 hours of having been observed alive and symptom free (un-witnessed event)*¹¹.

Subjects with non-cardiac chronic and terminal illnesses were excluded on the basis that such deaths were not sudden or unexpected. Cases of sudden cardiac arrest associated with electrocution, poisoning, overdose, drowning, and suicide were not included. Cases with positive toxicology screening for drugs or substances known to cause cardiac arrhythmias were excluded.

Method of case information retrieval for registry study

Garda or hospital pathologists referred all unexpected or unexplained deaths to the coroner of that jurisdiction. Cause of death details were then submitted to the General Registry Office, with data then registered periodically with the Central Statistics Office births and deaths section.

The SCDYR then, upon request to the CSO, received a 512-bit encrypted spreadsheet containing case information, arranged by coroner jurisdiction or hospital pathology department.

The SCDYR then contacted all coroner and hospital pathologists for each individual post-mortem report, toxicology report, and inquest report where appropriate. These records were reviewed by a panel to determine whether they were cardiac or non-cardiac. The panel included a consultant cardiac electrophysiologist, consultant cardiologist, and independent review by two consultant pathologists in cases requiring adjudication

Screening for toxicology

A toxicology screen was carried out as routine on all autopsy cases by the local pathologist, with either local or state pathology laboratory results being supplied to the SCDYR where available. Both blood and urine were screened where possible, in all cases.

Specialist pathologist analysis

Cases deemed appropriate or requiring second opinion by the certifying pathologist were referred to a specialist cardiac pathologist outside of Ireland. This included slide blocks, background information, and relevant post mortem information. Specialist opinion was sought at the discretion of the certifying pathologist.

Ethics Approval and Data Protection

Ethical and statutory data collection permissions were obtained from Connolly Hospital, the Department of Health and Children, the Data Protection Commissioner, and the Central Statistics Office. The registry designed a purpose-engineered encrypted database for housing the SCDYR registry data.

Statistical Methods

Data was collected and stored using a purpose-built database with Microsoft Excel 2000© interface. Statistical analysis was carried out using PASW 18.0 (SPSS©). Data were presented as frequencies and counts using simple tables, bar charts and pie charts.

A comparison was also performed for all SADS cases to compare the accuracy of the CSO coding system using the cause of death as stated by the death certificate, versus the expert SCDYR panel-judged cause of death. Using standard methods¹⁰, incidence calculations were composed using CSO National Census Figures 2006 for males and females aged between 15 and 34 years inclusive. Incidence rates were calculated as follows-

$$100,000 * (n/N) = \text{Incidence rate per } 100,000$$

Where n=number of SCDs in the age and gender-specific population, and N=the CSO estimate of the national population of that specific age group and gender.

SECTION III

Results

III (a) Ascertainment of SCD cases

Results are reported for the deaths registered during the years 2005-2007. The population for this registry includes the entire population of the Republic of Ireland, aged 15 to 34 years, estimated by Census Ireland 2006 figures¹⁰.

For the period 2005-2007 inclusive, there were a total of 292 cases fulfilling the ICD-9 and ICD-10 sudden death criteria identified to the SCDYR by the Central Statistics Office (Figure 2). A total of 119 deaths (40.7% of the 292 eligible cases) were considered by the panel to represent true sudden cardiac deaths. This approximates 3 sudden cardiac deaths per month, in the 15-34 year age group, over a 3-year period.

Eleven cases were referred for adjudication to the pathology panel, as to whether death was cardiac or non-cardiac. Table 1 shows breakdown of case selection by year. Figure 2 demonstrates the case selection process for cases registered during the years 2005 to 2007, inclusive. 292 possible cases were identified by the CSO using death certificate/ ICD code data. 86 post mortems were not located, insufficient, or outstanding, despite multiple attempts and requests on behalf of the SCDYR to obtain them.

Total cardiac cases comprised 119/206, or 57.8% of the total eligible for analysis.

Table 1– Cardiac and non-cardiac cases, as identified by the SCDYR case ascertainment methodology, for the years 2005 to 2007 inclusive

	2005	2006	2007	Total number of cases	Percentage of total cases (%) where n=292
CSO identified cases	95	85	112	292	-
Outstanding cases / reports not located	39	24	23	86	29.5%
Non-cardiac cases	14	26	47	87	29.8%
Confirmed cardiac cases by SCDYR protocols	42	35	42	119	40.7%

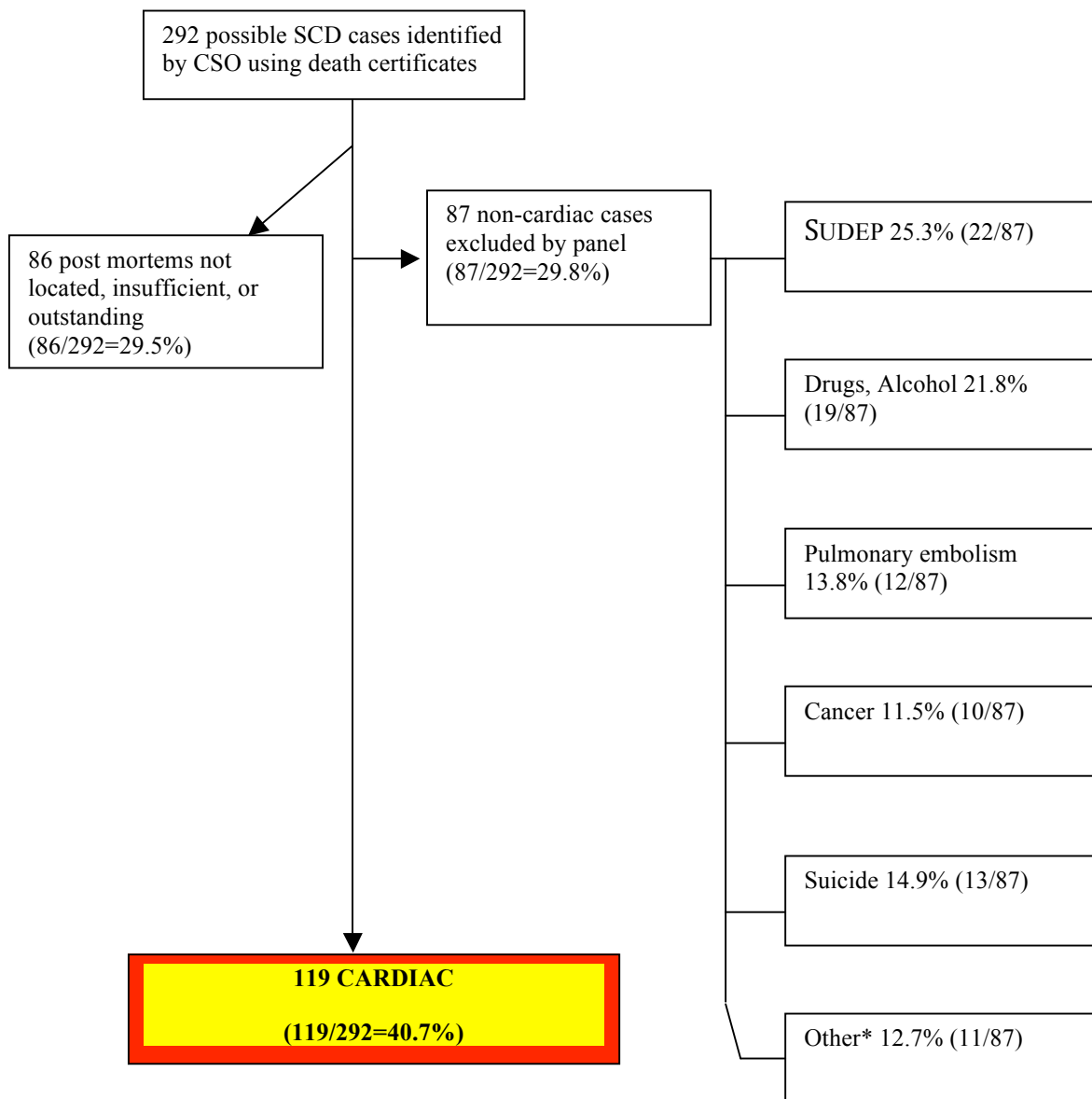
Table 2– Demographic characteristics of confirmed cases of Sudden Cardiac Death in the Young, by year and using the SCDYR retrospective review strict ascertainment methodology.

	2005	2006	2007	Total
Number *	42	35	42	119
Male	88.9% (n=37)	60% (n=21)	76.1% (n=32)	75%
Age in years: mean (SD†),	24.91 (6.83)	26.59 (5.67)	26.03 (6.37)	25.84 (6.29)

* Number of confirmed SCD

† Standard deviation

Figure 2- Flow chart of registry (SCDYR) case-selection process for the cases registered during the years 2005-2007 inclusive. * ‘Other’ denotes deaths as a result of trauma/accidents, infections, organ failure, neurologic causes, and deaths not otherwise categorized.



III (b) Causes of SCD in confirmed cases

Of the 119 cases of SCD, the gender was predominately male (75%, n = 90). The average age was 25.84 yrs (range 15-34), as described in Table 2.

The most common finding at autopsy, in this unselected sudden cardiac death population, was 'morphologically normal heart' or SADS. Other common findings from highest to lowest were:

- SADS – 26.1% n = 31/119
- Coronary Artery Disease with evidence of MI - 20.1% n = 24/119
- HCM - 14.3% n = 17/119)
- Idiopathic LVH - 10.1% n = 12/119
- Congenital heart disease - 8.4% n=10/119)
- Myocarditis - 5.9% n = 7/119
- Aortic dissection 2.5% n = 3/119

Figure 3- Pie chart of the causes of SCD in Ireland, registered for the years 2005 to 2007 inclusive, for persons aged between 15 and 34 years. Data based on persons with SCD as confirmed by SCDYR*.

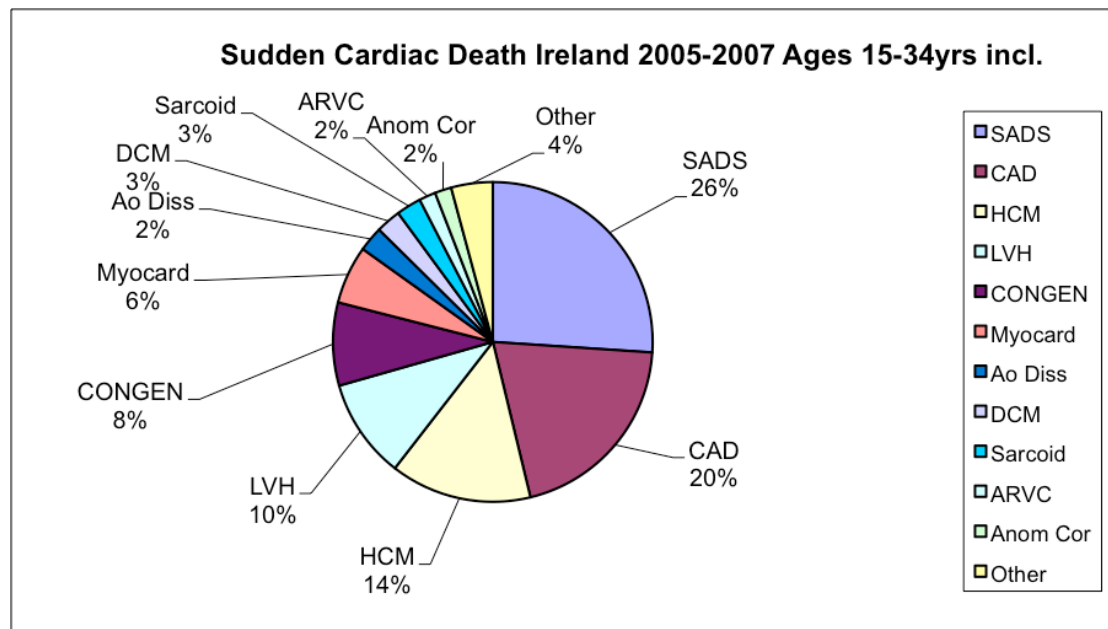


Figure 4– Cause of sudden cardiac death for the years 2005 to 2007 inclusive, by year and frequency.

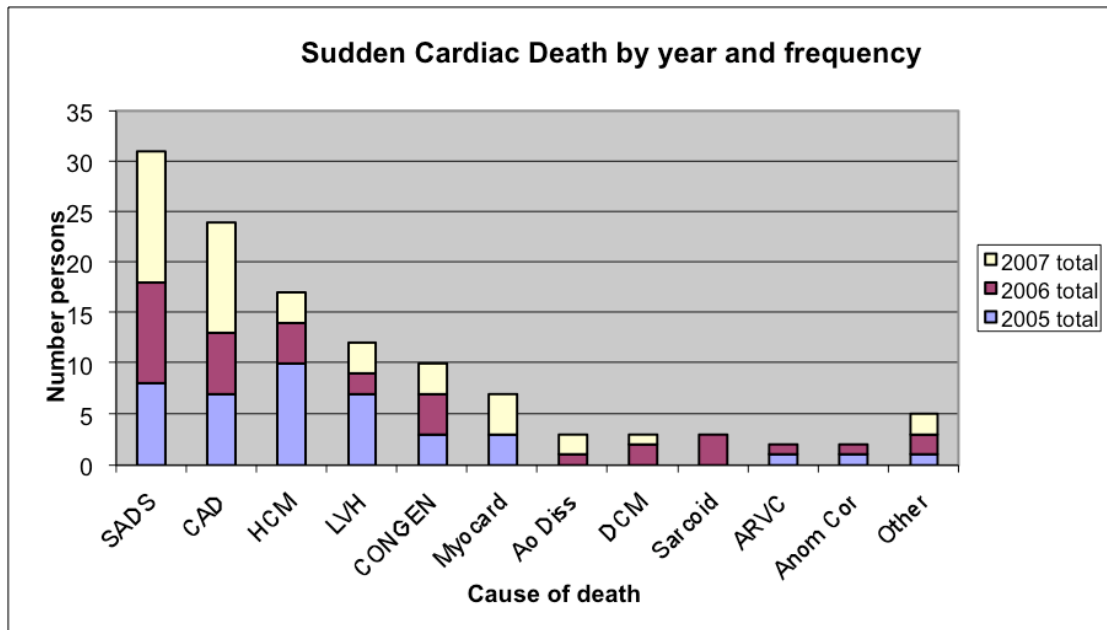
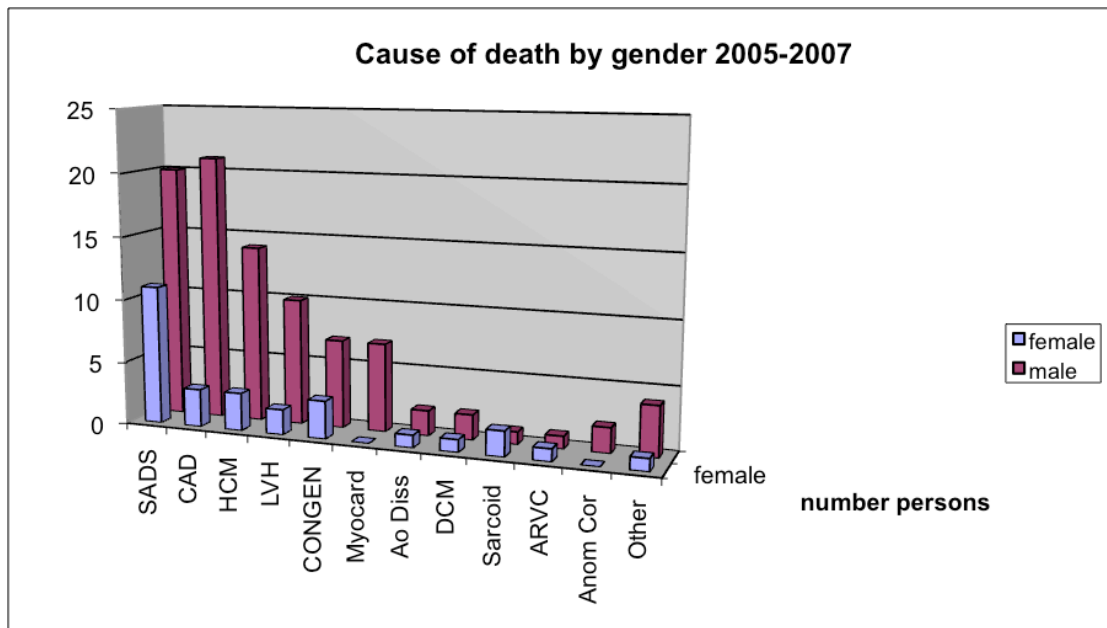


Figure 5- Cause of sudden cardiac death by gender for the years 2005 to 2007 inclusive, for the ages 15-34 years *.



Legend for figures 3 to 5

SADS= Sudden Arrhythmic Death Syndrome;
CAD= Coronary Artery Disease;
HCM= Hypertrophic Cardiomyopathy;
LVH= Left Ventricular Hypertrophy;
CONGEN= Congenital Heart Disease;
Myocard= Myocarditis
Ao Diss= Aortic dissection;

DCM= Dilated Cardiomyopathy;
Sarcoid = Cardiac Sarcoidosis
ARVC= Arrhythmogenic Right Ventricular Cardiomyopathy;
Anom Cor = Anomalous coronary artery
Others includes anomalous coronary arteries, infective endocarditis, aortic aneurysm, mitral valve prolapse, acute cardiac transplant rejection, and Duchenne’s muscular dystrophy

III (c) Incidence rates and ascertained causes of SCD

During the period 2005-2007 inclusive, the total national incidence for sudden cardiac death in the 15-34 year age group was 2.68 per 100,000 persons/year. This equated to a male incidence of 4.11 per 100,000 persons/year, and female incidence of 1.19 per 100,000 persons/year for sudden cardiac death from all causes. According to Census Ireland 2006 figures, SCD accounted for 2.9% of all deaths in the 15-34 years group, in 2006 (n = 25/849) alone.

The national incidence of SADS in the 15-34 year age group was 0.76 per 100,000 persons/year, for the total population. This comprised of males (0.96 per 100,000 per year) and females (0.54 per 100,000 per year).

The national incidence of SCD due to Coronary Artery Disease in the 15-34 year age group was 0.59 per 100,000 persons per year. Males accounted for 1.01 per 100,000 persons/year, and females 0.14 per 100,000 persons/year respectively.

The national incidence of death due to hypertrophic cardiomyopathy (HCM: the commonest form of cardiomyopathy noted) in the 15-34 yr age group, was 0.41 per 100,000 persons /year. Males comprised of 0.67 per 100,000 persons/year, and females 0.14 per 100,000 /year, respectively.

III (d) - Specific results relating to common causes of SCD

Sudden Arrhythmic Death Syndrome (SADS)

The diagnosis of SADS on post mortem evaluation remains a significant challenge. There has traditionally been a heavy onus on the pathologist to identify a cause of death, and therefore a tradition of identifying likely minor insignificant abnormalities as the cause of death, in the absence of any clearly significant abnormality.

Furthermore, SADS deaths may be thought to be due to a toxin, and the diagnosis of SADS is then delayed, pending the report of the toxicology analysis. Of the 31 SADS cases identified by the SCDYR panel, only five (16.1%) had been referred to Dr Mary Sheppard, Specialist Cardiac Pathologist in the Royal Brompton Hospital, UK. Importantly, in all cases, findings were corroborated with the opinion of the referring local pathologist. Slides were retained with permission in all cases.

Family screening for first-degree relatives of SADS cases was recommended on the official coroner post-mortem reports in 11/23 (47.8%) cases, during the years 2006-2007. This may represent an underestimation, as individual local practitioners may have undertaken their own referrals once report findings were made available.

Idiopathic Left Ventricular Hypertrophy

The distinction was made between HCM and a diagnosis of idiopathic left ventricular hypertrophy on the basis of both macroscopic and microscopic findings. Left ventricular wall thickness of ≥ 15 mm, or weight > 500 g, with microscopic findings of myocyte hypertrophy with or without fibrosis, and no myocyte disarray were considered adequate for diagnosis. A total of 12 patients fulfilled the criteria.

Congenital Heart Disease

There were 10 sudden cardiac deaths associated with congenital heart disease identified from the death registration from 2005-2007. It is important to highlight the ongoing risk posed by lethal cardiac arrhythmias, as post-operative survival improves. Estimates for sudden cardiac death post Mustard or Senning repair for transposition of the great arteries (TGA) have been calculated at 7.9 per 1,000 patient years¹².

III (e) - Activities at time of death

The circumstances of individual deaths may be useful in ascertaining cause, as fatal events in HCM, arrhythmogenic right ventricular cardiomyopathy (ARVC), and the long QT syndrome (LQTS) types 1 and 2, may be more during exertion, as opposed to Brugada syndrome and LQTS type 3 which may occur more commonly during sleep.

Table 3 details the activity undertaken at the time of death, in cases where this information was recorded or known when the post mortem report was compiled. 29% of deaths in patients with HCM occurred during exertion (5/17).

Figure 6 shows the circumstances of death in the 119 confirmed cardiac deaths as ascertained by the SCDYR team. In 42% (50/119) of cases the circumstance were unknown, or not stated on post mortem reports. From the data from 2006 and 2007, 24/77 (31.2%) deaths were witnessed, with 34/77 (44.2%) occurring in the home. Eighteen deaths occurred in bed, with four deaths occurring in the bathroom. Paramedic/accident and emergency staff attempted resuscitation in 30/77 (39.0%) of cases.

Figure 6- Circumstances of sudden cardiac death for the years 2005 to 2007 inclusive

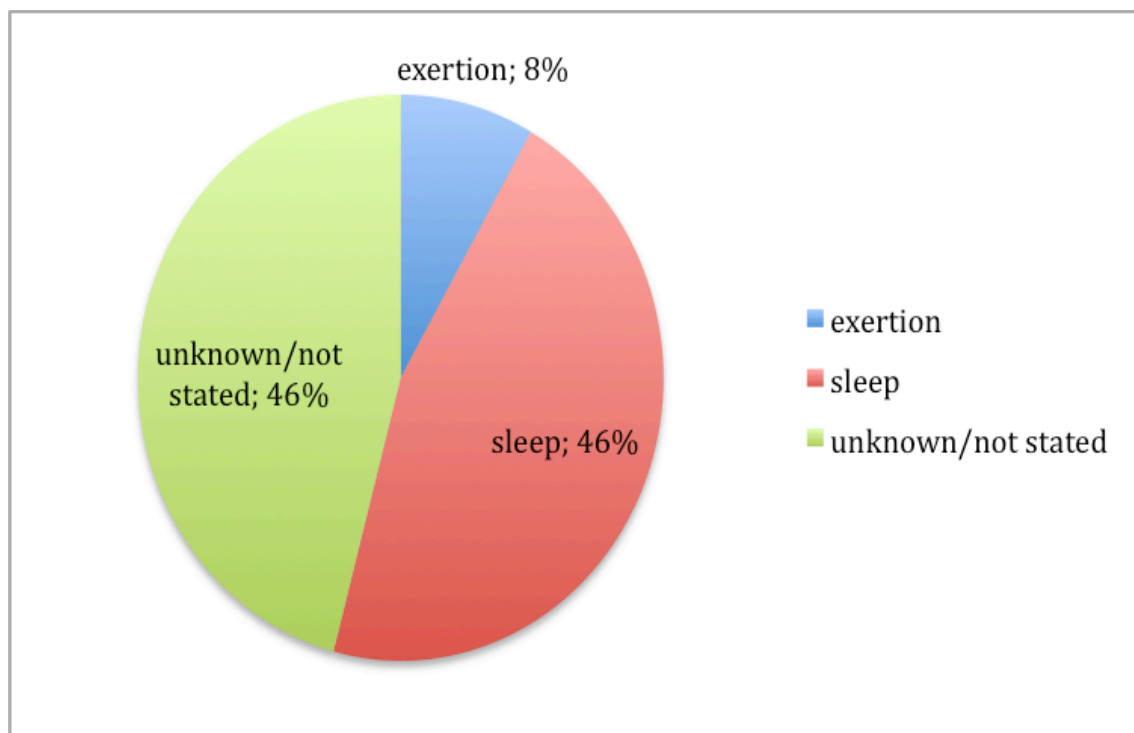


Table 3: Exertion-related cardiac deaths, and type of activity undertaken at time of SCD for the years 2005 to 2007 inclusive.

Post mortem diagnosis	Total SCD cases	No of exertion - related deaths	Types of Activity at time of exertion-related death
SADS	31	2	Football (both cases)
HCM	17	6	Herding Cattle Tag Rugby Football (2 cases) Skipping Cycling
CAD	24	1	Basketball
Anomalous coronary artery	2	1	Football

III (f)- Results of the comparison between CSO-assigned ICD coding and those assigned after post mortem review, for the years 2006 and 2007

Coding of causes of death

One of the key limitations of retrospective death certificate-based data collection is the variability in case definition and ICD code assignment for cause of death. When an unexpected death occurs, and the case data arrives in the CSO, an ICD code is assigned by the coding department, based on death certificate data provided. This process can often be subjective, particularly if the information on the death certificate is ambiguous. Systematic errors in how death certificates are interpreted and coded can therefore lead to inaccurate national estimates for SCD, as well as other medical conditions.

A review of the CSO data provided to the SCDYR was carried out of all the cardiac cases identified by the Registry, to compare the accuracy of ICD coding carried out using death certificate data by the CSO coding department, with ICD codes assigned directly by the SCDYR using findings from autopsy/inquest data. This was done by year, as ICD-9 coding was upgraded to ICD-10 in 2007. It must be noted that the majority of death certificates were completed by the coroner, as the nature of sudden deaths meant these cases were automatically referred to the relevant coroner/pathologist for autopsy.

In 2006, 18/25 (72%) death certificate findings matched those of the post-mortem findings to the word. The major discrepancies arose with coding for SADS: 2/10 cases were not allocated ICD-9 codes, as findings were listed as ‘unascertained’ in Part 1A of the death certificate. This is despite the opinion noted that death was most likely due to SADS (sudden cardiac death with morphologically normal heart and negative toxicology), with the completing coroner preferring to list cause as ‘unascertained’.

A similar situation arose in 2007, where, despite the change to the ICD-10 coding system, 11/13 (84%) of SADS cases were allocated at least four different codes. This has implications for both the level of family screening recommended for first degree relatives, and indeed for the need for a review of how coding is standardized with respect to what defines a SADS case, to minimize inter-coder variability.

Tables 4 and 5 demonstrate the variability in coding for what the SCDYR panel had agreed as being SADS as cause of death.

Table 4 – Variation in coding for SADS cases 2006: SCDYR SADS case coding versus CSO coded cases (based on death certificate information).

ICD-9 code as allocated by CSO	Description	Number of cases classified as SADS by the SCDYR panel
426	Conduction disorders	1
427	Cardiac dysrhythmias	1
428	Heart failure	0
429	Ill-defined descriptions and complications of heart disease	2
798	Sudden death cause unknown	2
Unascertained		2
307	Special symptoms of syndromes not classified elsewhere	1
WPW	Not coded	1

Table 5- Variation in coding for SADS cases 2007: SCDYR SADS case coding versus CSO coded cases (based on death certificate information).

ICD-10 code as allocated by CSO	Description	Number of cases classified as SADS by the SCDYR panel
R96.0	Other sudden death, cause unknown-instantaneous death	1
R96.1	Other sudden death, cause unknown-death occurring less than 24 hours from onset of symptoms, not otherwise explained	1
I49.9	Cardiac arrhythmia, unspecified	2
I46.1	Sudden cardiac death, so described	4
E108	Insulin-dependant diabetes with unspecified complications	1
No Code		3

Discussion

This report has described the rationale of the SCDYR, and the methodology used and the ongoing results of the retrospective review of SCD in the young in the Republic of Ireland. It is clear from these findings that SCD in the young, whilst a rare event at population level, represents a significant challenge in Ireland, with an estimated incidence of three cases every month. It can also be assumed that this figure is something of an underestimate.

The case ascertainment methodology used by the SCDYR meant that cases that may have been due to SADS were assumed due to drugs or alcohol because of a toxicology report. Furthermore, we were unable to ascertain any cases of SADS that may have manifested themselves as apparent drownings, or single vehicle accidents.

The incidence of SADS noted in the 15-34 year age group was 0.76 per 100,000 persons/year (0.96 per 100,000 per year in men and 0.54 per 100,000 per year in women). This however does not represent the total population burden of SADS, as it is well documented that people below 15 or beyond the age of 34 are still at risk of fatal events relating to such channelopathies as the LQTS or Brugada syndrome. Catecholaminergic Polymorphic Ventricular Tachycardia is described in the literature to have also caused SADS deaths in the under-15 year age group.

Therefore, while these figures represent a singular advance in our understanding of SADS in Ireland, they must be interpreted in context.

Non-cardiac sudden deaths

In total 87 cases of sudden death reviewed were deemed to be non-cardiac in aetiology. The commonest finding as a non-cardiac cause of sudden death was sudden unexpected death in epilepsy (SUDEP). This accounted for 25.2% (22/87) of non-cardiac sudden deaths for the years 2005 to 2007 inclusive.

It is known that epilepsy is associated with a two- to three- fold increase in mortality compared to the general population. SUDEP is defined as non-traumatic and non-drowning death in patients with epilepsy that is sudden, unexpected, witnessed or un-witnessed, and with or without evidence of a seizure. The incidence of SUDEP has been estimated to be between 3.5-5.9/1000-person years¹⁵. Myofibrillar degeneration, cardiac conduction system oedema, and morphological abnormalities of the conduction system have been described on post-mortem SUDEP analysis. These may represent underlying abnormalities, or may be the consequence of repeated hypoxaemia or catecholamine surge sometimes seen during seizures, and warrant further investigation.

It is recognized that some SUDEP deaths may be due to cardiac arrhythmias in subjects with undiagnosed arrhythmic heart disease. In one series, 39% of patients with long QT syndrome had diagnoses delayed during diagnostic work-up for epilepsy, with 4 SADS occurring in young family members while evaluations were being carried out¹⁵. In this post mortem review, it is worthy of note that in the SUDEP cases, therapeutic levels of anti-epileptic medications were detected on post-mortem toxicology studies in only one-third of cases.

The next most common cause of non-cardiac sudden death in this population was sudden death associated with drugs or alcohol, termed overdoses in this analysis, which made up 21.8% (19/87) of non cardiac cases. These were categorised separately from suicide, and include deaths associated with alcohol, cocaine, and other drugs, with significant positive findings on toxicology reports.

While there may be underlying cardiac arrhythmias as true causes of death, especially for non-intentional overdoses, the distinction has been made for accuracy of SCD estimates. In 2007 alone, cocaine or its metabolites (including lignocaine, an anti-arrhythmic often used for cocaine preparation) were present in the toxicology screens of 5 overdose or toxicity deaths identified by the CSO as sudden deaths. It is well known that cocaine-associated death is not dose related, and can occur after the ingestion of trivial amounts of drug and be associated with very low plasma levels¹⁷.

Other non-cardiac causes of sudden death in this population included pulmonary embolism – (13% of all non cardiac sudden deaths), Acute Respiratory Distress Syndrome, acute post surgical bacterial endocarditis, and cerebral haemorrhage.

National post-mortem figures

Over the period 2005 to 2007 inclusive, there was an average of 5,427 post mortems carried out per year in Ireland. With 292 suspected cardiac death cases occurring in the 15-34 yr age group during that period, this accounts for an average workload of up to 1.8% of all post mortems per year. The feasibility of adapting national guidelines for autopsy investigation of suspected cardiac death with structurally normal heart, such as those in use in the United Kingdom, should be strongly considered given the relatively low overall burden posed by SCD. This also has implications for the design, implementation, and economic feasibility of post-mortem molecular autopsies.

For the years 2005-07, 29.5% (n = 86/292) of cases were unaccounted for, insufficient, or not provided. This included reports not located in the CSO listed source location/jurisdiction, reports not found, or reports not provided despite multiple requests. Given the variability and inaccuracy in using death certificate reporting for SADS, no reference to death certificate diagnosis was made for inclusion in overall figures if post-mortem reports were not available for review by the panel.

Once again, this no doubt accounts for an underestimation of total estimates of SCD incidence. For 18 CSO registered SCD cases, the CSO held incorrect information as to which coroner had been associated with the case. This meant that the SCDYR team experienced difficulty in obtaining the post mortem reports, often with no other means of reference to locate reports. One explanation for this discrepancy is that source jurisdiction information is used, rather than location of death. This is an issue that highlights some of the limitations of retrospective as opposed to prospective data analysis for accuracy of SCD estimation and case investigation.

ICD coding and death certification information

The CSO coding department uses the World Health Organization International Classification of Disease codes to classify causes of death. As part of the coding process, the CSO coding department selects the underlying cause of death from the death certificates, and translates the literal text of the listed conditions into ICD codes. The ICD system has undergone a number of modifications to date, and at present, there are two ICD code revisions in use in Europe (ICD-9 and ICD-10).

In spite of the common underlying principles, these two versions have important differences, such as the number of codes in each version (5000 in the ICD-9 and 10000 in the ICD-10). Furthermore, ICD coding can either be performed manually, or with an automated process. The automated method is in use in some countries¹⁰, and can be a successful way of limiting coding biases and improving coding comparability. Ireland uses the manual coding system, with final coding decisions being made by the relevant coding departments in the Central Statistics Office.

We have demonstrated that for the diagnosis of SADS, there is a substantial discrepancy between the CSO-attributed ICD code, and the death certification and post mortem information. This is important when considering the true underlying frequency of SADS deaths in this age group. Using CSO data to estimate, for example, the SADS death rates from 2005-2007, would lead to an incidence of 0.14 deaths / 100,000 per year. The estimate as calculated by the SCDYR team panel review methods is actually five times higher, at 0.70 deaths / 100,000 per year.

The assignment of ICD-10 codes by the person completing the cause of death on the death certificate would be one way to minimize error and potential mis-classification. Final coding decisions lie with the coding department in the CSO, staffed by non-medical personnel, who must make coding decisions based on findings, which may not clearly satisfy one coding option. This highlights the need for consensus opinion amongst those providing final cause of death statements, with avoidance of statements leaving interpretation open to non-medical coders, and potentially delaying the initiation of family screening recommendations. In cases where no consensus can be reached, referral for specialist pathologist review should be considered.

Registration timeframe

Registration of deaths occurs for either the calendar year of death, or the next year. Delays usually occur due to coronial inquests. The CSO states approx 2.5% of cases are included in the Late Register, which is retrospectively included into overall annual figures. As all deaths are legally obliged to be registered, non-registration is rare because of necessity of death certificates for many legal purposes.

In a review of timeframes of death certificate/post-mortem reporting, Ireland had favorable timeframes within which queries were processed. These queries were often initiated by the CSO in order to complete demographic or clinical data in cases where information was incomplete. Some European countries had virtually non-existent query systems, or ones that could take up to or over a year.

The implications for completion of death certificates, ICD coding, and recommendation for Family Screening are clear. The average interval between death and CSO death registration is 129 days (SD=81.3), using data from 2006, seen in Figure 7. Ireland is among only 6 EU countries with report rate averages nearing 4 months – the other countries being Northern Ireland, Scotland, Belgium, Austria, and Portugal. Of note Sweden, Norway, and Finland report time interval averages of up to one year.

Collaboration with other groups & future directions

Since 1994, the ISIDA funded Sudden Infant Death register has successfully reported annually on the incidence and epidemiology of sudden infant death (SIDS) cases in Ireland. It has performed detailed case-controlled studies of the environmental and socio-economic factors that may contribute to SIDS. It has helped to raise the standard of paediatric post-mortem examination of a suspected SIDS infant, and helped to reduce the incidence of SIDS through dissemination of information to the public.

The SIDS Registry initially collected data on sudden deaths in infants from birth to 2.99 years. The Paediatric Mortality Registry (PMR), run by Temple St Children's Hospital, aims to collect data on sudden deaths in children from birth to 14 years inclusive. Unlike the SCDYR study, the PMR is designed as a case-control study focusing on the socio-demographic factors associated with the cases, as well as specific pathologic considerations. The intention is for collaborative and comparative purposes to ultimately include the SIDS Registry and PMR 0-14yrs data in the SCDYR, via case notification.

From this publication, it is hoped that in continued collaboration with bodies such as the IHF, HIQA and the HSE, we will aim to complete an SCD prospective register in the Dublin region, as a pilot for a nationwide registry, to improve our knowledge and accuracy in data collection regarding the incidence, and causes of sudden death in Ireland. The age group targeted in the pilot is from 15 until 34 years of age inclusive, with the future intention to produce a national report annually on cases of sudden death from 1 until 34.99 years of age, using data forwarded from the paediatric mortality registry.

The long terms objectives of the Republic of Ireland SCD in the Young Registry are:

1. To create a national Prospective Registry
2. To record the frequency of sudden death in young adults aged less than 35 years of age.
3. To collect key epidemiologic, demographic, and geographic information on these deaths.
4. To elucidate the causes of sudden death in this population.
5. To make public an annual report to highlight this information to the public and health professionals.

There are some limitations to our data. Two areas of potential data error have been identified by the CSO itself, which are reflected by the registry study findings. First, that the details of death may have been entered incorrectly at registry office - usually the original intent of the attending doctor can be deciphered by CSO cause of death coder in the CSO coding department.

Second is the issue of Cause of death coding – this can be subjective and complicated. The editing process may identify where the deceased has been assigned an underlying cause of death inappropriate for age/sex. It is not an automated process. Furthermore, selective bias may occur during the coding procedures.

Retrospective Registry

The inherent selection bias that occurs with retrospective registries, such as strict toxicology exclusion criteria, or reliance on non-standardized pathology reports, will always account for the current study limitations. Accurate sensitivity and specificity figures could not be used for comparison between death certificate data, and post mortem data for estimation of SCD figures, due to the high number (29.5%) of reports either not available or insufficient for analysis.

Conclusion

These figures represent the first comprehensive, retrospective analysis of sudden cardiac death rates in the young (ages 15-34yrs), in Ireland. The national SCD yearly incidence of 2.68 per 100,000/yr is higher compared with other similar European studies, although the heterogeneity of different studies makes accurate, direct comparison more challenging.

The incidence rates in this report are likely an underestimation of the true figure due to missing data resulting in case exclusions. Gender distribution with male preponderance for SCD has been previously reported in multiple studies, and this holds true for both total SCD, and SCD due to HCM, CAD, and SADS, in the SCDYR figures.

Previous studies have reported SCD rate estimation by death certificate data as accounting for an overestimation of cases, such as the large US study by Chugh et al¹⁶. It is clear from our study that, when using death registration data in Ireland, the true incidence of SADS/inheritable cardiac disease/SCD is underestimated. Comparing coded cause of death versus panel review cause of death, up to 20% of SADS cases were not correctly identified, and CSO coding underestimated true SADS cases by a factor of 5.

It is important to highlight that all deaths occurring in persons with positive toxicology screens for drugs of abuse, or deaths classified as SUDEP, were not included in our SCD registry. This may underestimate the true incidence of SCD in those cases where drugs could have masked pre-existing conditions, such as cocaine use in the setting of congenital LQTS or Brugada syndrome.

This re-affirms the need for the implementation of prospectively collected data, where focused demographic, clinical, and autopsy information can be examined, and screening of first-degree relatives can be recommended without delay. This will rely on an increased national awareness amongst coroners, pathologists, physicians and general practitioners, for notification of potential cases.

The use of clear case definitions, with regards to the standard SCD autopsy procedure, and accurate source ICD coding at source when cause of death is certified, will certainly contribute towards the early detection of those at risk, as well providing up to date epidemiological data as knowledge of the causes of SCD evolve. Tissue samples should be routinely retained in cases of SADS, for 'molecular autopsy', or analysis for genetic mutations responsible for the cardiac ion channelopathies, known to cause SADS (LQTS, Brugada syndrome, CPVT).

The current burden of the investigation of SCD in the young, as evidenced by national autopsy figures, is currently minimal and should allow for the development and implementation of a nationally agreed standard SCD autopsy protocol, as occurs throughout the UK and parts of Europe.

Multiple studies^{9,13} have reported a frequency of 25-50% of inheritable cardiac disease known to cause SCD, in relatives of those who had sudden, unexplained cardiac deaths. As these cases are likely to be heritable in nature, the importance of early family screening cannot be understated.

The current specialist cardiac centers providing family screening offer appropriate support, diagnostics, counseling, and referral to specialist genetics services where indicated. The use of these services, in combination with the efficacious implementation of Taskforce recommendations, and a national awareness of the scale of SCD in Ireland, should enable earlier detection and prevention of heritable cardiac conditions associated with lethal cardiac arrhythmias, thereby reducing overall SCD rates in the young in the Republic of Ireland.

Abbreviations

Ao Diss-	Aortic Dissection
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
CAD	Coronary Artery Disease
Congenital HD	Congenital Heart Disease
CSO	Central Statistics Office
DCM	Dilated Cardiomyopathy
ECG	Electrocardiogram
HCM	Hypertrophic Cardiomyopathy
ICD	International Classification of Diseases (ICD-9 or 10)
ICD	Implantable Cardioverter Defibrillator
LVH	Left Ventricular Hypertrophy
SADS	Sudden Arrhythmic Death Syndrome
SCD	Sudden Cardiac Death
SCDYR -	Sudden Cardiac Death in the Young Registry
SUDEP	Sudden Unexplained Death in Epilepsy
TGA	Transposition of the Great Arteries

Glossary of terms (adapted from The Report of the Taskforce on Sudden Cardiac Death)

Aortic aneurysm - bulging weak spot in the body's main arteries which may rupture and cause death.

Atherosclerosis- a group of diseases characterized by thickening and loss of elasticity of the arterial walls.

Brugada syndrome- an inherited condition due to an abnormality in the sodium channels in the membranes of the heart muscle cells which can lead to life threatening ventricular arrhythmias.

Cardiac pathologist- a qualified medical doctor (pathologist) specially trained to identify disease in organs and tissue, in particular in the examination of the heart.

Cardiomyopathy- a disease of the heart muscle, which may cause thickening (hypertrophy), thinning and weakness, or replacement of muscle with fibrous tissue or fat. Patients with cardiomyopathies are at increased risk of arrhythmias.

Channelopathy- a disease involving dysfunction of an ion channel, due to an abnormal chemical reaction in the molecular pores in the heart's muscle cells.

Commotio cordis- sudden cardiac arrest from a blunt, non-penetrating blow to the chest.

Congenital heart disease- malformation of the heart or the large blood vessels near the heart caused by deformed development of the heart in the womb. It means "born with" or "present at birth".

Coronary Artery Disease- can also be referred to as ischaemic heart disease, or coronary heart disease. The coronary arteries arise from the aorta adjacent to the heart and supply the heart muscle with blood that is rich in oxygen. Coronary Artery Disease refers to narrowing or blockages in the vessels, usually due to atherosclerosis.

First degree relative- a person's mother, father, sister or brother (parents and siblings).

Implantable cardioverter defibrillator- a self-contained device implanted under the skin or muscle of the upper chest wall and connected via electric leads that pass through the veins to be fixed to the muscle of the atrium and/or ventricles of the heart. The defibrillator corrects the heart rhythm by delivering precisely calibrated and timed electrical shocks, when needed, to restore a normal heartbeat.

Long QT syndrome- an inherited defect in the heart rhythm that predisposes to syncope without warning (sudden fainting spells), dizziness, palpitations, seizures and sudden death. The name of the syndrome comes from the QT segment in the tracing on the ECG.

Myocardial infarction- death of some of the heart muscle (myocardial tissue) usually caused by arteriosclerosis with narrowing of the coronary arteries, the culminating event being a thrombosis (clot).

Myocarditis- inflammation of the muscular walls of the heart.

Pulmonary embolism- the obstruction of the pulmonary artery or branch of it leading to the lungs by a blood clot, usually from the veins in the leg, or foreign material causing sudden closure of the vessel.

SADS/ Sudden Adult or Arrhythmic Death Syndrome- a term used when sudden death occurs in an adult and no definite cause of death can be found, even after the heart has been examined by an expert cardiac pathologist.

Sudden cardiac death- death due to natural causes within an hour of the onset of symptoms, in the absence of any other cause, proven or assumed to have a cardiac cause. SADS deaths are included in this category.

Wolff-Parkinson-White syndrome- a heart condition with an additional abnormal electrical connection between the heart's chambers that may cause the heart to race.

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