

**UNIVERSITY OF SOUTHAMPTON**

**The Epidemiology of Ventricular Arrhythmias**

**By**

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ABSTRACT

FACULTY OF MEDICINE, HEALTH AND BIOLOGICAL SCIENCES

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Five research methods were adopted to explore the epidemiology of ventricular arrhythmias and provide the context for decisions about the use of Implantable Cardioverter Defibrillators (ICDs): (1) A systematic review, (2) An analysis of the national database of ICDs, (3) A national survey of UK ICD centres, (4) A population based cohort study of the incidence and prognosis of patients diagnosed with ventricular arrhythmias and (5) A case series of sudden cardiac death (SCD).

Findings were as follows: No UK studies on the incidence of ventricular arrhythmias had been published prior to this work. An assessment of the relationship between ICD use and need, suggested that those English regional areas in most need also had the lowest rates of ICD implantation. Respondents to a national survey of ICD centres perceived patient identification as the greatest barrier to ICD use.

The incidence rate (2001-2002) of diagnosed ventricular arrhythmias was estimated as 202 (95% CIs 164, 248) per million population for all patients who had survived the first day after their diagnosis and 88% of these patients survived to 12 months. Incidence was two fold higher in males than females and significantly increased with age. Most patients presented with syncope or palpitations.

Expert opinion was that less than 1% of the SCD case series could have been identified prior to their death and considered for an ICD. 49% of cases would have required further investigations to determine ICD appropriateness. Most of these cases had suffered an MI and/or were diagnosed with heart failure during their lifetime but were not referred for heart rhythm monitoring.

In conclusion, the incidence of ventricular arrhythmias is dependent on the case definition, prevalence of coronary heart disease, referral patterns and duration of diagnostic testing. Future work should focus on developing care pathways for patients presenting with symptoms suggestive of ventricular arrhythmias and indications for ICDs.

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## List of abbreviations

A&E	Accident and Emergency
AMI	Acute Myocardial Infarction
ARR	Absolute Risk Reduction
BPEG	British Pacing and Electrophysiology Group
CA	Cardiac Arrest
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCU	Coronary Care Unit
CHD	Coronary Heart Disease
CI	Confidence Intervals
CM	Cardiomyopathy
DGH	District General Hospital
DHA	District Health Authority
ECG	Electrocardiogram
EF	Ejection Fraction
EP	Electrophysiology
EPS	Electrophysiological study
ER	Emergency Room
GP	General Practice
HCM	Hypertrophic Cardiomyopathy
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
ICD	Implantable Cardioverter Defibrillator
ICD-10	International Classification of Disease (version 10)
IDC	Idiopathic Dilated Cardiomyopathy
IHD	Ischaemic Heart Disease

LMS	Left Main Stem
LVEF	Left Ventricular Ejection Fraction
LVF	Left Ventricular Function
MI	Myocardial Infarction
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NSVT	Non-sustained Ventricular Tachycardia
NYHA	New York Heart Association
ONS	Office of National Statistics
PAS	Patient Administration System
PCT	Primary Care Trust
PM	Post Mortem
PMP	Per Million Population
PTCA	Percutaneous Transluminal Coronary Angioplasty
R&D	Research and Development
RBH	Royal Bournemouth Hospital
RCT	Randomised Controlled Trial
RHA	Regional Health Authority
RHCH	Royal Hampshire County Hospital
RR	Relative Risk
RRR	Relative Risk Reduction
RSH	Royal South Hants
SCD	Sudden Cardiac Death
SD	Standard Deviation
SEPHO	South East Public Health Observatory
SF-36	Short Form (36 questions)
SFS	Syncope Functional Status
SGH	Southampton General Hospital
SMR	Standardised Mortality Ratio

SPR	Specialist Registrar
SUHT	Southampton University Hospitals Trust
SVT	Supra-ventricular Tachycardia
SWHHA	South West Hampshire Health Authority
UK	United Kingdom
US	United States
VA	Ventricular Arrhythmia
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WTE	Whole Time Equivalent

## **Publications resulting from work from this thesis**

Parkes J, **Chase D**, Grace A, Cunningham D, Roderick P. Inequity of use of implantable cardioverter defibrillators in England: retrospective analysis. *British Medical Journal* 2005; 330: 454-5.

Burnley H, **Chase D**, Gallagher PJ, Roderick P. Pathological findings in sudden cardiac death. *Virchows Archiv (Journal of the European Society of Pathology)* 2005; 447. Number 2. 463 (abstract P 727).

## **Conference presentations resulting from work from this thesis**

**Chase D**, Roderick P, Milne R, Morgan JM. 'Incidence and prognosis of ventricular arrhythmias'. British Cardiac Society. Annual Scientific Conference, Glasgow, April 2006. Judges' Choice session. Oral presentation.

**Chase D**, Roderick P, Gallagher P, Burnley H, Roberts P, Morgan JM. 'Case series of sudden cardiac death'. British Cardiac Society. Annual Scientific Conference, Glasgow, April 2006. Oral presentation.

**Chase D** 'Epidemiology of ventricular arrhythmias'. Post-graduate Society Conference, University of Southampton, June 2005. Oral Presentation.

**Chase D**, Cunningham D, Grace A, Roderick P, Roberts P, Morgan JM 'The provision of ICD implantation in England and Wales'. British Cardiac Society Annual Scientific Conference, Glasgow, April 2003. Oral presentation.

## **Related publications**

**Chase D**, Roderick P, Cooper K, Davies R, Quinn T and Raftery J. Using simulation to estimate the cost effectiveness of improving ambulance and thrombolysis response times after myocardial infarction. *Emerg. Med. J.*, Jan 2006; **23**: 67 - 72.

*Submitted to Europace*: Morgan J, **Chase D**, Earles S, Paisey JR, Yue AM, Nicholson T, Roberts PR, Roderick P. Diagnostic yield and cost per diagnosis of an implantable recorder in unexplained syncope.

## **Declaration**

This thesis is the result of work done wholly whilst I was in registered postgraduate candidature. It was supported by a research studentship from the South East Research and Development Directorate, any opinions expressed, however, are my own.

# 1. Introduction

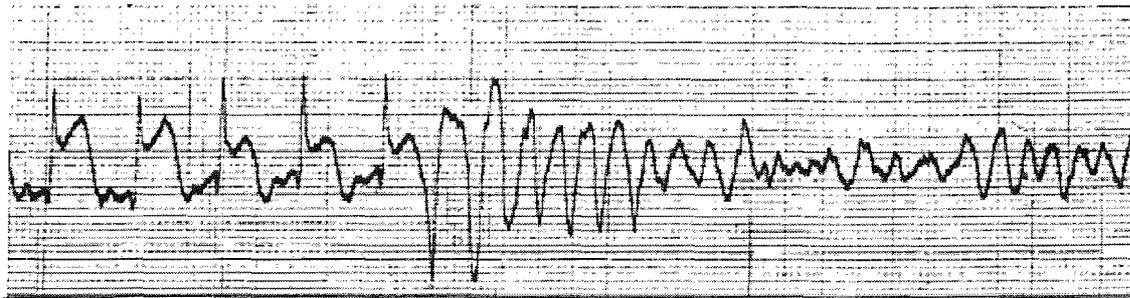
## 1.1 Prelude

The heart's contractions are controlled by an electrical signal that arises from the sinoatrial node (the heart's natural pacemaker) and follows the natural pathways of the heart. An arrhythmia is a change in the normal heart rate or control of the heart's contractions<sup>1</sup>. Ventricular arrhythmias are abnormal heart rhythms generated from the heart's ventricle. These rhythms follow an irregular pathway through the heart resulting in rapid contractions which consequently prevent the heart from completely filling with blood. This can result in a cardiac arrest and asystole<sup>1</sup>.

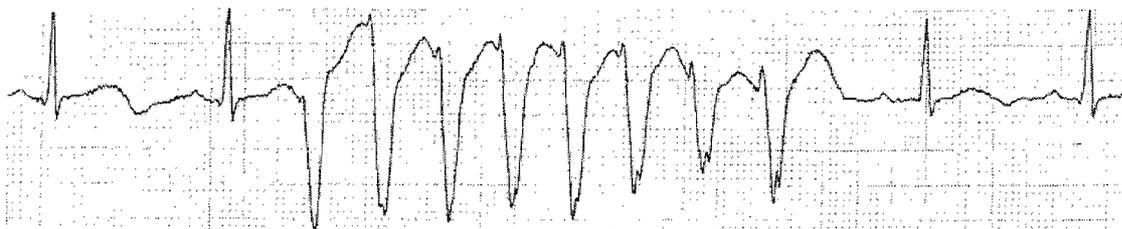
There are two main types of ventricular arrhythmias; ventricular tachycardia and ventricular fibrillation. Ventricular tachycardia (VT) is further sub-divided into two groups; non-sustained VT (NSVT) and sustained VT. This distinction relates to the duration of this abnormal rhythm. Ventricular fibrillation and sustained VT (with haemodynamic compromise) are life threatening forms of ventricular arrhythmias. Figure 1.1 demonstrates (A) a run of ventricular fibrillation and (B) a run of NSVT on a recording of the heart's electrical rhythm (a heart rhythm strip).

**Figure 1.1: Heart rhythm strips showing runs of ventricular arrhythmias**

**(A) Ventricular Fibrillation**



**(B) Sinus rhythm, followed by a run of non-sustained ventricular tachycardia and then reversion back into sinus rhythm**



There are a number of causes of ventricular arrhythmias and these are shown in table 1.1.

**Table 1.1 Causes of ventricular arrhythmias<sup>2</sup>**

<b>Causes</b>	<b>Details</b>
Idiopathic	Occurring in otherwise normal individuals
Underlying cardiac conditions	Coronary artery disease, cardiomyopathy, mitral valve prolapse
Familial conditions	Long QT syndrome, Brugada syndrome
Infection, inflammation or degeneration of the heart muscle	
Abnormal levels of electrolytes in the blood	Decreased potassium and/or magnesium e.g. by use of diuretics
Toxins and stimulants	Caffeine, nicotine, cocaine, some medications and herbal formulations

The prevalence of these causes in patients presenting with ventricular arrhythmias is unclear. However, studies of cardiac arrest survivors show that about 75% have coronary artery disease<sup>3</sup>. 10-15% of patients have dilated cardiomyopathy (which may be idiopathic, or due to other causes such as alcohol). Patients with identified familial conditions are known to be rare<sup>3</sup>.

## **1.2 Why is it important that patients with ventricular arrhythmias are identified?**

Evidence of symptomatic ventricular arrhythmias (in patients who also have underlying cardiac disease) is an important independent predictor of sudden cardiac death (SCD). These patients are at a 12 fold increased risk of SCD<sup>4</sup>. Patients with non-sustained ventricular tachycardia with no underlying heart disease do not appear to be at any increased risk<sup>5</sup>. However, for patients with underlying heart disease, cardiomyopathies or familial conditions, the occurrence of non-sustained ventricular tachycardia is independently associated with an adverse prognosis. The extent of this risk appears to be dependent on the degree of underlying disease<sup>5</sup>. The epidemiology of ventricular arrhythmias is explored further in a systematic review in chapter 3.

Implantable Cardioverter Defibrillators (ICDs) have been acknowledged in national guidance (in 2000) to be an effective and cost-effective intervention in the management of patients with life threatening ventricular arrhythmias; reducing this risk of an SCD<sup>6</sup>. It is therefore important that these patients are identified prior to a fatal event and managed appropriately.

## **1.3 Presentation of patients**

Ventricular arrhythmias can range from being asymptomatic and benign to symptomatic and life threatening<sup>7</sup>. Patients with symptomatic ventricular arrhythmias present to the health service in a number of ways: as an SCD or an SCD survivor (suffering a cardiac arrest) or with symptoms such as syncope, pre-syncope (dizziness), palpitations, chest pain or shortness of breath. The severity of presentation is both dependent on the sustainability and rate of the arrhythmia and the presence or absence of any underlying heart disease.

Asymptomatic patients with NSVT can be identified during diagnostic testing. Asymptomatic in this context means the patient had no symptoms at the time of testing when this arrhythmia was identified. These patients may or may not have presented for diagnostic testing with symptoms suggestive of ventricular arrhythmias.

Below are some details of the epidemiology and causes of the most common presentations with symptomatic ventricular arrhythmias: SCD (with further information on failed SCD/cardiac arrest) and syncope.

### ***Sudden Cardiac Death***

SCD is defined as 'natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected' by the European Society of Cardiology<sup>8</sup>. However, this definition varies slightly in the literature with some researchers not incorporating a time element from symptoms to death due to the large number of unwitnessed deaths. SCD incidence rates in the literature vary considerably probably both due to differences in case definitions and true variations between populations and time.

It has been estimated (in 2000) that about 75,000 people die of an SCD annually in the UK<sup>9</sup>. SCD represents about half of the deaths attributable to cardiovascular disease<sup>10</sup>. In developed countries, the underlying disease of the majority of SCDs (75%) is coronary artery disease. Most of the remainder are due to cardiomyopathies (dilated and hypertrophic)<sup>11</sup>.

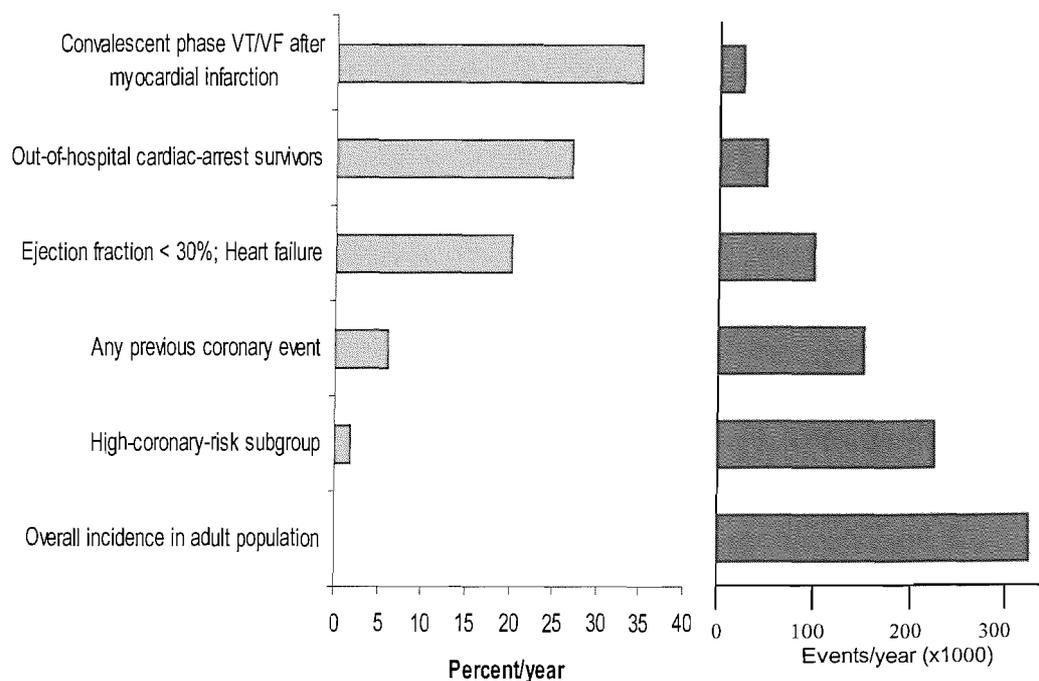
An SCD is the result of a triggering event and an abnormal substrate that induces electrical instability and VT that degenerates into VF<sup>11</sup>. In about 20%-30% of cases,

this abnormal substrate takes the form of an acute MI. Heart rhythm monitoring of patients experiencing an SCD suggests that about 85% of deaths are due to ventricular arrhythmias. About 15% are due to bradyarrhythmias (this usually represents end stage heart failure).

The risk of SCD in the general population is age-related<sup>12</sup>. The greatest increase in risk occurs between the ages of 40 and 65 years. However, in patients with advanced heart disease, the extent of disease rather than age has a larger impact on risk and age-related curves are not so distinct in this sub-group of the population<sup>12</sup>.

Patients with the highest risk for SCD; survivors of cardiac arrest and patients with low left ventricular ejection fraction (LVEF) and inducible or spontaneous non-sustained VT), are a small proportion of the total population burden of SCD. The lowest risk subgroups have a very large denominator relative to event rates; making identification of those patients that could potentially benefit most from therapy difficult<sup>13</sup>. Figure 1.2 shows US data on the proportion of sudden cardiac death in subgroups at different levels of risk on the left hand side and the absolute number of events in the adult population per year for these same risk groups on the right hand side of the diagram<sup>13</sup>.

**Figure 1.2 Sudden Cardiac Death among population subgroups (USA, 1990)**



The SCD incidence in the USA was estimated as 0.1% to 0.2% of the general population aged 35 years and over per annum<sup>12</sup>. As can be seen from figure 2, patient groups known to be at highest risk of a SCD e.g. those with low ejection fractions, patients with a history of heart failure and survivors of a cardiac arrest have a much higher SCD incidence rate; between 20% and 30% per annum but these sub-groups do not account for the majority of overall SCD events per annum<sup>13</sup>. Thus, the predictive power of these high risk characteristics only applies to small subgroups of patients suffering an SCD. The greater number of events occurs in the larger, general population.

The largest international SCD incidence study published to date (electronic database search undertaken in 2003) was a retrospective national surveillance study

undertaken in the U.S. of sudden cardiac deaths in all persons within the U.S.<sup>14</sup>. The overall age adjusted SCD rate was 206.5 per 100,000 in males and 140.7 per 100,000 in females but rates varied by state; ranging from an age-sex adjusted rate of 114.2 per 100,000 in Hawaii to 212.2 per 100,000 in Mississippi.<sup>15</sup>

### ***Survivors of an out of hospital cardiac arrest***

SCD victims experience a cardiac arrest. Outcomes of out-of-hospital resuscitation for episodes of cardiac arrest are generally poor (about 3–10% survive in most studies), and those people who survive a first episode of a life-threatening ventricular arrhythmia are at high risk of further episodes. Half are re-hospitalised within 1 year and 40% die within 2 years<sup>16</sup>.

A population based study undertaken in Seattle, Washington, U.S. was published in 2002<sup>17</sup>. This suggested that the incidence of out-of-hospital cardiac arrests, with ventricular fibrillation as the first identified rhythm, had fallen by about 56% between 1980 and 2000 (from 0.85 to 0.38 per 1000). This reduction was most evident in males (57% reduction in incidence). The authors suggested that this decline in incidence rates probably reflected a national decline in coronary heart disease mortality<sup>17</sup>.

A systematic review of the incidence of cardiac arrest was published in 1993<sup>18</sup>. Studies reporting incidence and survival rates from peer-reviewed journals identified through automated searching (methods not reported) from 1970 to 1989 were considered. If more than one study for a given community fulfilled the criteria, the authors used the one conducted for the longest duration and/or largest population. Studies of 20 communities met the inclusion criteria. Incidence rates varied from 35.7 to 128.3 per 100,000. Survival rates ranged from 1.6 to 20.7 per 100 cases. The

authors found that incidence rates in the communities were related negatively to survival rates i.e. as the incidence rate increased, the survival rate to discharge decreased. Unfortunately, this review provided no information on the case definitions, case identification methods or calculation of survival for each of the individual studies. It is unclear whether these studies are comparable enough in their methods to examine this relationship. The authors comment that inconsistencies existed and could have resulted in the under and over-reporting of cases and the effect of reducing or increasing the survival rate.

Uniform reporting of cardiac arrest studies, using a standardised format known as the 'Utstein' template, was initiated in the early 1990s. The Heartstart Scotland project has published results using this template<sup>19</sup>. The population based rate was 33 patients arresting per 100,000 per year. The authors noted that this figure was likely to be an underestimate probably due to under-reporting. Of 1676 cases for which medical records could be identified, 1383 (83%) were declared dead on arrival at hospital or in the emergency department. 119 (7%) died in a hospital ward, 174 (10%) were discharged alive, of whom 148 (9%) were alive at 1 year.

### ***Syncope***

Syncope is a sudden transient loss of consciousness with concurrent loss of postural tone<sup>20</sup>. The incidence of syncope varies between 1.3 and 2.7 episodes per thousand population per annum with up to 40% of episodes being recurrent. Causes of syncope range from common benign problems to severe life threatening disorders. Causes and proportions of patients with these causes (taken from a summary of case series) are listed in table 1.2<sup>3</sup>.

**Table 1.2 Causes of syncope**

<b>Cause</b>	<b>Percentage of syncopal patients (%)</b>
<b>Neurocardiogenic causes</b>	
Vasovagal	8-41%
Situational	1-8%
Carotid sinus syncope	0.4%
<b>Orthostatic hypotension</b>	4-10%
<b>Decreased cardiac output</b>	
Obstruction to flow	1-8%
Arrhythmias*	4-38%
<b>Neurologic and Psychiatric diseases</b>	3-32%
<b>Unknown</b>	13-41%

\*Arrhythmias: sinus node dysfunction, atrioventricular conduction system disease, paroxysmal supraventricular and ventricular tachycardia and inherited syndromes

As can be seen from table 1.2, vasovagal, arrhythmias and neurologic and psychiatric causes are the most common known causes. However, there is great variation in the contribution of causes between studies. Even after extensive investigations, a large proportion of patients (up to 41%) have no identified cause for their syncope.

In exploring the cause of unexplained syncope, the most important issue is the presence of structural heart disease and/or an abnormal heart rhythm<sup>21</sup>. Cardiac syncope, as opposed to non-cardiac syncope, is an independent predictor of mortality and sudden death<sup>21</sup>.

The only way of diagnosing or excluding an arrhythmia as the aetiology of syncope is by capturing the cardiac rhythm during symptoms. This is difficult with conventional testing due to the infrequency and unpredictability of syncopal episodes.

## **1.4 Case definition of ventricular arrhythmias**

The case definition of ventricular fibrillation and sustained VT is widely accepted and is detailed below. The definition of what constitutes NSVT varies in the literature both in terms of the amount of required consecutive ventricular beats and the heart rate experienced during this run of beats.

### **1.4.1 Ventricular ectopic activity**

A very brief run of ventricular beats is known as ventricular ectopic activity<sup>22</sup>. This is not a type of ventricular arrhythmia but should be distinguished from non-sustained ventricular tachycardia. Activity is described in terms of the number of beats in a run e.g. salvos of three or more beats. Heart rate during this run of beats is rarely described. Ventricular ectopic activity is highly prevalent on Holter monitoring in screening studies of asymptomatic persons, particularly in the elderly<sup>23</sup>. There is no evidence to suggest an increase risk of SCD associated with ventricular ectopic activity<sup>22</sup>.

### **1.4.2 Ventricular tachycardia**

There is evidence to suggest an increased SCD risk associated with runs of ventricular tachycardia for persons with underlying cardiac disease<sup>5</sup>. Ventricular tachycardia is defined as either non-sustained (occurring for 30 seconds or less) or sustained (occurring for more than 30 seconds). Although this is a widely accepted differentiation, the definition of exactly what constitutes non-sustained ventricular tachycardia is not. Definitions in the literature range from a salvo of three to five

ventricular beats. Some stipulate a required heart rate of between 100 and 120 beats per minute, and others do not note a required heart rate at all<sup>24, 25, 26</sup>.

Patients with sustained VT tend to present with syncope, but can also present with palpitations, chest pain or other type of cardiac symptom. Patients with non-sustained VT can also present with these symptoms or they can be asymptomatic. At slower rates, ventricular tachycardia may be asymptomatic<sup>8</sup>. Symptoms also depend on the morphology of the arrhythmia: this can be monomorphic or polymorphic in nature (polymorphic ventricular tachycardia tends to be faster and less stable than monomorphic tachycardia); the severity of underlying heart disease; vascular tone; geometry of the ventricular contraction and whether the patient is upright or supine<sup>8</sup>.

### **1.4.3 Ventricular fibrillation and sudden cardiac death**

Ventricular fibrillation is widely defined as a chaotic disorganised arrhythmia. This arrhythmia causes instant haemodynamic collapse and loss of consciousness. Over a period of a few minutes, the heart becomes less viable and if defibrillation is not undertaken or is unsuccessful, all electrical activity ceases. This is a type of SCD<sup>8</sup>.

Heart rhythm recordings of patients at the time of sudden cardiac death usually show an acute increase in ventricular ectopic activity, followed in a few seconds or minutes by ventricular tachycardia, which degenerates (in seconds to minutes) into ventricular fibrillation. Five to seven minutes later electrical activity ceases<sup>8</sup>. Patients who are successfully resuscitated during such an episode are known as 'sudden cardiac death survivors' or, more commonly as, cardiac arrest survivors.

## **1.5 Identification of cases**

There are no screening programmes for the identification of patients with ventricular arrhythmias. These arrhythmias are uncommon and less severe forms i.e. non-sustained ventricular tachycardia are transient. More severe forms of ventricular arrhythmias i.e. sustained ventricular tachycardia and ventricular fibrillation, are potentially life threatening and if the patient does not present to the health service quickly their condition could worsen and presentation would be as a sudden cardiac death or resuscitated cardiac arrest survivor<sup>7</sup>.

Ventricular arrhythmias can only be diagnosed using some form of electrocardiogram (ECG) monitoring, and then only if the patient is experiencing this arrhythmia at the time of monitoring. An ECG can be undertaken over different time periods. The types of ECGs used to diagnose ventricular arrhythmias and the time period over which the rhythm is recorded are listed below.

### **1.5.1 Electrocardiogram (ECG)**

The ECG is usually the first investigation used to investigate a heart rhythm disturbance. It generates a graphical record of the heart's rhythm. A 12-lead ECG is commonly used. To record the ECG, patches with wires are placed on the chest and the wires are connected to a monitor. ECGs can be undertaken in all healthcare settings.

An ECG can record the patient's heart rhythm over a matter of minutes or patients can be continuously monitored using a bedside ECG during hospital admission. It can confirm a patient is in VF or sustained VT at the time of collapse. Non-sustained VT is very rarely diagnosed using an ECG.

### **1.5.2 Holter monitoring**

The Holter monitor is a device that measures and records heart rhythm continuously over a certain time period, usually 24 to 72 hours. Most patients have 24 hour Holter monitoring. Holter monitors use a portable cassette recorder worn on a shoulder-strap harness. Six skin electrodes are attached at the recorder port. The patient keeps a diary of symptoms that occur, and when they occur, during the recording period. This test tends to be undertaken when an ECG does not demonstrate the arrhythmia and it is still suspected to be the cause of symptoms.

Patients are encouraged to attempt to actively reproduce their symptoms during 24 hour recording. If symptoms are reproducible or occur on a daily basis, Holter monitoring is an efficient method of correlating symptoms with cardiac rhythm. More commonly, symptoms are less predictable and longer term ECG event recording is indicated.

### **1.5.3 Implantable loop recorder**

These experimental devices enable ECG recording during transient infrequent events. The implantable loop recorder is inserted under the skin under local anaesthetic. It continuously monitors heart rhythm for up to 14 months. These recorders are designed for patients with syncope or transient presyncope. However, they may also have value for patients with transient palpitations or other symptoms potentially related to an abnormal heart rhythm.

When the device is activated, ECGs immediately preceding the event are retained along with subsequent ECG recordings; providing a continuous recording of ECG prior to, during and after onset of symptoms e.g. a patient with syncope could regain consciousness and activate the device 3 minutes after passing out and still record the

ECG before and after the event. Longer ECG recordings and automated devices are becoming available (allowing a 20 min recording to be transmitted in less than 7 minutes)<sup>27</sup>.

### 1.5.4 Electrophysiological Study (EPS)

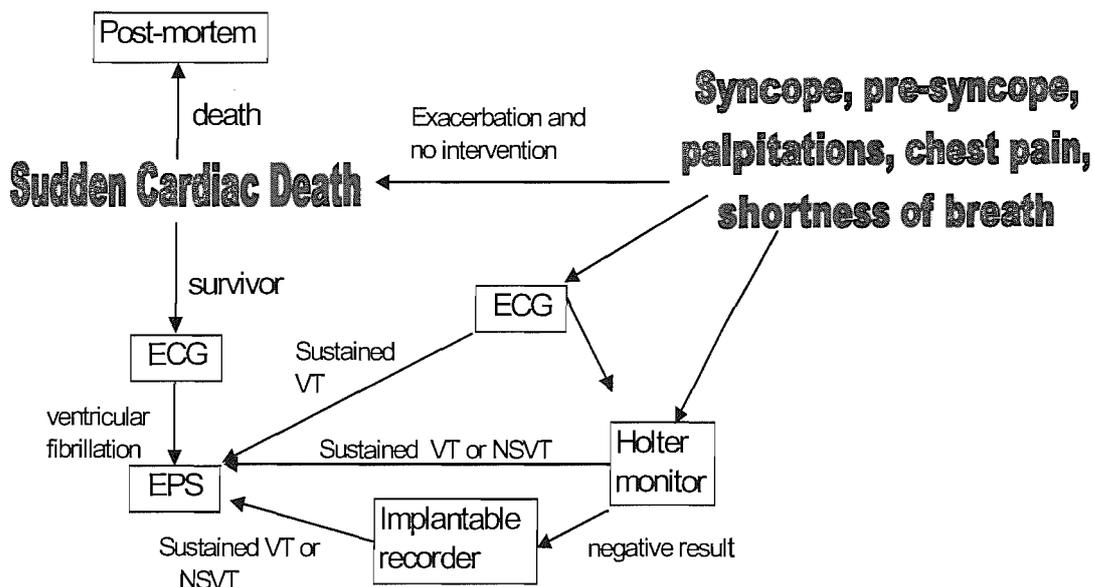
The EPS is undertaken in a catheter laboratory and can take several hours. It is a recording of the electrical activity in the heart. A catheter is placed inside the heart. This catheter delivers impulses to the heart to trigger VT or VF. EPS helps pinpoint the location and type of arrhythmia and can be used to assess the effectiveness of treatments.

Indications for EPS are: (1) The investigation of symptoms i.e. a history of persistent palpitations, recurrent syncope or presyncope with impaired left ventricular function and (2) interventions; ablation and investigation of arrhythmias<sup>28</sup>.

### 1.5.5 Presentation and diagnosis

Figure 1.3 shows patients' presenting symptoms and the pathways to diagnosis.

**Figure 1.3 Presentation and diagnosis of patients to hospital and within hospital with ventricular arrhythmias**



Patients in VF present de novo as an SCD or if defibrillated successfully are survivors of a cardiac arrest and can be readily diagnosed by the emergency services using an ECG. Those patients identified as suffering VF outside of the context of an acute MI would be referred for an EPS.

Patients with ventricular tachycardia commonly present with syncope or palpitations, but they can also present with chest pain, dyspnoea or dizziness<sup>27</sup>. These symptoms, especially syncope, can indicate a number of possible cardiac and other causes. Patients therefore may undertake a cascade of tests to determine cause<sup>29</sup>.

The aims of diagnostic testing for this group of patients are both to identify the ventricular arrhythmia and the underlying cause of this arrhythmia<sup>30</sup>. Ventricular arrhythmias can be transient e.g. due to an electrolyte imbalance post acute myocardial infarction, peri-operative or immediately post-operative. These ventricular arrhythmias are generally reversible. Circumstances and immediate biochemical tests identify these patients. In all other patients, the likelihood of underlying cardiac disease needs to be established.

Non-sustained ventricular tachycardia (NSVT) is generally diagnosed using Holter monitoring. Because of the transient nature of NSVT, the sensitivity of testing is low. The specificity of testing is moderate<sup>27</sup>. There is potential for misdiagnosis of ventricular tachycardia; as supraventricular tachycardia with left bundle branch block. However, clinicians tend to err on the side of caution and query potential ventricular tachycardia before diagnosing the less severe alternative. Non-sustained ventricular tachycardia can also be diagnosed on continuous ECG monitoring, such as in a coronary care unit. It is also possible to identify non-sustained ventricular tachycardia on an ECG e.g. in a doctor's surgery, ambulance or accident and emergency department whilst a patient is experiencing symptoms, but this is uncommon.

In practice, the definition of non-sustained ventricular tachycardia tends to depend on the type of test being undertaken. For Holter monitoring at the Southampton General Hospital, the definition is four or more consecutive ventricular beats at a rate of 100 beats per minute or more. For ECG monitoring, a run of three or more consecutive beats would be considered possible non-sustained ventricular tachycardia, and the patient would be investigated for underlying cardiac disease. Sustained ventricular tachycardia is widely defined as a run of consecutive ventricular beats occurring for more than 30 seconds regardless of type of diagnostic test<sup>24, 31, 26</sup>.

Sustained ventricular tachycardia can also be diagnosed on Holter monitoring or ECG<sup>27</sup>. This is more readily diagnosed than NSVT because the run of consecutive beats is for a much longer duration and patients tend to experience more severe symptoms.

Inducible ventricular tachycardia is not a type of ventricular arrhythmia as such, but the ability to reproduce this arrhythmia in an electrophysiological study (EPS). Definitions of what constitutes a positive EPS ventricular stimulation can vary, but a generally accepted definition is the inducibility of 10 beats or more of ventricular tachycardia by programmed simulation<sup>8</sup>.

Patients with inducible VT on EPS are at a higher risk of an SCD than patients with VT that is not inducible during EPS<sup>5</sup>. The sensitivity and specificity of EPS is low and dependent on the morphology of the induced ventricular arrhythmia, its sustainability and whether the patient is at high risk of suffering an SCD<sup>8</sup>.

### **1.5.3 Subsequent diagnostic testing**

Once a ventricular arrhythmia has been diagnosed there is a cascade of tests a patient may undertake to determine underlying heart disease. Non-invasive tests include an exercise ECG, to establish degree of ischaemia and an echocardiogram to establish left ventricular function. Angiography is an invasive test undertaken to establish the degree of coronary artery narrowing. Left ventricular function can also be determined using this test but measurements are less precise than echocardiography.

## **1.6 Management of patients**

This section describes the acute and subsequent health care management of patients with ventricular arrhythmias. Management is dependent on the severity of the arrhythmia and the presence or absence of underlying cardiac disease.

### **1.6.1 Acute management of ventricular fibrillation**

For patients presenting in VF; and thus experiencing a cardiac arrest, the immediate aim of treatment is to save the patient's life. This involves cardiopulmonary resuscitation and external defibrillation. The speed at which these life saving measures are employed is crucial to the patient's survival<sup>32</sup>. In the UK, there is a national target for ambulance response to life threatening calls: to reach 75% of patients within 8 minutes<sup>33</sup>. The aim of this target is to save more lives. Programmes for educating public on undertaking cardiopulmonary resuscitation have been met with limited success<sup>32</sup>.

### **1.6.2 Acute management of ventricular tachycardia**

For patients experiencing sustained ventricular arrhythmia, the aim of management is to revert patients back to their normal heart rhythm. This can involve the use of drugs such as amiodarone and/or giving the patients a DC shock. As with a cardiac arrest, once a normal rhythm has been achieved and the patient has been stabilised, the aim is to locate any underlying cardiac disease through the diagnostic testing described in the previous section. A risk profile is built up prior to testing based on previous history, family history and results of biochemical and other standard admission tests.

Patients with non-sustained ventricular tachycardia are much more heterogeneous. If the patient is known to have a cardiac history, then this arrhythmia could be treated with amiodarone and the underlying cardiac disease explored further. If the patient has no previous cardiac history it is unlikely that the arrhythmia would be treated. However, if patients present as an emergency with syncope or palpitations and run/s of non-sustained ventricular tachycardia, an echocardiogram would be undertaken to establish if there is any degree of left ventricular dysfunction. Any abnormalities detected on echocardiogram would result in the patient having further tests to establish the degree of cardiac disease.

### **1.6.3 Subsequent management**

The aim of subsequent management for patients with underlying cardiac disease and a ventricular arrhythmia that is not transient or reversible is 1. to manage the cardiac disease and 2. to reduce risk of sudden cardiac death from recurrent episodes of the arrhythmia. Managing the cardiac disease can involve revascularisation either by Percutaneous Transluminal Coronary Angioplasty (PTCA) or Coronary Artery Bypass Grafting (CABG).

The management options for ventricular arrhythmias are: 1. Radiofrequency ablation, 2. Anti-arrhythmic drug treatment and 3. Implantable Cardioverter Defibrillator<sup>16</sup>.

Radio-frequency ablation destroys the specific area of the heart that begins the abnormally fast signals. It is a potential cure but the procedure is often unsuccessful. Most types of ventricular arrhythmias aren't amenable to ablation. Anti-arrhythmic drugs are another option. However, most can worsen a ventricular arrhythmia and their use requires close monitoring. Anti-arrhythmic drugs are restricted to patients with well-tolerated arrhythmias or those whose life expectancy is poor despite aggressive therapy. These drugs are not a cure, but suppress the beginning of a tachyarrhythmia episode. The most widely used anti-arrhythmic drug is amiodarone<sup>16</sup>. The Implantable Cardioverter Defibrillator (ICD) is the current treatment of choice for patients with life threatening ventricular arrhythmias.

#### **1.6.4 The place of Implantable Cardioverter Defibrillators in patient management**

ICDs are similar in size to a pacemaker (30–40 cm<sup>3</sup> in capacity), weigh less than 80 g, and are surgically implanted using local anaesthesia under the skin in the pectoral region<sup>16</sup>. The latest devices provide graded responses to a sensed ventricular arrhythmia. Antitachycardia pacing, low-energy synchronised cardioversion and high-energy defibrillation shocks can be delivered via a single transvenous lead, terminating a potentially life-threatening arrhythmia. Devices last about 7 years before replacement is required.

Electrophysiological studies (EPS) are sometimes used prior to implantation of an ICD in order to confirm the need for ICD and/or to provide information on pacing the device. Appendix 1 shows management pathways from presentation to ICD implantation for patients presenting with: (A) a failed sudden cardiac death (out-of-

hospital cardiac arrest), (B) sustained ventricular tachycardia and (C) post-MI with non-sustained ventricular tachycardia.

## **1.7 Justification for ICDs**

The high cost of ICDs; at about £20,000 per device in 2000, and concerns about the effectiveness of these devices led to demands from health authorities for national guidance on ICD use. A HTA report for the National Institute for Clinical Effectiveness (NICE) of evidence for ICDs was published in 2000<sup>16</sup>. Seven RCTs, eight cost-effectiveness analyses and two good quality literature reviews were reviewed. Overall, these studies showed changes in absolute mortality risk ranging from an increase of 1.7% to a reduction of 22.8% for the use of ICDs as opposed to current management (relative risk reductions of -7% to +54%)<sup>16</sup>.

Cost-effectiveness was estimated in this report using UK cost data from three hospitals and trial survival data from one RCT, ranging between £20,250 and £87,000 per life year saved. The cost per quality adjusted life year was estimated as between £21,300 and £108,800 (using quality of life indices derived from clinical opinion)<sup>16</sup>.

NICE considered cost-effectiveness, amongst other considerations, and recommended the use of ICDs for primary and secondary prevention in specified groups of patients<sup>6</sup>. In this context, implantation of patients with a previous SCD episode and/or previous VT is known as secondary prevention. Implantation of patients with a prior MI, coronary artery disease, family history of SCD and familial cardiac conditions e.g. long QT syndrome, poor cardiac function (low left ventricular ejection fraction) or heart failure is called primary prevention.

The patient groups recommended for an ICD by NICE were:

Secondary prevention i.e. for persons who present in the absence of a treatable cause, with:

- (1) Cardiac arrest due to either VT or VF,
- (2) Spontaneous sustained VT causing syncope or significant haemodynamic compromise,
- (3) Sustained VT without syncope/cardiac arrest, and who have an associated reduction in ejection fraction (less than 35%) but are no worse than class 3 of the New York Heart Association functional classification of heart failure.

Primary prevention for patients with:

- a history of previous MI and all of the following:
  - i) non-sustained VT on Holter monitoring,
  - ii) inducible VT on electrophysiological study
  - iii) left ventricular dysfunction with an ejection fraction less than 35% and no worse than class 3 of the New York Heart Association functional classification of heart failure
  
- a familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia and following repair of Tetralogy of Fallot.

The NICE report acknowledged the lack of epidemiological data on indications for ICDs. Despite this, NICE set a target figure of 50 ICDs to be implanted per million

population in the UK. This figure was based on modelling undertaken by an industry representative.

Subsequent to these recommendations, several further trials, two systematic reviews and a meta-analysis<sup>34</sup> have been published. The NICE report and recommendations were updated in 2005 to incorporate new evidence.

Results from the published meta-analysis are shown below to provide an indication of the variation in benefit achieved using ICDs in primary and secondary prevention<sup>34</sup>. Nine RCTs with over 5,000 patients were included in the meta-analysis. This included the 3 primary prevention and 4 secondary prevention trials in the NICE report plus two further primary prevention trials. These additional trials did not require evidence of ventricular arrhythmias, they were: CAT which included patients with dilated cardiomyopathy and an LVEF  $\leq 0.30$  and MADIT II which included patients with an MI  $\geq 4$  weeks before entry and LVEF  $\leq 0.30$ . The pooled relative risk reductions in all cause mortality associated with ICDs compared with conventional management using a random effects model are shown in the table below.

**Table 1.3 Pooled relative risk reductions in all cause mortality associated with ICDs for primary and secondary prevention of ventricular arrhythmias**

Indication for ICD	Number of patients ICD vs conventional	Relative risk reduction	95% CIs Random
Primary prevention	1494 vs 1636	0.66	0.46, 0.96
Secondary prevention	963 vs 1060	0.75	0.64, 0.87

There was no statistical evidence of heterogeneity in either meta-analysis. In the primary prevention analysis, exclusion of the MADIT 1 and MADIT 2 studies still demonstrated a relative risk reduction of 0.73 (0.57, 0.94). However, the removal of the MUSTT study resulted in a non-significant risk reduction of 0.74 (0.51, 1.08).

The 2005 NICE recommendations are discussed in the 'future ICD use' section of this chapter.

## **1.8 Trends in ICD use**

### **1.8.1 International and European ICD implantation rates**

The first ICD was implanted in 1980. Since that time, it has become widely accepted as the treatment of choice for patients with ventricular arrhythmias. However, there is wide variation between countries in implantation rates.

Rates in the UK are lower than that in many European countries, and markedly lower than USA (which implanted 83% of the world's ICDs in 2000 with an estimated annual cost of \$1.34 billion). In 1997, a world survey of ICD use was undertaken. This showed large variation in ICD rates, from 7 per million population (pmp) per year in the UK to 133 pmp in the U.S<sup>35</sup>. Figure 1.4 below shows the ICD implantation rate pmp in 2000 in selected European countries<sup>35</sup>.

Figure 1.4 ICD implantation rates per million population in 2000<sup>35</sup>

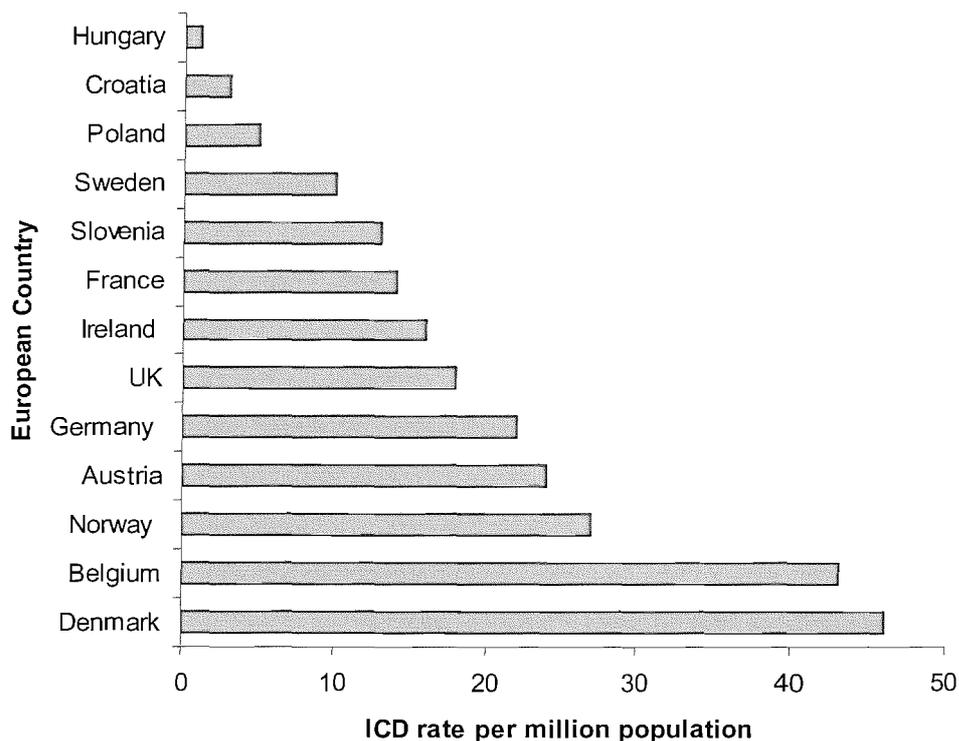


Figure 1.4 shows that there was still wide variation in ICD use between European countries in 2000. The original NICE guidance was published in 2000. As can be seen from figure 1.4, the UK ICD rate fell far below that recommended by NICE; at about 20 per million per year as opposed to the recommended 50 per million for England and Wales alone.

One paper has been published that explored potential reasons for temporal and geographical trends in ICD use in Europe (between 1993 and 1998), the authors considered 2,257 patients from ten European evaluation studies of Medtronic defibrillators and defibrillation electrodes<sup>36</sup>. Rates of implantation differed greatly

between countries and did not correlate with indices of health related expenditure (number of patients per physician and number of patients per hospital bed). Indications for ICDs in Europe are shown in table 1.4. The relative proportion of patients with indications for ICDs differed between countries.

**Table 1.4 Overall indications for ICD implantation in Europe (% of patients)**

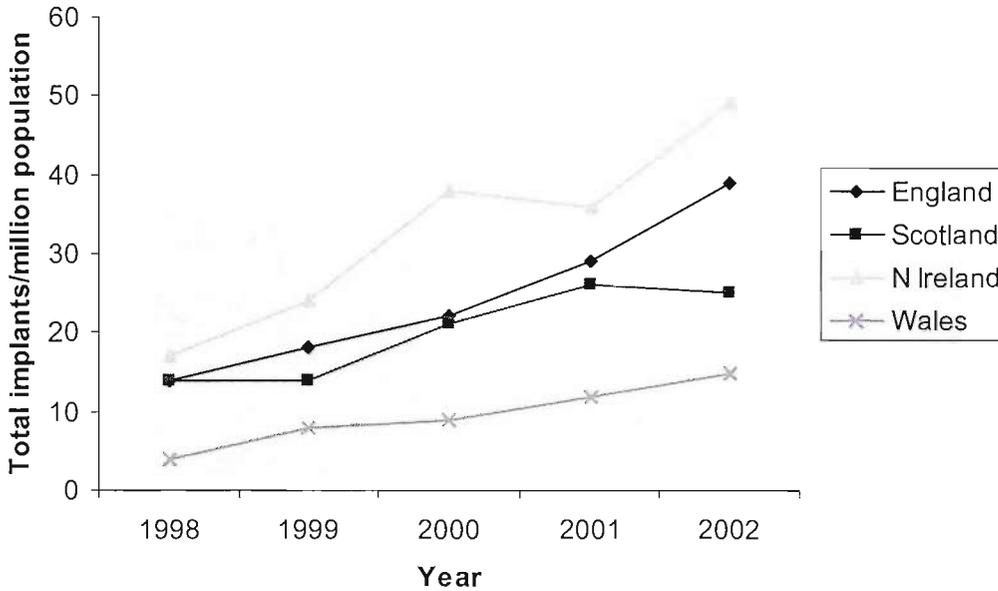
Indication for ICD	% of patients
Sudden cardiac death only	34.3%
Ventricular tachycardia only	45.8%
Sudden cardiac death and ventricular tachycardia	16.3%
Others (possibly unexplained syncope or awaiting heart transplant)	3.6%

Temporal trends showed a significant decrease in implantation of defibrillators for history of SCD only (39% vs 21%) and an increase in ICDs in patients with a history of ventricular tachycardia (56% vs 74%). The authors concluded that the increasing age of patients during the study period and the increased use of ICDs for less severe cases suggested an increased acceptance for ICDs. A major limitation to this paper was that the analyses were only based on the use of Medtronic devices and patients could have been preselected for European trials on the basis of indications. It is therefore difficult to generalise the information on indications to all patients receiving an ICD. Chapter 4 in this thesis details an analysis of all patients receiving ICDs in the UK during a two year period.

### 1.8.2 UK ICD implantation rates

There is also variation in ICD use between UK regions. Figure 1.5 shows ICD implantation rates in the four UK countries (England, Scotland, Northern Ireland and Wales) between 1998 and 2002.

**Figure 1.5 ICD implantation rate pmp in UK countries 1998-2002<sup>35</sup>**



As can be seen from figure 1.5, implantation rates were increasing within this time period in all four countries; the largest relative increase occurring in Northern Ireland and the smallest in Wales<sup>37</sup>. The publication of the NICE guidance in 2000, was followed by a significant increase in ICD implantation in England.

Further data on geographical and time trends and indications for use in the UK are presented in chapter 4 of this thesis.

### 1.8.3 Future ICD use

Since the 2000 NICE guidance, a large trial of ICD use known as MADIT-2 has been published. Results from this study suggest that patients who suffer an acute MI and have left ventricular dysfunction (but not necessarily a ventricular arrhythmia) have a mortality benefit from having an ICD implanted. This patient group is of a much greater size than that of patients suffering a ventricular arrhythmia. If ICDs were routinely implanted in this patient group the cost to the NHS would be substantial.

In 2005, NICE updated their recommendations for ICDs. They included an additional group in the primary prevention category:

- Patients with a history (> 4 weeks) MI and left ventricular dysfunction with LVEF of less than 30% and a QRS duration of equal to or more than 120 milliseconds.

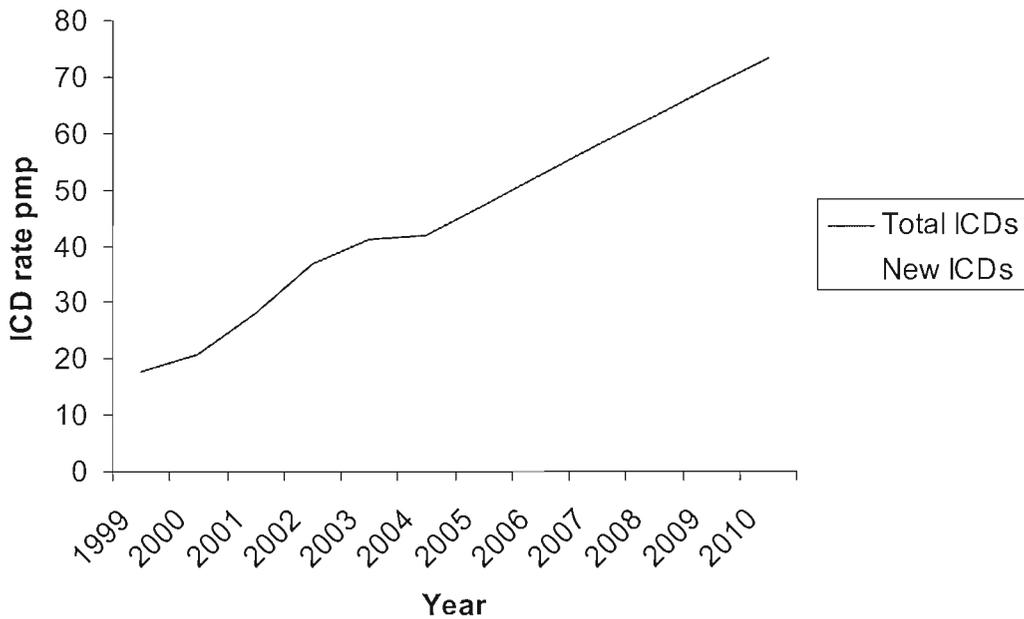
Thus, this additional patient group would not require any evidence of a ventricular arrhythmia and therefore an EPS would be unnecessary. This group is a sub-group of the MADIT-2 study population (the sub-group that benefited most from ICD implantation).

An audit of patients admitted to three coronary care units during one month in Newcastle in 2001, supplemented with figures from the literature has been published<sup>38</sup>. This study is the only published attempt to estimate the number of new patients meeting the NICE recommendations in 2000 (and the MADIT-2 study criteria) and is based on a very small number of patients. Six patients were identified who met the criteria. Extrapolating from this, the authors suggested an incidence of 150 ICDs pmp per annum using the current NICE guidance. If the MADIT-II criteria were

applied, 11 actual and 7 hypothetical patients would have been considered for an ICD with a total incidence rate of 504 pmp per annum. The authors noted that these figures were underestimated given that only patients admitted to coronary care units with acute illness were audited<sup>38</sup>.

Figure 1.6 below shows predicted trends in ICD use for the UK (actual and predicted trends provided by the national ICD database co-ordinator). Data up to 2004 are actual. Rates from 2005 onwards are based on projections using the 1999 to 2004 data.

**Figure 1.6 UK ICD rates per million population (pmp) from 1999 to 2004, and projected to 2010.**



As can be seen from figure 4, the NICE ICD rate of 50 per million population recommended in 2000, is predicted to be met in 2006. Future use of ICDs will be considered further in chapter 4 and in the final discussion of this thesis.

## **2. Study Objectives**

This short chapter presents a justification for assessing the epidemiology of ventricular arrhythmias, lists the research questions to be considered and outlines the research methods that will be employed to address them.

### **2.1 Justification for this work**

The NICE technology appraisal on ICDs published in 2000 acknowledged a lack of epidemiological data on ventricular arrhythmias<sup>16</sup>. Some modelling was undertaken by an industry representative with a figure of 50 ICDs per million population implanted suggested as health service demand for ICDs<sup>6</sup>. This figure was much higher than the UK ICD supply rate in 2000 of 17 per million population. However, this model was not substantiated with published epidemiological data. Subsequent to the NICE recommendations, health economic modelling work was commissioned by the National Health Technology Assessment Programme. Input on epidemiology was required to complement this modelling work.

There are no known published reviews of the epidemiology of ventricular arrhythmias and no UK population based studies of the incidence of this life threatening condition. This thesis will be the first attempt to explore the epidemiology of ventricular arrhythmias with a UK perspective. A multi-faceted approach will be adopted to provide health service planners with a detailed consideration of this issue.

## 2.2 Aim

The aim of this thesis is to explore the incidence, prognosis and current management of ventricular arrhythmias. This work will provide the context for decisions about the use of ICDs in England.

## 2.3 Research questions and study methodologies

The four main research questions to be answered are shown in bold with the study methods to be employed to answer these questions below (relevant thesis chapters are in brackets):

**1. What is the current knowledge on the incidence and prognosis of diagnosed symptomatic ventricular arrhythmias?**

- Systematic review (chapter 3).

**2. What are the current patterns of ICD management of patients with ventricular arrhythmias?**

- Analysis of the national database of ICDs - the British Pacing and Electrophysiology dataset (chapter 4).
- National survey of ICD centres (chapter 4).

**3. What is the incidence and prognosis in a defined population of diagnosed symptomatic ventricular arrhythmias?**

- Prospective population based cohort study (chapter 5).

**4. What is the scope for preventing sudden cardiac death from ventricular arrhythmias?**

- Consecutive case series of sudden cardiac death (chapter 6).

This thesis was initiated in September 2001.

### **3. Systematic review of the epidemiology of ventricular tachycardia**

This chapter addresses research question 1 in chapter 2 of this thesis: What is the current knowledge on the incidence and prognosis of diagnosed ventricular arrhythmias?

#### **3.1 Background**

This systematic review was undertaken to provide a synthesis of the literature and inform the design and analysis of the prospective population based cohort study. The epidemiology of ventricular tachycardia had not been previously reviewed.

The original objective for this review was to include broader literature on the epidemiology of ventricular arrhythmias and Sudden Cardiac Death. However, in searching for these studies, it was soon realised that the literature on cardiac arrests, including/excluding sudden cardiac death, was vast and fairly well reviewed already (discussed in chapter 1, section 1.3). It was therefore decided that a systematic review of epidemiology of ventricular arrhythmia alone would be a more feasible approach given resources and time constraints.

#### **3.2 Methods**

This section sets out the methods used to determine inclusion, searching for papers and quality assessment.

### 3.2.1 The inclusion and exclusion criteria

Studies considered for inclusion were population based incidence studies, and prognostic studies that included well defined consecutive cases. The inclusion criteria are shown in box 3.1.

#### Box 3.1 Inclusion criteria

##### **For incidence and prognostic studies**

- Prospective and retrospective population based observational studies of the incidence and/or prognosis of ventricular arrhythmia
- Cases were patients with newly diagnosed ventricular arrhythmias
- Studies including 30 or more ventricular arrhythmia cases.
- Restricted to adult populations (aged > 16 years)
- Studies in all languages published from 1989 onwards

##### **For incidence studies**

- Studies which provided (or at least allowed calculation of) an incidence rate.

##### **For prognostic studies**

- Studies with a representative, well-defined sample of patients at a similar point in disease at inception.
- Studies which provided (or at least allowed calculation of) a mortality and/or arrhythmia recurrence rate.

There were two reasons for including studies published from 1989 onwards: firstly, because of the large volume of studies identified through scanning; having a cut off

date reduced the number of papers and made the task more manageable within the timescale. Secondly, since the 1980s significant changes have occurred in the epidemiology and treatment of the main cause of ventricular arrhythmias, coronary artery disease. The incidence of ventricular arrhythmias associated with coronary heart disease has fallen. This decline is believed to be due to the reduction of risk factors associated with coronary heart disease and its management. Notably, the use of thrombolysis for acute myocardial infarction and earlier revascularisation in acute and chronic coronary artery disease acts to limit the degree of left ventricular impairment and ongoing ischaemia and consequently reduces the occurrence of ventricular arrhythmias<sup>7, 39</sup>. Studies previous to this time would provide a better picture of the natural history of this disorder but would not reflect the scale of the problem today.

The reasons for only including prognostic studies with 30 or more cases were as follows: precision of estimates would be greatly reduced with a small number of cases, it would not be possible to draw out results from different sub-groups and size of the study can also be used as a surrogate measure of the quality of a study.

### **Definition of ventricular tachycardia**

Due to varying definitions of ventricular tachycardia in the literature, all studies of 'ventricular tachycardia' were included. The precise heart rate and number of ectopic beats as defined are described.

Studies of ventricular arrhythmias, which included patients with ventricular tachycardia were also included.

### **Definition of population based**

There are no published quality criteria for evaluating how the population was defined. Therefore, some criteria were composed in consultation with PR and RM. Box 3.2 shows the criteria will be used to determine the quality of included incidence studies.

#### **Box 3.2 Definition of population based (in order of methodological quality)**

1. Investigators have tried to match cases to a geographically defined population (i.e. potential for inflows and outflows addressed, census population estimates),
2. The size of the local geographically defined population was presented and investigators stated that the hospital being studied provided all/most of the care for these resident patients,
3. The estimated size of the hospital catchment area was presented,
4. The size of the local geographically defined population was presented but there was no further information on care settings.

### **Definition of well-defined hospital based case series**

Well defined hospital based case series were defined as including consecutive patients who presented to secondary or tertiary care at a similar point in their disease e.g. patients presenting to the Accident & Emergency Department or as new out-patient referrals with palpitations or syncope or patients diagnosed with non-sustained VT post-MI. There is general agreement that a reliable prognostic study requires a well-defined cohort of patients at a similar stage of their disease<sup>40</sup>.

Box 3.3 shows the exclusion criteria for this review.

### **Box 3.3 Exclusion criteria**

- |  |
|--|
| <ol style="list-style-type: none"><li>(1) Studies specifically assessing incidence and prognosis of patients with familial conditions with a high risk of sudden cardiac death;</li><li>(2) Studies of patients experiencing transient ventricular arrhythmias during or immediately after surgery (and were presumed to be a result of surgery) and</li><li>(3) Studies of patients experiencing ventricular arrhythmias during or shortly after acute myocardial ischaemia i.e. with potentially transient and reversible arrhythmias.</li></ol> |
|--|

Studies specifically assessing patients with familial conditions have been excluded because of the complexity in interpreting their findings and converting these to an annual rate of ventricular tachycardia and its prognosis. Some of these patients experience ventricular tachycardia, others do not. Furthermore, methods for identifying such cases differ greatly to studies on a group of patients with ventricular arrhythmias. Patients with familial conditions tend to be identified through familial screening.

For patients experiencing transient and reversible ventricular arrhythmia, electrical rhythm disturbances during these times are associated with the event itself and should not be associated with an increased risk of a subsequent ventricular arrhythmia or SCD.

#### **3.2.2 Searching**

An electronic search was undertaken of the following databases: Medline from 1989 to April 2002, Embase from 1988 to August 2002 and the Citation index (searched in 2002) for published studies. Reference lists were also checked from included studies and identified editorials and reviews. The electronic database search strategies used are shown in appendix 2.

One reviewer (DC) searched the electronic databases and reference lists. Papers were requested for those studies believed to be relevant. One reviewer (DC) abstracted data from each paper using the incidence and prognosis data abstraction forms shown in appendix 3. This was checked against the original paper for precision and completeness by the second reviewer (RM). Any discrepancies about inclusion and specific data entries were resolved through discussion.

### 3.2.2 Validity assessment

Quality assessment questions were included in the data abstraction forms. These questions were developed using published guidance on applying these questions to prognostic studies and other types of observational studies<sup>41:42</sup> and in discussion with RM and PR. At the time of data abstraction, no published literature providing guidance on assessing the quality of incidence studies were identified; these were therefore created by adapting questions relating to other types of studies. The quality assessment questions used are shown in the boxes below.

#### Box 3.4 Quality assessment of incidence studies

1. Was the study prospective or retrospective?
2. What was the study duration?
3. Was the study population (denominator for incidence rate) well described? How accurately was the size (and age) of the population estimated?
4. Was there a clear definition of the condition (a case/the numerator for incidence rate)?
5. Was ascertainment of cases from the study population likely to be complete? Was there any potential for cross-boundary flow?
6. Can it be determined that cases were incident?

Studies met each of the respective criteria in box 4 if: 1. Cases were identified prospectively, 2. Study duration was one year or longer, 3. Study population was well

described, 4. The condition was clearly described, 5. Complete/almost complete cases ascertainment and 6. Cases were incident.

**Box 3.5 Quality assessment of prognostic studies**

1. Was the study prospective or retrospective?
2. What was the study duration? Was follow up sufficiently long and complete to assess prognosis?
3. Was there a significant loss to follow up?
4. Was there a consecutive well-defined sample of patients at a similar point in the course of their disease?
5. If subgroups with different prognoses are identified, was there adjustment for important prognostic factors?

Studies met each of the respective criteria in box 5 if: 1. Cases were identified prospectively, 2. Study duration was one year or longer, 3. There was no or minimal loss (<10%) to follow up, 4. Cases were consecutive and well described and 5. Adjustment was made for important prognostic factors.

**3.2.3 Data synthesis**

The studies reviewed were very heterogeneous both in terms of the patients themselves and the methods undertaken to identify and follow them. Therefore, incidence and survival rates were described for each study with reference to these issues rather than attempting to undertake a meta-analysis. Annual and two year survival probabilities were presented as described in papers or by calculation from presented survival curves. Comparisons of survival between prognostic groups within studies were described. Studies were grouped by type of ventricular arrhythmia and some were sub-grouped by whether they had known heart disease or other related underlying conditions.

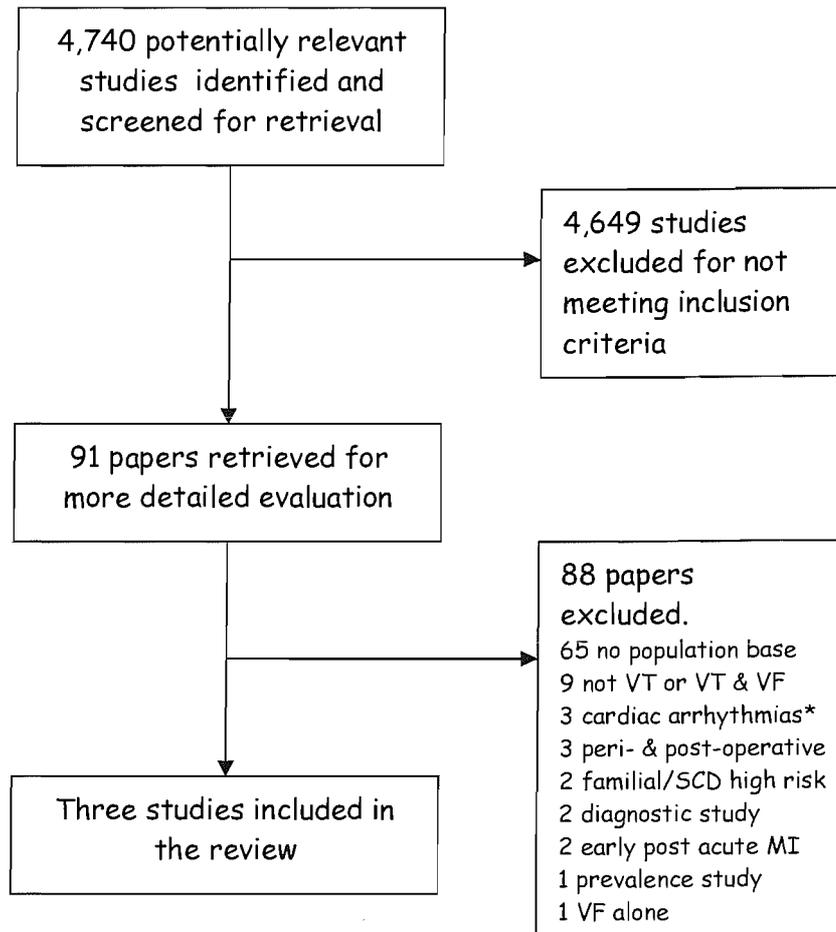
### **3.3 Results**

This section describes the number of studies meeting the inclusion criteria, the quality of these studies and their results.

#### **3.3.1 Number of studies meeting the inclusion criteria**

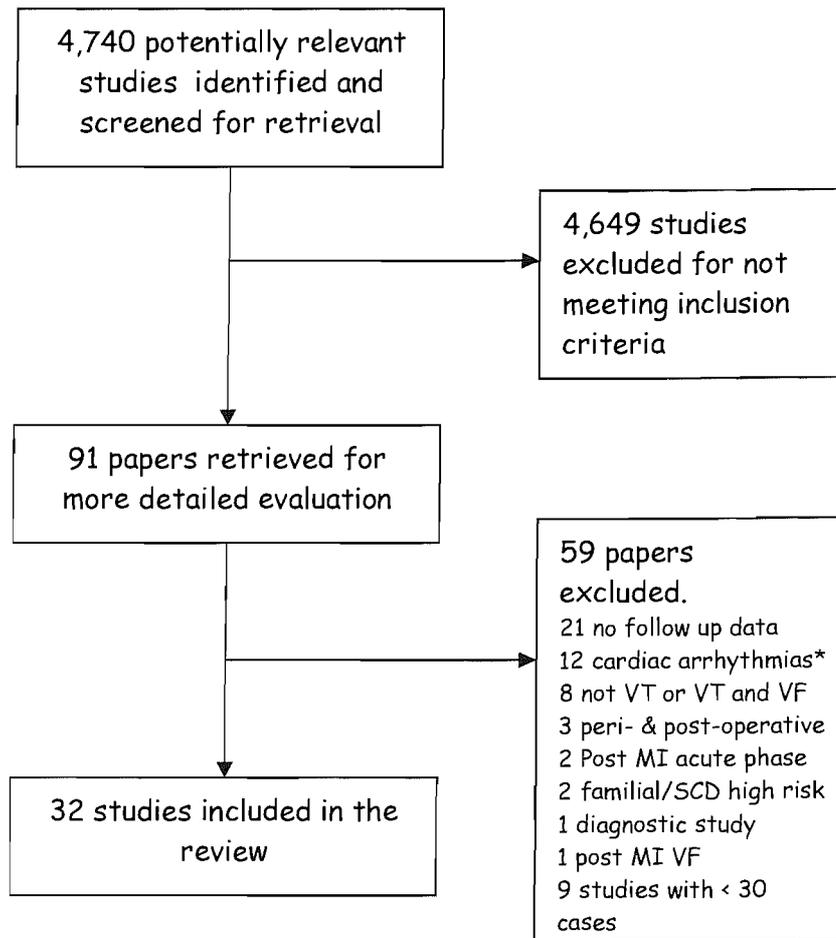
Figures 3.1 and 3.2 below shows the number of incidence and prognostic studies identified and included. All of the incidence studies also evaluated prognosis. However, for ease, these have been presented as two separate screening processes.

Figure 3.1 Flow-diagram for screening incidence studies



\*cardiac arrhythmias – these were studies where number and/or rate of ‘cardiac arrhythmias’ was a result but there were no details on type of cardiac arrhythmias. It was therefore not possible to calculate the number of persons experiencing ventricular arrhythmias.

Figure 3.2 Flow-diagram for screening prognostic studies.



\*cardiac arrhythmias – these were studies where number and/or rate of 'cardiac arrhythmias' was a result but there were no details on type of cardiac arrhythmias. It was therefore not possible to calculate the number of persons experiencing ventricular arrhythmias.

4,740 studies were identified through searching electronic databases and scanning reference lists. All these abstracts were scanned. The majority of these abstracts were clearly irrelevant. 91 papers were retrieved for more detailed evaluation. These 91 papers addressed the topic area but further information was required to determine inclusion. Inclusion and exclusion criteria were then applied to these 91 papers. The second right hand box on figures 3.1 and 3.2 shows how many of the 91 papers were excluded and the reasons for exclusion.

Searching for incidence and prognostic studies in Medline generated 3039 hits. Fifty-eight papers were scanned for potential inclusion (a yield of 2%). Searching Embase identified an additional 1700 hits. Thirty-three papers were scanned for possible inclusion. Of the papers scanned for possible inclusion, the Embase search tended to identify more papers meeting the inclusion criteria and also some useful reviews (for checking of references). The reason for this is unclear but could be due to the use of broader search terms in the Embase search strategy.

All 91 papers were checked against the inclusion criteria by the two reviewers. Of the 91 papers, just 3 papers met the criteria for incidence studies (and prognostic studies) and 32 met the inclusion criteria for prognostic studies.

### **3.3.2 Types of studies meeting inclusion criteria**

Patients and the tests used to diagnose patients in the 32 papers meeting the inclusion criteria differed considerably. Types of studies could be classified as assessing the incidence and/or prognosis of:

- (1) Sustained VT or VF (this includes some studies of life threatening/malignant ventricular arrhythmias which can be assumed to be sustained)

- (2) Inducible VT or VF on EPS (patients present with indications for testing, such as syncope)
- (3) Mix of Sustained VT and NSVT which were not separately identified (each study included both patients with sustained VT and patients with NSVT)
- (4) NSVT alone.

Table 3.1 below shows the type of ventricular arrhythmia studied, aetiology of underlying heart disease and the diagnostic test used to diagnose ventricular arrhythmias in each of the eligible studies. Most of these studies included a mixture of patients with and without underlying heart disease (left blank for underlying disease in the table). However, some studies exclusively considered patients with particular types (or no) underlying disease. Information on type of underlying disease is shown in the table. Studies in each of the four sub-groups are ordered alphabetically.

The diagnostic test used to diagnose ventricular arrhythmias varied between studies. It is important to acknowledge the type of test used because diagnostic accuracy varies between tests and the length of time patients are monitored. This would have an impact on both the number of cases diagnosed and the type (see glossary for details). Holter monitoring was used in the majority of studies to diagnose the ventricular arrhythmias. A 24 hour tape is standard, but 2 studies monitored patients for a longer time period. ECG bedside monitoring was used in a number of studies. Patients were monitored in hospital for varying time periods.

**Table 3.1 Eligible studies by type of arrhythmia studied, underlying disease of cases and diagnostic test**

Study	Details of VA	Underlying disease	Diagnostic test
<b>1. All cases in each study had sustained VT or VF</b>			
Alexander <sup>43</sup>	Primary diagnosis of VT/VF		Not stated
Andresen <sup>44</sup>	Non-inducible sustained VT		VT history, EPS
Coughlin <sup>45</sup>	Sustained VT	Idiopathic CM	Not stated
Hsu <sup>46</sup>	Life threatening VA		Not stated
Leclercq <sup>47</sup>	Sustained VT		ECG
McDonald <sup>48</sup>	Primary diagnosis of VT/VF		Not stated
Naccarella <sup>49</sup>	Malignant VT or VF	Late after MI	24 hr Holter
O'Hara <sup>50</sup>	Sustained VT or VF	Old MI	VT history, exercise ECG
Pinski <sup>51</sup>	1 <sup>st</sup> episode of sustained VT or VF, all candidates for EPS	76% had CAD	ECG
Rodriguez <sup>52</sup>	Sustained VT or VF		ECG
Saxon <sup>53</sup>	Sustained VT and inducible VT		ECG, EPS
Wiesfeld <sup>54</sup>	Sustained VT or VF	Post MI	ECG
<b>2. All cases in each study were presenting for EPS and had inducible VT or VF on EPS</b>			
Bhandari <sup>55</sup>	Inducible VT of 6 or more beats and VF	Acute MI	EPS
McCowan <sup>56</sup>	EPS all comers – inducible		EPS
<b>3. Cases within each study had sustained VT or NSVT not separately identifiable</b>			
Brodsky <sup>57</sup>	Spontaneous symptomatic VT	No underlying heart disease	ECG, 24hr Holter, EPS
Feleke <sup>58</sup>	VT of $\geq 4$ beats $\geq 120$ bpm	Acute MI vs no Acute MI	ECG with automated monitoring
Hosoda <sup>59</sup>	$\geq 6$ beats	MI	Not stated
Jull-Moller <sup>60</sup>	NSVT or sustained VT		24hr Holter
Kapoor <sup>61</sup>	Symptomatic, sustained or NSVT		ECG, $\geq 24$ hr ECG monitoring
Kofflard <sup>62</sup>	$\geq 3$ beats	HCOM	24 hr Holter
Maggioni <sup>39</sup>	$\geq 3$ beats $> 100$ bpm	MI	24 hr Holter
Spirito <sup>63</sup>	$\geq 3$ beats	HCOM	24 & 48hr Holter
Stewart <sup>64</sup>	$\geq 3$ beats $\geq 120$ bpm	DCM	24hr Holter
Tanabe <sup>65</sup>	$\geq 3$ beats $\geq 120$ bpm		24hr Holter
Wilber <sup>66</sup>	NSVT or sustained VT	Low ejection fraction, CAD and/or MI	24 hr Holter & EPS

<b>4. All cases within each study had NSVT</b>			
Algra <sup>4</sup>	Not defined, VT on 24 hr tape		24 hr Holter
Andresen <sup>67</sup>	NSVT		24 hr Holter
De Maria <sup>68</sup>	NSVT of $\geq 3$ beats	Idiopathic CM	24 hr Holter
Hammill <sup>69</sup>	Asymptomatic NSVT		24 hr Holter or ECG and EPS
Kadish <sup>70</sup>	Asymptomatic NSVT		24 hr Holter
Klein <sup>71</sup>	Asymptomatic NSVT	CAD	24 hr Holter
Takahashi <sup>72</sup>	NSVT	Acute MI	24 hr Holter

CAD: Coronary Artery Disease, MI: Myocardial Infarction, CM: Cardiomyopathy, HCOM: Hypertrophic Cardiomyopathy, DCM: Dilated Cardiomyopathy

### 3.3.3 Quality of included studies

The quality of incidence and prognostic studies were judged against the criteria in boxes 3.4 and 3.5 (shown in the methods section).

#### 3.3.3.1 Quality of incidence studies

Table 3.2 shows answers to quality assessment questions posed in the methods (box 3.4) for incidence studies. Two studies met 4 of the 6 quality criteria<sup>43, 46</sup>. The other study met 3 of the criteria<sup>48</sup>.

Only one of the studies identified cases prospectively<sup>46</sup>. Cases were identified over lengthy periods in all three studies. The study population was described in two studies but methods of derivation were only reported in one study<sup>46</sup>. In this case, the population were all patients known to have hospital membership<sup>46</sup>.

All three studies were reliant on routine hospital data to identify patients (using International Classification of Disease, ICD, codes). However, case-ascertainment

and accuracy of reporting was checked using two methods in the McDonald et al study<sup>48</sup> and found to be very good<sup>48</sup>.

**Table 3.2: Quality of incidence studies (relates to criteria in box 3.4)**

Study	Prospective study?	Study duration	Study popn	Case definition	Complete ascertainment?	Truly incident?
Alexander <sup>43</sup>	No	3 years	Described	ICD codes	Unclear	Yes
Hsu <sup>46</sup>	Yes	2 years	Described	ICD codes	Unclear	Unclear
McDonald <sup>48</sup>	No	10 years	Unclear	ICD codes	Almost complete	Unclear

Only one study attempted to identify all new cases of ventricular arrhythmias (Alexander et al<sup>43</sup>). However, it is unclear whether cases were appropriately matched to the population. Population statistics for California were used to estimate the size of the population yet only cases from non-federal hospitals were included in the study. This may have lead to an underestimate of incidence.

### 3.3.3.2 Quality of prognostic studies

Table 3.3 shows answers to quality assessment questions posed in the methods (box 5) for prognostic studies.

**Table 3.3: Quality of prognostic studies (relates to criteria in box 3.5)**

Study	Prospective study?	Study duration	Loss to follow up?	Cases consecutive?	Prognostic factors assessed?
<b>1. All cases in each study had sustained VT or VF</b>					
Alexander <sup>43</sup>	No	12 months	No	Unclear	No
Andresen <sup>44</sup>	Yes	21 months	No	Yes	Yes
Coughlin <sup>45</sup>	Yes	13 months	No	Unclear	Yes
Hsu <sup>46</sup>	Yes	24 months	No	Yes	Yes
Leclercq <sup>47</sup>	No	61 months	5%	Yes	Yes
McDonald <sup>48</sup>	No	96 months	No	Unclear	No
Naccarella <sup>49</sup>	Yes	78 months	No	Yes	Yes
O'Hara <sup>50</sup>	Unclear	34 months	No	Yes	Yes
Pinski <sup>51</sup>	No	17 months	No	Yes	Yes
Rodriguez <sup>52</sup>	No	40 months	No	Yes	Yes
Saxon <sup>53</sup>	No	Subgroups:18, 23 & 32 months	No	Unclear	Yes
Wiesfeld <sup>54</sup>	Yes	21 months	No	Yes	Yes
<b>2. All cases in each study were presenting for EPS and had inducible VT or VF</b>					
Bhandari <sup>55</sup>	Yes	18 months	6.1%	Yes	Yes
McCowan <sup>56</sup>	Unclear	6 months	No	Unclear	No
<b>3. Cases within each study had sustained VT or NSVT</b>					
Brodsky <sup>57</sup>	No	50 months	2.7%	Unclear	Yes
Feleke <sup>58</sup>	No	72 months	2.6%	Yes	Yes
Hosoda <sup>59</sup>	Yes	33 months	No	Yes	Yes
Jull-Moller <sup>60</sup>	Yes	53 months	No	Yes	Yes
Kapoor <sup>61</sup>	Yes	40 months	2.3%*	Yes	No
Kofflard <sup>62</sup>	Yes	96 months	No	Unclear	Yes
Maggioni <sup>39</sup>	Yes	6 months	2%	Yes	Yes
Spirito <sup>63</sup>	Yes	58 months	2.4%	Yes	Yes
Stewart <sup>64</sup>	No	43 months	3.2%*	Yes	Yes
Tanabe <sup>65</sup>	Unclear	31 months	2.6%	Unclear	Yes
Wilber <sup>66</sup>	Yes	16 months	3%	Yes	Yes
<b>4. All cases in each study had NSVT</b>					
Andresen <sup>67</sup>	No	17 months	No	Unclear	Yes
De Maria <sup>68</sup>	Yes	29 months	3.2%*	Yes	Yes
Takahashi <sup>72</sup>	Unclear	31 months	4.4%	Yes	Yes
Algra <sup>4</sup>	No	24 months	Unclear	Yes	Yes

Study	Prospective study?	Study duration	Loss to follow up?	Cases consecutive?	Prognostic factors assessed?
Hammill <sup>69</sup>	Yes	Subgroups: 17 & 14 months	No	Yes	Yes
Kadish <sup>70</sup>	No	19 months	3.8%	Yes	Yes
Klein <sup>71</sup>	Unclear	14 months	No	Unclear	Yes

\*Loss to follow up from whole cohort which includes VT patients amongst others. Not possible to determine loss to follow up for VT patients alone.

Overall, the quality of these studies was good. Most, (13 studies) met 4 of the 5 quality criteria. 10 of the studies met all of the quality criteria. The table below shows the number of studies meeting criteria by type of ventricular arrhythmia studied.

**Table 3.4: Number of prognostic studies meeting up to 5 quality criteria in box 5 by ventricular arrhythmia grouping**

Group	1	2	3	4	5
(1) Sustained VT or VF			3	5	4
(2) Inducible VT or VF			1		1
(3) Sustained or NSVT			2	5	4
(4) NSVT alone			3	3	1
<b>Total</b>			9	13	10

Of the 32 studies, a prospective design could be certain for 19 studies. The design was uncertain for seven of these studies. All studies followed up patients for 6 months or longer. Losses to follow up were identified in 18 of the studies but were minimal. Cases were reported as being consecutively recruited in all but 10 studies. However, for three of these 10 studies, routine data were used to identify cases. Although not stated, we would expect routine data to be based on consecutive cases. The impact of various prognostic factors on case fatality rates was assessed in all but 4 studies.

### **3.3.4 Results from incidence studies**

The three incidence studies included over 260,000 patients hospitalised with a primary diagnosis of ventricular arrhythmias. They were all undertaken in the U.S. Table 3.5 summarises the methods and findings of these studies.

**Table 3.5 Summary of methods and results from the 3 incidence studies**

<b>Author, Place, dates</b>	<b>Cases and method of identification</b>	<b>Population</b>	<b>Baseline characteristics</b>	<b>Results: Incidence rates per 100,000</b>
McDonald <sup>48</sup> U.S. Deaths from 1990 to 1994 and admissions from 1985 to 1995	U.S. Medicare patients who died in the Emergency room ER (1990-1994) and those discharged from hospital with a principal diagnosis of VT or VF/CA (1985-1995). Patients identified from inpatient hospitalisation file. ICD-9 codes used to identify hospital discharges	All U.S. Methods not described.	Patients less than 65 years excluded. In 1990, average age of patients who died in ER & those admitted to hospital was 75.6 years. 99.8% of those who died in ER were in VF, 40% female, 9.6% of all were black. 35.4% of those admitted were in VF (64.6% in VT), 40.2% female, 7.2% of all were black.	<b>1990 In ER:</b> Males 65-79 years = 256, ≥80 years = 529 Females 65-79 years = 101, ≥80 years = 330. <b>1990 Admitted to hospital:</b> Males 65-79 years = 115, ≥80 years = 175. Females 65-79 years = 49, ≥80 years = 100 <b>1994 In ER:</b> Males 65-79 years = 212, ≥80 years = 496 Females 65-79 years = 92, ≥80 years = 311. <b>1994 Admitted to hospital:</b> Males 65-79 years = 104, ≥80 years = 147. Females 65-79 years = 40, ≥80 years = 71
Alexander <sup>43</sup> California, U.S. Admissions from 1992 to 1994	Patients discharged from all non-federal California hospitals who had a primary diagnosis of VT or VF. Discharges identified from the data files of OSHPD using codes (I assume these are ICD codes)	Estimates of the overall 1992 to 1994 California population by age, sex and ethnicity from California State Department of Finance.	Patients with a prior admission for VT/VF in 1991 were excluded. 67% were males. 7% black, 7% Latino & 4% asian. 64% were aged 65 years and over. 58% of whites, 61% blacks, 53% of Latinos and 52% of asians had a cardiac co-morbidity	No overall rate. Age-adjusted hospitalisation rates* broken down by ethnicity: For males, whites had a rate of 24.5, blacks 14.2, Asians 7.4 and Latinos 4.3. For females, rates were 11 for blacks and whites, 3.8 for Asians and 3.1 for Latinos.

**Table 3.5 Summary of methods and results from the 3 incidence studies**

<b>Author, Place, dates</b>	<b>Cases and method of identification</b>	<b>Population</b>	<b>Baseline characteristics</b>	<b>Results: Incidence rates per 100,000</b>
Hsu <sup>46</sup> Northern California, U.S. Discharges from 1995 to 1998	Incident patients discharged alive with a primary diagnosis of CA, VT or VF. Patients identified through search of automated records of those admitted or discharged using ICD-10 codes	Given number of Health Maintenance Organisation Members in Northern California	Mean age was 61 years. 75% were males and 79% were white. 44% had chronic heart failure. 47% had previous MI. Arrhythmia aetiology was ischaemic for 54%.	Rates derived from data: 53% of 598 patients presenting were new cases (using chart review to check) identified over 39 months in a population of 2.4 million healthcare members, this generates a rate of patients being discharged alive of 4.06 per 100,000 persons per year

OSHDP: Office of Statewide Health Planning and Development

\* Age-adjustment calculated using the direct method with California population used as reference.

The study by McDonald et al suggested that most patients with a primary diagnosis of ventricular arrhythmias who reached hospital were declared dead in ER (60% and 62% of those patients who reached ER in 1990 and 1994 respectively)<sup>48</sup>. The proportion of these patients who died prior to reaching ER was not stated, but it is likely to be the majority of deaths. There was no information in the paper about how many patients may have died in the community of a ventricular arrhythmia and not taken to ER. The incidence rate both to ER and hospital admission was higher in very old patients and in males more than in females. The age difference in incidence rates was much greater for all patients admitted to ER than those admitted to hospital. This would suggest greater case fatality rates in the older age groups. Unfortunately, this study only included patients aged 65 years and over and therefore these data cannot be generalised to patients under the age of 65 years.

Alexander et al explored variation in age-adjusted hospitalisation (hospital discharge) incidence rate by ethnicity<sup>43</sup>. The researchers found that amongst males, whites had the highest hospitalisation rate, followed by blacks, Asians and Latinos. Amongst females, blacks and whites had similar rates but rates of Latinos and Asians were lower. The age adjustment to incidence rates was necessary because blacks and Latinos presenting with VT/VF were significantly younger than whites and Asians with VT/VF. In comparison with the McDonald et al study, these incidence rates were lower. There are probably two main reasons for this difference: (1) Patients admitted in the previous year with VT/VF were excluded from the Alexander et al study and (2) Patients aged less than 65 years were excluded from the McDonald et al study. Another possible reason could be the place of study. U.S. national statistics on heart disease deaths show that white males living in North Western States have the lowest age-adjusted rates of heart disease mortality<sup>73</sup>. Consequently, these States may also have the lowest rates of hospitalisation for ventricular arrhythmias.

The third incidence study by Hsu et al, did not present an incidence rate, but this was derived from the data presented<sup>46</sup>. The rate derived was much lower than both the McDonald and the Alexander et al studies. This is likely to be because this rate was for patients discharged from hospital alive. Case fatality rates in hospital are high. Another reason is that great efforts were taken to exclude prevalent cases. The other two studies probably included some prevalent patients (the McDonald study much more so than the Alexander et al study).

In summary, only three U.S. studies were identified that evaluated the incidence of patients hospitalised with ventricular arrhythmias. No UK based studies were found. These were large studies with cases identified from routine data. The Alexander et al study probably provides the best estimate of the incidence of ventricular arrhythmias because attempts were made to ensure cases were newly diagnosed. However, cases may not have been matched appropriately with the population.

The generaliability of results from these studies to the UK population is highly questionable. Only hospitalised patients with a primary diagnosis of ventricular arrhythmias were included in all three studies. These patients would probably represent a large proportion of those patients with life threatening ventricular arrhythmias i.e. patients with sustained VT or VF. However, patients hospitalised for other conditions e.g. an MI, who experience a ventricular arrhythmia during their stay and the much larger group of patients suffering a ventricular arrhythmia who are not hospitalised e.g. diagnosed with NSVT as an out-patient would have been excluded.

Furthermore, the incidence of ventricular arrhythmias will vary with time, place and person. Over time, incidence rates of ventricular arrhythmias mirror those of coronary heart disease (given that it is the most common underlying aetiology). By place, there are great variations in CHD mortality and morbidity rates both between and within countries. By person, as these studies have shown, rates are higher for males and older persons.

### **3.3.5 Results from prognostic studies**

All three of the incidence studies discussed in section 3.1 also reported on prognosis. Another 29 studies have assessed prognosis. These studies are considered in this section under the 4 sub-groupings detailed in section 3.2. Studies in each sub-grouping are ordered alphabetically. Appendix 4 shows details of study methods, case definitions, details of testing and treatments received during follow up in the 32 prognostic studies. Results are summarised in the text and, along with baseline characteristics, in the accompanying tables.

Almost all of these 32 studies identified patients who were at the same point in a diagnostic or treatment pathway e.g. all admitted to CCU with life threatening arrhythmias or all selected for EPS testing on the basis of previously recorded non-sustained ventricular arrhythmias etc. However, patients may have experienced their symptoms for different periods of time.

Survival analyses were stratified by possible prognostic factors in most of the studies. These factors varied and included: ethnicity, treatment strategies, underlying heart disease (in particular, left ventricular function), presenting symptoms and ability to induce ventricular arrhythmias on further testing. Follow up times varied. Survival probabilities at 12 and 24 months are presented in this chapter (where possible) to enable some comparison of results between studies.

Important prognostic factors appear to be left ventricular dysfunction, underlying heart disease, time interval since MI and type of ventricular arrhythmia. Results in this chapter are stratified by these factors where possible.

### **3.3.5.1 All cases in each study had sustained VT or VF**

Twelve studies assessed the prognosis of patients with sustained VT or VF. Survival rates were presented in 10 of these studies (duration of follow up is shown in table 3.3) and broken down by prognostic factors in all but one study. Table 3.6 shows the baseline characteristics of patients, prognostic factors assessed, one and two year survival rates and the key findings from each study. Two of the 12 studies did not present survival data, but arrhythmia recurrence rates. The results of these studies are shown in table 3.7.

**Table 3.6 Survival probabilities at 12 and 24 months by prognostic groups in studies where all cases had sustained VT or VF**

Author, place & publication date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilities of survival, unless otherwise stated (%)		Key findings	
			At 12 months	24 months		
<b>Alexander<sup>43</sup></b> <b>California</b> <b>U.S.</b> <b>2002</b>	8713 patients admitted with VT/VF. Patients with a prior admission for VT/VF in 1991 excluded. 64% of patients aged 65 years or over.	<b>Black</b> (n = 576). 45% female. 42% had heart failure. <b>87% survived to discharge</b>	70% survival from admission		Case fatality risk ratio from discharge to 12 months was 1.18 for black patients as opposed to whites (95% CI 1.03, 1.36) controlling for multiple confounding risk factors	
		<b>Latino</b> (n = 610). 40% female. 32% had heart failure. <b>89% survived to discharge</b>	76%			
		<b>Asian</b> (n = 370). 36% female. 34% had heart failure. <b>89% survived to discharge</b>	78%			
		<b>White</b> (n = 7157). 32% female. 35% had heart failure. <b>90% survived to discharge</b>	76%			
<b>Andresen<sup>44</sup></b> <b>Germany</b> <b>1992</b>	60 patients with documented ventricular arrhythmias that were not inducible on EPS: 39 with cardiac arrest due to noninfarction VF and 21 with sustained VT	39 patients <b>with VF</b> . Mean age of 55 years. 74% males. 54% had coronary artery disease. 44% had a previous MI. Mean LVEF was 55% +/- 14%.	EF ≤40%		At mean follow up, survival rates were significantly lower in patients with an LVEF EF ≤40% than those with an LVEF EF > 40% within the VF group (p = 0.005) and within the VT group (p = 0.01)	
			EF > 40%	30%		95%
		21 patients <b>with VT</b> . Mean age of 50 years. 81% males. 48% had coronary artery disease. 43% had a previous MI. Mean LVEF was 50% +/- 13%.	EF ≤40%			50%
			EF > 40%	50%		100%

**Table 3.6 Survival probabilities at 12 and 24 months by prognostic groups in studies where all cases had sustained VT or VF**

Author, place & publication date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilities of survival, unless otherwise stated (%)		Key findings
			At 12 months	24 months	
Coughlin <sup>45</sup> , U.S. 1994	126 IDC patients. Mean age was 59 years. 53% were males. 102 (81%) were black. 50 patients had ventricular arrhythmias	<b>All Black IDC patients</b> (n = 102) (LVEF < 25% = 53% of patients)	71.5%	63.6%	No statistical analyses comparing groups with ventricular arrhythmias. Survival analyses were based on all IDC patients and ethnicity of IDC patients.
		<b>Black IDC patients with ventricular arrhythmias</b> (n = 42)	58%*	46%*	
		<b>All White IDC patients</b> (n = 24) (LVEF < 25% = 60% of patients)	92%	86.3%	
		<b>White IDC patients with ventricular arrhythmias</b> (n = 8)	100%*	88%*	
Hsu <sup>46</sup> , U.S. 2002	264 incident VT/VF cases <b>discharged alive</b> . Mean age of 61.3 years. 75% were males. 79% were white. 44% had CHF, 47% had a previous MI. 67% had VT, 29% VF and 4% cardiac arrest (rhythm unknown). Arrhythmia aetiology was ischaemic for 54%, nonischaemic for 19% and unknown for 27%.	All patients (n = 264)	92% survival from discharge	87%	At 24 months, patients with ICDs implanted were significantly more likely to survive than patients treated with amiodarone or other treatments (p<0.05)
		Patients who received amiodarone (n = 91). 62% CHF. 24% had VF.		75%	
		Patients who had an ICD implanted (n = 94). 47% CHF. 52% had VF.		94%	
		Patients receiving other treatments (n = 79). 22% CHF. 8% had VF.		92%	

\*Survival probabilities estimated from survival curves

**Table 3.6 Survival probabilities at 12 and 24 months by prognostic groups in studies where all cases had sustained VT or VF**

Author & publication date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF where stated)	Probabilities of survival, unless otherwise stated (%)		Key findings
			At 12 months	24 months	
<b>Leclercq<sup>47</sup></b> <b>France,</b> <b>1991</b>	295 VT patients. Patients divided into 4 prognostic groups: (1) 156 patients: 140 males and 16 females, mean age of 58 years. (2) 43 males and 12 females, mean age 50 years (3) 54 males and 11 females, mean age 33 years and (4) 10 males and 9 females; mean age 38 years.	(1) <b>Coronary heart disease</b> (and usually old MI) (n = 156) 81 had LVEF > 30% 75 had LVEF < 30%	85%*	81%*	Survival rates at mean follow up were significantly lower in groups 1 and 2 than groups 3 and 4 (p<0.01). The rate was also lower in group 1 than group 2 (p<0.05). Survival rates were lower still in groups 1 and 2 for patients with LVEF < 30% (p<0.01)
		(2) <b>Nonischaemic left ventricular disease</b> (n = 55) 37 had LVEF > 30% 18 had LVEF < 30%	92%* 80%*	85% 76%	
		(3) <b>Right ventricular disease</b> (n = 65)	95%*	92%*	
		(4) <b>No detectable heart disease</b> (n = 19)	100%* 90%*	97%* 80%*	
<b>McDonald<sup>48</sup></b> <b>U.S. 2002</b>	255,029 patients with <b>new VT/F admissions</b> . Excluded patients aged < 65 years.	1987 cohort (no data for this year)	53% survival from admission		A multivariate model comparing data from 1994 to 1987 suggested a significantly improved survival after the index admission with odds ratios of 0.98 (p = 0.0001) at 30 days, 0.97 (p = 0.0001) at 1 year and 0.94 (p = 0.0001) at 2 years
		1994 cohort (n = 22,357 admitted). Mean age 75.5 years. 37% females. 33.8% had VF. <b>86.5% survived first day.</b>	58%		

\*Survival probabilities estimated from survival curves

**Table 3.6 Survival probabilities at 12 and 24 months by prognostic groups in studies where all cases had sustained VT or VF**

Author, place & date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilities of survival, unless otherwise stated (%)		Key findings
			At 12 months	24 months	
Naccarella <sup>49</sup> , Italy, 1992	122 patients with VT or VF late after an acute MI (≥60 days). Mean age of 65 years. No gender breakdown. 96 patients had their LVEF measured, for 17 ejection fraction was < 20% and for 79% it was > 20%.	VT occurrence 60-180 days post MI N = 28	86%	86%	Factors significantly associated with survival were: post MI CAD (p<0.01), multiple AMI (p<0.05), NYHA class ≥III (p<0.001), EF ≤ 20% (p<0.01), ≥2 morphologies of VT (p<0.01), heart rate ≥ 180/min of VT (p<0.001) and previous cardiac arrest (p<0.05)
		VT occurrence 181-2 years post MI N = 21	100%	100%	
		VT occurrence > 2 years post MI N = 31	100%	100%	
		LVEF > 41% N = 34	97%	94%	
		LVEF 31-40% N = 15	93%	80%	
		LVEF 21-30% N = 30	83%	63%	
		LVEF < 20% N = 17	65%	35%	
Previous cardiac arrest N = 36	92%	72%			
No previous cardiac arrest N = 86	94%	81%			
O'Hara <sup>50</sup> , the Netherlands, 1992	150 patients with sustained monomorphic VT (n=116) or ventricular fibrillation (n=34) late after an acute MI. Mean age in group 1 was 62 years vs 60 years in group 2. 6% of group 1 had suffered a previous cardiac arrest vs 25% of group 2.	Group 1: Had reproduction of their VT during exercise testing (n = 17)	Free of sudden death		Patients with exercise induced VT had a significantly increased risk of SCD than those patients without exercise induced VT p = 0.02
			77%	47%	
		Group 2 : No exercise induced VT (n = 133)	Free of sudden death		
			80%	56%	

**Table 3.6 Survival probabilities at 12 and 24 months by prognostic groups in studies where all cases had sustained VT or VF**

Author, place & date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilities of survival, unless otherwise stated (%)		Key findings
			At 12 months	24 months	
<b>Pinski</b> <sup>51</sup> , U.S., 1992	42 cases. Mean age of 63 years. 32 (76%) males. 32 (76%) had coronary artery disease. NYHA class III-IV 38%.	First episode of VT or VF and all candidates for EPS (n = 42)	64%	62%	The only independent predictor of death was NYHA class III or IV
<b>Saxon</b> <sup>53</sup> , U.S., 1989	121 VT/VF patients. Mean age was 57.4 years. 99 (82%) males and 18% females. 77% of patients had CAD. 27% had congestive heart failure.	Cardiac arrest (n = 53) LVEF 31% +/- 14%	70%*	55%*	There were no significant differences in survival between the 3 groups over 48 months. However, the incidence of sudden death was significantly higher for cardiac arrest patients than those with palpitations. Of note, these patients had a significantly lower LV EF than patients with palpitations (p <0.05)
		Syncope (n = 20) LVEF 30% +/- 11%	78%*	55%*	
		Palpitations/dizziness (n = 48) LVEF 39% +/- 15%	85%*	74%*	

\*Survival probabilities estimated from survival curves

**Table 3.7 Probabilities of arrhythmia recurrence at 12 and 24 months by prognostic groups in studies where all cases had sustained VT or VF**

Author, place & date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilities of survival, unless otherwise stated (%) At 12 months      24 months		Key findings
Rodriguez <sup>52</sup> , the Netherlands, 1992	364 patients who suffered VA after a previous MI. Study group: 172 males and 34 females. Mean age 59 years.	Study group: 75% with VT and 25% with VF. 47% had arrhythmia 2 months post-MI. Mean LVEF was 35% +/- 11%	Free of non-fatal VT recurrence 64% in 40 months		Aim of this study was to develop a prognostic index for non fatal recurrence of VT post MI. The clinical variables in the index were: Interval from MI to arrhythmia, drug therapy with or without sotalol and VT or VF as presenting arrhythmia. On validation, the sensitivity, specificity and predictive values were high.
		Test group: 51% with VT and 49% with VF. 28% had arrhythmia 2 months post-MI. Mean LVEF was 38% +/- 10%	Free of non-fatal VT recurrence 83% in 28 months		
Wiesfeld <sup>54</sup> , The Netherlands, 1995	82 patients who suffered VA after a previous MI. Mean age was 64 years. 79% were males. Patients split into 3 treatment groups on basis of angiography results.	Group A: 14 patients. 71% had VF. Mean LVEF 46% +/- 17%. 45% had 3 vessel disease. <b>Ischaemia believed to be primary cause and treated with revascularisation</b>	Arrhythmia free rate (recurrent VT and sudden death) 100%*      100%*		In a univariate analysis of the whole cohort, predictors of arrhythmia recurrence were LV EF and time from the old infarct to the index arrhythmia (a longer time interval was associated with increased arrhythmia recurrence independent of LVEF)
		Group B: 13 patients. 54% had VF. Mean LVEF 35% +/- 14%. 75% had 3 vessel disease. <b>Ischaemia considered coexistent factor.</b>	75%*      56%*		
		Group C: 55 patients. 35% had VF. Mean LVEF 27% +/- 12%. 22% had 3 vessel disease. <b>Ischaemia did not play a role.</b>	68%*      52%*		

\* Survival probabilities estimated from survival curves

These 12 studies stratified their results by different prognostic factors. No two studies considered exactly the same factors. Thus, survival probabilities differed greatly between studies over the same time period. At 12 months, these ranged from 100% survival to 50% and at 24 months, from 100% to a survival probability of 30%.

Furthermore, patients were followed up at different time points after their ventricular arrhythmia and this also affected cumulative survival probabilities. Some studies assessed prognosis from hospital admission, some hospital discharge and in others timing is unclear. Case fatality rates have been shown to be high during hospital admission. For these reasons, it is difficult to compare results between studies.

However, confounders were controlled for in some studies (although, only one study, by McDonald et al<sup>48</sup>, undertook multivariate modelling of their survival data) and some tentative conclusions can be drawn from these. Statistically significant independent prognostic risk factors were ethnicity (black vs white), left ventricular function (ejection fraction  $\leq 40\%$  vs  $> 40\%$ ), history of MI, presence of ischaemia and timing from acute MI (on arrhythmia recurrence) and earlier year of diagnosis (probably associated with available treatments at that time).

### **3.3.5.2 All cases in each study were presenting for EPS and had inducible VT or VF on EPS**

Two studies assessed the prognosis of patients presenting for EPS who were found to have inducible VT or VF on EPS. Bhandari et al<sup>55</sup> explored the risk of arrhythmia free events (including death) in stable survivors of an acute MI with and without inducible VT or VF (see table 3.8 for results). The occurrence of arrhythmic events was not significantly different between these two groups ( $p < 0.4$ ).

McCowan et al documented their experience of EPS. The evaluation of patients diagnosed with inducible VT on EPS was considered alongside patients with supraventricular tachycardia, syncope and other reasons. Inducible VT/VF patients were followed up for a mean of 6.4 months. For this reason, results from this study are not tabulated. Of the 45 patients with inducible VT or VF, there were 2 deaths during follow up; both cardiac.

The results from the Bhandari et al<sup>55</sup> study suggest that the presence of inducible VT in post MI patients is not associated with a statistically significant increase in arrhythmic events. However, studies of patients presenting with VT or VF prior to EPS have shown that these patients are at an increased risk of suffering arrhythmic events (see next section 3.3.5.2). Although the McCowan et al<sup>56</sup> study met the inclusion criteria for this review, it was not informative; it simply provided information on the number of deaths within a 6 month period.

**Table 3.8 Probabilities of arrhythmia recurrence at 24 months by prognostic groups in a study of cases presenting for EPS and having inducible VT or VF**

Author, place & date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilites of survival, unless otherwise stated (%) 24 months	Key findings
Bhandari <sup>55</sup> U.S. 1989	75 patients who had EPS $\geq$ 48 hours post acute MI. 19 patients with induced sustained VT and 14 patients with VF on EPS. 6 patients with non-sustained induced VT and 36 patients without inducible VT or VF.	Inducible sustained VT or VF. 33 patients. Mean LVEF was 47%.	Free of arrhythmic events 0.83	The occurrence of arrhythmic events was not significantly different between the two groups (p<0.4). A cox regression analysis suggested that mild congestive heart failure was the only significant predictor (p<0.01) of subsequent arrhythmic events
		Non-inducible VT or VF or inducible non-sustained VT. 42 patients. Mean LVEF was 48%.	Free of arrhythmic events 0.95	

### **3.3.5.3 Mix of sustained VT and NSVT in each study**

Eleven studies considered both patients with sustained VT or non-sustained VT at baseline in the same study i.e. the study case definitions were broad but did not include patients with inducible VT at baseline (although, patients may have had an EP study during follow up). Survival probabilities by prognostic factors considered in each study and key findings are shown in table 3.9.

Table 3.9

Survival probabilities at 12 and 24 months by prognostic groups in studies with a mix of patients with sustained VT and NSVT

Author, place & date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilities of survival, unless otherwise stated (%)		Key findings
			At 12 months	24 months	
Brodsky <sup>74</sup> , U.S. 1993	37 patients with symptomatic VT and no apparent heart disease. 14 males and 23 females. Mean age 39 years +/- 16 years. 4 patients were in VF, 15 in sustained VT and 18 patients in NSVT	All 37 patients		At 50 months 1 non-cardiac death	No cardiac deaths occurred. Patients with inducible VT were significantly more likely to have recurrence of major arrhythmic symptoms (requiring an intervention for termination) (p<0.05)
		VT inducible N = 12		At 50 months 5 recurrences	
		VT not inducible N = 25		At 50 months 1 recurrence	
Feleke et al <sup>58</sup> , Sweden, 1989	VT was detected in 211 (38%) out of 548 cases with AMI and in 109 (4%) out of the remaining 800 non-AMI cases. Mean age in each group was 67 +/- 9 years. 27% were women. 48% of non-AMI patients with VT had suffered a previous MI vs 27% of AMI patients with VT.	109 non-AMI patients with VT	0.67*	0.61*	The 1-6 year survival curves did not differ significantly between the 3 groups. However, there were no data on timing of VT post MI and LVF. Of note, a significantly higher proportion of VT patients without acute MI had suffered a previous MI. No multivariate modelling was undertaken.
		211 AMI patients with VT	0.61*	0.54*	
		237 patients with AMI without VT	0.67*	0.59*	

\* Survival probabilities estimated from survival curves

**Table 3.9 Survival probabilities at 12 and 24 months by prognostic groups in studies with a mix of patients with sustained VT and NSVT**

Author, place & date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilities of survival, unless otherwise stated (%)		Key findings
			12 months	24 months	
Hosoda et al <sup>59</sup> , Japan, 1995	2733 MI patients discharged from hospital. Baseline data for MI cohort, 2,232 males, 501 females, mean age of 58.8 +/- 11.3 years. LVEF was measured for all MI patients but not described for only those with VT or VF.	MI patients with VT during hospitalisation vs MI patients without VT during this time	2.9 years 0.88 vs 0.93		Case fatality rate was significantly higher for patients who had experienced VT (p<0.001) or VF (p<0.001) during hospitalisation than those who did not. No multivariate modelling was undertaken.
		MI patients with VF during hospitalisation vs MI patients without VF during this time	2.9 years 0.81 vs 0.93		
Juul-Moller et al <sup>60</sup> , Sweden, 1991	394 68 year old men with VAs identified through screening. 13.5% had IHD. 6.6% had suffered an MI.	116 men with 'serious' ventricular arrhythmias	53.1 months 0.94		There was no significant difference in case fatality between men with and without serious ventricular arrhythmias.
		278 men without 'serious' ventricular arrhythmias	53.1 months 0.97		
Kapoor <sup>61</sup> , U.S., 1990	433 syncopal patients. Mean age 56 years. 40% Males. 49% had syncope in past year. 12% had had an MI, 16% had had a ventricular arrhythmia. 12% had congestive heart failure.	49 syncopal patients diagnosed with VT	SCD survival 40 months 0.67		Results focused on the prognosis of cardiac vs non cardiac causes of syncope. In a Cox proportional hazard model, a cardiac cause of syncope was an independent predictor of case fatality RR 2.2 (95% CI 1.45, 3.22)
		110 patients. Cardiac cause of syncope (including the 49 patients with VT)	0.73*	0.62*	
		144 patients. Noncardiac cause of syncope	0.92*	0.86*	
		179 patients. No diagnosis.	0.96*	0.88*	

\*Survival probabilities estimated from survival curves

**Table 3.9 Survival probabilities at 12 and 24 months by prognostic groups in studies with a mix of patients with sustained VT and NSVT**

Author, place & date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilities of survival, unless otherwise stated (%) 12 months    24 months	Key findings
<b>Maggioni et al<sup>39</sup>, Italy, 1993</b>	8676 post acute MI patients. 81% were ≤70 years. 82% were males. 14% had suffered a previous MI.	586 patients had VT. 5.1% of these patients had EF > 35%.	At 6 months 0.95	In a univariate analysis Acute MI patients with VT were at a higher risk of death, OR 1.99 (1.21, 3.27) but not in a multivariate analysis.
<b>Kofflard et al<sup>62</sup>, the Netherlands 1993</b>	113 patients with hypertrophic cardiomyopathy. Mean age at diagnosis 37 years. 53% were males. 14% of patients were in NYHA class III. 0% in class IV. 1% had suffered a previous cardiac arrest.	37 of 98 HCM patients (38%) had VT	Survival from cardiac death at 96 months 0.95	There was no significant difference in cardiac case fatality between HCM patients with or without VT.
		61 of 98 HCM patients (62%) did not have VT	Survival from cardiac death at 96 months 0.90	
		8090 patients without NSVT. 1.5% patients had EF > 35%.	At 6 months 0.97	
<b>Spirito et al<sup>63</sup>, Geneva, Bologna &amp; Rome. 1994</b>	151 patients with hypertrophic cardiomyopathy. Baseline data were broken down by whether or not patients experienced VT.	42 HCM patients had VT. Mean age 46 years. 74% were males. 33% had LVOT obstruction.	Free of sudden death 1*            0.96*	The relative risk of cardiac death in patients with VT as opposed to those without was 1.4 (95% CI 0.6, 6.1). Relative risk of sudden death was 2.4 (95% CI 0.5, 11.9)
		109 HCM did not have VT. Mean age 37 years. 68% were males. 25% had LVOT obstruction.	Free of sudden death 1*            1*	
<b>Stewart et al<sup>64</sup>, England, 1990</b>	124 patients with dilated cardiomyopathy. No baseline data presented. Apart from NYHA class. 23% being in NYHA class III.	79 patients with VT or >250 ventricular ectopics. 24% were in NYHA class III.	Free of sudden death 0.93*        0.85	No significant difference in survival between DCM patients with VT as opposed to those without.
		45 patients without VT or > 250 ventricular ectopics.	Free of sudden death 1            0.97	

\*Survival probabilities estimated from survival curves

**Table 3.9 Survival probabilities at 12 and 24 months by prognostic groups in studies with a mix of patients with sustained VT and NSVT**

Author, place & date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilities of survival, unless otherwise stated (%)		Key findings	
			At 12 months	24 months		
Tanabe et al <sup>65</sup> , Japan, 1989	117 patients with VT. Mean age 56.1 years.	IHD group. 40 patients who have suffered a previous MI or angina pectoris with coronary stenosis. Mean age 62.8 years.	Survival at 46.8 months	0.5	At 46 months, the incidence of SCD was significantly lower in patients with idiopathic VT than those with IHD, idiopathic cardiomyopathy or those having miscellaneous heart disease.	
		18 patients with idiopathic cardiomyopathy. Mean age 49.4 years.	Survival at 46.8 months	0.65		
		26 patients with miscellaneous heart disease. Mean age 62.9 years.	Survival at 46.8 months	0.56		
		33 patients with idiopathic VT. Mean age 46 years.	Survival at 46.8 months	0.97		
Wilber et al <sup>66</sup> , U.S., 1990	97 patients with VT, chronic coronary artery disease and EF < 40%	57 patients without inducible sustained ventricular arrhythmias	Cardiac arrests or SCD	0.98	Multivariate analysis identified persistence of inducible sustained VAs as the only independent predictor of sudden death or recurrent sustained arrhythmias (p < 0.001, RR 3.5, 95% CI 2.1, 4.9)	
		20 patients with inducible ventricular arrhythmias that were suppressed	Cardiac arrests or SCD	1		0.89
		20 patients with persistently inducible sustained ventricular arrhythmias	Cardiac arrests or SCD	0.66		0.5

These eleven studies attempted to identify both patients with sustained or non-sustained VT. However, given that most of these studies used Holter monitoring to identify patients it is likely that most, if not all patients in these studies, had non-sustained VT. Again, survival probabilities varied greatly: from 100% survival to 61% at 12 months and from 100% to 50% at 24 months.

These studies were of a small size and had variable inclusion criteria, patients' underlying heart disease and follow up periods. Multivariate modelling was only undertaken in one study. This suggested that although NSVT post acute MI was an independent prognostic risk factor in a univariate model; this was no longer the case in a multivariate model. This study was of a very large cohort of post acute MI patients and these results concur with those from the Feleke et al<sup>58</sup> study of acute MI patients also detailed in this section. Hosoda et al<sup>59</sup> also considered the prognosis of acute MI patients with VT (or VF) and found that these patients had a higher case fatality rate. It is likely that this study mostly included patients with life threatening ventricular arrhythmias. There were very few patients with life threatening arrhythmias in the Maggioni et al<sup>39</sup> study.

Some conclusions can be drawn from the studies. Three studies evaluated patients with either hypertrophic or dilated cardiomyopathy. All of these studies concluded that patients suffering from cardiomyopathy and VT did not have a significantly increased case fatality rate above patients with cardiomyopathy without VT. Patients with idiopathic VT in another study were also found to have a low case fatality rate.

Only one study in this review was a population based screening study (by Jull-Moller et al<sup>60</sup>). This found that patients with VT on Holter monitoring were not at an increased risk of an SCD. However, the case definition of VT was very broad and included patients with very short runs of ventricular ectopic beats. It is not clear whether any of the patients in this study suffered from sustained VT.

#### **3.3.5.4 NSVT alone**

Seven studies evaluated prognosis in patients with NSVT i.e. no patients with life threatening ventricular arrhythmias at baseline were included in these studies. Survival probabilities by prognostic factors considered in each study and key findings are shown in table 3.10.

Table 3.10

Survival probabilities at 12 and 24 months by prognostic groups in studies of NSVT alone

Author & date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilities of survival, unless otherwise stated (%)		Key findings
			At 12 months	24 months	
Algra et al, the Netherlands, 1993	6693 patients who had 24 hour ECGs for various indications. 58% were males. 50% were aged 60 years or older. 32% had suffered a previous MI. 16% had congestive heart failure.	674 patients with NSVT	Free of sudden death	0.88	Patients with NSVT had an unadjusted RR of SCD of 11.5 (95% CIs, 6.5, 27.3). Unclear why only 1835 were tested for occurrence of NSVT.
		1161 patients without NSVT	Free of sudden death	0.99	
Andresen et al, Germany, 1992	191 patients with spontaneous asymptomatic NSVT. 64% were males. Mean age 68 years. 33% of patients suffered a previous MI.  Overall results and by underlying heart disease  Results by NYHA class and number of NSVT episodes in 24 hours	All 191 patients	Free of sudden death at 17 months	0.94	Apart from 1 case, all SCDs were in the CAD or cardiomyopathy groups. SCD rate in patients having $\leq 6$ episodes of NSVT was significantly lower than patients having $> 6$ episodes ( $p \leq 0.02$ ). Patients with both LVD and frequent NSVT episodes were at a 12 fold increased risk of sudden death ( $p = 0.05$ ).
		119 patients with CAD, previous MI or DCM		0.91	
		18 patients with valvular disease		0.83	
		54 patients with other or no underlying heart disease		1	
		106 patients in NYHA class II having $\leq 6$ NSVT episodes in 24 hours	Free of sudden death at 17 months	0.98	
		39 patients in NYHA class III having $> 6$ episodes		0.93	
		26 patients in NYHA class II having $\leq 6$ episodes		0.92	
		20 patients in NYHA class III having $> 6$ episodes		0.75	

**Table 3.10 Survival probabilities at 12 and 24 months by prognostic groups in studies of NSVT alone**

Author, place & date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilities of survival, unless otherwise stated (%)		Key findings
			12 months	24 months	
De Maria <sup>68</sup> , Italy, 1986-1990	218 IDC patients. 67 patients had VT on Holter monitoring. No baseline data on VT group. Overall IDC group: 161 males (74%), mean age 41 years	All IDC patients N = 218	0.93*	0.88*	In a multivariate analysis of data on all IDC patients; LVEF, cardiac index and VA severity were independent predictors of cardiac death
		IDC patients with VT N = 67	0.93*	0.82*	
Hammill et al <sup>69</sup> , U.S., 1990	110 patients with asymptomatic NSVT. 85% were male. Mean age of 63 years. 43% had suffered a previous MI. 25% had DCM.	53 patients had ejection fraction <40%. 57% of these patients had had a previous MI. 43% had DCM.	CHF class I and II 0.9*	0.58*	In a univariate analysis, only history of CHF and ejection fraction were independent predictors of death and cardiac death. Presence of inducible VT on EPS did not predict outcome.
			CHF class III and IV 0.4*	0.4*	
		57 patients had ejection fraction ≥ 40%. 30% had suffered a previous MI. 7% had DCM.	0.96*	0.94*	
Kadish et al, U.S., 1993	280 patients with asymptomatic spontaneous NSVT. 77% were males. Mean age was 58 years. Mean ejection fraction 0.37 +/- 0.17.	79 patients with no evidence of structural heart disease. Mean age 52 years. Mean EF 0.62 +/- 0.06.	1*	0.97*	Patients without structural heart disease had a probability of survival that was significantly higher than in all other groups (p<0.01). In a multivariate analysis, only lower EF and inducible VT correlated with sudden death during follow up.
		134 patients with CAD or presence of Q wave infarction. Mean age 62 years. Mean EF 0.36 +/- 0.15.	0.9*	0.81*	
		43 patients with idiopathic dilated cardiomyopathy. Mean age 58 years. Mean EF 0.26 +/- 0.14.	0.68*	0.59*	
		24 patients with other types of heart disease, mostly valvular heart disease. Mean age 54 years. Mean EF 0.43 +/- 0.19.	0.84*	0.73*	

\*Survival probabilities estimated from survival curves

Table 3.10

Survival probabilities at 12 and 24 months by prognostic groups in studies of NSVT alone

Author & date	Baseline characteristics	Prognostic groups considered in each study (with information on mean LVEF +/- SD where stated)	Probabilities of survival, unless otherwise stated (%)		Key findings
			12 months	24 months	
Klein et al <sup>71</sup> , U.S., 1989	40 males with CAD and NSVT. Aged 44 to 71 years.	22 NSVT patients with inducible VT. Mean age 60 years. 86% had suffered a previous MI. Mean EF 31% +/- 13.	0.62*	0.54*	All sudden deaths occurred in patients with NSVT and inducible VT (p<0.01).
		18 NSVT patients with noninducible VT. Mean age 61 years. 78% had suffered a previous MI. Mean EF 42% +/- 14.	1*	1*	
Takahashi et al <sup>72</sup> , Japan, 1994	68 patients with NSVT. 65% were males. Mean age 50 years. 16% had suffered a previous MI. 13% had cardiomyopathy. 3% had valvular disease. 63% had no underlying heart disease.	20 NSVT patients with inducible VT. Mean EF 57% +/- 12.	1*	1*	There were no cardiac deaths during follow up. VT was induced more frequently in patients with organic heart disease but was not related to history of syncope.
		48 NSVT patients with non-inducible VT. Mean EF 60% +/- 13.	0.96*	0.96*	

\*Survival probabilities estimated from survival curves

A number of these studies suggest that patients with NSVT on Holter monitoring are at an increased risk of a sudden cardiac death. However, further analysis in some studies suggested that this is related to underlying heart disease. In particular, patients with left ventricular dysfunction were at a much higher risk of an SCD. Survival probabilities varied greatly: from 100% survival to 40% at 12 and 24 months.

The value of inducible VT on EP testing for patients presenting initially with NSVT seems to be debatable. Two studies suggested that Inducible VT was a significant predictor of case fatality (and SCD alone). However, another two studies found that the ability to induce VT in patients initially presenting with NSVT did not predict outcome. Unfortunately, none of these studies provided information on why these patients with NSVT had been referred for EP testing. The discrepancy in findings could be related to the test itself: Diagnostic accuracy of EPS is related to underlying heart disease and the definition of a positive test result by investigators. More likely, the difference was due to chance. In all four of these studies, the number of patients with inducible VT was small.

### **3.4 Discussion**

The objective of this chapter was to identify and critique studies on the incidence and prognosis of ventricular tachycardia (including studies of both VT and VF). Electronic searching resulted in thousands of potential studies for consideration. However, only a very small proportion of these were relevant.

No UK based incidence studies were identified. Only three studies met the inclusion criteria for incidence studies and these were all undertaken in the U.S. using routine statistics to identify cases. These studies considered patients hospitalised with a primary diagnosis of ventricular arrhythmias i.e. mostly, if not all, having life threatening ventricular arrhythmias. One study considered incidence from the point of arrival at hospital and found that most cases were dead on arrival<sup>48</sup>. Incidence rates, both at hospital arrival and admission, were higher in males and in much older age groups. Unfortunately (probably due to the type of data used in these studies) there was no breakdown of incidence rates by presenting symptoms, age bands, and/or underlying heart disease.

The best estimate of the incidence of life threatening ventricular arrhythmias came from the Alexander et al study with an age adjusted incidence of hospital admission for ventricular arrhythmias (as a primary diagnosis) of 24.5 per 100,000 for white males and 11 per 100,000 for white females<sup>43</sup>. However, this estimate did not include patients who died prior to admission (including those who died in the emergency room). The main limitation of this study was that cases may not have been correctly matched to the population. Furthermore, although care was taken to exclude cases presenting in the previous year, some prevalent cases may have been included.

Thirty-two studies met the inclusion criteria for prognostic studies (and included the 3 incidence studies). These studies were of good methodological quality but most did not undertake detailed analysis of prognostic data i.e. multivariate analysis due to their small size. However, the patient populations were very heterogeneous; being diagnosed with VT for varying lengths of time after onset of symptoms.

In studies assessing the prognosis of patients suffering a life threatening ventricular arrhythmia, case fatality rates in hospital were high. Long term survival probabilities varied greatly; both of patients with life threatening ventricular arrhythmias and those with NSVT. Survival was heavily dependent on specific prognostic factors: degree of heart failure (ejection fraction recording and/or NYHA class), previous MIs, extent of coronary artery disease and whether the patient has suffered a cardiac arrest. The degree of heart failure, measured as ejection fraction or as a heart failure class had the greatest independent influence on prognostic rates.

The main limitation of these studies was the lack of information on case finding i.e. how the patients were identified and referred for diagnostic testing. It is therefore difficult to determine how representative these study patients are of patients presenting to the health service. Furthermore, the primary aim of many of these studies was not to assess the prognosis of ventricular arrhythmias; this was an additional finding. Consequently, the number of patients with and without ventricular arrhythmias and the number of ventricular arrhythmia patients broken down by prognostic groups was small.

Summarising findings from these studies was also difficult because so many of the studies considered different combinations of: presentations, prognostic factors,

diagnostic tests and types of ventricular arrhythmias. Each of these factors could have been associated, in some way, to survival. Very few of the studies included a multivariate analysis of prognostic data due to their small size. None of the studies attempted to identify and assess the prognosis of all patients presenting with ventricular arrhythmias. Each study was specific to a particular setting, mostly referral to a specialist cardiac service.

There are some limitations to this review. In searching for eligible studies, some studies may have been missed for a number of reasons: Firstly, the nature of this topic area. Some of the studies included in this review did not aim to assess the prognosis of VT. These studies were of patients (experiencing a certain symptom) that had a diagnostic test and were followed up or all patients having a diagnostic test for whatever reason and followed up. In an attempt to reduce this problem, all papers with the word 'arrhythmias' in the abstract that weren't obviously irrelevant were checked.

Although the electronic search strategies may not have been sensitive enough. It is difficult to test this without the identification of papers via another source and then checking electronically indexed words. However, no additional studies were identified from checking references of papers. Potential for error in assessing inclusion of the 91 papers retrieved for more detailed evaluation is likely to be minimal; given that two reviewers independently assessed inclusion and the second reviewer checked abstracted data.

Secondly, no handsearching was undertaken. Studies could have been identified through handsearching that wouldn't have been identified through electronic searching. This was not a method I intended to use because of time constraints, but if I had, it would have been difficult to decide which journal/s to include. The included studies were published in a number of journals.

Thirdly, the exclusion of papers written in languages other than English. Due to resource constraints, papers written in other languages were excluded. Generally, these studies have English language abstracts and no such abstracts were identified when searching the electronic databases.

The generalisability of the incidence estimate from the Alexander et al study<sup>43</sup> is questionable due to the limitations of the study and the exclusion of ventricular

arrhythmia cases not admitted to hospital with a primary diagnosis of ventricular arrhythmias e.g. patients admitted with an acute MI or other cardiac problem and out-patients diagnosed with non-sustained VT. The latter group would probably represent the majority of patients suffering ventricular arrhythmias. This will be explored further in chapter 5, a prospective cohort study of ventricular arrhythmias.

Another concern is the application of incidence rates from one geographical setting and time to another. Although no studies were identified that assessed incidence across different countries, the McDonald et al study considered rates in different U.S. states and found that states with higher CHD mortality rates had a higher incidence of ventricular arrhythmias. Furthermore, the data in this study were also assessed in two years; 1989 and 1994 and rates had decreased in this time<sup>48</sup>.

The prospective study detailed in chapter 5 of this thesis will be the first attempt to undertake a UK based incidence study. Unlike published studies to date, emphasis will be placed on matching cases to the population. However, published studies do provide some ideas for the design of this study. It is clear that the identification of patients reaching hospital who die in A&E (and preferably community deaths) is of high importance in determining the incidence of ventricular arrhythmias. A&E deaths contributed the largest proportion of patients reaching hospital with ventricular arrhythmias in the McDonald et al study<sup>48</sup>. The identification of differences between those patients reaching hospital admission alive and those who die prior to admission could be of use in better targeting resources to save lives. However, the difficulty exists in determining which of these community deaths are primarily due to ventricular arrhythmias.

Another idea is the use of routine data to identify cases. The UK based study will use other methods to better identify all cases, but routine data will serve as a useful cross-checking case identification method. It will be interesting to compare the yield of cases between methods and the number of false positives i.e. cases that weren't actually ventricular arrhythmias as determined by routine data.

Despite the limitations of previously published prognostic studies, these papers have provided useful information on the most important prognostic factors associated with ventricular arrhythmia case fatality. This will also help in the design of the UK study; medical note data extraction forms will include the need for data on left ventricular function/heart failure disease class, evidence of previous MI,

coronary artery disease and the severity of the ventricular arrhythmia. Unlike previous studies, the UK study will explicitly document case finding methods and how patients presented to the health service i.e. their symptoms and method of referral for diagnostic testing.

Did a systematic review of the incidence and prognosis of ventricular arrhythmias add anything to this field of study? This was the first attempt to systematically identify, critique and assess these studies. I believe that it has provided a more complete picture of existing work. However, further large studies are needed to gain a better understanding of the prognosis of this disorder. The practical limitation of such studies would be the ability to identify large enough cohorts of consecutive patients with life threatening and non-life threatening ventricular arrhythmias to enable consideration of potential confounders to prognostic indicators.

## **4. Current and future ICD management in the UK**

This chapter addresses research question 2 in chapter 2 of this thesis: What are the current patterns of ICD management of patients with ventricular arrhythmias?

### **4.1 Methods**

A study was undertaken to determine the geographical pattern of ICD use and barriers to the use of ICDs. This was achieved by an analysis of the national ICD database and a national survey of ICD centres.

### **4.2 Declaration**

A declaration of a significant contribution to this work is required. Methods and results from this work have been published\*. This piece of work was part of a nationally funded study on the cost-effectiveness of ICDs (*HTA Programme monograph in press*). The work was supervised by Dr Parkes, who provided the idea for the study, cleaned the dataset and gave advice and assistance on the analysis and Dr P Roderick, as PhD supervisor and editor of the published paper. The study investigator, myself, co-ordinated the survey and undertook all the analyses.

### **4.3 Current ICD use and use/need analysis**

The objectives of this analysis were to assess current geographical patterns of ICD management and to relate measures of use to estimates of need for ICDs. Specific objectives were to:

1. Provide descriptive information on the characteristics of patients having new ICDs implanted and type of ICDs.
2. Derive regional rates (and rates by Strategic Health Authority areas) of ICD use.
3. Derive use/need ratios using two proxy measures of need: Coronary Heart Disease mortality and deprivation.

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\* Parkes J, Chase D, Grace A, Cunningham D, Roderick P. Inequity of use of implantable cardioverter defibrillators in England: retrospective analysis. *British Medical Journal* 2005; 330: 454-5.

This section will begin with a description of the national ICD database. The methods of analysis will then be described. Finally, results relating to the three specific objectives above will be presented and conclusions drawn.

### **4.3.1 National ICD database**

The British Pacing and Electrophysiology Group (BPEG) ICD database is a national dataset of all first and replacement ICD implantations undertaken in the UK over the past 15 years<sup>75</sup>. Every UK ICD implanting centre provides data to BPEG on the characteristics of patients receiving ICDs, type of ICD and date of implantation. In 2002, there were 41 UK NHS ICD centres, all of which provided data to BPEG. The location of these centres is shown in appendix 5 (please note that there were 9 centres in London and not 12 as stated on map).

### **4.3.2 Methods**

BPEG ICD data from the national database were provided from 1998 to 2000. The dataset held 2983 records of new and replacement ICD implantations. The information provided in the dataset was: Year of implantation, country of implantation, age, sex, postcode, District Health Authority (DHA) code, date of implantation, whether the ICD was a dual chamber device, aetiology, ECG findings, presenting symptom/s, indications for having an ICD, whether the ICD was new or a replacement and date of death. No information was given on which centre implanted these ICDs. This was considered confidential information by the BPEG administrators.

This dataset had been cleaned by the BPEG administrators and was believed to be 100% complete. However, it was clear from viewing the database that further data cleaning was required.

#### **4.3.2.1 Data cleaning**

One person (Dr Parkes) checked through this dataset for possible duplicate records. Records were deleted from this database if they were:

1. Obvious duplicates i.e. same id number, age, sex, date of implant and postcode.

2. Same person had a repeat ICD within 3 days (it is likely that the first implant was actually a pacing lead implant)
3. Same person had a repeat ICD within 4 weeks (also unlikely).

The total number of deleted records was 80. The dataset now contained 2903 records of ICDs undertaken.

#### **4.3.2.2 Methods of analysis**

This section described the methods of analysis applied to the dataset to describe the patients, calculate rates and assess need.

##### ***ICD and patient characteristics***

Descriptive data on all ICDs and the characteristics of patients having ICDs implanted were derived using SPSS.

##### ***Rates of ICD implantation***

Rates of new ICD implantation for the UK and indirectly standardised rate ratios by age and gender for English Regions (using the English ICD implantation rate 1998-2000 as a standard) were derived.

English regions were defined as: (1) the 'old' Regional Health Authority areas (RHAs). There were 8 RHAs, which served populations of between 4.9 million and 8.7 million persons and (2) The current (in 2002), Strategic Health Authority areas (SHAs). There were 28 SHAs serving populations of between 1.2 million and 2.6 million persons. The BPEG ICD dataset held information on District Health Authorities (DHAs) in which each patient resided. The Department of Health website provided information on the composition of RHAs and SHAs by DHA.

Population estimates for English Regions were taken from the Public Health Common Dataset (2000). The expected number of new ICDs for each region was generated by multiplying the English new ICD implantation rate with regional population data for each specific age group and gender. Observed numbers of new ICDs for each region by age group and gender were also derived. The overall observed over expected ratio was then generated for each Region and 95%

confidence intervals, assuming a Poisson distribution, were calculated. A Chi squared test for heterogeneity was performed to determine any significant differences in rates of new ICD implantation across regions.

Population estimates for Scotland and Wales were mid 2001 estimates for Scotland and Wales and Census information for 2002 for Northern Ireland. Age-sex standardised rates for England, Northern Ireland, Scotland and Wales were derived using the UK as standard (the sum of population data for the 4 UK countries) and employing the methodology for indirect standardisation detailed above.

Geographical comparisons were made of new ICDs alone because patients having a replacement ICD could have had different characteristics to those having a new ICD. It could introduce bias if comparisons were made using both new and replacement ICD data.

### ***Derivation of use/need ratios***

To assess need for ICDs between geographical areas, ideally we would require data on the number of persons having indications for an ICD by area. These data are not available. A 'second best' measure would be sudden cardiac death rate by area. As already noted, most sudden cardiac deaths are due to ventricular arrhythmias. These data are not routinely collected.

Two proxy measures of need were therefore used: 1. Ischaemic Heart Disease (IHD) mortality and 2. Area deprivation. The majority of IHD deaths are sudden, so this measure could approximate sudden cardiac death rates. Moreover, ventricular arrhythmias are more prevalent in patients with underlying heart disease than in those without. Deprivation is well recognised as a measure of population need for IHD interventions; there is a strong relationship between this proxy measure and IHD prevalence.

### ***Ischaemic Heart Disease***

Regional standardised mortality rate ratios (SMR) for IHD (ICD 9 codes 410-414) were taken from the Public Health Common Dataset 1997-1999. Use-need ratios were derived by comparing the SMR to the age-sex standardised ICD use, where

1.0 represented a situation where use exactly matched the English standard of implantation, and  $>1$  represented use exceeding the standard for England and  $<1.0$  represented use not reaching the standard for England.

### ***Deprivation***

To derive deprivation scores each patient having a new ICD was linked by residential postcode to deprivation data at the 1991 Census ward level using look-up tables available from MIMAS<sup>76</sup>. Each ward in England and Wales in 1991 was assigned a Townsend deprivation score on the basis of Census response as part of the available dataset.

The Townsend deprivation score is a measure of material deprivation and comprises four variables: Household ownership, car ownership, unemployment and overcrowding<sup>77</sup>. Standardised scores from each of these variables are summed to generate a deprivation score. High scores represent more deprivation and lower scores represent less deprivation.

Census data on deprivation score and population size (broken down by age group and gender) at an electoral ward level were downloaded from the MIMAS website. These data were ordered and split into quintiles by ascending Townsend score and size of population (about 9.4 million people were included in each quintile) i.e. those wards with the lowest Townsend scores were in the first quintile and those with the highest Townsend score (and most deprived) were in the fifth quintile.

Data on the electoral ward in which each ICD patient resided were not available in the BPEG dataset. However, each patient's residential postcode was recorded. MIMAS provided codes for assigning postcodes to relevant electoral wards.

This use/need analysis using deprivation as a proxy measure of need was based on a subset of the ICD database: 1666 new ICDs (of 2004 new ICDs with sufficient data to perform this analysis). The expected values of ICDs were generated by applying the national age sex specific rates of ICD use (where national data was based on only those with a deprivation score) to each deprivation quintile. Observed values were numbers of ICDs by deprivation quintile. A statistical test for trend using a poisson regression model was undertaken.

### 4.3.3 Results

#### 4.3.3.1 Descriptive data on implantations

In the UK, 2903 ICDs implanted between 1998 and 2000, of which the majority (81%) were new ICDs i.e. implanted in patients who had not received a device in the past. Figure 4.1 shows that the use of both new and replacement devices in the UK increased between 1998 and 2000.

**Figure 4.1** Number of new and replacement ICDs undertaken in the UK

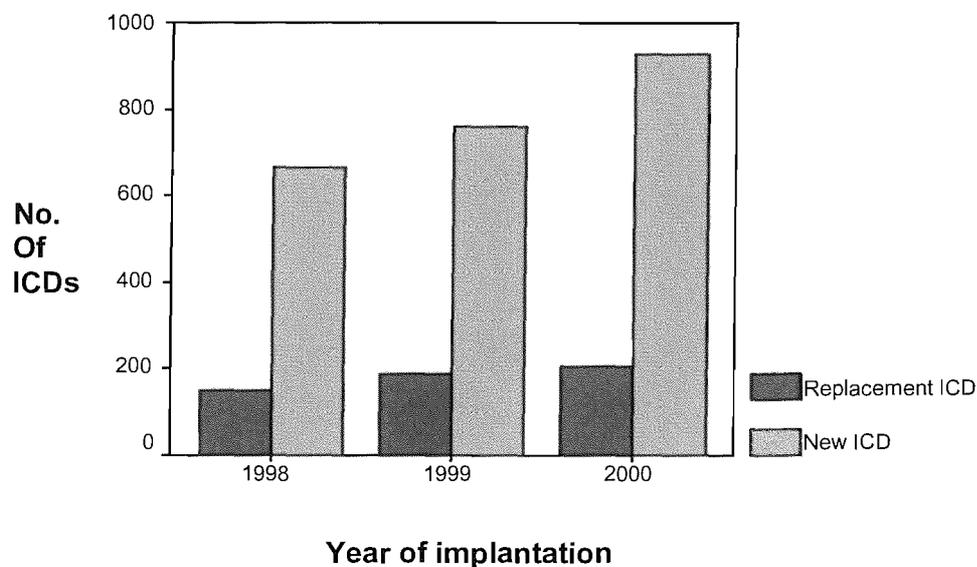


Table 4.1 shows the number of ICDs undertaken by country and by year. The table shows increasing ICD implantation in all four countries. The largest relative increases in use appeared to be in Northern Ireland and Wales.

**Table 4.1 ICD use by country and year of implantation**

			Year of implantation			Total
			1998	1999	2000	
Country of implantation	England	Count	711	818	951	2480
		% within Country of implantation	28.7%	33.0%	38.3%	100.0%
	N Ireland	Count	27	41	63	131
		% within Country of implantation	20.6%	31.3%	48.1%	100.0%
	Scotland	Count	72	71	95	238
		% within Country of implantation	30.3%	29.8%	39.9%	100.0%
	Wales	Count	9	21	24	54
		% within Country of implantation	16.7%	38.9%	44.4%	100.0%
Total		Count	819	951	1133	2903
		% within Country of implantation	28.2%	32.8%	39.0%	100.0%

Presenting symptoms were available on 1777 of 2903 (61%) patients. Of these, most (37%) presented with a cardiac arrest, followed closely by syncope (35%). Table 4.2 shows the symptoms of patients presenting for implantations.

**Table 4.2 Presenting symptoms of patients having ICDs**

<b>Presenting symptoms</b>	<b>No. of patients (%)</b>
Cardiac arrest	655 (23%)
Syncope	619 (21%)
Dizzy spells	246 (9%)
Palpitations	164 (6%)
Other	48 (2%)
Prophylactic	45 (2%)
Missing	1126 (39%)
<b>Total</b>	<b>2903</b>

There were slight variations in the types of presenting symptoms recorded for patients having new and replacement devices (excluding missing data). 34% of patients implanted with new devices initially presented with a cardiac arrest compared with 49% of patients having replacement ICDs. 36% of those implanted with a new ICD initially suffered syncope compared with 31% of those having a replacement device.

ECG findings were recorded in 2015 of 2903 patients (70%), of these most were recorded as suffering ventricular tachycardia (54%), (table 4.3).

**Table 4.3 ECG findings for persons implanted**

<b>ECG finding</b>	<b>No. of patients (%)</b>
Ventricular tachycardia	1097 (38%)
Ventricular fibrillation	624 (22%)
Ventricular tachycardia & fibrillation	274 (9%)
Other	20 (0.7%)
Unknown	888 (30%)
<b>Total</b>	<b>2903</b>

Aetiology was described for 1441 (50%) persons implanted and this is shown in table 4.4. Thus, half of the implantations had no recorded aetiology of the patient. Of those with information, most patients presented post myocardial infarction. There were very little differences in the aetiology of those patients having new implants compared with those having replacement devices.

**Table 4.4 Aetiology of ICD patients**

<b>Aetiology</b>	<b>No. of patients (%)</b>
Post MI	809 (28%)
Cardiomyopathy	324 (11%)
Coronary artery disease (no MI)	149 (5%)
Idiopathic	46 (2%)
Long QT syndrome	38 (1%)
Valvular heart disease	36 (1%)
Brugada	2 (<1%)
Other	37 (1%)
Unknown	1462 (50%)
<b>Total</b>	<b>2903</b>

#### **4.3.3.2 Descriptive data on individuals having implantations**

The BPEG dataset was of all ICDs undertaken between 1998 and 2000. Each record in the dataset represented an ICD. 103 patients had either a primary and revision ICD or two revision ICDs in this time period. The dataset was therefore individualised to provide patient based information i.e. each record in the new dataset represented an individual.

This dataset holds information on 2802 patients who had one or more ICDs between 1998 and 2000. 81% of these patients were males. For 19 patients, there was no gender information.

Table 4.5 shows the age of patients who had an ICD implanted (age at time of first implant on database). Age was not known for 158 patients. Most patients were aged between 45 and 64 years at implantation. The implantation rate in this age group was also the highest of all age groups. Rates by age and gender showed small increases by age for females and very large increases for males.

**Table 4.5 Number of patients having a new or replacement ICD and rates per million population (pmp) by gender**

Age group	Number (%)	Male ICD rate pmp	Female ICD rate pmp
0 to 4 years	3 (<1%)	1.3	0.7
5 to 14 years	12 (<1%)	2.1	1.6
15 to 24 years	49 (2%)	8.2	8.3
25 to 44 years	309 (12%)	27.0	13.7
45 to 64 years	1169 (44%)	172.5	29.6
65 to 74 years	888 (34%)	393.0	62.1
75 to 84 years	201 (8%)	157.6	20.6
85 years and over	13 (<1%)	34.3	5.6
Age unknown	158		
<b>Total</b>	2802	87.9	18.9

### **Summary of findings**

The descriptive analyses showed that the majority of ICDs implanted between 1998 and 2000 were new rather than replacement devices. However, provision of both new and replacement devices increased over the 3 year period.

There were lots of missing data on symptoms and aetiology. It is not compulsory for ICD centres to provide this information. Of those ICD records where symptoms and aetiology were described, most patients' presenting symptom was a cardiac arrest and underlying aetiology was mostly post myocardial infarction. It is striking that the ICD rate for males was more than four fold that of females and, as expected, rates increased with age up to 65 to 74 years but decreased from 75 years onwards.

#### **4.3.3.3 Geographical differences and measurement of need**

##### ***UK country and English region analyses***

Table 4.6 below shows the average number of new ICDs undertaken per year within the 3 year period (1998-2000), the crude new ICD rate per million population and the age-sex standardised ratio for the 4 UK countries and each English region. The table shows that there was variation between countries with Northern Ireland having the highest ICD rate (Chi squared test for heterogeneity,  $p < 0.005$ ) using the UK as a standard. It should be noted that age and sex information were not available for all cases and data from these cases were therefore not included in the table below.

There was also significant variation between RHA areas in the use of new ICDs (test for heterogeneity,  $p < 0.005$ ). Two regions had particularly low use of ICDs: West Midlands and North West . There was no consistent geographical pattern (eg north –south gradient) at regional level.

**Table 4.6: Analysis of new ICD implantations by UK country and English region (RHA) 1998-2000**

Country	Number of new ICDs per annum (mean from 1998-2000)	Crude Use rate per million per annum*	Age sex standardised rate** (95% CI)	Number of ICD implanting centres
England	668	13.7	1.11 (1.06-1.16)	35
Wales	17	5.8	0.39 (0.28-0.51)	1
Scotland	77	15.1	0.92 (0.80-1.07)	3
N Ireland	41	24.3	1.86 (1.53-2.26)	2
Health region of England	Number of new ICDs per annum (mean from 1998-2000)	Crude Use rate per million per annum*	Age sex standardised rate (95% CI)	
Eastern	63	11.7	0.95 (0.82-1.09)	1
London	90	12.2	1.04 (0.92-1.18)	9
North West	68	10.2	0.86 (0.75-0.99)	5
Northern & Yorks	96	15.2	1.11 (0.98-1.26)	5
South East	132	15.1	1.02 (0.91-1.14)	4
South West	83	9.1	1.25 (1.10-1.42)	6
Trent	74	14.4	1.16 (1.02-1.33)	4
West Midlands	40	7.4	0.61 (0.51-0.73)	1

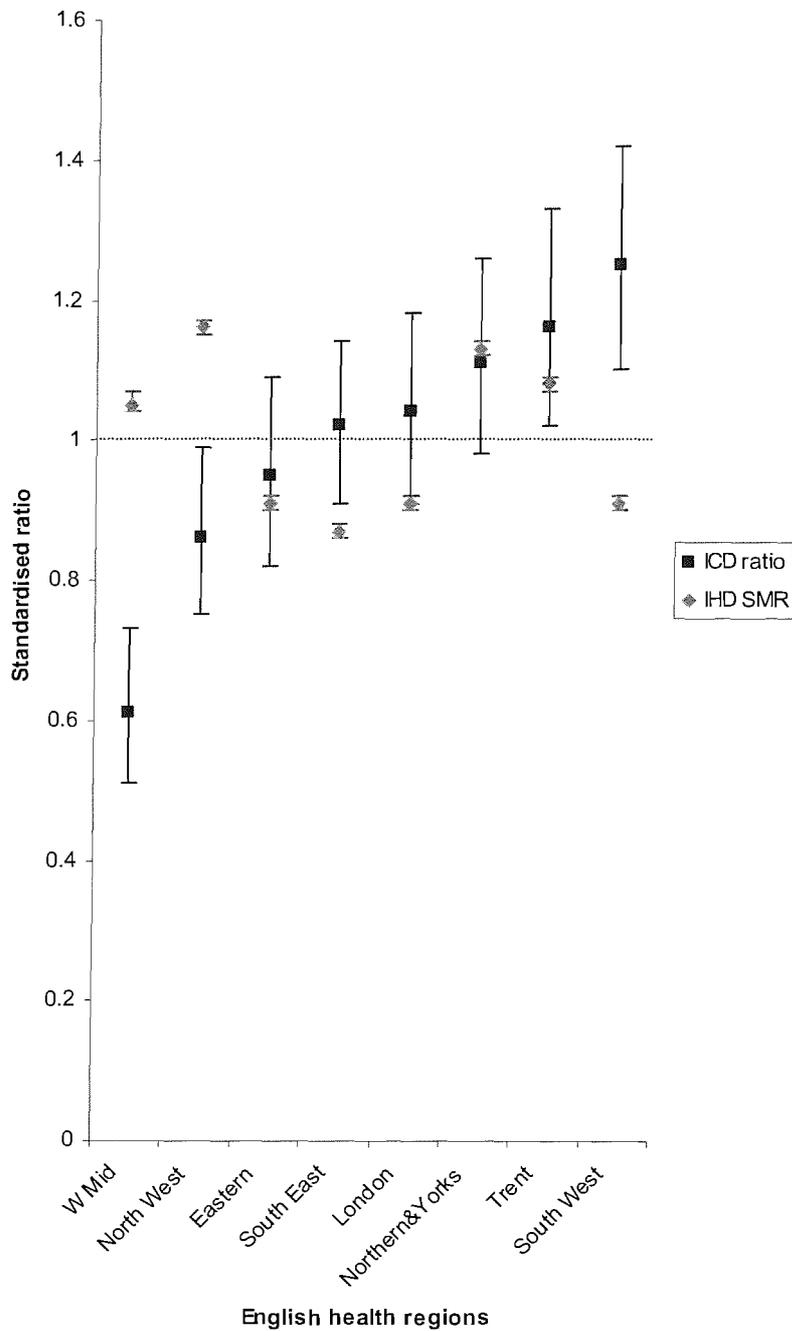
\*using data for which age and sex available to allow for comparison with age standardised rate

\*\* ICD rates by country were standardised against the UK population and English regional rates were standardised against the population of England.

### ***Use/need ratios using IHD as a proxy measure of need***

Figure 4.2 shows the age-sex standardised ICD ratios and SMRs for IHD for each English health region. This suggests that there may be an inverse relationship between ICD use and need with people with potentially most need (highest SMR for IHD) receiving the lowest rate of ICD implantation.

**Figure 4.2** Age sex standardised ICD ratios and SMR for IHD for English health regions (1998-2000)



**Strategic Health Authorities (SHA) analysis**

The age sex standardised SHA rates are shown in table 4.7. The confidence intervals around the age-sex ratios of use were wide because of the small number of ICDs undertaken in each SHA. This table also shows the number of ICD centres situated in each SHA.

**Table 4.7 Age-sex standardised ICD use by SHAs**

<b>Strategic Health Authority</b>	<b>ICDs pmp per annum</b>	<b>Age-sex standardised use</b>	<b>Number of centres</b>
Kent & Medway	24.4	0.82(0.62-1.09)	0
Somerset & Dorset	24	1.80 (1.45-2.23)	1
County Durham & Tees Valley	18.1	0.85(0.61-1.17)	1
North and East Yorkshire& North Lincolnshire	18.1	1.39(1.12-1.71)	1
Leicestershire, Northampton shire & Rutland	17.9	1.51(1.22-1.88)	1
Surrey & Sussex	16.1	1.16 (0.97-1.40)	2
South West Peninsula	15.3	1.10 (0.87-1.39)	4
Essex	14.7	1.18 (0.94-1.49)	0
West Yorkshire	14.6	1.29(1.05-1.58)	2
Cheshire & Merseyside	14.5	1.20(0.99-1.46)	1
Trent	14	1.12(0.93-1.35)	2
North West London	13.1	1.59(1.0-1.26)	3
Northumberland, Tyne Wear	13	1.05(0.81-1.37)	1
Avon, Gloucestershire & Wiltshire	12.5	1.04 (0.84-1.29)	1
South East London	12	0.75 (0.54-1.05)	2
North East London	11.8	1.16 (0.88-1.56)	2
Hampshire & Isle of Wight	11.6	0.92(0.71-1.18)	1
Shropshire & Staffordshire	11.4	0.61 (0.43-0.85)	0
South West London	10.8	0.99 (0.73-1.35)	1
Thames Valley	10.8	0.95(0.75-1.20)	1
Cumbria & Lancashire	10.6	0.81 (0.62-1.04)	2
North Central London	10.4	1.02 (0.74-1.4)	1
South Yorkshire	10.2	0.86 (0.63-1.17)	1
Norfolk Suffolk & Cambridgeshire	10.1	0.8 (0.63-1.02)	1
Bedfordshire & Hertfordshire	9.7	0.82 (0.62-1.10)	0
Coventry, Warwick &Worcestershire	7.9	0.63 (0.45-0.87)	1
Birmingham & the Black Country	7	0.61 (0.46, 0.81)	0
Greater Manchester	5.7	0.53(0.40-0.70)	2

The SHA were ascribed by DHA code of the patient's residence. Thus the population of Dorset and Somerset who had no implanting centre in the SHA still had a relatively high age-sex standardised rate of 1.80, as they were implanted in centres outside their own SHA area. There were 9 NHS centres in London, almost one quarter of the total number of centres, which may be accessible to those in the environs but not those living further away. Between North Essex and

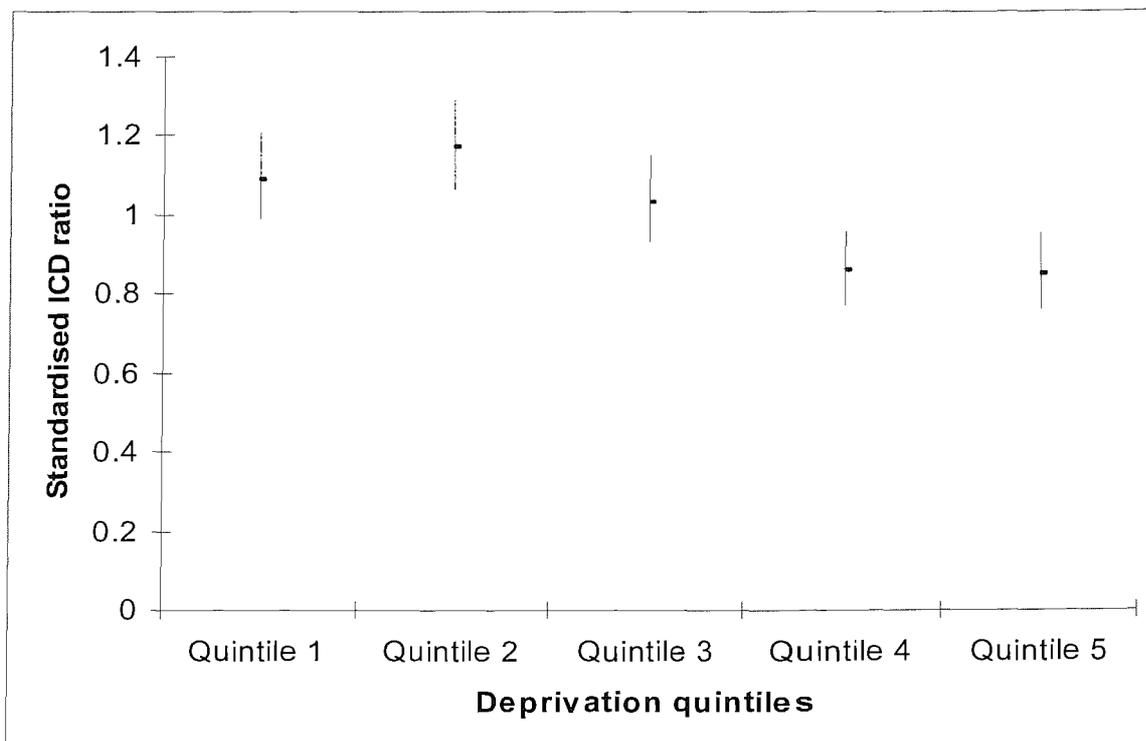
Cambridgeshire there were no centres, thus patients referred would have had a greater distance to travel. There were 4 SHAs that had no centre.

There was no obvious pattern of crude or age-sex standardised ICD use by SHA (using England as standard), although, SHAs with lower implanting rates tended to be in the Midlands and the North West and those with higher rates in the rest of the North.

***Needs assessment using deprivation as a proxy measure of need***

Figure 4.3 below shows age-sex standardised rates for ICD use by deprivation quintile. Quintile 1 includes persons in wards with the lowest Townsend scores (and thus least deprived). Quintile 5 includes persons in wards with the highest Townsend scores (and thus most deprived).

**Figure 4.3 Standardised ICD ratio by deprivation quintiles**



Slightly more ICDs than expected were undertaken in the least deprived quintiles and less ICDs than expected in the most deprived quintiles. However, confidence intervals included one for three of the quintiles. A test for trend using a poisson regression model (with null hypothesis being that there is no relationship between ICD use and deprivation) and ICD use showed a statistically significant trend with

$p = 0.005$ . ICD use decreased with increased deprivation (at a small area level). If need was being met, and deprivation is an appropriate measure of need, we would expect the inverse of this result i.e. increasing ICD use with increasing deprivation.

#### **4.4 National survey of ICD implantation centres**

This section describes the methods and results of a national survey of ICD implantation centres. The specific aims of this survey were to ascertain the activity of each centre, staff capacity, some information on clinical practice, perceived barriers and drivers to managing patients for ICD therapy, and comments on future directions of practice in ICD therapy.

There were 41 UK centres that were undertaking ICD implantation in 2002. All were situated in tertiary hospitals and run by one or more Consultant Cardiologists (Electrophysiologists). Staff involved in running an ICD service varied between centres. Generally, it consists of a Consultant, one or more Specialist Registrars, cardiac technicians and nurses. Roles of staff were orientated towards both the implantation of the devices and following up patients; especially those experiencing shocks. Section 5.1 of this chapter has provided information on the location of these centres and a map can also be found in appendix 5 (please note that there are 9 centres in London and not 12 as on map).

##### **4.4.1 Methods**

The BPEG management team provided a list of current (in 2002) implanting centres. A survey letter and short questionnaire were developed with the help of a Consultant Cardiologist (Electrophysiologist) (see appendix 6 for copies of these documents). These were not piloted due to time constraints.

The letter and questionnaire were sent to all centres in January-February 2002. Questionnaires were sent to a named Consultant in each implanting centre. Non-responders were contacted via phone, e-mail and fax and repeat questionnaires were sent out to maximise response rate.

#### 4.4.2 Results

The response rate to the survey was 78% (32 of 41 centres). The 9 non-responding centres were evenly spread throughout England (all centres in Scotland, Northern Ireland and Wales responded).

Most of the centres (81%) served populations above that of a typical DGH i.e. greater than a population of 500,000 persons. The majority (63%) served populations of more than 1 million persons. This reflects the tertiary nature of many of the centres for this service.

Overall, the median staffing levels for consultant grade was 2 whole time equivalents (WTE), with 1 WTE NHS Specialist Registrar (SPR) and 2 technical staff. 10% had no technical staff whilst 16% had more than 5 WTE technical staff working in the ICD service. There was no statistical association between the number of staff or the professional craft of the staff and the activity of the unit. However, in units implanting higher numbers of ICDs, there were higher numbers of consultants available, but this did not reach statistical significance.

Table 4.8 shows the respondents' perceived barriers to ICD implantation.

**Table 4.8: Barriers to care for eligible patients**

	<b>Strongly agree/agree %</b>	<b>Unsure %</b>	<b>Strongly agree/disagree %</b>
<b>Patient identification</b>	93		7
<b>Staff Capacity</b>	57	7	36
<b>Funding for treatment</b>	46		54
<b>Skillmix</b>	36	7	57
<b>Clinic waiting times</b>	25	4	72
<b>Implantation waiting times</b>	25	11	64
<b>EPS waiting times</b>	22	14	64
<b>Patient refusal</b>	11		89
<b>Non-attendance</b>		4	96

By far the most commonly identified barrier to care for patients that were eligible for ICD therapy was patient identification. Staff capacity and funding for treatment were the next most commonly identified barriers. Comments on barriers included the difficulties in getting referrals of eligible patients from secondary /DGH level of

care, and the problems of evidence being in the public domain influencing professional equipoise on eligibility criteria, preceding national guidance and therefore funding (for example the recently published MADIT 2 study providing evidence for ICD therapy in patients with heart failure that had not yet been approved by NICE).

43% of respondents reported that they had a waiting list for ICD implantation. The median waiting time for an ICD was 3-4 weeks. 71% of respondents said that they submitted 100% of their ICD data to the national BPEG database, with 86% submitting 90% or more and 7% submitting less than 19% of their data routinely.

Comments from respondents on how they envisaged practice changing over the next few years fell into four broad categories, shown in table 4.9 below.

**Table 4.9 Comments made by respondents on changing practice**

	<b>Comments</b>
<b>Increase in numbers</b>	<ul style="list-style-type: none"> <li>• Numbers will increase as the centres become more widely known</li> <li>• Steady increase in numbers mainly limited by staffing and hardware resources</li> <li>• Great increase in numbers-double in next year</li> </ul>
<b>Expansion of eligibility criteria</b>	<ul style="list-style-type: none"> <li>• Continued expansion of primary prevention indications</li> <li>• More primary prevention being done (MADIT 2 will further increase this)</li> <li>• Primary prevention indications will expand service</li> </ul>
<b>Configuration &amp; practice</b>	<ul style="list-style-type: none"> <li>• Devolvement to larger DGHs. Increasing number of biventricular units.</li> <li>• Devolution to implantation at DGH level in hub and spoke arrangement</li> <li>• Less EPS used</li> <li>• Shorter implant times less GA devolvement to DGHs home-based monitoring better distributed support (wider knowledge base)</li> <li>• Need to expand facilities for implanting ICDs Expansion of hub and spoke model of practice to DGH</li> <li>• Expansion of service hopefully supported by devolution of service into surrounding DGH</li> <li>• Devolution of DGH with stated quality criteria &amp; minimum activity levels, staff &amp; resources and out of hours cover.</li> <li>• No specific recommendations have been made about replacements which are increasing and these are being included in the allocation of all ICD at a 50pmp by health authorities</li> <li>• NICE is out of date</li> </ul>
<b>Staffing</b>	<ul style="list-style-type: none"> <li>• Need designated and funded staff</li> <li>• Need for a dedicated fully funded staffed ICD clinic with a Staff grade or similar attached and at least 3 days of WTE time for 2 cardiac technicians.</li> <li>• Our ICD clinics will have to go to technician only due to increasing workload</li> </ul>

All of the respondents recorded that they expected to have a large increase in number of implantations over the next few years. Nearly all mentioned setting up of services in DGH settings either in hub and spoke arrangement, or accreditation of centres with specific quality criteria with support from larger centres provided on a needs basis.

## 4.5 Discussion

This chapter has described current patterns of ICD management, considered the relationship between use and need and reported ICD centre electrophysiologists' views on current and future management.

An analysis of routinely collected national ICD data from 1998 to 2000 showed that ICD rates were increasing annually, particularly the implantation of new devices rather than replacement ICDs. The rate of new ICD implants in England was just 13.7 per million population in this time period. Where symptom data was available, cardiac arrest was the most common presentation with post-MI being the most common underlying aetiology. The ICD rate for males was more than four fold that of females and rates increased with age up to 74 years but decreased there onwards.

A comparison of ICD implantation rates from 1998 to 2000 in England with regional rates showed that implantation rates in some areas fell well below that of the national rate (and much further below the rate recommended by NICE). An assessment of the relationship between use and need, using IHD mortality and deprivation data as two proxy measures of need suggested possible inequity of ICD utilisation within England. Results from the deprivation analysis strongly suggested that the inverse care law was operating; those areas where need was highest also had the lowest rates of new ICD implantation.

Barriers and the future direction of ICD implantation were explored in a national survey of ICD centres. The results suggested that patient identification was the greatest barrier to ICD use; with perceived under referral of patients with indications for ICDs from clinicians in primary and secondary care. Future direction was seen as a shift towards providing ICDs in secondary care and changing indications for ICDs (the MADIT-2 study criteria: patients post myocardial infarction with low left ventricular ejection fraction). Anxieties were expressed about the potential explosion of numbers as a result of these changing indications and the ability of the current providers to give a high quality service.

The limitations of this work were mainly those usually associated with routinely collected data. The BPEG ICD database relies on paper manual returns from ICD centres and is believed to be incomplete (a 20% underestimate of industry returns). The 1998-2000 BPEG ICD dataset was believed to be complete and cleaned. However, further data cleaning was necessary to exclude erroneous records. There were lots of missing data on symptoms, aetiology, age, gender and residential postcode of patients. Where there was no gender or age recorded, these data could not be used in the age-sex standardisation. The missing data were assessed and distributed fairly evenly between deprivation quintiles. However, there were some differences in the amount of missing data from various regions but these were not those regions with the lowest ICD rates.

Ideally, need would be measured as the number of patients with indications for an ICD. However, there is no routinely available measure of ICD need. Therefore, proxy measures were used: the Townsend score as a measure of deprivation and IHD SMR. The use of these proxy measures should be justified given that the underlying aetiology of the majority of ventricular arrhythmias is IHD and IHD mortality is positively related to deprivation.

An important limitation of the national survey was non response of 28% of ICD centres despite repeated requests. Due to confidentiality issues, BPEG would not release data on which centres implanted which ICDs. Therefore, it was not possible to determine whether the non-responding centres implanted significantly more or less ICDs than responders. However, the non-responders were evenly distributed geographically.

Annual reports of national ICD use have been available from BPEG since the early 1990s (now part of Heart Rhythm UK) and can be found on the national cardiac interventions database website<sup>75</sup>. However, this is the first analysis of regional data with consideration of need. One paper had been published prior to this study that attempted to explore reasons for variation in ICD rates across Europe (discussed in chapter 1, section 1.8.1). This study did not identify any statistically significant associations between various factors and ICD use<sup>36</sup>. No UK surveys of ICD use, other than the one described here, have been published.

Variations in ICD rates between health regions could be due to inaccessibility to ICD centres. Some SHAs did not have implanting centres; London had almost one

quarter of these centres. There could be variation in ease of access for those patients referred for an ICD with those living furthest away from a centre having reduced access.

The devolution of ICD implantation to a secondary care setting may enable better identification of patients who could benefit from an ICD. This would need to be accompanied by wider dissemination of best practice guidelines and effective education about indications leading to appropriate patients being identified and referred. However, staff and funding shortages were perceived as problems that could hinder such a change.

The policy implications of the national ICD centre survey results are: (1) the need for referral guidelines and targeted education to ensure appropriate identification and referral of patients and (2) consideration of the practicalities and resource commitment associated with the devolution of ICD services to the secondary care setting. A recommendation from this work is to encourage ICD centres to provide more complete data returns. There were a large number of missing data variables in the BPEG ICD database, especially on patients' underlying aetiology.

Analyses on the BPEG ICD database performed in this study to investigate potential geographical inequity could be repeated at a future date to determine whether changes have occurred over time.

## **5. Population based study of the incidence and prognosis of ventricular arrhythmias**

This chapter addresses research question 3 in chapter 2 of this thesis: What is the incidence and prognosis of diagnosed symptomatic ventricular arrhythmias in a defined population? A prospective cohort study of newly diagnosed ventricular arrhythmias was established in the Southampton and South West Hampshire Health Authority area to:

- (1) Estimate the incidence rate of diagnosed symptomatic ventricular arrhythmias,
- (2) Characterise patients and document current management (including number of ICDs implanted) and
- (3) Determine the survival rate and quality of life over 12 months in this defined incident cohort.

### **5.1 Methods**

The research design and methods are described, beginning with a statement about the research design, a definition of cases and then a description of the study population. Two feasibility studies undertaken to determine methods of identifying cases and clarify the study setting are then presented.

Methods for determining the completeness of case ascertainment and ensuring minimal cross-boundary flow of cases are also described. Ethical issues are documented and methods of data collection highlighted. Finally, the statistical analyses undertaken and the required sample size calculation are given.

#### **5.1.1 Study design**

A population based prospective cohort study was chosen as the most appropriate design as it enables the identification and follow-up of newly diagnosed cases over a specified time period with the assessment of the prognosis of an inception cohort providing more robust data than that of a prevalent group. A prospective design was chosen because there were no simple methods of identifying cases retrospectively; cases would need to be identified as they occurred. The intention

was to identify new cases over a 12 month period in a defined geographical area and follow-up all such cases for 12 months.

### **5.1.2 Who were the cases?**

Cases in this study were consecutive patients with newly diagnosed:

- Non-sustained Ventricular Tachycardia (VT),
- Sustained VT,
- Inducible VT,
- VT or ventricular fibrillation (VF) in the chronic phase subsequent to a myocardial infarction
- Out of hospital cardiac arrest with VF as the presenting rhythm.

As previously discussed (see chapter 1 section 1.4), the definition of ventricular tachycardia varies in the literature and in practice. For this study, a pragmatic definition of VT of four or more consecutive ventricular beats at a rate of 100 bpm or higher was used. This definition is used by analysers of heart rhythm recording devices, such as the Holter monitor, at Southampton University Hospitals Trust and the Royal Hampshire County Hospital to identify patients with ventricular tachycardia. If a broader definition of VT was used, as described in the literature, some of these more broadly defined, and less severe, cases would not be considered VT by analysers and doctors at these hospitals. These undiagnosed cases would be very difficult to identify.

Non-sustained VT was defined as a run of VT lasting for less than 30 seconds. Sustained VT was defined as a run of VT lasting for 30 seconds or longer. Inducible ventricular tachycardia was defined as the ability to reproduce ventricular tachycardia using programmed stimulation during an Electrophysiological study.

The exclusion criteria were:

- Persons under 16 years of age.
- Patients with ventricular tachycardia that was transient and reversible i.e. during acute ischaemia (at the time of infarction), peri- or post-operatively or during catheterisation.
- Patients suffering an in-hospital cardiac arrest.

- Patients suffering VT or VF in the acute phase i.e. within the first 48 hours, subsequent to a myocardial infarction.

Patients surviving an out-of-hospital cardiac arrest (not associated with acute ischaemia) and those who suffered ventricular fibrillation in the chronic phase post-myocardial infarction were included in this study. However, other patients who suffered a cardiac arrest whilst in hospital have been excluded. The reason for this distinction is because evidence suggests that patients in the former two health states could benefit from an Implantable Cardioverter Defibrillator (ICD)<sup>16</sup>. However, an in-hospital cardiac arrest not associated with a previous myocardial infarction could be due to numerous underlying aetiologies. A few of these patients could plausibly benefit from an ICD but it would be difficult both identifying these patients and determining their eligibility.

Patients with transient and reversible ventricular arrhythmias were also excluded because these arrhythmias are generally caused by a chemical imbalance that can be corrected, or corrects itself, and not the result of the underlying cardiac aetiology. These patients would not be considered for an ICD.

Patients with previous episode/s of ventricular tachycardia and/or cardiac arrest due to a ventricular arrhythmia were excluded wherever possible to ensure that the cohort represented newly diagnosed patients.

### **5.1.3 Setting and Study population**

The geographical setting of the study and the demographics of the study population who resided within that area during the timeframe of the study are described. Where possible, these demographics are compared with national data.

#### **5.1.3.1 Geographical Setting**

Cases were identified in the former Southampton and South West Hampshire Health Authority (SWHHA) area and Winchester City and surrounding suburbs. The two NHS providers of secondary and tertiary care in these areas are Southampton University Hospitals NHS Trust (SUHT) and the Royal Hampshire County Hospital (RHCH).

SUHT has two hospitals. The main provider of inpatient care for SUHT is Southampton General Hospital (SGH). SGH provides secondary care for SSWHA and tertiary care for a population of about 3 million persons (including the SSWHA area). A specialist electrophysiological service is provided at SGH for this wider population. The second SUHT hospital is the Royal South Hampshire Hospital (RSH) which provides secondary care for SSWHA. The RHCH is part of the Winchester and Eastleigh NHS Trust and provides secondary care for residents in central Hampshire.

### 5.1.3.2 Study population

The study population was those persons resident in the geographical area served by SUHT and RHCH. The boundaries of this area were defined firstly by assessing the feasibility of identifying cases within this area in a feasibility study and secondly by undertaking a detailed analysis of cross-boundary flow using routine Hospital Episode Statistic data (see section 6.1.8).

#### 5.1.3.2.1 Southampton and South West Hampshire Health Authority Area (SSWHA)

In 2001 the SSWHA area had a population of 548,220 persons, 443,824 adults aged 16 years or older. A map of the area is shown in appendix 7. At this time, SSWHA was composed of three PCT areas: Southampton City, Eastleigh and Test Valley and New Forest. The PCTs, number of electoral wards and population size are shown in table 5.1 below.

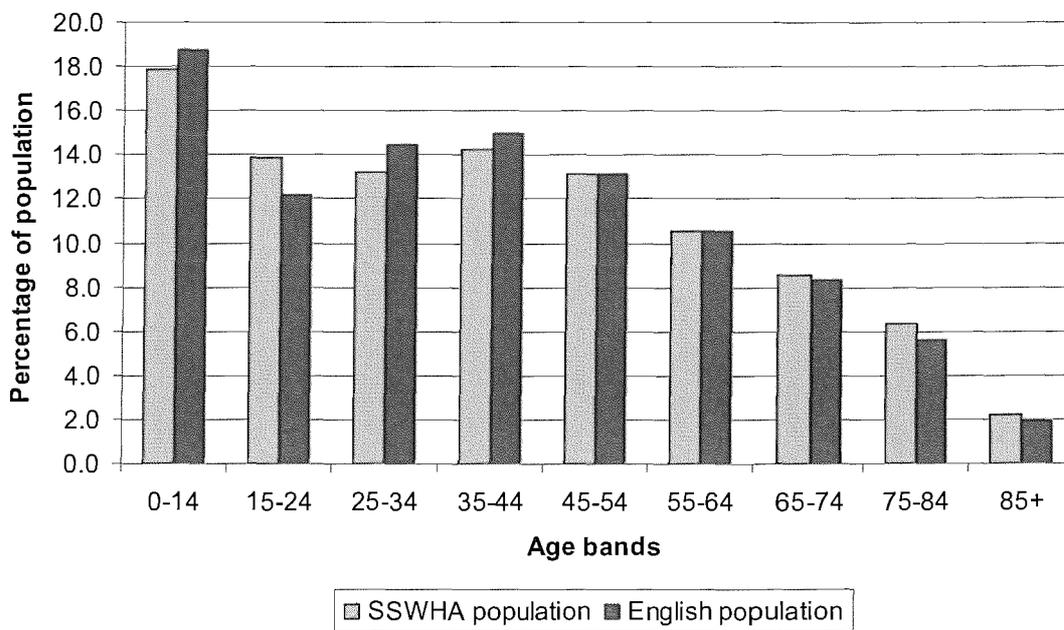
**Table 5.1: Population data and number of electoral wards by the 3 PCTs within SSWHA in 2001**

PCT area	Number of electoral wards	Population – number of persons resident in area*
Southampton City	16	217,444
Eastleigh and Test Valley	28	161,448
New Forest	34	169,328

\*Resident population data downloaded from Census 2001 website

In 2001, 49.1% of SSWHA residents were males compared with 48.7% of English residents. The age distribution was also similar to national data. The figure below shows the proportion of SSWHA residents and residents of England in 10 year age bands in 2001. The proportion of SSWHA persons in each age band was very similar to that of England. The average life expectancy was 79.6 years in the SSWHA compared to 79.0 for England in the same period.

**Figure 5.1 Proportion of persons by age bands in the SSWHA and England**



In 2001, 4.1% of people in SSWHA belonged to an ethnic group other than white. However, this proportion varied greatly between SSWHA localities; from 1% in Avon Valley and the South West of the New Forest to 17.3% in Central Southampton. In comparison, 9.1% of the English population belonged to ethnic groups other than white.

Age-standardised rates for all cause mortality and CHD mortality in England and SSWHA by gender are shown in the table below.

**Table 5.2 Age standardised mortality rates per 100,000 persons in SSWHA (Census 2001 data)**

	<b>Males</b>	<b>Females</b>
<b>All cause mortality rate</b>		
England	806.5	553.1
SSWHA	736.8	500.7
<b>Standardised CHD mortality rate</b>		
England	209	170
SSWHA	178.8	79.6

In conclusion, the demographics of SSWHA are similar to that of England except that SSWHA has a smaller proportion of persons from ethnic minority groups and mortality rates are slightly lower.

#### **5.1.3.2.2 Winchester City and suburbs**

The boundaries for care of patients at the RHCH are not clearly defined. Patients can reside in the districts of: Basingstoke and Deane, East Hampshire, Hart, Rushmoor, Test Valley and Winchester<sup>78</sup>. In 2001, these 3 districts were covered by the following four PCTs: North Hampshire, Eastleigh and Test Valley South, Blackwater Valley and Hart and Mid-Hampshire PCT. Significant cross-boundary flow of patients residing in the Blackwater and Hart and North Hampshire areas was likely (this was later confirmed in a Hospital Episode Statistic Analysis, see section 6.1.9). These areas were therefore excluded from the study catchment area. Table 3 shows the number of electoral wards and population size of the two remaining PCTs.

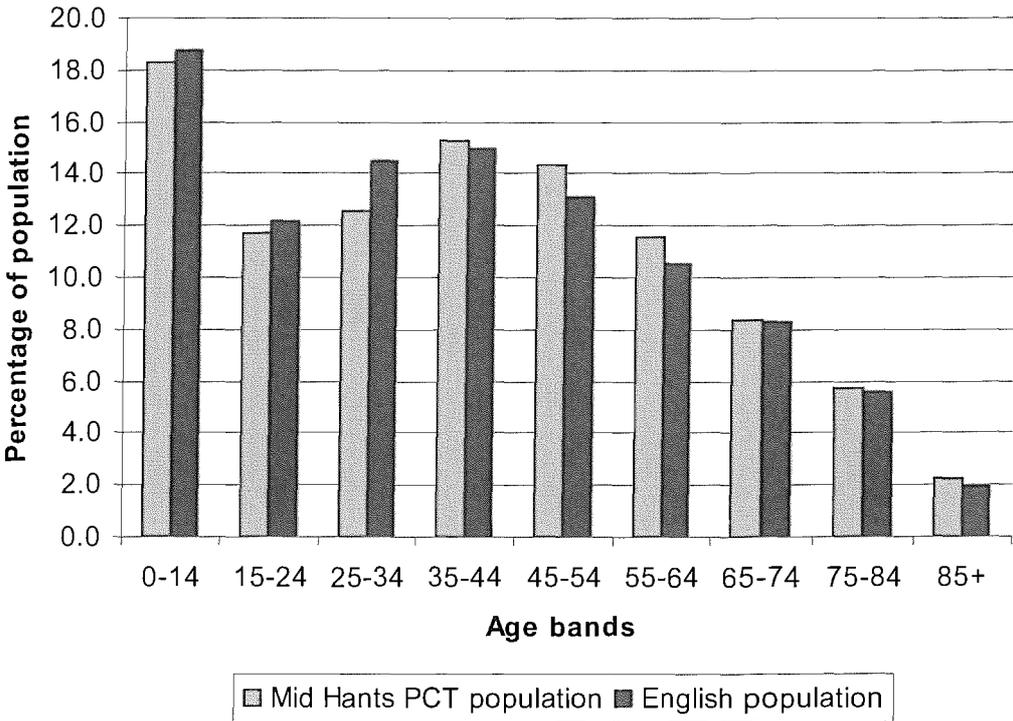
**Table 5.3: Population data and number of electoral wards by 2 of the PCTs RHCH provides care**

<b>PCT area</b>	<b>Number of electoral wards</b>	<b>Population</b>
Eastleigh and Test Valley South	28	161,448
Mid-Hampshire	41	172,250

Residents in the Eastleigh and Test Valley South area are served by either SUHT or RHCH. Eastleigh and Test Valley South is part of SSWHA and demographical data on this area have been discussed in the previous section (6.1.3.1).

Appendix 8 shows a map of the Mid Hampshire PCT area. This area was populated with 172,250 persons in 2001. There were 140,775 adults (aged 16 years and over). Figure 5.2 shows the proportion of residents in 10 year age bands compared with the English population. There was a slightly higher proportion of older persons and associated smaller proportion of younger persons in the Mid Hampshire PCT area compared with England. Life expectancy data were not available for this area but average life expectancy in Winchester City Local Authority was 80.5 years and 79.7 years in East Hampshire compared with 79.0 years in England. Only 2% of the PCT population belonged to an ethnic group other than white, compared with 9.1% of the English population.

**Figure 5.2 Proportion of persons by age bands in Mid Hampshire and England in 2001**



All cause mortality and CHD mortality data are available for the Mid Hampshire PCT area and Winchester Local Authority for the pooled years of 2001 to 2003. Age standardised rates per 100,000 persons are shown by gender in the table 5.4 below.

**Table 5.4 Age standardised all cause per 100,000 persons and age-sex standardised CHD mortality rates**

	<b>Males</b>	<b>Females</b>
<b>All cause mortality rate</b>		
England	806.5	553.1
Winchester Local Authority	653.8	474.6
Mid-Hampshire PCT	683.7	489.3
<b>Standardised CHD mortality rate</b>		
England	209	170
Winchester LA	59	58
Mid-Hampshire PCT	70	74

In conclusion, in comparison with England, the Winchester area has a smaller proportion of persons from ethnic minority groups and a much lower standardised mortality rate and CHD mortality rate.

#### **5.1.4 Feasibility study 1**

Feasibility study 1 was undertaken to determine the methods that would feasibly identify all cases meeting the inclusion criteria in the main study.

The aims of this study were to:

- Explore methods of case ascertainment,
- Consider the number of cases identified by each method, including consideration of the threshold for defining NSVT,

##### **5.1.4.1 Feasibility study 1 methods**

Staff involved in admitting, diagnosing and managing these patients were consulted about possible ways of identifying cases. The methods were piloted at one site (SUHT) as this was the main provider of care for this study population and

it was crucial that case ascertainment methods were feasible and sustainable at SUHT.

It was clear from initial discussions with the Consultant Cardiologist (Electrophysiologist) that there were no registers, log books or other type of central recording of patients with ventricular arrhythmias. The only records of a diagnosis were in a patient's hospital and/or GP notes i.e. test results, in consultant letters, letters to GPs, hospital admission and discharge details, and ward notes.

It would not have been possible to look through the hospital and GP notes of every patient within the study population who presented to the health service within the time period. Indeed, even if this was possible it would have to be undertaken retrospectively and would therefore be prone to the problem of missing results, letters etc.

It was therefore decided that a 'hot pursuit' method of case identification would be the most systematic way of ensuring a minimal number of missed cases. Hot pursuit is an approach adopted by the MONICA study group to identify new cases of myocardial infarction<sup>79</sup>. This approach involves actively searching for new cases of disease as they occur.

A number of staff working in SUHT Cardiac, Elderly Care and Accident and Emergency departments were consulted for ideas of case identification methods: a Consultant Cardiologist (Electrophysiologist), doctors, technicians and nurses working in cardiac care, a Consultant in Elderly Care and a Consultant in Accident and Emergency (A&E). They suggested setting up case identification systems in three areas: (1) Coronary Care, (2) Accident and Emergency, (3) non-invasive cardiac investigations and (4) invasive cardiac investigations. Methods and justification for setting up systems in these areas are described below.

### **(1) Coronary care**

Theoretically, all patients with life threatening ventricular arrhythmias (within the study catchment area) should have been referred to the SUHT Coronary Care Unit (CCU). The Consultant Cardiologist recommended setting up a case ascertainment system in CCU. Past experience of leaving a list with CCU staff to be completed when new cases arose had been met with little success (unless the

study researchers worked on the CCU). Therefore, it was recommended that the investigator visit or phone the CCU every other day to ask the Sister in charge if there had been any new cases. A poster was also placed in the nurses' station and the coffee room to heighten awareness.

The Sister in charge also recommended a cross-check of the MI rehabilitation book for any missing cases. Although all cases of ventricular arrhythmias are not centrally logged, all MI survivors are logged in a cardiac rehabilitation book held in the CCU. This book provides details of whether patients' MIs were complicated with ventricular arrhythmias in the acute and/or chronic phase post acute MI.

This system was piloted for three months prior to the start of the main study.

## **(2) Accident and Emergency (A&E)**

Survivors of an out-of-hospital cardiac arrest or sustained ventricular tachycardia (as identified on ambulance or A&E ECG) would have been admitted as an emergency via A&E (if not referred straight to CCU from another hospital). In consultation with an A&E consultant, it was agreed that the only method of identifying these emergency cases would be regular checks of the resuscitation log book entries.

These books were kept in the A&E resuscitation room and a brief record of each patient managed in this room was entered in the log book. All patients presenting with ventricular arrhythmias were managed in the resuscitation room and each event, including pre-hospital and A&E deaths, with details of heart rhythm recorded on ECG (if available), patient's name, date of birth, hospital number and where the patient was transferred to should have been recorded in this book. However, an entry was not always completed for every patient and the amount of details on each event varied.

A retrospective analysis of resuscitation log book entries over a one year period (in 2001) and a three month prospective pilot were undertaken to determine the number of cases that could be identified using this method.

### **(3) Non-invasive diagnostic testing**

The source that was expected to identify the most cases was results of non-invasive diagnostic testing i.e. Holter monitoring (24 and 48 hour testing), Cardiomemos, King of Hearts and Reveal implantable recorders. SUHT Cardiac technicians and doctors were consulted for the most systematic and timely way of identifying diagnosed patients.

The system at SUHT worked as follows; both in-patient and out-patient tapes were analysed at Southampton General Hospital and outpatient tapes alone were analysed at the Royal South Hants Hospital (RSH); both part of SUHT. Holter monitor tapes supplied to nursing homes, in the community and Lymington Hospital were also all analysed at SGH. Tapes were analysed approximately one week after testing, and appeared to be dealt with in a priority order, with cardiac patients and paediatric cases given the highest priority and out-patients given the lowest priority.

The technicians recommended using two methods to ensure complete identification. Both captured cases post analysis and after the medical registrar's consideration of results. These methods were:

- (1) The top copy of every SGH analyser's report was placed in a tray for the investigator to check. All were logged and ones showing VT (as per case definition) were kept to be enclosed with patient records.
- (2) The analysers' log book was checked to ensure all reports were identified. Tapes showing salvos of 4 or more consecutive ventricular beats in this book were highlighted with a marker pen by the Holter analyser (for the majority of the time the analyser was the same person). The analyser and the investigator met weekly to collate information on new cases.

The RSH analyser was contacted once a week for new RSH out-patient cases (there is only one analyser at the RSH). Results of rhythm testing were not logged at RSH, but identification of ventricular arrhythmia runs was rare and therefore weekly phone calls to the analyser were sufficient. Both the analyser's reports and the log book held information on the patient's name, hospital number, ward/out-patient, Consultant in charge of care, date of birth and findings. However, the

analysers report held much greater details of test results including heart rate and number of beats.

Use of Reveal implantable heart recorders was not logged. However, it was not common practice to use these diagnostic devices. At the time of the study, Reveals were only being implanted as part of an ongoing clinical trial, known as CIRUS. Close links with the CIRUS research nurse ensured that no cases would be missed.

These approaches were piloted in the feasibility study over a three month period.

#### **(4) Invasive diagnostic testing**

The final source of cases for this study was through invasive cardiac investigations. The only invasive diagnostic test for VT is the electrophysiological study (EPS). This approach is called 'VT stimulation'. These tests are undertaken to determine the inducibility of VT in patients with symptoms suggestive of VT or those who have been diagnosed with VT on other tests. Results of EPS were logged in a diary. The technician responsible for this log book recommended checking the diary for patients having 'positive VT stimulations' on a weekly basis. Patient's name, hospital number, date of birth and results of testing were logged in this book. A retrospective pilot study of EP diary entries over a one year period (2001) was undertaken.

#### **5.1.4.2 Feasibility study 1 results**

Results of the first feasibility study are detailed below. These are described for each of the four pilot areas and changes made as a result of the feasibility study highlighted.

##### **(1) Coronary Care**

Eight cases were identified over 3 months. One patient had survived an out of hospital cardiac arrest, 3 patients suffered sustained VT and 4 patients suffered runs of non-sustained VT whilst in CCU. No further cases were identified in the MI rehabilitation book.

The number of cases identified seemed low, but the Sister in charge stressed that the frequency of VT occurrence was highly variable.

## **(2) A&E**

Seventy-six cardiac arrests were recorded in the log book over 12 months. The majority of patients (61 patients, 80%) were certified dead in A&E. Five patients were referred to ITU, two to CCU and six patients to other wards. None of the entries provided information on presenting heart rhythm.

To increase recording of ventricular arrhythmia occurrence, the A&E consultant met with A&E staff and informed them of the study. He stressed the need for staff to note the type of rhythm recorded on ambulance and/or A&E ECG in the log entry. He also recommended frequent visits to check the log book to remind staff of the study. A three month prospective pilot was undertaken to assess the feasibility of frequent A&E visits and to increase study awareness. No problems were identified during this pilot phase.

Two additional methods were added to the main study methods to help identify those cases most likely to have been primarily caused by a ventricular arrhythmia i.e. excluding acute MI cases, cases where the presenting rhythm was an atrial arrhythmia and arrests due to other causes. Most of the cardiac arrest logs were of patients who had died before entering the resuscitation room. There was no information on the heart rhythm of these patients. Ambulance reports held in the A&E department were accessed for information on heart rhythm. Furthermore, using hospital numbers, the post-mortem database (explained in more detail in Chapter 6) was checked for causes of death.

## **(3) Non-invasive diagnostic testing**

The yield of VT from non-invasive diagnostic testing over a 3 month period is shown in table 5.5 below. At the time of piloting, it wasn't clear whether to use the broader case definition of VT as described in the literature or the pragmatic definition. Data were therefore recorded on both definite VT (four or more consecutive ventricular beats at a rate of 100 bpm or higher) and possible VT (three or more consecutive beats at a rate of 100 bpm or higher). The table shows the number of definite VT cases and definite and possible VT cases (all VT)

identified at SGH and RSH. It also shows the total number of Holter monitor reports analysed during this time period in both hospitals. The monthly yield was the total number of cases identified in both hospitals divided by the total number of Holter monitoring reports analysed.

**Table 5.5 Tabulation of all 24 hour tapes undertaken and number of definite and definite and possible VT (all VT)**

Month	No. cases @ SGH	Total no. tapes @ SGH	No. cases @ RSH	Total no. tapes @ RSH	Monthly yield
<b>Jan</b>					
Definite VT	2	89	1	145	1.3%
All VT	6		3		3.9%
<b>Feb</b>					
Definite VT	5	95	0	118	2.4%
All VT	7		1		3.8%
<b>Mar</b>					
Definite VT	5	73	2	125	3.5%
All VT	6		2		4%
<b>Total</b>					
Definite VT	12	257	3	388	2.3%
All VT	19		6		3.9%

Fifteen definite VTs were logged and 10 possible VTs. 645 analysers' reports were available (a further 151 tapes were logged in the Holter monitor book but no report was identified). The diagnostic yield of definite VT over this period was 2.3%. For possible and definite VT the yield was 3.9%.

Thus, if a pragmatic definition of NSVT was used in this study about half of the textbook defined NSVT would be excluded from the study. The problem is whether identification of what wouldn't be deemed Doctor diagnosed VT would be feasible and comprehensive over 12 months duration, particularly when looking for these cases using other methods. It was decided that many of the more broadly defined, least severe, VT cases would be missed and therefore a pragmatic case definition would be adopted.

The CIRUS study had been running for over 12 months prior to this study's start date and no patients had been diagnosed with ventricular arrhythmias using the REVEAL implantable device in that time period.

#### **(4) Invasive diagnostic testing**

Sixty-five 'VT stimulations' were undertaken during EPS in 2001. Thirty-two patients (49%) had inducible VT. 40% (26 patients) did not have inducible VT. One patient had inconclusive test results and 6 patients had no decision recorded.

##### **5.1.4.3 Feasibility study 1 conclusions**

All four methods identified potential cases. Apart from the minor changes described, it was decided that these methods would be used in the main study. Non-invasive diagnostic testing identified the largest number of cases. Although, invasive diagnostic testing (EPS) identified 32 cases, some of these cases may not have been newly diagnosed. Furthermore, EPS was provided as a tertiary service; some patients may have resided outside of the study catchment area. A small number of cases were identified in coronary care. It was clear from discussions with the staff that due to the variability of cases presenting and the lack of central logging, a hot pursuit method would be the only way of identifying cases in this setting.

It would have been useful to have determined the amount of overlap in identified cases between these methods; each may have been identifying the same cases. This was not an objective of the feasibility study but would have helped determine which methods were serving as sole providers of cases and which as cross-checking methods. Unfortunately, two methods were piloted over different time periods and very little information was available on each patient due to the lack of ethical permission at that time.

##### **5.1.5 Feasibility study 2**

The aims of this feasibility study were to:

- Determine potential cross-boundary flow from the proposed study catchment area and then,

- Assess the feasibility of identifying cases at hospitals other than SUHT

At this stage, it was not clear whether cases from two local hospitals just outside the boundaries of the SSWHA i.e. the RHCH and the Royal Bournemouth Hospital would be included in this study or whether wards with a significant flow of cases to these hospitals would simply be excluded. If cases from these hospitals were included, this would provide a much larger number of cases; increasing precision in the assessment of differences between groups of cases and assessing different referral patterns and management. The issues were whether: (1) this was a feasible task for one investigator and (2) ease of identifying cases.

#### **5.1.5.1 Feasibility study 2 methods**

The potential for cross-boundary flow of cases from the SSWHA catchment area to these hospitals was explored with a routine data analysis (Hospital Episode Statistics, HES) of admissions for diagnostic codes of ventricular arrhythmias or syncope over a 12 month period (2000-2001). HES data were requested from the National Casemix Office on all admissions for residents within the SSWHA area with information on hospitals providing care and the patients' ward of residence.

As non-invasive diagnostic testing yielded the largest number of cases in feasibility study 1, the intention was to undertake a retrospective audit of the number of cases that would be identified using this source at the RHCH and RBH. This was undertaken over a 7 month period at the RBH. Unfortunately, there were no logs of rhythm testing results at the RHCH. It was not possible to undertake a retrospective study of cases within this hospital. The feasibility of setting up systems to identify cases at these hospitals was discussed with resident Consultant Cardiologists and Cardiac technicians.

#### **5.1.5.2 Feasibility study 2 results and conclusions**

Results and conclusions of the HES analysis and feasibility study at the two hospitals are described below.

##### **Hospital Episode statistics analysis**

Over 12 months, 1,474 spells were recorded with diagnostic codes for ventricular arrhythmias, cardiac arrest, syncope, palpitations or collapse. Of these, 1,066

were treated at SUHT and 408 at another Trust. There was a significant flow of patients in the New Forest PCT section of the SSWHA area to the RBH (70% of spells). There was also a significant flow of patients from the Eastleigh North section of the SSWHA area to the RHCH (63% of spells). A very small number of cases (14) were admitted to Salisbury Healthcare Trust, but other than this, residents were not admitted to any other hospital.

These results highlight the need to either include cases at these hospitals to reduce the likelihood of missed cases within the catchment area or to exclude parts of the catchment area where there was significant cross-boundary flow.

### **Royal Bournemouth Hospital**

The 7 month retrospective analysis of consecutive Holter monitoring reports yielded only one case resident within SSWHA.

A link was made with the resident Consultant Cardiologist but there was little interest in the project. Setting up systems to identify cases at this hospital would have been difficult.

Due to the number of cases identified in the feasibility study, the lack of interest and system for case identification at the Royal Bournemouth Hospital and the infeasibility of one investigator frequently travelling to this hospital to enable hot pursuit of cases it was decided that cases identified at this hospital would not be included in this study. But, population data from electoral wards within the New Forest area with significant movement of cases to the Royal Bournemouth Hospital would be excluded from the study (see section 5.1.9 for method of excluding wards).

### **Royal Hampshire County Hospital**

Although a retrospective audit was not possible, the Consultant Cardiologist at this hospital was keen to provide advice and support for the study. The Senior Cardiac Technician was happy to set up a system for prospectively logging new cases of VT.

Systems were set in place to prospectively identify cases and ethical permission was sought. Due to time constraints, it was not possible to pilot these case identification methods. However, lessons learnt from piloting at SUHT helped determine methods at RHCH. These methods were:

(1) Weekly telephone calls to Holter monitor analysers. A notebook of identified VT cases was kept and a poster placed in the non-invasive cardiac department reception as a reminder of the study.

(2) A poster was placed at the nurses station on the cardiac ward. Doctors were asked to phone when a case was identified.

(3) A&E admissions log book. All admissions and details of the admission were logged. Presenting rhythm was recorded. This log book was checked on a monthly basis.

The methods set up at the RHCH were not as intensively monitored as those at SUHT because cases of life threatening ventricular arrhythmias were known to be rare and, if the patient survived the initial 24 to 48 hours, they were referred to SUHT for further management.

The following methods sections describe methods of the main study.

### **5.1.6 Case identification**

Following the feasibility studies; the finalised case identification methods and timeframe for the main study are outlined below.

Cases would be identified at SUHT and RHCH through:

- Visiting SGH CCU and checking the cardiac rehabilitation book
- Checking Accident and Emergency log books, ambulance reports and post-mortem causes of death
- Checking with analysers, the Holter monitor book and analysers reports
- Checking the EP diary and liaising with the CIRUS research nurse
- Liaising with Doctors involved in the care of cardiac patients

It was intended that cases would be identified over a 12 month period.

### **5.1.7 Cross-checking**

Attempts were made to determine the completeness of case ascertainment using routine data sources. Three methods were used; each having limitations and these are detailed below.

#### **(1) *Hospital Episode Statistics***

Hospital episode statistics (HES) data on all patients presenting at SUHT and RHCH between October 2002 and October 2003 with any one of three ICD codes during their hospital admission, namely: I47.2 Ventricular tachycardia, I46 Cardiac arrest (outside hospital) and I49 Ventricular fibrillation & flutter were requested from the Trusts. Each individual patient could be identified but newly diagnosed patients could not be distinguished from prevalent cases.

SUHT Cardiothoracic Directorate discharge summaries and out-patient clinic letters were made available. These were checked for further information on patients identified from HES data who were not screened for potential inclusion in the study.

#### **(2) *Prescriptions for anti-arrhythmic drugs***

As a validation exercise, it was intended that an audit of anti-arrhythmic drug prescriptions linked to READ code diagnosis of ventricular arrhythmias would be undertaken in one local PCT over one year. However, there were practical difficulties in undertaking such an exercise. Consultation with two General Practitioners (GPs) within this area who use READ codes revealed that patients suffering ventricular arrhythmias may simply be coded as having 'arrhythmias'. It would then be necessary to exclude the great majority of patients who suffer atrial arrhythmias alone and receive the same anti-arrhythmic drugs as patients with ventricular arrhythmias through checking patients' GP notes. It was decided that this was not feasible within the timeframe of the study.

### **(3) Southampton ICD database**

The Southampton Implantable Cardioverter Defibrillator (ICD) database was checked for cases. This database holds details of all patients, both NHS and private, who had an ICD implanted at SGH or BUPA Southampton Hospital since this service was initiated. All patients having an ICD implanted from October 2002 until March 2004 were cross-checked against the study cohort (ICDs implanted in 5 months after the study identification period ended were considered due to possible waiting time).

#### **5.1.8 Status of cases**

In screening cases for potential eligibility, hospital notes (general and cardiac notes) were checked prior to patient consent to ensure that patients were newly diagnosed. Ethical approval for this activity was granted. It was intended that all patients not meeting the inclusion criteria or living outside the catchment area would be excluded from this study using this method.

#### **5.1.9 Cross-boundary flow**

For the calculation of incidence rates it is imperative that cases are correctly matched to the population from which they reside and that there is no (or very minimal) flow of cases from this population into other populations. Cases from other populations are excluded to ensure matching. However, wards on the boundaries of the catchment area could include patients presenting to hospitals outside of the area i.e. these would be missed cases in this study.

Potential for significant cross-boundary flow was considered in feasibility study 2. It was decided that this would be dealt with by: (1) only including patients diagnosed at the Royal Hampshire Hospital who lived within a defined catchment area and (2) excluding wards where there is likely to be significant cross-boundary flow e.g. those in the New Forest where patients may be diagnosed at the Royal Bournemouth Hospital.

Retrospectively (request made in 2005), Information analysts at Southampton City PCT and North Hampshire PCT were asked to provide a list of all PCT areas (and all electoral wards contained within them) within the catchment area for services at SUHT or RHCH during the years 2002 and 2003. This included PCTs where only a

few residents required care at these centres. A request was then made to the South East Public Health Observatory (SEPHO) for data on all hospital episodes (with specific ICD-10 codes) by these electoral wards in 2002 and 2003 and by Trust where care was provided.

Hospital episode data by electoral ward were made available by SEPHO provided that 5 or more episodes were recorded for wards (patient confidentiality is considered to be breached if information on wards with less than 5 episodes is provided). Ventricular arrhythmias are relatively rare and can be miscoded. The investigator therefore requested data on all in-patient and day case episodes where the following diagnoses were recorded: Cardiac arrest, paroxysmal tachycardia, other cardiac arrhythmia, palpitations and syncope and collapse. Respectively, the ICD-10 codes for these diagnoses are as follows: I46, I47.2, I49, R00.2 and R55. An episode was a Finished Consultant Episode, either as a day case or an in-patient.

Data were made available for the period 2002 to 2003 (financial year). In the 6 PCT areas (incorporating 191 electoral wards), 2,340 episodes were recorded with the above diagnostic codes (1,959 episodes excluding suppressed data). Rules were then devised to determine which wards should be excluded from the incidence analysis due to significant cross-boundary flow of patients to hospitals outside of the study catchment area.

The following rules were applied to the electoral ward data:

If SUHT or RHCH:

1. Were the sole providers of care, this ward would be included in the catchment area.
2. Did not provide any of the care, this ward would be excluded from the catchment area.

In electoral wards where less than 5 episodes were recorded at SUHT and/or RHCH i.e. the exact number of episodes was suppressed by HES to preserve patient confidentiality. If SUHT and/or RHCH:

3. Provided 50% or more of the care i.e. another provider had suppressed data for this ward, this ward would be included in the analysis.
4. Provided suppressed data but another/other providers had more than 5 episodes recorded or more than 1 provider had suppressed data for this ward, this ward would be excluded from the analysis

In electoral wards where 5 or more episodes were recorded at SUHT and/orRHCH. If SUHT and/or RHCH:

1. Provided more than 5 episodes of care but other providers had 'suppressed data', this ward would be included.
2. Provided 50% or more of the episodes of care, this ward would be included in the analysis.

Using these rules, 111 of the 191 electoral wards were excluded from the analysis. Table 5.6 below shows the number of electoral wards and population of adults in each of the PCT areas included in the final study catchment area (excluding those 111 wards with high cross-boundary flow). Population data from a total of 80 electoral wards were included in the incidence analysis, with a population of 450,959 adults (16 years and over).

**Table 5.6 Number of electoral wards and adult population of PCTs in the study catchment area**

<b>PCT area</b>	<b>Number of electoral wards</b>	<b>Population of adults</b>
Southampton City	16	177,696
Eastleigh and Test Valley	28	127,612
New Forest	24	96,929
Mid Hampshire	12	48,722
<b>Total</b>	<b>80</b>	<b>450,959</b>

### **5.1.10 Ethics**

Ethical permission for this study was requested; firstly with the Southampton and South West Hampshire Local Research Ethics Committee and then at later date with the North and Mid Hampshire Local Research Ethics Committee. Permission was granted from both bodies with no major changes to the proposed project.

### **5.1.11 Consent of patients**

Eligible in-patients were approached regarding study consent during their stay in hospital (once clinically stable). For out-patients, and those patients too ill to discuss the study during their hospital stay, the patient information sheet and consent forms were sent to their homes (see appendix 9 for study letter, consent form and information sheet).

Once patients had consented to study entry, they were asked to complete a brief questionnaire about themselves and two quality of life questionnaires (the SF-36 and the syncope functional status questionnaire). Questionnaires were self-completed either in hospital or at home. The two quality of life questionnaires were re-sent to patients after 12 months within the study. Patients were asked to complete the syncopal functional status questionnaire only if they had experienced syncope/blackouts in the past.

### **5.1.12 Questionnaires**

Three questionnaires for self-completion by patients were used in this study: A baseline questionnaire, the Short-Form Health Survey Questionnaire and the Syncopal Functional Status Questionnaire.

The aim of the baseline questionnaire was to capture basic but essential information about each respondent such as age, gender, ethnicity, socio-economic status, care at home, whether the patient drove and their heart conditions. Information on heart condition was cross-checked against hospital notes. Appendix 10 shows the baseline questionnaire.

The Short-Form Health Survey Questionnaire with 36 items (SF-36) is a well-validated and reliable generic quality of life questionnaire<sup>80;81</sup>. The SF-36 is shown in appendix 11. Version 1 of the SF-36 was used in this study. It has 36 items and

measures health status through eight multi-item dimensions: physical functioning, social functioning, and role limitations due to physical problems, role limitations due to emotional problems, mental health, energy/vitality, pain and general health perception. Each scale is scored on a 0-100 possible range. These scores can be combined into two weighted scores: PCS and MCS. Higher scores indicate a better quality of life.

The reliability of the SF-36 has been reported in 14 studies<sup>82</sup>. Results from these studies have been pooled and the median of reliability coefficients across studies equalled or exceeded 0.8 for each scale i.e. 80% or more of the measured variance is reliable (with the exception of the Social Functioning Scale, with a median of 0.76)<sup>82</sup>. The content validity of this questionnaire has been evaluated by comparing the SF-36 with seven other widely used survey forms. The SF-36 includes all of the most frequently represented health concepts in these survey forms and its results correlate well ( $r^2=0.4$ ) with omitted general health concepts. Construct validity has been analysed using factor analytic tests, criterion-based approaches and correlational studies<sup>82</sup>.

Syncope is one of the commonest presentations for patients experiencing ventricular tachycardia. The Syncopal Functional Status (SFS) Questionnaire has been designed to measure quality of life associated with experiencing syncope. This questionnaire is shown in appendix 12. The SFS questionnaire has been designed to measure quality of life associated with experiencing syncope. An 11 question matrix of yes/no questions assesses the ways that syncope interferes with a patient's life and three Likert-scale questions assess the fear and worry a patient may experience about syncope. Higher scores indicate a greater degree of syncope associated impairment.

The validity of this disease specific questionnaire has been assessed in one study<sup>83</sup> The SFS questionnaire was pilot tested on 84 subjects and validated on a separate cohort of 49 patients. Scores from the 49 patients correlated with both physical and psychosocial dimension scores on the Sickness Impact Profile (a measure of functional status) ( $r^2 = 0.35-0.36$ ,  $p = 0.01$ ) and with five of ten subscale scores on the Symptom Checklist 90-R (a measure of psychological distress) ( $r^2 = 0.3-0.43$ ,  $p = 0.004-0.02$ ). Recently, the SFS questionnaire has been used to measure quality of life in a randomised trial of a diagnostic test for unexplained syncope (the CIRUS trial) in Southampton.

All three of these questionnaires were self-completed. The reasons for not administering these questionnaires as part of an interview were time and travel costs. Both the SF-36 and the SFS questionnaire have been designed, and used, as self-completion questionnaires, although a lower response rate for completion of the SF-36 has been reported in patients over the age of 65 years.

### **5.1.13 Information on patient characteristics**

The baseline questionnaire provided some information on patient characteristics. Hospital notes provided further information. Data collected were: age; sex; date of diagnosis; presentation, severity of arrhythmia i.e. whether sustained VT, non-sustained VT, inducible VT or cardiac arrest; CHD history (e.g. past history of MI, angina, heart failure); other co-morbidities and current and previous health care management for symptoms. The clinical data extraction form is shown in appendix 14. It is based on a data extraction form used in a local RCT (CIRUS) on unexplained syncope but adapted slightly (with advice from a Consultant Cardiologist) for this study.

### **5.1.14 Follow-up**

All new cases of diagnosed ventricular arrhythmias were identified and followed up for 12 months.

Centralised flagging of deaths via the ONS was the intended method of identifying deaths and accessing data on cause. Unfortunately, this was not possible. ONS requested a change to the patient information sheet, informing the study participant of this data access requirement. This request was received subsequent to the majority of the patient information sheets being distributed to study participants.

Therefore, deaths occurring within the period were identified via the Hospital Patient Administration System. Information on causes of death within the entire study catchment area was provided by New Forest PCT with permission from the Office of National Statistics (ONS).

Prognosis and health care management were followed up using hospital case notes. All relevant hospital admissions, out-patient visits, management and drug

use data were recorded. Patients alive at 12 months were re-sent the two quality of life questionnaires.

### **5.1.15 Analysis of results**

#### **Incidence analyses**

Postcode analysis was undertaken to match cases to the study catchment area. The patients' residential postcode was matched to electoral wards using the mapping facility on the ONS Census 2001 website<sup>84</sup>.

Incidence rates were calculated as the number of new cases of diagnosed ventricular arrhythmias in 12 months within the catchment area divided by the number of adult persons resident within the catchment area (population data taken from the 2001 Census, as previously described). All new cases were included in the analyses i.e. consenting eligible patients and non-consenting potentially eligible patients. Confidence intervals for rates, assuming a Poisson distribution, were derived.

Age-sex standardisation of incidence rates was undertaken using the direct method of standardisation. The English population was used as a standard (data broken down by gender and 10 year age bands were taken from the 2001 Census; with a total English adult population of 39,861,017).

#### **Prognostic study data**

Descriptive data were presented on presenting symptoms, severity of ventricular arrhythmia, CHD history and health care management.

#### **Quality of life analysis**

Results from the SF-36 were presented as the mean scores (and standard deviations) for the Physical (PCS) and Mental Health Component (MCS) Summary Scales at baseline i.e. at the time of diagnosis and at 12 months follow up. Results from the SFS syncope questionnaire were presented as mean scores (and standard deviations) for syncope dysfunction at the same time points. The

difference between scores from baseline to follow-up was assessed using a Student t test for paired data. A value of  $p < 0.05$  was considered significant.

Mean PCS and MCS scores were derived using an SPSS syntax based on the scoring algorithms in the SF-36 Health Survey manual<sup>82</sup>. Inferences were made for missing values. U.S. population norms were used<sup>85</sup>. U.K. population norms were not available for this version of SF-36 at the time of the study.

### **Survival analysis**

Survival data were presented in a Kaplan-Meier plot. No assumptions were made on these data for this analysis. Time to event was defined as the time from diagnosis to date of death. Cases were censored at end of follow up or loss to follow-up. All patients consenting to study entry and meeting the inclusion criteria were included in this analysis.

The log rank test was undertaken to assess differences in survival between: (1) patients aged 65 years and over and those patients younger than 65 years and (2) patients with life threatening ventricular arrhythmias as opposed to those patients with non-sustained ventricular arrhythmias. The null hypothesis in both of these analyses was that there was no difference in survival between prognostic groups. The alternative hypothesis being that there was a difference in survival between the groups.

A Cox regression analysis was attempted to assess the effect of prognostic factors on survival. The prognostic factors selected for inclusion were; age ( $\geq 65$  years vs  $< 65$  years), gender, severity of ventricular arrhythmia (life threatening vs non-sustained ventricular arrhythmia), left ventricular function as assessed on echocardiogram and previous history of an MI. Plots of each prognostic factor were viewed to determine whether the proportional hazards assumption was met (if the lines representing each strata crossed, this was considered a violation of the assumption and the factor was excluded from the analysis).

### **5.1.16 Sample size**

No previous studies on the epidemiology of ventricular arrhythmias had been identified when designing this study. This was an exploratory study and an estimated proportion of events within a specified sized population were calculated using limited information from the literature.

The NICE estimate of potential ICD need (50 per million population) and the USA ICD rate in 1998 (169 per million population) were used to calculate the expected number of events. The estimated study population size was 1.5 million (the final study population size was 450,959). If the population size was 1.5 million, between 75 (95% CI 56 to 99) and 254 (95% CI 217 to 295) incident cases would be identified in 12 months.

## **5.2 Results**

The number of identified cases and some basic characteristics are described, then the incidence analysis and finally prognosis.

The intention was to identify cases over a 12 month period. However, due to personal reasons (maternity leave) the investigator completed recruitment at SUHT at 11 months and 6 months at RHCH. These data were converted into an annual incidence rate. All consenting eligible patients were followed up for 12 months.

### **5.2.1 Screening cases for study inclusion**

The study started in SUHT on 21st October 2002 and in Winchester on 21st March 2003. Case identification ended on 16<sup>th</sup> September 2003.

363 patients presenting at SUHT or RHCH (or having community based test results analysed at these hospitals) were screened for study inclusion. The flow-diagram below (figure 5.3) shows the screening process. 132 patients had died of a suspected out-of-hospital cardiac arrest i.e. died in the community or in A&E. 225 patients were alive at the time of screening. 117 of these patients were excluded from this study for the reasons shown in the first box of figure 1. 114 patients were believed to have met the inclusion criteria at the time of study entry. However, 30 of these patients did not provide consent to study inclusion and 4

patients were not identifiable i.e. these patients were identified on screening but could not be found due to insufficient information. Twelve further patients were later excluded due to reasons shown in the second box on figure 5.3.

**Figure 5.3 Number of patients screened for study entry, included and excluded cases with reasons for exclusion**

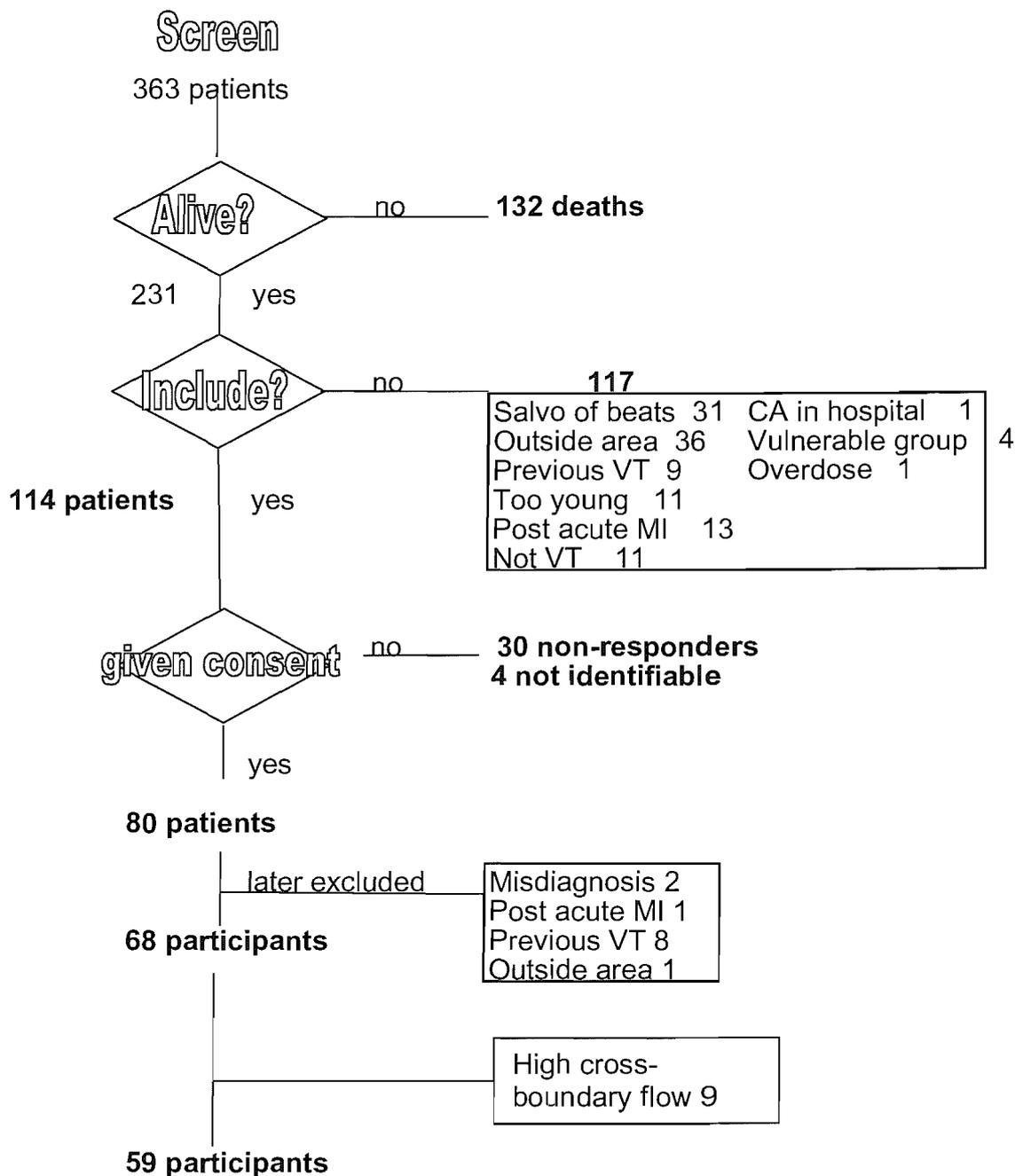


Table 5.7 shows the case identification methods used and the number of cases primarily identified by each method. There was some overlap between sources,

but this was not comprehensively recorded. The results shown are therefore of the source that first identified the patient.

Most patients screened were initially identified through the A&E resuscitation log (136 patients) and the Holter monitoring log and reports (115 patients). Even though cases were only identified at RHCH over a 6 month period (as opposed to 11 months at SUHT), the number of cases identified was very much lower than at SUHT.

**Table 5.7 Primary case identification methods and number of cases identified**

<b>Method</b>	<b>Number identified (%)</b>
<b>SUHT</b>	
A&E resus log	136 (37.5%)
SGH Holter log & reports	115 (31.7%)
CCU visit	50 (13.8%)
EP diary	36 (9.9%)
RSH Holter analyser	9 (2.5%)
ICD code check	2 (0.6%)
Cardiac rehab book	1 (0.3%)
<b>RHCH</b>	
Dr contact	11 (3%)
RHCH Holter monitoring	2 (0.6%)
RHCH event recorders	1 (0.3%)
<b>Total</b>	<b>363</b>

The groups within the screening flow-diagram (figure 5.1), in order of the diagram, are explained below.

- **Deaths prior to consent**

132 patients died prior to a request for study consent. Most of these patients died in SUHT A&E (or outside hospital, but were brought into the A&E resuscitation

room). Ambulance reports on these cases can be identified on the A&E system by hospital number, patient name, date of birth and date of admission. For 24 cases some or all of these data were missing. 108 cases were checked for ambulance reports to determine presenting heart rhythm. Table 9 shows the results from this exercise.

**Table 5.8: Rhythm recorded in ambulance report for patients who died of an out-of-hospital cardiac arrest**

<b>Presenting heart rhythm</b>	<b>Frequency</b>	<b>Percent</b>
Ventricular fibrillation	12	9%
Asystole	13	9.9%
Bradycardia	2	1.5%
No ambulance report or no information in report on presenting rhythm	105	79.5%
<b>Total</b>	132	100%

For the majority of patients who died of an out-of-hospital cardiac arrest, there was no information about heart rhythm in the ambulance report or (more often) an ambulance report was not even found. Due to the very high proportion of missing data, information on presenting rhythm was not used to determine the number of patients with cardiac arrests associated with ventricular arrhythmias. The post-mortem database was checked to identify the cause of death for those cases where a post-mortem was undertaken. The results of this exercise are described in the next chapter.

Alongside this study the investigator undertook a study of Sudden Cardiac Death (SCD) in Southampton and South West Hampshire Health Authority area (see chapter 6). These cardiac arrest data will be linked to data from the SCD study to help generate an estimate of the number of SCDs presumed to be caused by a ventricular arrhythmia in the community. These data will not be considered further in this chapter.

- **Patients excluded prior to consent**

117 patients were excluded from study entry. The reasons for exclusion are shown in the flow-diagram. The most common reason being living outside of the study catchment area (30.8% of those patients excluded). Another common reason for exclusion was 'salvo of beats' ie they did not fulfil the local Doctors' definition for VT (31 patients, 26.5% of excluded patients). Patients had been described, mainly in the Holter monitoring reports, as experiencing a run of ventricular ectopic beats but these patients did not have a run long enough and/or fast enough as described in the case definition (nor diagnosed as having VT). Four patients were excluded from this study for ethical reasons; they were deemed 'vulnerable' by nursing staff i.e. unable to provide consent.

- **Non-consenting and unidentifiable patients**

30 patients did not give their consent to the prognostic study (non-responders) and 4 patients were not identifiable (these patients were identified by doctors in Winchester (2 patients) and CCU nurses (2 patients) via the phone, but were not found on the wards nor checking other sources of patient identification.

Non-responders living within the catchment area were included in the incidence analyses. Some information is known about these 30 non-responders and we can make some comparisons between responders and non-responders, see table 5.9.

**Table 5.9 Comparison of baseline data on responders and non-responders**

<b>Group (Number)</b>	<b>Gender</b>	<b>Mean age (SD)</b>	<b>Type of ventricular arrhythmia % of group</b>
Responders N = 68	46 males (68%)	67 years (15.7)	69% NSVT, 16% Sustained VT, 10% inducible VT, 4% VF
Non-responders N = 30	19 males (63%)	76 years (12.9)	72% NSVT, 17% Sustained VT, 4% inducible VT, 7% VF

Non-responders tended to be older ( $p = 0.001$ ) and there were slightly more males ( $p = \text{NS}$ ). Type of ventricular arrhythmia was similar: with slightly more patients from both ends of the severity spectrum i.e. NSVT and VF in the non-responders group.

- **Consenting patients**

80 patients provided their consent to study entry and appeared to meet the study criteria at the time of study entry. However, further information resulted in the exclusion of another 12 patients (1 patient lived outside the area, 2 patients were misdiagnosed, 1 had VT within 24 hours post MI and 8 patients had a previous diagnosis of VT recorded in their notes). Therefore, 68 patients met the inclusion criteria and consented to this study.

Nine of the 68 consenting patients lived in wards with a high cross-boundary flow. These patients were therefore excluded from the incidence analyses. 59 consenting patients were therefore included.

### **5.2.2 Incidence study analyses**

Cases in the incidence analyses were patients known or believed to meet the inclusion criteria on the basis of available information i.e. for patients consenting to study entry, full information from hospital notes and patient questionnaires ensured these were incident ventricular arrhythmia cases. For non-consenting patients checks could only be made from available information at the time of screening (see methods section). Therefore, some non-consenting cases and deaths could have been misdiagnosed or suffered previous ventricular arrhythmias.

Table 5.10 below shows the number of consenting (responders) and non-responders, including patients who were deemed too vulnerable for consent, within the catchment area (excluding cases in wards with a high cross-boundary flow) by status at time of screening. Due to the exclusion of some consenting cases during study follow up (for the reasons shown on the flow-diagram), an assumption of the same proportion of non-responding patients being excluded has been made. Of the original 80 consenting patients, 21 were excluded.

**Table 5.10 Status and number of cases within the study catchment area**

<b>Status of cases at time of screening</b>	<b>Number of cases in catchment area</b>
Consenting patients	59
Non-responding patients (N = 30) and 'vulnerable group' patients (N = 4)	25 (59/80*34)

Case ascertainment took place over 11 months at SUHT and 6 months at RHCH. Only fourteen cases were logged at RHCH over the 5 month period, 3 of which were not identifiable. Of the 11 identifiable cases, just one lived within the study catchment area. This one case was referred to SUHT on the same day of admission to RHCH.

There are a number of options for dealing with this issue, these are: 1. Simply to assume that if one case was identified over 5 months then approximately two cases would be identified over 12 months and use this estimate in deriving an annual incidence rate of live cases within the whole catchment area, 2. Or assume that, as with the one RHCH case, ie to avoid double counting that all further RHCH cases would be referred on to SUHT and identified through SUHT case identification methods and 3. To exclude the 1 RHCH case and all wards within the catchment area where there is a high cross-boundary flow to RHCH to derive an incidence rate for SUHT cases and their catchment area only. Options 2 (this page) and 3 (page 141) will be undertaken and the pros and cons of these approaches discussed.

### **Option 2 Whole study catchment area incidence analysis**

The population is described in the methods. The total population size was 450,959 adults. 59 consenting patients and 25 non-consenting patients were identified during 11 months and alive at the time of case screening. The results are described in terms of person, place and time.

### 5.2.2.1 Overall incidence analysis

The overall incidence rates and confidence intervals are shown in the table below.

**Table 5.11 Annual incidence rates per million population for patients with ventricular arrhythmias alive at time of screening**

Status of cases at time of screening	Estimated number of cases in 12 months	Incidence rate per million population per annum	95% Confidence intervals
Consenting patients	64*	142	111, 181
Consenting and non-consenting patients	91**	202	164, 248

\*cases identified over 11 months (59/11 \*12)

\*\* $(25 \text{ cases}/11 * 12) + 64$  consenting patients

Therefore, the incidence rate of newly diagnosed ventricular arrhythmias in this study was 202 per million population. This incidence rate is of all persons who survived to hospital admission. It does not include SCDs due to ventricular arrhythmias. This will be considered in more detail in the next chapter of this thesis.

### 5.2.2.2 Incidence analysis by age and gender

Age-sex standardised incidence rates, rates by age and gender and type of ventricular arrhythmia are presented. Rates can be easily calculated for responders but not for non-responders. Assumptions were made about the exclusion of non-responder cases using information on the proportion of responders who were later excluded.

There were 34 non-responders. It was assumed that 9 would be subsequently excluded, leaving 25 patients. These 9 cases were excluded at random from the following analyses (in sections 5.2.2.2, 5.2.2.3, 5.2.2.4 and 5.2.2.5).

The age-sex standardised incidence rate (direct to England) of ventricular arrhythmias was 203 pmp (95% CIs 164, 252). Table 13 shows the annual

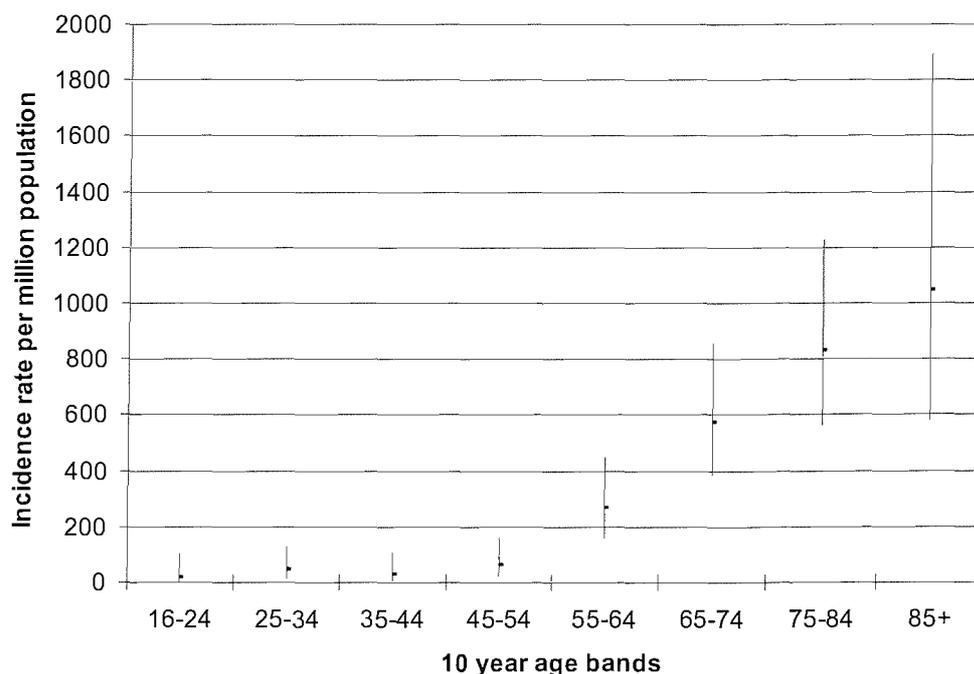
incidence rate broken down by gender. The incidence of ventricular arrhythmias in males was almost double that of females. Except one black male, all cases in this study were white.

**Table 5.12 Annual incidence rates per million population broken down by baseline factors**

Gender	Number of cases identified over 11 months	Incidence rate per million population per annum	95% Confidence Intervals
Males	55 males	273	210, 356
Females	29 females	137	95, 197

Figure 5.4 shows the annual incidence rate by age group. There was a steep increase in incidence rates with age group from 45 years onwards but confidence intervals were wide and overlapped between 4 age groups.

**Figure 5.4 Annual incidence rate by age group**



A chi-squared test for trend showed that this increase in incidence with age was highly statistically significant ( $p < 0.0001$ ).

### 5.2.2.3 Incidence analysis by type of ventricular arrhythmia

The table below shows the incidence of life threatening ventricular arrhythmias and the much less severe form; non-sustained ventricular tachycardia (again, non-responders were included in this analysis using the approach described in section 5.2.2.2). About one third of ventricular arrhythmia cases were life threatening i.e. sustained VT, cardiac arrest or inducible VT, with an incidence rate of 62 per million population. The proportion of life threatening cases considered for and implanted with an ICD will be discussed in the results of the prognostic study (section 5.2.4).

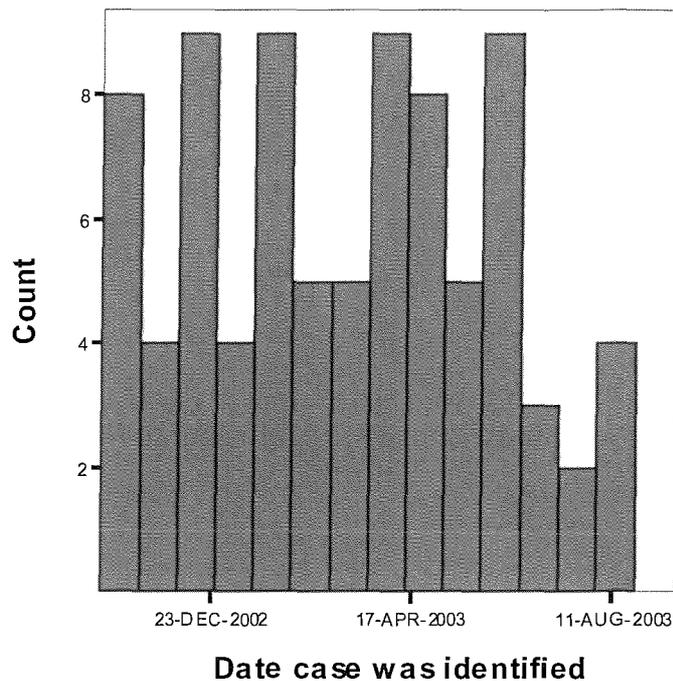
**Table 5.13 Incidence of ventricular arrhythmias by severity**

Type of ventricular arrhythmia	Number of cases identified over 11 months	Incidence rate per million population per annum	95% confidence intervals
Life threatening ventricular arrhythmia	26	62	43, 90
Non-sustained VT	58	140	109, 179

### 5.2.2.4 Analysis by time

Seasonal variations in case identification were explored. Figure 5.5 below shows the dates when consenters and non-responders were diagnosed. There does not appear to be a pattern in the frequency of diagnoses during the timeframe of the study. There was no significant difference in the proportion of winter (October-March) (54%, 95% CIs 36%, 55%) and summer diagnoses (April-August) (46%, 95% CIs 45%, 65%). However, if rolling averages are calculated, these suggest a possible seasonal variation.

**Figure 5.5 Histogram of the frequency of diagnoses by date of diagnosis**



### 5.2.2.5 Incidence analysis by place

Incidence rates by PCT areas are shown in table 15 below. Population data for each PCT can be found in table 5.14.

**Table 5.14 Number of cases and incidence rates by PCT areas**

	<b>Number of cases identified over 11 months</b>	<b>Incidence rate per million population per annum</b>	<b>95% confidence intervals</b>
<b>Southampton City</b>	35	214	156, 294
<b>Eastleigh and Test Valley</b>	27	235	164, 336
<b>New Forest</b>	18	206	133, 320
<b>Mid Hampshire</b>	4	82	31, 219

Incidence rates in the 3 SSWHA PCTs were very similar. However, the rate in Mid Hampshire was much lower. Gender, median age and proportion with life threatening ventricular arrhythmias by PCT area are shown in the table below. Patients in the New Forest area tended to be older. The percentage of males was greater in Eastleigh and Test Valley and Mid Hampshire (where patients tended to be younger). The rate of life threatening ventricular arrhythmias was highest in the New Forest area and lowest in the Eastleigh and Test Valley area. The confidence intervals around these estimates were wide. However, one could hypothesise that the high rate in the New Forest area could be due to the higher average age of the population. The lower rate in the Eastleigh and Test Valley area could be due to access problems i.e. these cases could be admitted to either SUHT or the RHCH and the distance for these patients to travel to these hospitals is possibly the greatest.

**Table 5.15 Median age, proportion of male cases and incidence of life threatening ventricular arrhythmias by PCT area**

<b>PCT</b>	<b>Median age in years (minimum, maximum age)</b>	<b>Proportion of males % of cases</b>	<b>Incidence of life threatening ventricular arrhythmias per million population (95% CIs)</b>
<b>Southampton City</b>	71 (25, 89)	60%	56 (30.3, 104.6)
<b>Eastleigh and Test Valley</b>	72 (24, 88)	72%	24 (7.6, 72.9)
<b>New Forest</b>	74 (54, 90)	67%	93 (48.3, 178.5)
<b>Mid Hampshire</b>	61 (25, 85)	75%	62 (19.9, 190.9)

### Option 3 SUHT catchment area incidence analysis

If we apply the same cross-boundary flow rules to the study catchment area, but treat RHCH as a hospital outside of the study boundaries, this would exclude all Mid-Hampshire PCT wards and 7 wards in the Eastleigh and Test Valley PCT area. The total population of adults in this catchment area is 358,244 persons. Five consenting patients and 4 non-consenting patients resided in wards with high cross-boundary flow and were therefore excluded from the analysis. Thus, 54 consenting patients and 21 non-consenting patients were included in the analysis.

The table below shows the number of cases in this catchment area and the incidence rates per million population with 95% confidence intervals.

**Table 5.16 Annual incidence rates per million population for patients with ventricular arrhythmias**

Status of cases at time of screening	Estimated number of cases in 12 months	Incidence rate per million population per annum	95% Confidence intervals
Consenting patients	59*	165	128, 213
Consenting and non-consenting patients	82**	219	176, 272

\* $((59-5)/11) * 12$

\*\* $((25 - 4 \text{ cases})/11) * 12 + 59 \text{ consenting patients}$

Therefore, the incidence of ventricular arrhythmias in the SUHT catchment area was 219 per million population. This is comparable to the incidence rate of 202 per million population generated from the whole catchment area. The confidence intervals are wide and overlap between these two estimates. The age-sex standardised incidence rate in the SUHT catchment area was 228 pmp (95% CIs, 182, 286).

### 5.2.3 Cross-checking

SUHT and RHCH hospital episode statistics and the Southampton ICD database were checked after completion of the study case identification phase to determine whether cases may have been missed. The results of this exercise are presented below.

#### **SUHT HES data**

Three hundred and ninety-three patients with episodes of care where an ICD-10 code of I47.2, I46 or I49 was recorded were identified in the SUHT hospital management system during the case identification phase. In comparing these data with the final study cohort, HES identified 26 of the 68 patients (38%). HES data identified 18 of the 21 life threatening VA cases (86%) and 8 of the 47 non-sustained VT cases (17%). Coding of non-sustained VT as a diagnosis of ventricular arrhythmia appears to be rare.

Ninety-eight of the 393 patients were screened for inclusion in the study. Therefore 295 patients were coded with a diagnosis of ventricular arrhythmias during the case identification phase but not identified in screening for study cases.

Six of these 295 patients were under the age of 16 years, leaving 289 potentially missed cases. Fifty patients were selected at random (17% of cases) and their discharge summaries and/or out-patient clinic letters checked for further details of their arrhythmia. Table 5.17 below shows the results of this exercise.

**Table 5.17 Information relating to inclusion criteria of 50 SUHT HES cases not identified during screening**

<b>Further information</b>	<b>Number (%) of patients</b>
<b>Cases not meeting inclusion criteria n = 42</b>	
Residing outside catchment area	19 (38%)
ICD implanted prior to study entry	6 (12%)
Peri-operative VT/VF	6 (12%)
Atrial arrhythmia or AV nodal arrhythmia (inappropriately coded VAs on discharge summaries)	7 (14%)
Previous history of VT	4 (8%)
Fatal VT/VF during hospital admission	3 (6%)
<b>Potentially missed cases n = 5</b>	
Acute MI, VT/VF during hospital admission but timing unclear	5 (10%)
<b>Total</b>	<b>50</b>

Of the 50 cases checked, 42 (90%) did not meet the inclusion criteria for this cohort study. Most of these patients lived outside of the catchment area. Interestingly, seven patients appeared to be miscoded as suffering ventricular arrhythmias during admissions; only information regarding atrial arrhythmias was detailed in their discharge summaries.

Further information would be required on 5 (10% of checked summaries) to determine study inclusion. If these randomly selected cases were no different to the remaining cases, there would be about 39 potentially missed cases. However, these 5 patients who suffered an acute MI may have had VT or VF during the acute phase. These patients were not identified on screening but this could be because the Coronary Care nurses were made aware of the study inclusion and exclusion criteria and did not inform the study investigator of their occurrence.

### **RHCH HES data**

Sixty-one patients had a diagnosis of ventricular arrhythmias during an episode of care at RHCH during the case identification phase at this hospital. Unfortunately, the hospital numbers at RHCH do not correspond with those of SUHT. Therefore, it is not possible to compare these patients with those screened for the study. However, some checks can be made.

All of the 61 patients were over 16 years of age. However, 49 of these cases had a 'discharge destination' code of 'death'. Many of these patients probably died in A&E.

Of the 12 patients who survived to hospital discharge, one was included in the cohort study, another appeared to meet the inclusion criteria but did not respond to requests for study consent and a third patient was excluded; living outside of the study catchment area.

Details of the remaining 9 patients were: 4 acute MIs with cardiac arrest/ventricular tachycardia (timing unspecified), 2 overdoses leading to cardiac arrest and 3 cardiac arrests in hospital associated with other disorders. If the 4 patients suffering a cardiac arrest post MI did so in the chronic phase, these patients should have been considered for study inclusion. They were not identified using case identification methods set up at RHCH, but may have been transferred to SUHT and identified using SUHT methods.

### ***Southampton ICD database***

For the period: 1<sup>st</sup> October 2002 to 31<sup>st</sup> March 2004, 151 ICDs were implanted either at SUHT or at BUPA Southampton. Forty-eight (32%) of these were implanted in patients residing in the study catchment area. Seventeen of these patients were included in the study and six had suffered VT but were later excluded from the study because they were not incident cases. The remaining 25 ICD patients were checked against the study screening database to identify any missing cases or reasons for exclusion. These reasons are shown in the table below.

**Table 5.18 Patients having ICDs who were not screened for the study**

Reason for exclusion	Number of cases
No VT. Patient had ICD for hereditary condition, DCM or heart failure	7
Patient diagnosed before or after study case identification period	15
No information	2
Potential missed cases	1
<b>Total</b>	<b>25</b>

The main reason for not including these ICD patients in the study was that they were diagnosed before or after the case identification phase of the study. Another reason was that patients hadn't suffered a ventricular arrhythmia (an ICD was implanted to manage potential arrhythmias associated with heart failure). There was no further information on two patients; it was therefore not possible to determine their reasons for having an ICD.

One case should have been screened for study inclusion but was missed. This patient had been admitted to a cardiac ward. During their stay they suffered a cardiac arrest (presumably this patient was in ventricular fibrillation). The patient had an EPS, this was negative, but an ICD was implanted. The justification for an ICD was not given in the hospital discharge summary. In-hospital cardiac arrests were excluded from this study except when the cardiac arrest occurred post MI (not acute phase). This could have been a missed case from the study but without access to patient notes this cannot be confirmed.

### ***Conclusion of cross-checking***

In conclusion, a small number of cases may have been missed from this study. Without access to these patients hospital notes it is not possible to confirm or refute patient eligibility. These patients suffered an acute MI with the occurrence of a ventricular arrhythmia during their admission. However, if these patients

experienced a ventricular arrhythmia during the acute phase post-MI they would not have been eligible for this study.

## 5.2.4 Results from the prognostic study

Sixty-eight patients provided their consent to be included in the prognostic study. These were consecutive cases meeting the inclusion criteria and residing within the catchment area (**including** wards with high cross-boundary flow), see figure 5.1.

### 5.2.4.1 Baseline characteristics of consenting patients

Baseline characteristics are shown in the tables below – general baseline information, information relating to the arrhythmia and patient presentation and previous heart disease history.

**Table 5.19 Baseline characteristics of 68 patients consenting to entry to the prognostic study**

Characteristic	Number of patients
Gender	46 males (68%), 22 females (32%)
Median age (youngest, oldest)	71 years (25 years, 90 years)
Ethnicity	67 whites, 1 black
Marital status n = 66	45 married/couple (66%), 5 single (8%), 15 widowed (23%), 1 divorced (2%)
Home situation n =66	44 live with spouse/partner (67%), 18 live alone (27%), 2 live with family members (3%) and 2 live with non-family members (3%)

Most cases were males. Patients tended to be elderly but the age range was wide. All but one patient was white. Most patients were married and less than one third lived alone.

Patients were asked about their current, or last previous, occupation. Fifty-six of the 68 consenting patients provided information about occupation. There were similar proportions of patients in each socio-economic class compared with 2001 census data for the study catchment area and England as a whole. However, the study cohort was fairly elderly; many of the patients having retired. Age-adjusted census data would be required to make meaningful occupational comparisons.

Table 5.20 shows baseline data on the cohort relating to their presentation to the health service with ventricular arrhythmia.

**Table 5.20 Baseline data relating to presentation with ventricular arrhythmia**

<b>Characteristic</b>	<b>Number of patients</b>
<b>Type of ventricular arrhythmia</b>	
Non-sustained VT	47 (69%)
Sustained VT	11 (16%)
Inducible VT	7 (10%)
VF (cardiac arrest)	3 (4%)
<b>Type of diagnostic test</b>	
Holter monitor	43 (63%)
ECG	10 (15%)
EPS	8 (12%)
CCU continuous ECG	5 (7%)
Cardiomemo	1 (2%)
Event recorder	1 (2%)
<b>Symptoms/reasons for referral for diagnostic testing</b>	
Syncope/blackouts	13 (19%)
Palpitations	13 (19%)
Shortness of breath	12 (18%)
Chest pain	10 (15%)
Fall	5 (7%)
Cardiac arrest	4 (6%)
Presyncope/dizziness	2 (3%)
Other	2 (3%)
Patient monitoring	1 (2%)
No information/missing	6 (9%)
<b>Patients symptomatic during testing?</b>	
Yes	15 (22%)
No	28 (41%)
Not stated	18 (27%)
Not applicable	7 (10%)
<b>Nature of admission to hospital</b>	
Acute admission	36 (53%)
Elective admission	8 (12%)
Not admitted	24 (35%)

Over two thirds of patients presented with non-sustained VT (69%). The majority of patients with life threatening ventricular arrhythmias presented with sustained VT. Very few patients (7 cases) presented with inducible VT. Only 3 patients survived a cardiac arrest and consented to study inclusion. A much higher number of suspected cardiac arrest cases were screened but only 18 patients survived (14 of these patients did not meet the inclusion criteria and one patient was not identifiable).

Most patients were diagnosed using a Holter monitor. Forty-two of the 43 patients diagnosed using a Holter monitor had non-sustained VT, the other suffering sustained VT. Most patients diagnosed using an ECG had sustained VT. Seven of the eight patients having EPS had inducible VT, the other had inducible VF. 65% of patients were diagnosed with ventricular arrhythmias on admission or whilst admitted to hospital. The other 35% of patients were either referred for Holter monitoring by their GP or via a hospital clinic or had a monitor in the community.

The main reasons for diagnostic testing were syncope or palpitations (38% of patients). Chest pain and shortness of breath were also common (32% of patients). However, only 15 patients were reported as suffering symptoms during diagnostic testing. This included just 2 of the 27 patients who had Holter monitoring. 28 patients were asymptomatic during diagnostic testing: 25 during Holter monitoring and 3 diagnosed by ECG. For 18 patients there was no information on symptoms during testing (and for 7 patients this question was not applicable as they were sedated during EPS).

Table 5.21 below shows the proportion of patients with a previous history of heart disease. These data are presented by severity of ventricular arrhythmia i.e. the proportion of patients with life-threatening or non-sustained VT with a previous history. All subsequent baseline and health care management data will be presented in this way. The reason for this is that mortality risk is much greater for patients with life threatening ventricular arrhythmias. Consequently, these patients were managed differently.

**Table 5.21 Previous history of heart disease by severity of ventricular arrhythmias (N = 68 patients)**

<b>Factor</b>	<b>Life threatening ventricular arrhythmia N = 21 unless stated</b>	<b>Non-sustained VT N = 47 unless stated</b>
Previous MI	11 (52%)	11 (23%)
Heart failure diagnosed	1 (5%)	6 (13%)
Left ventricular function*		
Severe	6 (29%)	8 (17%)
Moderate/mild	7 (33%)	16 (34%)
Good	4 (19%)	5 (11%)
No information	4 (19%)	18 (38%)
Angina	10 (48%)	11 (23%)
Cardiomyopathy	3 (14%)	3 (6%)
Familial condition	0 (0%)	1 (2%)
Atrial arrhythmia	3 (14%)	19 (40%)
Revascularisation	6 (29%)	8 (17%)
Other cardiac surgery	0 (0%)	5 (11%)
Diabetes	1 (5%)	2 (4%)
Hypertension	10 (48%)	18 (37%)

\*Only 46 patients had had an echocardiogram prior to or at time of diagnosis

The proportion of patients with a life threatening ventricular arrhythmia suffering a previous MI was significantly greater than those with non-sustained VT, with  $p = 0.02$ . However, the proportion of patients with non-sustained VT suffering an atrial arrhythmia was significantly greater than those with life threatening ventricular arrhythmias ( $p = 0.03$ ). Differences between other factors were non-significant.

Differences in underlying heart disease by age and gender were explored. There were no statistically significant differences in underlying heart disease by gender. The only statistically significant difference in underlying heart disease by age i.e.

65 years and older vs under 65 years, was an increased proportion of older patients with cardiomyopathy ( $p = 0.01$ ).

#### **5.2.4.2 Management of patients**

The acute and long term management (over 12 months follow up) is described for patients with life threatening ventricular arrhythmias and those diagnosed with non-sustained ventricular tachycardia separately.

##### ***Life threatening ventricular arrhythmias (N = 21)***

All 21 patients with life threatening ventricular arrhythmias were admitted to hospital. Eight patients (38%) were diagnosed by emergency services, either in the ambulance or A&E. Twelve patients (57%) were diagnosed during their admission, eleven of these patients were under the care of a Consultant Cardiologist when they were diagnosed. One patient presented as an out-patient for diagnostic testing and was admitted.

Six of these patients (29%) required intravenous infusions of anti-arrhythmic drugs and three patients (14%) required DC cardioversion to revert them back to sinus rhythm. Three patients were administered oral amiodarone (14%) to restore normal rhythm. No information on the acute management of the other nine patients was found in hospital notes; these patients may have reverted back into sinus rhythm spontaneously. Table 5.22 below shows the management of these patients after the acute phase but still during hospital admission.

**Table 5.22 Management of patients with life threatening ventricular arrhythmias during hospital admission**

Management of VT during hospital admission	Number of patients (%)
ICD	5 (24%)
ICD and amiodarone	4 (19%)
Ablation and ICD	1 (5%)
Oral amiodarone	5 (24%)
Other anti-arrhythmic drug	1 (5%)
Atenolol	1 (5%)
No information	4 (19%)
<b>Total</b>	<b>21</b>

Most patients with life threatening ventricular arrhythmias had an ICD implanted during their hospital admission (48% of these patients). Use of oral amiodarone was also common (24%). During 12 months follow up, 14 patients (67%) had no change in their management. The table below shows changes in management for the 7 remaining patients.

**Table 5.23 Changes in management from hospital admission to 12 months follow up post diagnosis**

Change in management		Number of patients
During hospital admission	After hospital discharge	
Amiodarone	ICD and amiodarone	3
No information	ICD	1
	Re-investigated	1
	Cardiac transplant	1
Other anti-arrhythmic drug	ICD	1
<b>Total</b>		<b>7</b>

Thus, at the end of 12 months follow up, 15 patients (71%) with life threatening ventricular arrhythmias had had an ICD implanted. Six of the patients with life

threatening ventricular arrhythmias did not have an ICD implanted during follow-up. Two of these patients were referred for an EP study; one patient had a negative EPS and the other declined the EP study.

The other four patients were not considered for EPS or ICD implantation. After acute management for their arrhythmias, the severe underlying heart disease of the three of these patients was treated i.e. CABG and valve replacement, heart transplant and pacemaker respectively. The other patient had no further management after the acute phase (this patient suffered an acute MI and VF in the chronic phase).

### **Non-sustained VT (n = 47)**

The management of patients diagnosed with NSVT is described for patients who were diagnosed on admission or during admission in hospital and for patients diagnosed on an out-patient basis separately. This distinction was made to determine whether patients who were admitted were managed differently to out-patients.

### ***Patients admitted (n = 26)***

Three of these 26 patients (12%) were diagnosed by the emergency services. The other 23 patients were diagnosed during their stay in hospital. These 23 patients were admitted for a number of reasons. These are shown in the table below.

**Table 5.24 Reasons for admission in those patients who were diagnosed with NSVT during their hospital admission (N = 23)**

<b>Reason for Admission</b>	<b>Number of patients</b>
Recurrent syncope	2 (9%)
Syncope	1 (4%)
Collapse	1 (4%)
Palpitations	1 (4%)
Shortness of breath	4 (17%)
Fall	2 (9%)
Reduced left ventricular function	1 (4%)
Cardiac surgery	2 (9%)
Atrial fibrillation	1 (4%)
Deep Vein Thrombosis	1 (4%)
Pneumonia	1 (4%)
Crohn's disease operation	1 (4%)
Unknown	5 (22%)
<b>Total</b>	<b>23</b>

Eleven of these 23 patients (48%) were admitted to hospital with symptoms suggestive of NSVT i.e. recurrent syncope, syncope, collapse, palpitations, shortness of breath and fall. The other 10 patients were admitted for other reasons, but experienced symptoms during their admission and were diagnosed with NSVT.

Table 5.25 shows the management of all 26 NSVT patients during follow up who were admitted to hospital.

**Table 5.25 Management over 12 months of the 26 NSVT patients who were admitted to hospital by symptoms during diagnostic testing**

<b>Management</b>	<b>Number of patients</b>
Amiodarone	7 (27%)
Referred for EP study, then ICD (1 patient), ablation (1 patient), beta-blockers (2 patients)	4 (15%)
Beta-blocker	1 (4%)
None	14 (54%)
<b>Total</b>	<b>26</b>

The majority of these patients (54%) received no management for NSVT during their admission or follow-up. Seven patients were administered amiodarone but only two of these patients were symptomatic during diagnostic testing. Four of these seven patients may have been administered amiodarone because of evidence of both NSVT and poor left ventricular function on echocardiogram. The justification for use of this drug for the other three patients is unclear. Four patients were referred for an EP study and subsequent management was guided by EP test results. The two patients with positive tests had ablation and an ICD respectively. Beta-blockers were administered to the two patients with negative test results to alleviate symptoms. Of the 10 patients who were admitted for reasons other than symptoms suggestive of NSVT, one of these patients was managed with amiodarone, another with a beta-blocker, but the remaining 8 patients were not managed for NSVT.

***Out-patients (n = 21)***

The management of out-patients diagnosed with NSVT is shown in the table below.

**Table 5.26 Management over 12 months of the 21 NSVT patients who were diagnosed as out-patients**

<b>Management</b>	<b>Number of patients</b>
Amiodarone	3 (14%)
Referred for EP study, then ICD	1 (5%)
Other anti-arrhythmic drug	1 (5%)
Reveal implantable recorder	1 (5%)
Beta-blocker	3 (5%)
None	12 (57%)
<b>Total</b>	<b>21</b>

The majority of patients (57%) received no treatment for NSVT and were not referred for further investigations. One patient was referred for an EP study; this was positive. Consequently, this patient had an ICD implanted but had no previous history of MI or left ventricular dysfunction. One patient had a reveal implanted, this patient suffered recurrent dizziness, had suffered a previous MI and had poor left ventricular function. Of the 3 patients administered amiodarone, only one had had an echocardiogram and suffered from moderate left ventricular dysfunction. None of these patients had suffered a previous MI.

***All NSVT patients (n = 47)***

There was little difference in the management of NSVT patients who were admitted compared with those diagnosed on an out-patient basis. However, slightly more in-patients were referred for further investigation (EP study). In total, twenty-six patients with NSVT were not managed for their arrhythmia. The table below shows information recorded (or not) in these patients' notes subsequent to their diagnosis.

**Table 5.27 Information in hospital notes subsequent to NSVT diagnosis for those patients who were not managed for their arrhythmia (n = 26)**

<b>Information in notes</b>	<b>Number of patients (%)</b>
No further mention of NSVT after test result	14 (54%)
Decision to not manage NSVT recorded	6 (23%)
Management recommendation made after test result but no further mention	3 (12%)
Recommendation for further investigations made after test result but no further mention	3 (12%)
<b>Total</b>	<b>26</b>

The majority of patients who were not managed for their NSVT (54%) had no further mention of their NSVT after the test result. Most of these patients had a test report in their notes but some had no record of the test being undertaken. For 24% of patients, the results were acknowledged and a recommendation was made for further investigation (echocardiogram and/or EP study) or management (anti-arrhythmic drug or beta-blocker) but any actions or decisions made subsequent to this were not recorded.

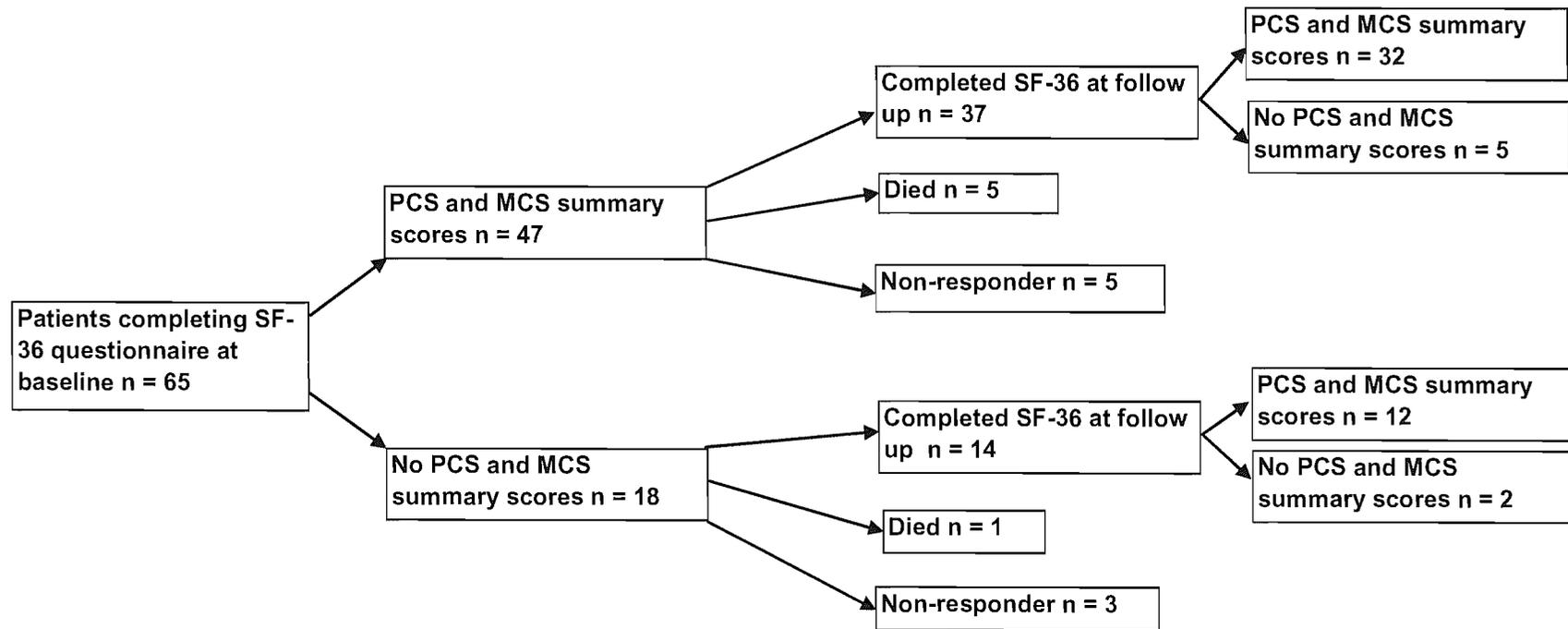
#### **5.2.4.3 Quality of Life**

Quality of life was assessed at baseline and 12 months follow up using the SF-36 and the syncope functional status questionnaire.

#### **SF-36**

Figure 5.6 shows the number of patients completing the SF-36 at baseline and follow up and the number of questionnaires providing sufficient information to calculate (and in some cases input) summary MCS and PCS scores.

Figure 5.6 Number of patients completing the SF-36 questionnaire at baseline and 12 months follow-up



65 of the 68 patients in the prognostic study attempted this questionnaire at baseline. All patients answered the first two questions but one or two patients missed each of the following questions. Consequently, summary scores could only be compiled for 47 patients. The main problem patients reported in answering questions was completing those which didn't appear to apply to them e.g. person in wheelchair asked about problems climbing stairs. 51 patients attempted this questionnaire at follow-up and summary scores could be compiled for 44 of these patients.

Of the 14 patients who completed baseline questionnaires but didn't at follow up, 8 died during follow up and 6 did not respond. The table below shows the mean summary scores for the PCS and MCS at baseline and follow up for those patients who provided a sufficient number of answers for summary scores to be compiled and the U.S. population norms for all persons and persons aged 65 and over.

**Table 5.28 Mean SF-36 summary scores (and standard deviations) at baseline and follow up and mean U.S. population norms for all persons and persons aged 65-74 years**

<b>SF-36 summary scale (number of persons)</b>	<b>Mean score at baseline (SD)</b>	<b>Mean score at follow-up (SD)</b>
<b>PCS scale</b>		
Study cohort	34.7 (11.3)	38.3 (11.5)
U.S. population norm (2,474)	50	
U.S. 65-74 years norm (442)	43.3	
<b>MCS scale</b>		
Study cohort	41.2 (11.2)	48.4 (11.8)
U.S. population norm (2,474)	50	
U.S. 65-74 years norm (442)	52.7	

The mean PCS and MCS scores at baseline were much lower than the U.S. population norms for all persons and those of similar age to the study cohort<sup>85</sup>. For both scales, there was an increase in mean summary score from baseline to follow up; this may represent an improvement in the patients' quality of life. A paired data

analysis is the appropriate method of assessing the change in quality of life and this is described below.

As shown in figure 3, summary scores for the PCS and MCS could only be paired for 32 patients i.e. for 32 patients there were sufficient data to derive a baseline summary score and a follow up summary score. The results of the paired data analysis are shown in the table below.

**Table 5.29 Mean differences in SF-36 summary scores for paired data**

	Mean score at baseline	Mean score at follow-up	Mean Difference (SD)	P value
PCS scale N = 32	36.1	37.1	1.1 (8.7)	.50
MCS scale N = 32	43.0	48.8	5.8 (12.3)	.01

The mean summary score increased for both scales from baseline to follow-up, which suggests an improvement in both physical and mental quality of life. This would be expected given that post diagnosis, most patients (all those with life threatening ventricular arrhythmias and some patients with NSVT) were managed for their symptoms. There was no significant difference in the PCS scale but there was a statistically significant difference in the MCS scale between baseline and 12 months.

Given that just 32 of 68 patients could be paired for analysis, it is important to consider whether these patients were representative of the cohort. Differences in the proportion of patients who were in the paired analysis compared to those who were not were considered. Five factors were compared: age, gender, ventricular arrhythmia severity, history of MI and left ventricular function. A Fishers Exact test showed no significant difference between the groups for all factors except gender. Paired data were available for 64% of females in the cohort compared with 39% of males with  $p = 0.05$ . Therefore, the quality of life results in the paired analysis may not represent the experience of males as well as the females in the cohort.

### **Patient reported syncope and the Syncope Functional Status Questionnaire**

Although syncope is a common symptom suggestive of ventricular arrhythmias, only twenty-eight patients (41%) reported suffering blackouts (syncope) in the 12 months prior to their diagnosis. Of these patients, only 71% (20 patients) completed the syncope questionnaire at baseline. Interestingly, a further 3 patients who reported that they hadn't suffered a blackout completed this baseline questionnaire.

Thus, just twenty-three patients completed the syncope functional status questionnaire at baseline. At follow-up, only 12 patients completed this questionnaire. Mean scores for these patients and individuals minimum and maximum SDS scores are shown in the table below.

**Table 5.30 Syncope Functional Status SDS scores at baseline and 12 months**

	Mean (SD)	Minimum score, maximum score
Baseline SDS (N = 23)	41 (29.3)	0, 87
SDS at 12 months (N = 12)	26 (22.2)	0, 79

Of the original 23 patients who completed the questionnaire at baseline, 8 completed the questionnaire at follow up, 3 patients died, 3 patients did not respond and 9 patients had not experienced a 'blackout' in the 12 months subsequent to the baseline questionnaire (the likely reason for not completing the follow up questionnaire).

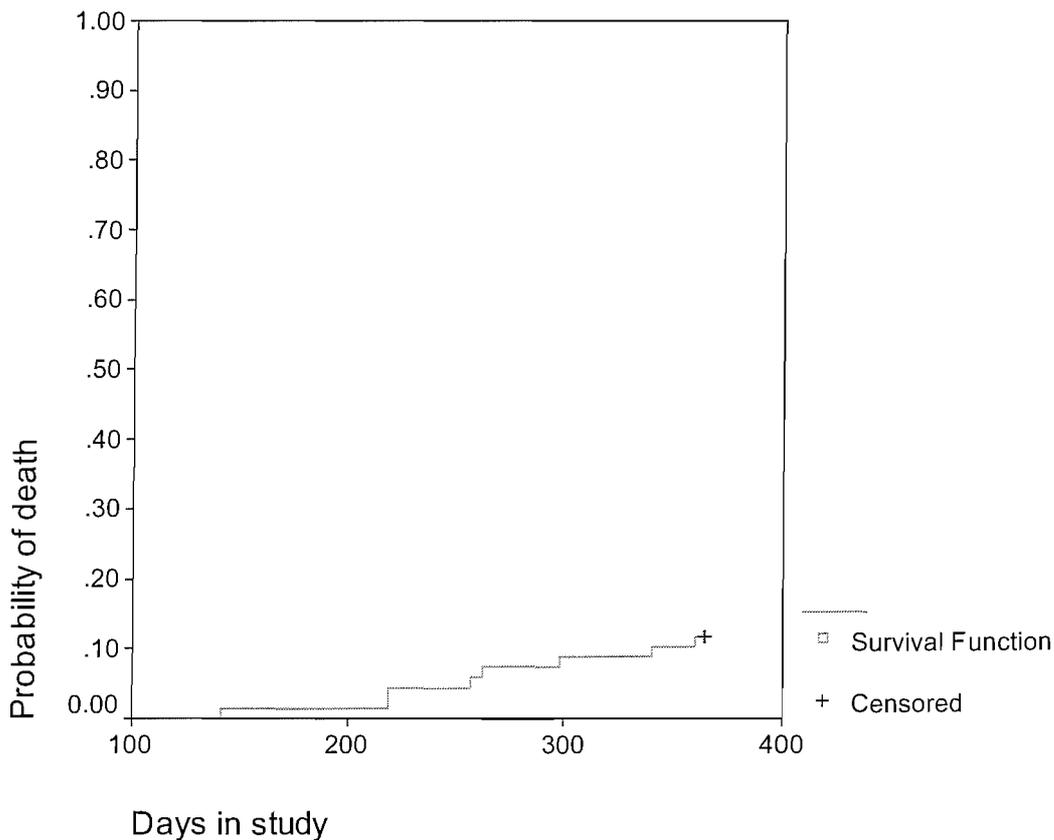
In a paired analysis of data from the 8 patients who completed questionnaires at baseline and follow up, there was a smaller improvement in quality of life but this was not statistically significant. However, this analysis would not take account of data from the nine patients who had not experienced a blackout during follow up.

#### **5.2.4.4 Survival**

There were eight deaths in the prognostic study. Eighty-eight percent of patients survived to end of follow up (12 months). Median survival could not be calculated,

given that more than 50% of the cohort was alive at the end of follow up. The Kaplan Meier plot below shows the probability of death for these patients.

**Figure 5.7: A Kaplan Meier plot of the cumulative probability of death for patients in the prognostic study (N = 68)**



### ***Representativeness of data***

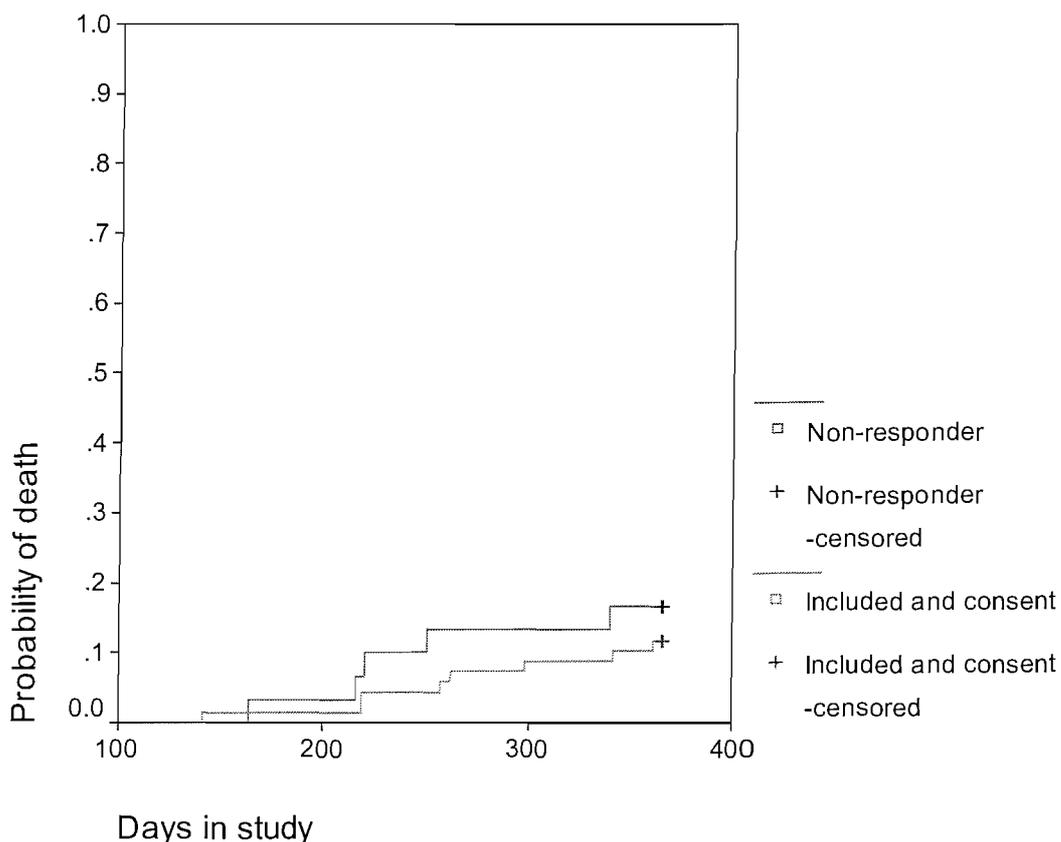
The number of patients in the cohort and the number of events within this cohort were small. We cannot be certain that these data are representative of all patients diagnosed with ventricular arrhythmias. About one third of the whole study cohort did not consent to study entry (30 non-responders) and a further small number of patients were excluded due to ethical reasons (4 vulnerable group patients). The survival experience of this group may have differed from those consenting.

Seven of the eight deaths in consenting patients were identified on PAS prior to checking with the General Practice. Questionnaires were sent to one patient known to be alive at time of sending, but this patient died between first and reminder posting. Their death was recorded on PAS very soon after the event.

If we could assume that PAS provides a complete record of all deaths we can retrospectively check the dates of death of all those patients who did not consent to study entry i.e. the 30 non-responders and 4 vulnerable group patients.

There were seven deaths in these 34 'non-responder'. The probability of survival was less than consenting patients; 79% at 12 months. Mean survival time was also less; 343 days. The survival functions (shown as the probability of death due to the small number of cases) of consenting patients (N = 68) vs 'non-responders' (N = 34) are shown in figure 5.8. Non-responders would appear to have a worse survival experience. However, a log rank test showed no significant difference in survival between the two groups ( $p = 0.23$ ). This was probability due to the small number of deaths in each group.

**Figure 5.8** A Kaplan Meier plot of the cumulative probability of death of consenting patients and non-responders



Another issue regarding the survival experience of these patients is that these data do not include patients who died on the day of diagnosis i.e. in the community or in A&E. The inclusion of these cases in the survival function would change average survival time and probability of survival enormously. The analyses in this section simply represent the survival experience of patients who had survived the first day after a ventricular arrhythmia. Sudden Cardiac Deaths are considered in the next chapter.

### Prognostic factors – impact on survival

With just eight deaths in the prognostic study cohort (N = 68), any differences between prognostic groups are likely to be very uncertain. For this reason, we will explore survival differences between dichotomous sub-groups. A Cox regression model will not be constructed because the proportional hazards assumption was violated for all factors except severity of ventricular arrhythmia i.e. life threatening vs NSVT. The table below shows cumulative survival for different prognostic groups and p values for differences using the log rank test.

**Table 5.31 Cumulative survival for prognostic groups**

Factor	Number of events/ cases	Cumulative survival in 12 months	p value
≥65 years vs < 65 years	6/44 vs 2/24	86% vs 92%	0.51
Male vs female	6/46 vs 2/22	87% vs 91%	0.66
Life threatening VA vs NSVT	1/22 vs 7/46	96% vs 85%	0.20
Previous MI vs no MI*	3/22 vs 5/45	86% vs 89%	0.78
Poor LVF vs moderate or good LVF**	1/14 vs 5/32	93% vs 84%	0.45

\*no information on one patient

\*\*LVF unknown at baseline for 22 patients

As would be expected, females and younger patients appear to have had a better survival experience. Interestingly, survival appeared better in patients with more severe ventricular arrhythmias and those with poor left ventricular function.

However, the log rank test results did not identify any statistically significant differences in survival between prognostic groups.

### ***Causes of death***

The causes of death of the eight consenting patients who died during follow up are shown in the table below. Five patients (63%) died of a cardiac cause, two patients of a non-cardiac cause and for one patient no cause of death information was identified.

**Table 5.32 Causes of death of patients who died during follow up**

<b>Cardiac causes of death</b>	<b>Non-cardiac causes of death</b>
<ul style="list-style-type: none"> <li>• Cardiomegaly</li> <li>• Dilated Cardiomyopathy</li> <li>• Congestive heart failure</li> <li>• Chronic ischaemic heart disease</li> <li>• Acute Myocardial Infarction</li> </ul>	<ul style="list-style-type: none"> <li>• Urinary tract infection</li> <li>• Chronic Obstructive Pulmonary Disease</li> <li>• No cause identified</li> </ul>

## **5.3 Discussion**

This study suggested that the age-sex standardised incidence of diagnosed symptomatic ventricular arrhythmias (for survivors of day one) was about 200 per million population. About one third of patients had life threatening ventricular arrhythmias, with an incidence rate of 62 per million population. Incidence was two-fold higher in males than females and significantly increased with age. However, there were wide confidence intervals around all incidence estimates due to the small number of incident cases.

This study cohort was fairly elderly with a median age of 71 years. Presenting symptoms varied, but were mainly: syncope, palpitations, chest pain or shortness of breath. Underlying heart disease was common, particularly for patients with life threatening ventricular arrhythmias. Over half of these patients had suffered a previous MI.

The majority of patients with NSVT were not managed for this arrhythmia, nor investigated further. Most patients with life-threatening ventricular arrhythmias were appropriately managed; 71% receiving an ICD. These devices were implanted in 17 patients in this cohort study, 65% of these patients received their ICD for secondary prevention i.e. to prevent a further life threatening ventricular arrhythmia and 35% received their ICD as primary prevention (five patients had suffered a previous MI and had NSVT and one patient suffered from a familial condition associated with a high risk of SCD).

Quality of life results were only available for a proportion of the cohort and a statistically significant improvement in the mental health component of the SF-36 was identified. This would be expected given that most patients (particularly those with life threatening ventricular arrhythmias) were managed for their symptoms. But these results may not have been representative of the whole cohort; males were significantly less likely to complete this questionnaire than females. Several of the elderly patients had difficulties answering some of the questions.

The survival experience of patients was good, with 88% of patients surviving to 12 months. This would be expected given that patients who died on the day of diagnosis (in the community, A&E or intensive care) were not included in the analysis. The probability of survival was less for non-responders but this was not statistically significant.

Twenty-six percent of patients who appeared to meet the study inclusion criteria at the time of screening did not give their consent to be included in the prognostic study. A response rate of 74% is reasonable. Non-consenting patients tended to be slightly older, with a poorer prognosis, but there was no difference in the proportion of patients with life threatening ventricular arrhythmias.

The strengths of this study were: (1) the number of methods and the hot pursuit approach used to identify cases. This should have reduced the number of missing cases, (2) the use of postcode analysis to define the study catchment area; excluding wards with potential for cases to present at hospitals outside of the catchment area and (3) follow up of an incident cohort.

The weaknesses were: (1) potential for missed cases. The cross-checking exercise identified a few cases that were not screened but could have met the

inclusion criteria. Furthermore, the case definition was a pragmatic one based on local practice; many 'literature defined' NSVT cases would have been missed, (2) non-diagnosed cases were not included. This study only identified patients diagnosed with ventricular arrhythmias. Patients who were not investigated or managed in primary care would have been missed. The SCD study, described in the next chapter, considers aspects of this issue, (3) private patients were not included. Patients diagnosed in private hospitals within the study catchment area would have been missed. A retrospective analysis of Holter reports at one private hospital in the catchment area identified eight patients with NSVT during the case identification period of this study; these patients may have been incident cases. All patients with life threatening ventricular arrhythmias would have been admitted to SUHT or RHCH.

Other weaknesses were, (4) the imprecision of estimates and the inability to explore these data further due to the small number of cases and deaths during follow up. This limitation could have been prevented if the study catchment area had been significantly larger and/or cases were identified and followed up over a longer time period. It would not have been possible for one investigator to identify cases using the hot pursuit approach at more hospitals. Furthermore, this study was time limited; therefore case identification and follow up periods could not have been extended, (5) assumptions were made about the number of non-responders meeting the inclusion criteria to determine the incidence rate and lastly, (6) the relatively high non-response rate to the quality of life questionnaires. In retrospect, an interview approach rather than postal questionnaire may have been a better method of assessing quality life in this fairly elderly study cohort.

In addition, the SF-12 would have been a more useful simpler tool to assess quality of life. Unfortunately, this version was not readily available at the time of initiating this study. One other prognostic study has assessed the quality of life of patients with ventricular arrhythmias (life threatening) using the SF-36. Hsu et al<sup>46</sup> found an improvement in patients' mean mental health and vitality scores from hospital admission to 24 months but this was not statistically significant.

As discussed in chapter 3 of this thesis, no UK studies of the incidence of ventricular arrhythmias have been published. The most comparable study was undertaken in the U.S. (Alexander et al) estimated the incidence of hospitalised ventricular arrhythmias as 245 per million population<sup>43</sup>. This study only included

patients with a primary diagnosis of VT or VF (this probably wouldn't have included patients with NSVT). This estimate is therefore more comparable to the rate of life threatening ventricular arrhythmias in this study i.e. a much lower rate of 62 per million population. The gender and age breakdown were similar for both of these studies.

There are a number of possible reasons for this variation in incidence estimates: (1) it may simply reflect a true difference in incidence rate by place i.e. the incidence of life threatening ventricular arrhythmias was much higher in the U.S. and/or the survival experience of patients suffering an SCD differed i.e. more patients in the U.S. were successfully resuscitated from a cardiac arrest in the community and reached hospital admission than in this UK study (furthermore, these two factors could also vary by time, the U.S. study was undertaken in the 1990s compared to 2002/3 for this study) or (2) Due to differences in case ascertainment methods. Cases in the U.S. study were identified using routine data. Although U.S. routine data are known to be more accurate than UK data, cases may have been miscoded.

Previous prognostic studies have shown significant differences in survival for factors such as: left ventricular dysfunction, previous MI and extent of coronary artery disease (see chapter 3 a systematic review of prognostic studies). There were no significant differences in survival between prognostic groups in this study; but this was probably due to the small number of deaths during follow up.

The demographics of study catchment area were similar to that of England, apart from a higher life expectancy, especially in the Winchester area, and lower proportion of persons from ethnic minority groups. This could suggest that the incidence rate is slightly lower than that of the UK. However, a number of factors such as the case definition, diagnostic accuracy and referral patterns need to be taken into consideration.

A pragmatic definition of ventricular arrhythmias was used to define cases in this study. The SUHT feasibility study suggested that about half of the 'textbook' defined NSVT could be missed by using this pragmatic definition. However, it would have been extremely difficult to identify these non-severe doctor undiagnosed cases. A routine data analysis suggested that very few (if any) pragmatically defined cases had been missed from the study. Conversely, this

analysis also highlighted the incorrect diagnostic coding and lack of coding of patients with ventricular arrhythmias (particularly those with NSVT) in routine data. Incidence rates in the 3 SSWHA PCT areas were similar. However, the rate for Winchester City and suburbs was much lower. This suggests that either there was a true difference between these areas or that some cases of NSVT were missed at the RHCH. The hot pursuit approach of identifying cases was not pursued as actively at the RHCH as SUHT. It is also possible that more patients with symptoms suggestive of ventricular arrhythmias living near a specialist centre i.e. SUHT are referred from primary care to such centres than patients living further away.

The number of cases in this study was much lower than expected. This expected number was uncertain being based on very little published data. Nevertheless, the catchment area was much smaller than expected i.e. just under half a million population compared with one and half million as estimated in the sample size calculation. The catchment area size was greatly reduced when attempts were made to exclude areas with high cross-boundary flow. A large number of screened cases were excluded because they resided outside of the final catchment area. The expansion of the catchment area would have necessitated case identification in at least two further hospitals on the boundaries of the study area. This would not have been feasible given the resources associated with this study. Furthermore, a small number of cases were misdiagnosed and were later excluded from the study.

It is difficult to determine why some patients were investigated further after an episode of NSVT and others were not. Reading through the notes it seemed that patients were investigated further if the Doctor was expecting to find NSVT given the patient's history. A number of factors would be considered including syncope history, known underlying heart disease and co-morbidities (in particular, evidence of other types of arrhythmias). Patients who were admitted with NSVT as opposed to presenting as an out-patient were more likely to have further investigations. Of concern was the number of patients who were diagnosed with NSVT but either their test results were not included in their notes or the results were included but not acknowledged further. The investigator's opinion is that this was due to the timing of test results; many were only available after the patient was discharged from hospital. Unfortunately, data from GP notes were not collected in this study it

was therefore not possible to determine whether the patient's GP had access to these test results and managed the patient in primary care.

There are no quality of life questionnaires specific for patients with ventricular arrhythmias. Syncope is the commonest symptom suggestive of ventricular arrhythmias, the syncope functional status questionnaire was therefore used to assess quality of life issues specific to this patient group. However, less than half of the study cohort reported experiencing syncope and very few patients completed the syncope functional status questionnaire at baseline and follow up. An arrhythmia specific quality of life tool, taking account of the various types of symptoms and the anxiety these patients suffer would be a useful development.

This is the first UK study of the epidemiology of ventricular arrhythmias. The methods and lessons learnt from undertaking this study could serve to aid the design of a much larger study of the epidemiology of life threatening ventricular arrhythmias with longer follow up. However, the usefulness of such a study is debatable for two reasons: (1) due to the very nature of ventricular arrhythmias; these are heavily dependent on diagnostic test accuracy and referral patterns and (2) since this study was initiated, ICD selection has moved on to include a much larger group of patients; those with a previous MI and left ventricular dysfunction (with or without evidence of a ventricular arrhythmia). Left ventricular dysfunction (with an ejection fraction < 30%) is a stronger independent predictor of sudden cardiac death than ventricular arrhythmias<sup>11</sup>.

Further epidemiological data on NSVT would probably be of little importance to the health service given that the prognosis for the majority of patients presenting (those with no underlying heart disease) appears to be unaffected<sup>86</sup>. However, an issue is whether certain symptomatic patients diagnosed with NSVT should be referred for further investigations to identify any unknown underlying heart disease. Guidelines are needed to clarify which groups of patients are at greatest prognostic risk and therefore in most need of further investigations. Furthermore, guidance primarily directed at primary care, on the referral and diagnostic testing of patients presenting with symptoms indicative of a ventricular arrhythmia i.e. syncope, pre-syncope and palpitations and subsequent diagnostic testing of patients who have suffered a previous MI would also be of benefit.

## **6. Case series of Sudden Cardiac Death**

Ventricular arrhythmias are the main triggers for SCD. These arrhythmias can arise with or without evidence of an acute coronary lesion i.e. acute myocardial infarction or acute thrombosis. Post-mortem studies have suggested that about 50% of SCDs are caused by an acute coronary lesion<sup>87</sup>. It is unlikely that patients suffering an SCD due to an acute coronary lesion would benefit from an ICD. However, the implantation of an ICD could prolong the life of a patient suffering an SCD not associated with an acute coronary lesion.

This chapter describes a study which addressed research question 4, the aim being:

- To establish whether victims of an SCD thought to be due to ventricular arrhythmia could have been identified prior to their death based on health service contacts and potentially been considered for an ICD.

### **6.1 Methods**

#### **6.1.1 Study design**

The research design was a 12 month consecutive case series of SCD within a defined population.

#### **6.1.2 Cases**

Cases in this study were consecutive post-mortem cases of sudden cardiac death presumed to be primarily caused by a ventricular arrhythmia as determined by a coroner's/pathologist report. A sudden cardiac death was defined as an unexpected Coronary Heart Disease (CHD) death that had no other probable cause. Inclusion/exclusion was then based on whether an acute MI or an isolated ventricular arrhythmia was the primary cause of their death, as only the latter would possibly benefit from an ICD.

### **6.1.2.1 Inclusion criteria**

Inclusion was based on pathological findings. Cases were included if they fell into any one of the following four adapted SCD categories devised by Professor Davies, St Georges Hospital, London (shown in box 6.1)<sup>88</sup>. These categories represent degrees of certainty that a case was a SCD.

#### **Box 6.1 Categories of SCD certainty**

1. More or less certain SCD. Evidence of a healed infarct with or without one or more coronary arteries < 1mm diameter.
2. A little less certain SCD. One or more coronary arteries < 1 mm in diameter but no evidence of old or recent myocardial infarction. All other features suggest a cardiac death.
3. Still probable SCD. No coronary artery < 1 mm in diameter but significant left ventricular hypertrophy in relationship to body build. All other features suggest a cardiac death.
4. Uncertain SCD. Moderate atherosclerosis but no coronary artery < 1 mm diameter. No old or recent infarction, no scars, no left ventricular hypertrophy.

Both witnessed and unwitnessed sudden cardiac deaths were included in the study. The time of death from onset of symptoms was not used as a criterion for defining a sudden death. However, the impact of using a stricter definition of sudden cardiac death i.e. a CHD death occurring within 1 hour of onset of symptoms that had no other probable cause of death was explored.

### **6.1.2.2 Exclusion criteria**

The exclusion criteria was certain SCD, that is: (1) With pathological evidence of haemopericardium with or without established myocardial infarction, (2) coronary thrombosis plus established acute myocardial infarction, (3) established acute myocardial infarct but no thrombus or (4) acute coronary thrombus but no myocardial infarction.

Cases aged less than 16 years at the time of death were also excluded.

### **6.1.3 Case finding**

Over a 12 month period, all SCDs were identified from the pathologist's post-mortem database at Southampton General Hospital (SGH). The catchment area for this Hospital was the former Southampton and South West Hampshire Health Authority (SSWHA) area and has been described in chapter 6, section 6.1.3.2. Cases who resided outside of this area were excluded from this study.

Reports from all SGH post-mortems were typed into a pathology database. A Specialist Registrar (HB) screened each report against the eligibility criteria during the timeframe of the study.

There were 19 Consultant Pathologists and 14 senior house officers and specialist registrars who undertook post-mortems at SGH. Pathologists were not asked to undertake more extensive investigations on these study cases but were asked to complete a 'new' cardiac death post mortem form after completing the post mortem for cases that they believed to be relevant (shown in appendix 13). Reports were completed and returned to HB. For cases where no cardiac death form was completed, but deemed eligible after studying the post-mortem report, a form was completed by HB.

HB checked each post-mortem report and cardiac death form against eligibility criteria. Cases were deemed eligible, definitely ineligible, unsure (for discussion), or incomplete (pending final report). All eligible cases were graded using the SCD grading scale (shown in box 1). These gradings were checked by the study investigator. A log was also kept of all certain SCD cases and the causes of death for all other post mortems undertaken during the study period.

### **6.1.4 Data collection and judging the appropriateness of cases**

#### **6.1.4.1 Data collection**

Previous health service history and pathological data were collected from: Post-mortem reports, police form (G28 form) and from hospital and GP notes. Health service history data were collected to determine whether patients could have been identified prior to their death from health service contacts. Pathological data were

collected both to describe the cases and to determine the completeness of health service history data.

The post-mortem reports provided some previous history and information on medications at the time of death, pathology and cause(s) of death. The police G28 form provided details of the event, whether or not it was witnessed and timing and details of symptoms prior to death. Hospital and GP notes provided information on previously known cardiac disease, cardiac management and medicines received, investigations undertaken, symptoms associated with ventricular arrhythmias, co-morbidities and family history. A standard proforma was used to extract data from hospital and GP notes (see appendix 16).

#### **6.1.4.2 Judging appropriateness of cases for ICDs**

There is a wealth of literature on methods for assessing the appropriateness of health care interventions for particular patients. Appropriateness here means that the benefits exceed the risks and that the procedure is worth doing<sup>89</sup>. For this study, a simplified version of the Rand method was adopted<sup>90</sup>. Experts were asked to independently rate the appropriateness of each case for an ICD, using information from each patient's health service history, and then to reach consensus through meeting and discussing any disagreements.

#### **Appropriateness criteria**

Guidance based criteria on the appropriateness for ICDs were developed by which each case could be judged. These criteria were based on national guidance (the 2000 NICE recommendations<sup>6</sup>). These criteria are shown in appendix 15. Those cases where one could be most certain that patients should have been considered for an ICD were those meeting the NICE criteria for an ICD.

Those cases where one could be most certain that patients would not have been identified prior to death for an ICD were those having no contact with the health service in association to cardiac problems and/or symptoms suggestive of ventricular arrhythmias. These were cases with definite 'de novo' disease; with no opportunity for secondary prevention.

For cases not considered to be at either end of this spectrum, the use of national and international recommendations and a Consultant Cardiologist's decision would be crucial in determining the level of certainty that each case could/or could not be identified.

### **Consensus method**

Two SGH Consultant Cardiologists (with special interest in cardiac electrophysiology); A and B, were provided independently with a standardised 'proforma' on each case in this study. The proforma provided information from hospital and GP notes on each patient's CHD history i.e. symptoms, test results and management (see appendix 14 for an example of a proforma).

The Consultants were familiar with the study case definition and case finding methods but were not provided with any pathological data on these cases.

A and B were asked to determine if cases should have been considered for an ICD or further testing to determine appropriateness for ICD during their lifetime on the basis of their health service history. They were asked to assign each case to one of the 5 categories shown in box 6.2.

#### **Box 6.2 Categories for determining ICD appropriateness**

- Appropriate for ICD
- Inappropriate for ICD (contraindications)
- Should have had further diagnostic tests
- No evidence to justify further testing
- De Novo

The two Cardiologists then met to discuss cases where they disagreed.

#### **6.1.4.3 Statistical analysis for judging appropriateness of cases**

The number of SCD cases that would have been appropriate for an ICD was presented. Characteristics of patients including, pathology and previous CHD history were detailed.

Agreement between hospital and GP notes in recording events was measured using the kappa statistic. Agreement between raters (A and B) in judging the appropriateness of cases was also measured using the kappa statistic.

### **6.1.5 Methods for identifying potential missing cases**

An assessment was undertaken to determine the generalisability of findings on this SCD case series to all SCDs presumed to be primarily due to a ventricular arrhythmia. Two methods were adopted to estimate the number of SCDs that occurred within the study catchment area and case identification period where a post-mortem was not undertaken. These are described below.

#### **(1) An analysis of mortality data on IHD and other forms of heart disease.**

Data on all deaths occurring between 1<sup>st</sup> October 2002 and 30<sup>th</sup> September 2003 in the study catchment area i.e. former SSWHA with a primary cause of death (1a, 1b or 1c) of IHD (ICD-10 IHD codes I20 to I25 and codes for other forms of heart disease I30-I52) were requested from the Office of National Statistics. Information on name, date of birth and death, sex, place of residence, place of death and underlying causes of death were provided.

It was assumed that patients dying of IHD in hospital did not die of an SCD. By definition, an SCD is unexpected and very few patients survive to hospital admission. IHD deaths in hospital were assumed to be due to end stage heart failure or an acute MI. Therefore, only data on IHD deaths in the community were examined.

These data were then cross-checked against the SCD study case series to determine the number of IHD cases where death was in the community and a post-mortem was not undertaken.

#### **(2) An analysis of out of hospital cardiac arrests**

In the prospective VT study (chapter 5), data were collected on all out of hospital cardiac arrests admitted to SGH A&E (dead or alive) from 21<sup>st</sup> October 2002 to 16<sup>th</sup> September 2003. Cases that died in the community or in A&E were cross-checked against the SCD study case series and the IHD analysis.

## 6.1.6 Ethics

Ethical permission for this study was granted from the Southampton and South West Hampshire Local Research Ethics Committee. The Committee decided that ethical permission from relatives of the deceased was not necessary.

## 6.1.7 Sample size

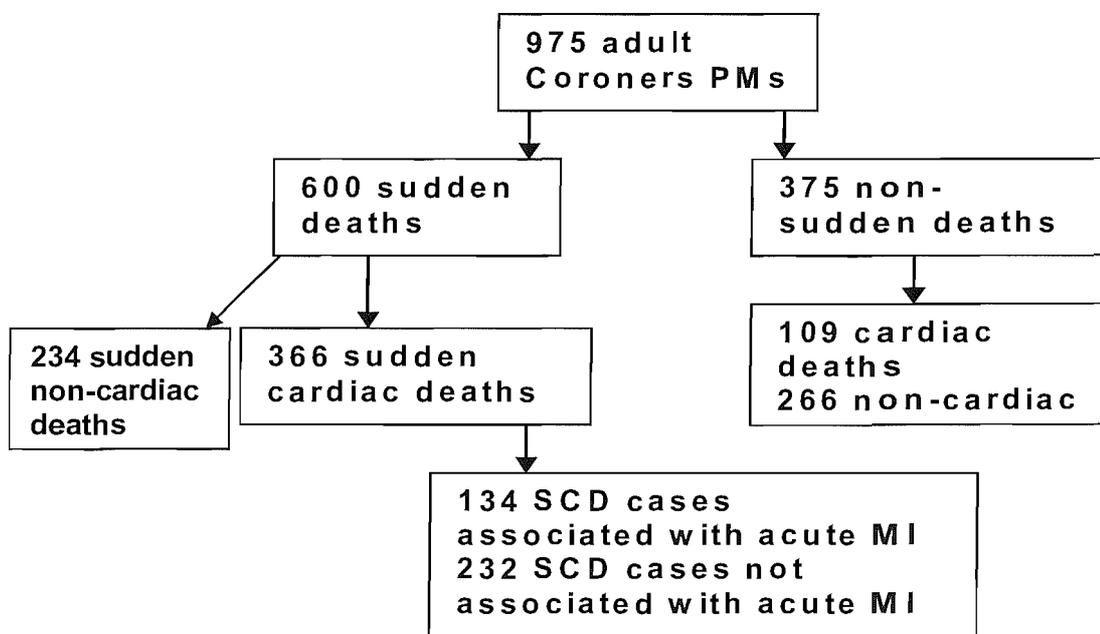
Published incidence studies suggest that there are about 600 sudden deaths per 500,000 persons per annum<sup>9</sup> (see chapter 1, section 1.3, Sudden Cardiac Death studies). About 50% of these are believed to be primarily due to ventricular arrhythmias<sup>87</sup>. Given that the population size of the catchment area was approximately 500,000 persons, we would expect about 300 cases (95% CIs, 267, 336) in 12 months.

## 6.2 Results

### 6.2.1 Information on post mortems and number of cases

Consecutive cases were identified in this study over 12 months; from 8<sup>th</sup> October 2002 to 7<sup>th</sup> October 2003. During this time, 1038 adult post-mortems on deaths in the community were undertaken at Southampton General Hospital. Of these, 975 (94%) were Coroners post-mortems. Figure 6.1 shows a breakdown of the number of SGH Coroner's post-mortems by sudden/non sudden and cardiac/non-cardiac causes.

**Figure 6.1 Breakdown of Coroner's post-mortems (PMs) undertaken at SGH**



600 (62%) of adult Coroner's PMs were sudden deaths, 366 (61%) of which were cardiac in nature. The main causes of the sudden non-cardiac deaths were attributed to pulmonary emboli, ruptured abdominal aortic aneurysms, stroke, gastrointestinal haemorrhage and dissecting aortic aneurysms. 89 were due to unnatural causes, e.g. drug toxicity, 23 road traffic accidents and 19 deaths due to malignant mesothelioma. There were 375 non-sudden deaths (39% of all adult Coroner's PMs). 29% of these were cardiac. Other causes were pneumonia and malignancy.

Of the 366 SCDs, 134 (37%) were thought to be associated with an acute MI by standard pathological investigation. These cases were excluded from the study. The remaining 232 SCDs met the criteria for this study. 215 (93%) of these cases resided within the study catchment area and were therefore included in this study.

### 6.2.2 Characteristics of the case series

The sudden cardiac death gradings of the 215 cases, as determined at post-mortem, are shown in table 6.1.

**Table 6.1 Certainty of cause of death in 215 cases**

<b>Grade &amp; degree of certainty</b>	<b>Brief description</b>	<b>No. of cases (%)</b>
<b>1 More or less certain</b>	Myocardial scarring with one or more coronary arteries < 1mm diameter. No coronary thrombosis.	109 (51%)
<b>2 A little less certain</b>	One or more coronary arteries < 1mm diameter. No scarring. No coronary thrombosis.	56 (26%)
<b>3 Still probable</b>	Cardiac hypertrophy. No coronary artery < 1mm diameter. No scarring.	44 (21%)
<b>4 Uncertain</b>	No cardiac abnormality (sudden arrhythmic (adult) death syndrome)	6 (3%)

For 51% of cases, it was 'very probable' that the patient died of a SCD. These cases were identified as having myocardial scarring with stenosed artery(ies). Only 6 cases were 'uncertain' SCDs; sudden arrhythmic (adult) death syndrome being the presumed cause.

Table 6.2 below shows the primary cause of death (cause 1a) on the post-mortem report. 98% (211) of cases had a 1a cause of death that would be coded as ischaemic heart disease (IHD) or other forms of heart disease. One case had no cause of death reported and the remaining 3 cases had IHD or other forms of heart disease as primary causes of death 1b and/or 1c.

**Table 6.2 Primary cause of death (1a) on post-mortem report in cases with SCD**

<b>1a cause of death on PM report</b>	<b>Frequency</b>	<b>Percent</b>
<b>IHD</b>		
	122	56.7
<b>Other forms of heart disease</b>		
Acute cardiac failure	46	21.4
Hypertensive heart disease	10	4.7
Congestive heart failure	9	4.2
Coronary artery atherosclerosis	7	3.3
Acute on chronic heart failure	6	2.8
Aortic stenosis	6	2.8
Left ventricular hypertrophy	2	.9
Coronary artery thrombosis	1	.5
Left ventricular aneurysm	1	.5
Presumed ventricular arrhythmia	1	.5
<b>Other causes</b>		
Pulmonary oedema	1	.5
Acute cardiorespiratory failure	1	.5
Asthma	1	.5
<b>No cause</b>		
	1	.5
<b>Total</b>	<b>215</b>	<b>100</b>

Descriptive data known at the time of post-mortem are presented in the tables below. Table 6.3 shows that most of the 215 cases were males and elderly. The youngest case was 40 years of age at time of death. No ethnic minority groups were represented.

**Table 6.3 Descriptive data on the case series (N = 215, unless otherwise specified)**

Gender	Males 64%, females 36%
Age, median (min, max)	Median age 75 years (40 years, 94 years)
Ethnic origin	White 100%
Marital status (N = 176)*	Married 47%, single 14%, separated 6%, widowed 34%

\*This information was not available at time of PM for 39 cases

Table 6.4 shows information relating to the event and symptoms preceding the SCD. These data were taken from police reports and the post mortem report itself. For some cases, these data were not available.

**Table 6.4 Data relating to the SCD event (N = 215, unless otherwise specified)**

<b>Place of death</b>	Home 72%, hospital 8%, public place 8%, care home 5%, other person's house 1%, work 2%, no details 3%	
<b>Death witnessed n = 194/215</b>	Yes 37%, No 63%	
<b>Symptoms reported prior to death? n = 139/215</b>	Yes 31% (67), No 34% (72)	
<b>Occurrence of symptoms prior to death n = 67/215</b>	<15 mins 28% (19) 16-60 mins 21% (14)	1-3 hrs 9% (6) 3-24 hrs 15% (10) > 24 hrs 27% (18)

Most of the deaths occurred at home(72%) and were unwitnessed(63%). For 35% of cases there was no information on symptoms prior to death. 31% experienced symptoms within 24 hours prior to death. 49% of these cases suffered these within 1 hour prior to death. Symptom descriptions varied considerably; breathlessness was reported as a symptom for 34% of the 67 cases, chest pain for 24%, blackout 5% and more ambiguous symptoms such as neck or shoulder pain (categorised under other in table), dizziness, 'felt unwell' etc. reported for other cases.

Table 6.5 below shows some pathological data on previous heart disease as identified by the post-mortem examination. 51% of cases were found to have

suffered a previous MI. Approximately two thirds of cases had one or more diseased (stenosed) coronary arteries, as one would expect from the inclusion criteria.

**Table 6.5 Pathological data on previous heart disease (n = 215)**

Previous MI	Yes 51%, No 49%
Left main stem disease (LMS)	Yes 3%
No. of vessels diseased (RCA, LAD, circumflex excluding LMS)	One vessel = 30%, two vessels = 26%, three vessels = 15%, no vessels diseased = 28%
Evidence of CABG	Yes 7%
Aortic valve disease	Yes 10%

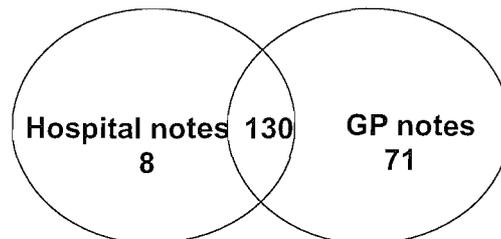
RCA = Right Coronary Artery, LAD = Left Anterior Descending, CABG = Coronary Artery Bypass Grafting, PTCA = Percutaneous Transluminal Coronary Angioplasty

This section has provided data on the pathology of cases and the event itself. These data enable comparison with other pathological and epidemiological studies of SCD and validation of health service history data. The following sub-section presents data extracted from hospital and GP notes on the health service history of these patients. These health service history data will be used to assess how appropriate these cases would have been for an ICD.

### 6.2.3 Information from hospital and GP notes

Of the 215 cases, hospital and/or GP notes could be identified for 209 (97% of cases). Figure 6.2 shows the number of cases for which hospital and/or GP notes were identified.

**Figure 6.2 Venn diagram of the number of cases for which hospital and/or GP notes could be identified**



The following analyses are based on the 209 cases with a health service history i.e. hospital and/or GP notes.

### **6.2.3.1 History of Coronary Heart Disease**

Table 6.6 shows the proportion of cases with a history of CHD as recorded in their notes. Only 2% of cases had a previous cardiac arrest and 5% a diagnosed ventricular arrhythmia recorded in their notes. As would be expected, high risk conditions for SCD i.e. cardiomyopathy (2% of cases) and hereditary conditions (<1 % of cases) were rare.

Just 18% of cases had a previous MI recorded in their notes. A diagnosis of heart failure was not common either (13%) and very few of these patients had had an echocardiogram to confirm their diagnosis. Diagnosis of another type of arrhythmia, mainly atrial arrhythmias, was more common (24%). Almost half the patients suffered hypertension and about a third of cases had angina in their lifetime.

**Table 6.6 CHD history in hospital and GP notes (n = 209)**

<b>CHD history</b>	<b>Evidence in hospital notes (n = 138 cases)</b>	<b>Evidence in GP notes (n = 201 cases)</b>	<b>Total number (n = 209) and % of these cases</b>
Suffered previous cardiac arrest	4	4	4 (2%)
Diagnosed with ventricular arrhythmia	9	6	10 (5%)
Suffered previous MI	35	45	37 (18%)
Diagnosed with heart failure	15	28	27 (13%)
Severe left ventricular dysfunction on echocardiogram	8	5	9 (4%)
Evidence of heart failure on angiogram or chest x-ray	5	5	10 (5%)
Diagnosed with other type of arrhythmia	35	45	50 (24%)
Radiofrequency Ablation	0	0	0
CABG	11	13	14 (7%)
PTCA	0	2	2 (1%)
Other cardiac surgery	4	5	6 (3%)
Pacemaker	2	4	4 (2%)
Cardiomyopathy	2	4	5 (2%)
SCD familial condition*	0	1	1 (<1%)
Angina	29	51	56 (27%)
Diabetes	20	19	20 (10%)
Hypertension	48	92	99 (47%)

\*excluding hypertrophic cardiomyopathy, this is included under cardiomyopathy

Data on symptoms experienced, investigations undertaken and referral patterns are considered in the assessment of ICD appropriateness and described in section 6.2.4.1. The next two sections describe agreement between hospital and GP notes and pathological data.

### **6.2.3.2 Discrepancies in recordings of events between hospital and GP notes**

An assessment of the amount of agreement between hospital and GP notes was undertaken because some discrepancy in CHD history between hospital and GP notes had been identified. For example, 6 patients were recorded as suffering a previous MI in their hospital notes but there was no information about these events in their GP notes and for 3 patients an MI was recorded in the GP notes but not the hospital notes. Possible reasons for these discrepancies could be that the GP was not notified about an event requiring hospital admission or the hospital notes did not contain information about an event managed at a hospital outside of the catchment area. The first and second columns of table 6 above show the number of patients with a CHD history as reported in either their hospital or GP notes.

Agreement in recording of CHD history between SUHT hospital and GP notes could be checked for those patients who had both sets of notes i.e. 130 cases. For MI, the overall agreement between notes was very good, with a Kappa score of 0.80. Although there were some discrepancies between hospital and GP notes CHD history, these were minor; with a Kappa score  $>0.5$  for all factors shown in table 6.6. Reassuringly, missed diagnoses were much more frequent in hospital notes than GP notes.

### **6.2.3.3 Discrepancies between notes and pathological data**

The objective of this exercise was to determine how accurately health service data reported previous CHD history against a 'gold standard' of pathological data from the post-mortem report. This was undertaken by comparing evidence of two factors: Occurrence of MI and CABG in the post-mortem report and the hospital and/or GP notes.

Evidence from hospital and GP notes showed that 18% of cases suffered from a previous MI. However, pathological data showed that 51% of cases suffered a previous MI. There could be a number of reasons for this variation. Events may not have been reported in the notes because: 1. notes of the event being reported to the health service have been lost or reported elsewhere and not consolidated in the patients' GP or SUHT notes or, most likely, 2. the patient suffered an MI and did not seek help from the health service. Some of these patients may have had a

silent MI. This is not an uncommon event in older people i.e. an MI occurred but there were no symptoms. Another concern is that there may be under reporting of events in hospital or GP notes; not all cases had both sets of notes.

A more useful indicator of potential missing health service history data would be reporting of a CABG. Fifteen cases had pathological evidence of a CABG. All of these cases had a CABG documented in their hospital and/or GP notes. This provides an indication that health service history is providing an accurate account of CHD history. However, the number of cases having a CABG was very small and one would expect this procedure to be well recorded in the notes.

#### **6.2.4 ICD appropriateness ratings**

This section describes the study investigator's deliberations on which cases would have been appropriate for an ICD and then the experts' ratings of appropriateness. The objective being to determine which cases could have been identified prior to their SCD and potentially considered for an ICD. The ICD appropriateness criteria are shown in appendix 15.

##### **6.2.4.1 Study investigator's appropriateness ratings**

The investigator constructed a list of potential indicators of CHD history. This was graded using the ICD appropriateness criteria (appendix 15). It was necessary to combine some of these indicators to determine how appropriate a patient was for an ICD. Only one of the indicators, cardiac arrest with recorded ventricular fibrillation, provides enough evidence in itself to justify ICD implantation. Combinations of other indicators are required to justify further testing to determine need for an ICD. Evidence of these indicators was checked against hospital and GP notes.

131 patients had one or more of these indicators as identified in their hospital and/or GP notes. 78 patients (37%) appeared to have de-novo disease i.e. none of these indicators were documented in their notes.

Table 6.7 below shows the graded list of indicators and the number of patients presenting with indicators and combinations of indicators. The numbers in the table below are mutually exclusive. Where patients had evidence of more than one of these indicators they were assigned to the indicator with most appropriateness

for an ICD. The table is ordered by ICD appropriateness i.e. those in the top row 'cardiac arrest with VF' would be most appropriate for an ICD. Indicators below 'sustained VT and MI with non-sustained VT' in the table are much less certain.

**Table 6.7 Number of patients with evidence of indicators**

<b>Indicators ordered by certainty of ICD appropriateness</b>	<b>No. of patients</b>
<b>Certain</b>	
Cardiac arrest with VF as recorded rhythm	4
Familial cardiac condition with high risk of SCD	1
Cardiac arrest with no rhythm recorded	1
Inducible VT/VF on EPS	0
<b>Less certain</b>	
Sustained VT	4
MI & Non-sustained VT	3
<b>Much less certain</b>	
Cardiomyopathy	5
Echocardiogram evidence of poor LVF	6
Heart failure diagnosis	21
Cardiac catheter/CXR evidence of poor LVF	2
Drug history (2 or more - frusemide/bumetanide, ACEI/All antagonist, beta-blocker, spironolactone)	28
MI with no evidence of ventricular arrhythmias or heart failure	19
Syncope	16
<b>Most unlikely</b>	
Use of amiodarone	2
Other arrhythmias	6
CABG or PTCA	2
Coronary Artery Disease on angiogram	2
Abnormal rhythm on Holter (ventricular ectopics)	1
Abnormal rhythm on ECG	8
<b>Total</b>	<b>131</b>
EPS = Electrophysiological Study, LVF = Left Ventricular Function, CXR = Chest X-Ray, CABG = Coronary Artery Bypass Grafting, PTCA = Percutaneous Transluminal Coronary Angioplasty, ECG = Electrocardiogram	

### **Certain**

Of the 131 patients with indicators of cardiac abnormalities, only 4 (3%) would have been considered appropriate for an ICD (having suffered a cardiac arrest with ventricular fibrillation as the recorded rhythm). Another 2 cases (2%) may have been appropriate for an ICD but further information would be required for certainty.

Further details on each of these cases revealed that two of these cases would not have been appropriate for an ICD: They suffered a cardiac arrest in the acute phase post-MI i.e. within 48 hours of an MI. VF would have been transient and associated with the MI. The two eligible cases are also debatable. One patient suffered a cardiac arrest post MI but there was no information on the timing of the arrest (only that it occurred during the same hospital admission) and the other patient suffered an arrest in hospital 72 hours prior to death (perhaps insufficient time for consideration of an ICD). This patient had suffered previous symptoms but declined investigations.

The other two cases in the certain category were: One patient who suffered from Wolff-Parkinson White syndrome (a familial condition with high risk of SCD) and was on a waiting list for EPS and ablation at the time of death and another who suffered a cardiac arrest but the heart rhythm at the time of arrest was not recorded. None of the patients in the case series had had an EPS.

### ***Less certain***

The 'less certain' cases were the seven patients who had suffered from a form of ventricular tachycardia (but had not suffered a previous cardiac arrest). Three of these patients suffered from sustained VT in the acute phase post-MI. These patients would not have been considered for an ICD. One patient suffered with sustained VT not associated with an acute MI and was commenced on amiodarone but was not referred for consideration of an ICD, possibly due to the patient's age at time of diagnosis (84 years).

Three patients suffered NSVT. One patient was symptomatic on testing, and managed for their ischaemia. This patient had an episode of NSVT post-MI but the timing of this arrhythmia post-MI was unclear. One patient suffered with shortness of breath and had Holter monitoring. The other patient had an exercise ECG to determine their level of ischaemia prior to having a CABG. Both patients experienced asymptomatic NSVT on testing and were not managed further. Notably, one of these patients was known to have poor left ventricular function on echocardiogram. These three patients would not have been eligible for an ICD on the basis of the 2000 NICE guidelines.

### ***Much less certain category***

This category includes patients with cardiac abnormalities and symptoms suggestive of ventricular arrhythmias i.e. patients with (a) cardiomyopathy and heart failure, (b) MI and (c) syncope. However, further investigations would have been required to determine if they were appropriate for an ICD. 97 cases were included in this category (see table 6.7). As before, this category is graded by level of certainty.

#### ***a) Cardiomyopathy and heart failure***

Patients at highest risk of a SCD and therefore most eligible for further investigation would have been those with cardiomyopathy and heart failure. Five patients had cardiomyopathy (4%). Fifty-seven patients were either diagnosed with heart failure (Doctor diagnosed and/or through investigations) or receiving a combination of drugs suggesting treatment for heart failure but had not suffered a ventricular arrhythmia or been diagnosed with cardiomyopathy during their lifetime.

Table 6.8 below shows the number of patients with cardiomyopathy and heart failure who (1) had an echocardiogram and/or angiogram/chest x-ray to confirm their diagnosis and (2) had an ECG and/or Holter monitor during their lifetime to determine whether they had an abnormal heart rhythm.

**Table 6.8      Investigations undertaken during the lifetime of patients with cardiomyopathy and heart failure**

	<b>Echocardiogram evidence of HF</b>	<b>Angiogram/CXR evidence of HF</b>	<b>Holter monitoring</b>	<b>ECG</b>
<b>Cardiomyopathy N = 5</b>	3 (60%)	2 (40%)	0	3 (60%)
<b>Heart failure N = 57</b>	6 (11%)	5 (9%)	16 (28%)	27 (47%)

Table 6.8 shows that most cardiomyopathy patients (60%) had their severe heart failure confirmed on echocardiogram. However, very few heart failure patients (11%) had an echocardiogram during their lifetime. Most patients had their heart

rhythm monitored at some time in their life, but few (28%) had had a Holter monitor. None of these patients were found to have VT on testing.

**b) MI**

In total, fifty-two patients had suffered an MI. According to the NICE guidelines, these patients would have been eligible for an ICD if found to have both non-sustained VT on Holter monitoring and left ventricular dysfunction on echocardiogram. The table below shows the number, and percentage, of patients having a record of having these investigations **at any time in their lifetime** (some patients suffered more than one MI in their lifetime, the date of the event closest to death is recorded in the table) and the decade in which the MI occurred.

**Table 6.9 Date of ‘latest’ MI and number of patients having investigations post-MI**

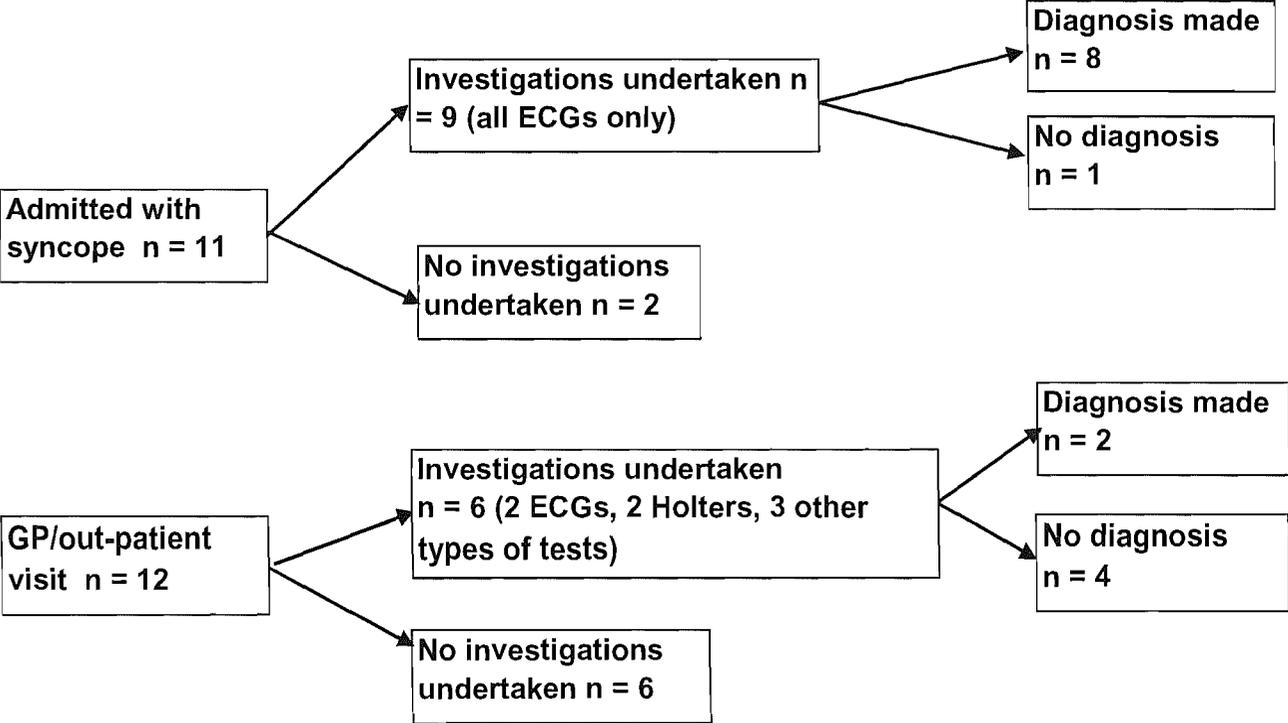
<b>Decade</b>	<b>Number of MIs</b>	<b>Echocardiogram undertaken</b>	<b>Holter monitoring undertaken</b>
<b>1970 – 1979</b>	3	2 (67%)	1 (33%)
<b>1980 – 1989</b>	14	3 (21%)	1 (7%)
<b>1990 – 1999</b>	18	9 (50%)	0
<b>2000 -</b>	15	7 (47%)	2 (13%)
<b>No information</b>	2	-	-
<b>Total</b>	52	21 (40%)	4 (8%)

Only 3 of the 52 patients (6%) suffering an MI had had an echocardiogram and Holter monitoring undertaken at some time in their life. These three patients did not have non-sustained VT on testing. Echocardiography is a relatively new technique for assessing the degree of heart failure. Angiography and chest x-rays have also been used to assess the degree of heart failure. However, only 9 of these 52 patients had had an angiogram or chest x-ray in their lifetime.

### **c) *Syncope***

Twenty-three patients suffered from syncope (blackouts) during their lifetime but were not diagnosed with a ventricular arrhythmia, heart failure or MI. Just 3 (13%) of these patients had suffered from recurrent syncope. However, others had suffered from dizziness and falls during their lifetime. Figure 6.3 shows the number of patients with syncope admitted or managed in primary care during their lifetime. It also shows whether investigations were undertaken after the event and if a diagnosis was made (for the 3 patients suffering from recurrent syncope, the flow-diagram shows the flow after the event for which most active management was provided).

Figure 6.3 Investigations undertaken and suspected diagnoses after admission or GP or out-patient visit for syncope



Ten (43%) of the 23 patients with syncope were diagnosed. Diagnoses varied from definite diagnoses i.e. atrial fibrillation, brain stem stroke, ventricular standstill and hypertension to possible diagnoses i.e. smoking related, anxiety state, exhaustion and possible vascular episodes. Fifteen patients (65%) had investigations to identify the cause of their syncope.

Most of the patients admitted with syncope were investigated (82%). However, this was only in the form of an ECG. Although fewer patients (50%) managed in primary care or in an out-patient setting had investigations, this included Holter monitoring and other types of investigations as well as ECGs.

None of the patients experiencing syncope but not having suffered a ventricular arrhythmia, MI or heart failure were rigorously investigated for the cause of their syncope. Most patients who were investigated had an ECG and no further testing.

### ***Most unlikely***

There were 21 patients in this category (see table 6.7). These patients had cardiac abnormalities or indications of cardiac abnormalities but these were not indicative of a ventricular arrhythmias and therefore would be insufficient to justify further investigation for ICD appropriateness e.g. evidence of other types of arrhythmias, CABG or PTCA.

### ***Conclusions of investigators ratings***

Of the 209 patients in the case series for whom hospital and/or GP notes could be identified, only 4 patients (3%) may have been appropriate for an ICD. Forty percent of cases appeared to have de novo disease; leaving the majority of these cases (57%)

with some form of cardiac abnormalities or symptoms suggestive of ventricular arrhythmias.

These 'less certain' and 'much less certain' cases were graded by certainty of ICD appropriateness in table 6.7 and investigations undertaken discussed. The results suggested that many patients with heart failure, previous MI or syncope were not investigated further to determine potential for suffering ventricular arrhythmias.

#### 6.2.4.2 Experts appropriateness ratings

Two experts were provided with proformas on all 209 cases and asked to rate the appropriateness of each case for an ICD as described in the methods (section 6.1.5). The results are shown in table 6.10 below. The kappa score was 0.50; suggesting a moderate strength of agreement between the two experts. However, there was agreement that only one case was appropriate for an ICD. Their reasons for deeming this case to be appropriate were A: 'known to be at high risk of SCD' and B: 'left ventricular function less than 35%'.

**Table 6.10 Appropriateness ratings by the two experts: Expert A's ratings in columns and expert B's in rows.**

A/B ratings	Appropriate	Inappropriate	Further tests	No evidence	De Novo	Total
Appropriate	1	0	0	0	0	1
Inappropriate	0	2	2	0	0	4
Further tests	0	28	51	14	3	96
No evidence	0	8	4	10	1	23
De Novo	0	2	2	7	74	85
Total	1	40	59	31	78	209

The majority of cases were categorised as 'de novo'. Disagreements on cases categorised as de novo were due to incorrect assessment by expert A or B e.g. not noting the occurrence of an MI or particular test results.

The reason for so much disagreement on who was inappropriate for an ICD was an issue about setting an age limit. Expert A used older age, i.e. over 80 years, as a contraindication to ICD implantation and therefore classified these cases as inappropriate for an ICD. Expert B commented on the older age of patients but did not use this information to determine appropriateness. Consequently, this reduced the number of cases expert A classed as 'should have had further tests'. Expert A recommended that 59 patients should have had further tests. Expert B recommended that 96 patients should have had further tests. The main reason for this discrepancy was the age contraindication used by Expert A. A's reasons for assigning cases to these two categories can be easily categorised and are shown below.

**Table 6.11 Expert A's reasons for assigning cases to the 'should have had further tests' categories**

<b>Reason for further testing</b>	<b>Expert A Number of cases (%)</b>
VT and CAD	1 (2%)
Symptomatic VT	1 (2%)
Possible MADIT 1* patient	46 (78%)
CAD not investigated	2 (3%)
Heart failure unexplained	5 (9%)
Syncope not investigated	2 (3%)
Supra-Ventricular Tachycardia misdiagnosis?	2 (3%)
<b>Total</b>	<b>59</b>

\*MADIT-1:NICE recommendation for primary prevention - MI, non-sustained VT and LV dysfunction

Expert B's reasons for assigning cases to these two categories were more specific and are shown in table 6.12. As far as possible, these have been sub-grouped under the reasons given by expert A.

**Table 6.12 Expert B's reasons for assigning cases to the 'should have had further tests' categories**

<b>Expert A's grouping for reasons</b>	<b>Expert B's reason for further testing</b>	<b>Number of cases</b>
VT & CAD/symptomatic VT	VT	3
Possible MADIT 1 patient (primary prevention)	MI NSVT	2
	Heart failure, MI	4
	MI	7
	MI ?EF	28
	MI ?revas	1
	MI & reduced LVF	1
	MI & syncope	2
CAD not investigated	Positive exercise tolerance test	3
	Previous CABG, ?EF	1
Heart failure unexplained	?Ejection fraction	18
	Heart failure, ?EF	5
Syncope not investigated	Syncope ?EF	4
	Syncope	7
SVT misdiagnosis?	?arrhythmia	8
?	DCM ?EF	1
<b>Total</b>		<b>95</b>

Reasons for assigning cases to the 'should have been considered for further testing' varied. The main reason being exploration of whether patients met the MADIT 1 study criteria i.e. the NICE recommendation for primary prevention of SCD.

### Exclusion of cases over 80 years of age at time of death

Expert A categorised all cases aged 80 years and over at time of death as inappropriate for an ICD because of their older age. We can exclude these cases to better compare reasons for disagreement between the two experts. If cases aged 80 years or over at the time of death are excluded from the cohort, this leaves 146 cases with hospital and/or GP notes. Appropriateness ratings by the two experts for this sub-group are shown in table 6.13. The kappa score for agreement between experts A and B was stronger than for the whole cohort; with  $k = 0.64$ .

**Table 6.13** Appropriateness ratings by the two experts for cases aged less than 80 years at time of death: Expert As ratings in columns and expert B's in rows.

A/B ratings	Appropriate	Inappropriate	Further tests	No evidence	De Novo	Total
Appropriate	1	0	0	0	0	1
Inappropriate	0	0	1	1	0	2
Further tests	0	2	48	4	1	55
No evidence	0	0	14	10	7	31
De Novo	0	0	1	0	56	57
<b>Total</b>	1	2	64	15	64	146

### ***Experts agreed appropriateness ratings and conclusion***

There were 31 cases where there was disagreement between experts. These cases were discussed at a joint meeting between the experts. Final decisions on all cases aged less than 80 years at time of death (n = 146) are shown in table 6.14.

**Table 6.14 Final appropriateness ratings as agreed by the two experts**

<b>Category</b>	<b>Number of cases (%)</b>
<b>Appropriate for an ICD</b>	1 (<1%)
<b>Inappropriate for an ICD</b>	0
<b>Should have had further tests</b>	72 (49%)
<b>No evidence to justify further testing</b>	11 (8%)
<b>De Novo</b>	58 (40%)
<b>Further information required</b>	4 (3%)
<b>Total</b>	146

In conclusion, the experts agreed that only one case aged less than 80 years at the time of death would have been appropriate for an ICD. Forty percent of cases could be classed as de novo. Most cases, 49%, required further investigations to determine appropriateness of an ICD. For 4 cases, the experts requested further information on heart rhythm recordings to determine whether these patients had been misdiagnosed with a supra-ventricular arrhythmia rather than a ventricular arrhythmia during their lifetime.

## 6.2.5 Identification of potential missing cases

This section presents results of an assessment of the number of SCDs where a post-mortem was not undertaken i.e. potential missing cases from this study. To determine the total number of SCDs (presumed to be primarily due to ventricular arrhythmias) in the community, cases were identified using the three methods described in the methods sections: 6.1.3 and 6.1.5. Cases were: (1) IHD deaths in the community, (2) post mortem SCDs and (3) out of hospital cardiac arrest cases.

### 6.2.5.2 Mortality data on IHD and other forms of heart disease

ONS data showed that 1843 adults died of ischaemic heart disease or other forms of heart disease who resided in the SSWHA area from October 2002-03. 774 (42%) of these adults died in the community. The ICD-10 codes of part 1a<sup>2</sup> of the death certificate for these cases, by place of death, are shown in the table below.

**Table 6.15 ICD codes of primary cause (1a) for IHD deaths**

<b>1a Cause of death</b>	<b>Hospital</b>	<b>Community</b>	<b>Total</b>
I20-I25 IHD	295 (28%)	330 (43%)	625 (34%)
I30-I52 Other forms of heart disease	284 (27%)	223 (29%)	507 (28%)
Other codes	490 (46%)	221 (29%)	711 (39%)
Total	1069 (100%)	774 (100%)	1843 (100%)

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<sup>2</sup> Cause of death is described in part 1 and part 2 of the death certificate. Part 1a is the 'disease or condition directly leading to death'. Part 1b 'other disease or condition, if any, leading to 1a. Part 1c 'leading to 1b. Part2 'other significant conditions contributing to the death but not related to the disease or condition causing it'.

Most of the community IHD deaths had IHD or other forms of heart disease as cause 1a in their death certificate (72%). However, 221 (29%) of community IHD deaths had codes other than IHD or other forms of heart disease for cause 1a. It was assumed that none of these 221 community IHD deaths with a 1a cause other than IHD or other forms of heart disease were SCDs. This leaves 553 community deaths that may be SCDs.

#### **6.2.5.1 Post-mortem SCDs**

As shown in results section 6.2.1, figure 6.1, there were 366 SCDs, of which, 232 (63%) were not associated with an acute MI and therefore presumed to be primarily caused by a ventricular arrhythmia. These cases were identified over 12 months (October 2002-03). Two-hundred and fifteen of these cases resided within the study catchment area.

Although the intention is to estimate the total number of SCD cases primarily caused by ventricular arrhythmias, in order to link data, it is helpful to know of other SCDs where a post-mortem was undertaken. 134 SCD cases associated with an acute MI were also identified. Further data on these cases were not collected. It is therefore unclear whether all or some of these cases resided within the catchment area. In the absence of further information, we will assume that the same proportion of SCD cases associated with an acute MI as those without an acute MI resided in the catchment area i.e. 93% of 134 cases; 124 cases.

It is important to note that all these cases were SCDs occurring within the catchment area where the person resided. If a resident had an SCD outside of the catchment area within the timeframe of the study this case would have been missed.

### **6.2.5.2 Out of hospital cardiac arrests**

During the case identification phase of the VT study (see chapter 6 for study details), 132 out of hospital cardiac arrest cases were identified at SUHT A&E department from October 2002 – September 2003).

The Post-Mortem database was checked to find out the cause of death for these 132 cardiac arrest cases. 108 cases had hospital numbers. Sixty-two of these 108 cases (57%) had Post-Mortem reports. For 45 cases (73%) the primary cause of death (cause 1a) was Ischaemic Heart Disease (33 of which were Sudden Cardiac Deaths, 11 of these were associated with an acute MI). Causes of death for the other 17 cases with a PM report included overdose, subarachnoid haemorrhage, pulmonary embolism, bronchopneumonia and gastro-intestinal haemorrhage. Clearly, some cases coded as a cardiac arrest in the resuscitation log book were miscoded.

Using data on the proportion of out of hospital cardiac arrest cases certified as suffering an IHD death by post-mortem examination, we can estimate the proportion of out of hospital cardiac arrest cases suffering an IHD death where a post-mortem was not undertaken. There were 70 out of hospital cardiac arrest cases, assuming 73% (percentage of post-mortem cases having IHD as cause of death 1a) died of IHD, this would account for 51 non-post mortem community based SCDs.

### **6.2.5.4 Estimation of the number of SCDs in the community**

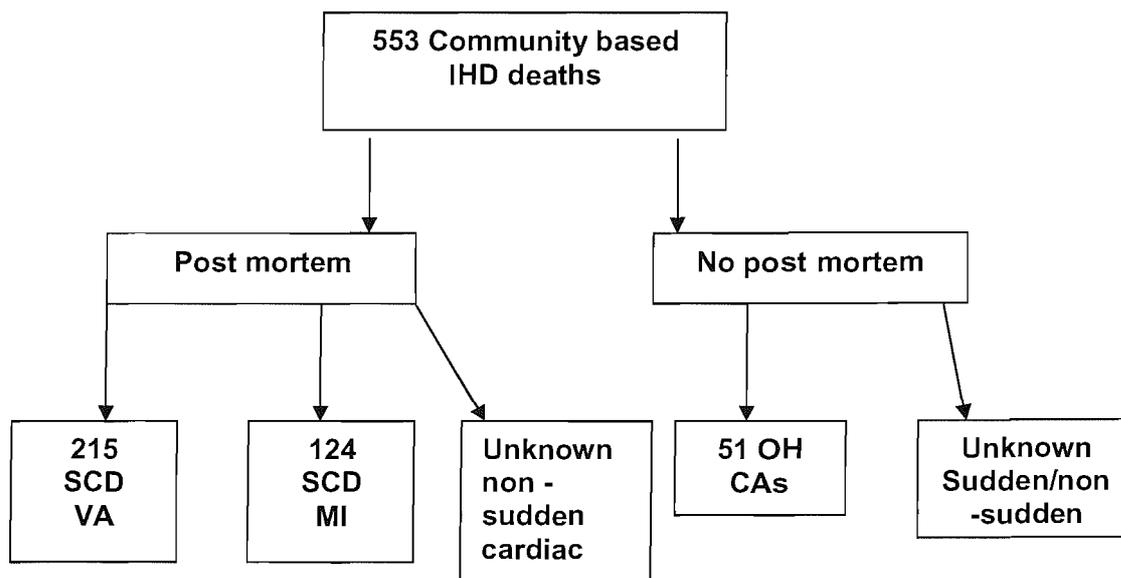
Attempts were made to link these three sources of data to estimate the number of SCD primarily caused by ventricular arrhythmias where a post-mortem was not undertaken. Unfortunately, due to a large amount of missing data on hospital numbers (from the IHD mortality data) and/or date of birth (from the out of hospital cardiac arrest cases and PM cases of SCDs associated with acute MI) this was not possible.

Therefore, assumptions and extrapolations from these data were made to estimate numbers.

It was assumed that all the SCD study cases (215 cases) and post-mortem cases of SCD associated with an MI (estimated 124 cases) would be included within the 553 IHD community deaths. Likewise, the estimated number of out of hospital cardiac arrest cases where a post-mortem was not undertaken and the primary cause of death (1a) was assumed to be IHD (estimated 51 cases).

Figure 6.4 is a diagram of all 553 IHD community deaths and the proportion of these deaths identified in the SCD study and A&E out of hospital cardiac arrests.

**Figure 6.4** Diagram of IHD community deaths showing the proportion identified by post-mortem and non post-mortem sources



As can be seen from figure 6.4, 390 (71%) of the IHD community deaths have been identified; from the SCD study (215 cases), SCDs associated with acute MI (124 cases) and out of hospital cardiac arrests (51 cases) where a post-mortem was not undertaken. This leaves 163 (29%) of IHD community deaths not identified. Can anything be said about whether any or all of these deaths were SCDs?

If 63% of the out of hospital SCD cases were primarily due to ventricular arrhythmia (as found with the post-mortem data), this would amount to 32 (51\*63%) out of hospital SCD cases (where a post-mortem was not undertaken). Similarly, if all 163 IHD community deaths were SCDs (and 63% of these were primarily due to ventricular arrhythmia) this would amount to 103 cases (163\*63%). Potentially, therefore, we could have missed as many as 135 (32 + 103) cases from our case series. This is unlikely to be the case though given the number of Coroners post-mortems undertaken on non-sudden cardiac deaths (see figure 6.1). It is more likely that none of the uncertain community deaths were sudden. This would mean that we have missed 32 cases (out of hospital cardiac arrest cases presumed to be SCDs primarily due to ventricular arrhythmias) from our SCD case series i.e. about 8% of all cases.

### **6.3 Discussion**

The aim of this study was to establish whether SCD cases thought to be due to a ventricular arrhythmia could have been identified prior to death and potentially considered for an ICD. This study has suggested that very few of the 215 cases (<1% as agreed by experts and 3% as determined by the investigator) could have been identified. Only 9 patients (4%) had survived a previous cardiac arrest or life threatening ventricular tachycardia. About 40% of SCD cases had no prior health service history of cardiac abnormalities or symptoms suggestive of ventricular arrhythmias.

Results from further investigations would have been required to determine the appropriateness of a large number of cases. The experts agreed that 49% of cases under 80 years at time of death required further investigations to determine ICD appropriateness. Their reasoning for assigning the majority of these cases (about 80%) for further investigations was that the patient had suffered an MI with/without heart failure or NSVT. There was also concern that a small number of cases may have been misdiagnosed i.e. as supra-ventricular tachycardia as opposed to a ventricular arrhythmia during the patients' lifetime.

Extrapolation from IHD mortality data on deaths in the community and out of hospital cardiac arrest data was undertaken to determine the number of possible SCD cases not already identified in this study case series. It was estimated that 32 SCDs primarily due to ventricular arrhythmias occurred within the catchment area but post-mortems were not undertaken. This suggests that the SCDs in this case series represented the majority of cases occurring in the community in 2002-3.

Reliance on notes for information on previous medical history is prone to the potential for lost information e.g. details of investigations not recorded, missing letters and lost information on episodes of care. Apart from accessing hospital and GP computer databases, there is no other method of identifying the health service history of these deceased patients. Furthermore, there may be differences between general practices and hospitals in comprehensiveness of notes. A comparison of data from hospital and GP notes for all those patients having both sets of notes was therefore undertaken. This suggested good agreement between the notes for events such as MI, ventricular arrhythmias and heart failure. GP notes tended to identify more cases and these notes were available for the majority of cases.

Only one person extracted data from the notes. It is possible that information could have been missed. Concurrence of information from hospital and GP notes is reassuring. Ideally, data extraction should be checked by a second person. Unfortunately this was not feasible within the timeframe of the study.

Agreement between experts on appropriateness for an ICD was good; with only one case considered appropriate. The main disagreement was the use of a criterion not addressed in guidelines; an age limit for ICD appropriateness i.e. the implantation of ICDs in patients aged 80 years and over would be inappropriate. Consensus between experts on appropriateness ratings was achieved on all cases under the age of 80 years at the time of death.

There is a large literature on consensus methods<sup>91</sup>. A simplified version of the Rand method was used to assess the appropriateness of cases for an ICD. This method was adopted because it has been widely used to assess the appropriateness of healthcare interventions, aggregation of results is explicit and the approach is not greatly time consuming. Most importantly, it enables participants to elicit private decisions which are then fed back to the group who meet to reach an agreement<sup>91</sup>. This provides an indication of the amount of difference in individual's judgements as well as enabling consensus.

Appropriateness was assessed by two experts working within the same specialist centre. Ratings from a group of experts from different centres would have provided a better indication of national consensus on appropriateness. We would expect the two experts helping with this study to have similar opinions on appropriateness (this wasn't always the case though). It was not feasible to convene a group of national experts within the timeframe of the study. However, the study investigator also considered the cases using the NICE ICD recommendations as a guide and drew similar conclusions on appropriateness.

Another limitation is the potential for missed cases. Ideally, all fatal SCD cases would have had a post-mortem. However, only 22% of deaths in England are followed by post-mortem. This rate is lower still in Scotland and Northern Ireland (12% and 9% respectively). SCD is not a certifiable cause of death; these deaths would probably be certified as deaths due to heart disease. Of concern, is whether the cases in the SCD case series are representative of all SCDs primarily due to ventricular arrhythmias. Therefore, an assessment of the potential number of missing cases was undertaken.

The limitations in undertaking such an assessment are associated with the sources of data and the extrapolations and assumptions made: (1) Routine mortality data was used to determine the total number of community IHD deaths. Incorrect ICD-10 coding could lead to an under or overestimate of the number of deaths and consequently number of SCD cases, (2) It was assumed that all deaths occurred in the community. In the SCD case series, 8% of deaths occurred in hospital. Any SCD patients surviving to hospital admission, who died during their admission, but did not have a post-mortem would have been missed and (3) assumptions were made about the proportion of SCDs primarily caused by a ventricular arrhythmia in cases where a post-mortem was not undertaken and the proportion of non-sudden cardiac post-mortem deaths occurring in the community.

Data from this case series of SCDs compares well with other studies; with very similar proportions of witnessed cases, gender and age breakdown<sup>87</sup>,. Pathological data comparisons showed that a smaller proportion of SCD cases were identified as 'certain' SCDs than larger and more detailed pathological studies<sup>87, 92, 93</sup>. About 50% of cases had evidence of acute MI or acute coronary thrombosis in these studies (compared with 37% in this series). Extensive pathological investigation was not undertaken in this case series and this may explain the difference. Therefore, it is

possible that some cases in this series had undetected acute MI or acute coronary thrombosis at post-mortem.

Pathological findings in SCD cases also vary by the age of the patient studied. In adults, coronary artery disease is by far the leading cause of death. Congenital heart disease, cardiomyopathy and unexplained left ventricular hypertrophy are more common causes in younger patients, especially athletes<sup>94, 95</sup>. The median age of patients in this study was 75 years, with the youngest being 40 years of age, consequently these causes were uncommon (just 3% of cases were unexplained).

There are no previous published studies that have assessed whether SCD victims could have been identified prior to their death and potentially considered for an ICD. Other studies have assessed the scope for preventing SCDs by identifying risk factors for SCD and found that the presence and severity of underlying heart disease is one of the most predictive risk factors for the future occurrence of SCD<sup>9</sup>. However, about 50% of SCDs occur in patients without diagnosed coronary heart disease<sup>96</sup>.

Studies of SCD incidence were discussed in chapter 1 of this thesis. The largest of these studies, undertaken in the U.S. in 1999 suggested an age adjusted incidence rate of 2070 per million population (pmp) for males and 1410 pmp for females. In this study, the incidence of SCD primarily due to ventricular arrhythmias (including the estimated number of cases where a post mortem was not undertaken) would be 557 pmp (95% CI, 491, 630).

We would expect these rates to differ because: (1) this study considered the number of SCDs primarily caused by ventricular arrhythmias, the U.S. study assessed the incidence of all SCD. In this study, 63% of SCDs where a post-mortem was undertaken were presumed to be primarily caused by a ventricular arrhythmia and (2) incidence rates differ by person, place and time and (3) the definition of SCD. We

used a broad definition that didn't require the death to be witnessed. Other definitions include just those cases known to have experienced symptoms 1 hour before death. Only 37% of cases in this study were witnessed. If only those cases known to have experienced symptoms within 1 hour prior to death were included, this would have constituted just 33 cases!

More recently, a study undertaken in Northern Ireland (published in 2006), estimated the European age standardised SCD incidence as 1220 per million population for males and 410 per million population for females<sup>97</sup>. 54% of the 300 victims of SCD had no known history of cardiac disease yet 94% of the pathology reports showed severe coronary artery disease in one or more of the coronary arteries. This compares well with our study, with 40% of victims having no known history yet 77% showed severe coronary artery disease. Unlike our study, the Northern Ireland study included all SCDs (including those with acute thrombosis) and also the small number of survivors. Similar to our study, unwitnessed deaths were included if the patient had been seen alive and asymptomatic within 24 hours of being found collapsed.

The 2000 NICE guidance recommendation is that patients suffering an MI with left ventricular dysfunction (heart failure) and non-sustained VT should be considered for an ICD for primary prevention of a SCD. This study has shown that very few patients who had suffered an MI were having further investigations i.e. echocardiograms and Holter monitoring to assess the level of ventricular function, and heart rhythm respectively post MI. In addition, very few of the cases who had suffered with heart failure during their lifetime had had their diagnosis confirmed on echocardiogram, chest x-ray or angiogram. Slightly more of these patients had had their heart rhythm monitored.

There could be a number of reasons for this block in referral: (1) the current NICE recommendations were made in 2000; information from this case series would not

show a change in practice as a result of these recommendations., (2) the resource implications of testing every patient who has suffered a previous MI would be great, (3) patient's co-morbidities and preference and (4) availability of these investigations.

Syncope is very prevalent and has a number of causes and many cases remain unexplained after extensive investigation (see chapter 1, section 1.3). In this study, syncope (blackouts) were reported in the notes of 11% of SCD cases. Suspected causes were recorded for some of these cases (see figure 6.3), but many cases remained undiagnosed.

Ventricular arrhythmias contribute to a very small proportion of known syncopal causes. i.e. the positive predictive value of syncope as symptom for detecting ventricular arrhythmias is very low. However, these arrhythmias are potentially fatal and it is therefore important to exclude this as a diagnosis for syncope. The problem is being able to record the patient's heart rhythm at the time of collapse. Implantable heart recorders are now available which are more sensitive and these may help to identify more patients who survive a life threatening ventricular arrhythmia. A recent trial 'CIRUS', undertaken at SGH, has established the cost-effectiveness of these devices for patients with unexplained recurrent syncope (unpublished, for citation see 'publications and presentations').

None of the patients in this study who experienced syncope had one of these devices implanted. Commonly, Holter monitoring is employed as a means of determining heart rhythm after an episode of syncope. Only 9% of syncopal patients not suffering an MI or heart failure had a Holter monitor during their lifetime.

Given that very few of the SCD cases suffered previous ventricular arrhythmias (as recorded in their health service notes), research should focus on identifying other risk indicators for an SCD and/or assess the cost-effectiveness of measures to prevent an

SCD at the time of the event e.g. the use of automatic external defibrillators<sup>11</sup>. Another research need is an assessment of the cost-effectiveness of heart rhythm monitoring and echocardiography post-MI (both incident and prevalent cases) to identify patients who may be appropriate for an ICD.

Policy implications should be: (1) to make SCD a certifiable cause of death and (2) the use of the SCD grading scale (devised by Davies et al) nationally by pathologists to determine the level of certainty associated with a SCD. The implementation of both of these measures would better enable epidemiological analysis of variations in SCD rates and associated factors between geographical areas.

## 7. Final Discussion

The objectives of this final chapter of the thesis are to summarise the main findings of this study and to reflect on results in relation to ICD provision.

This thesis has explored the incidence, prognosis and current management of ventricular arrhythmias to inform need for ICDs. A multi-faceted approach was employed. Five research methods were utilised:

- Systematic review of the epidemiology of ventricular arrhythmias
- Prospective cohort study of the incidence and prognosis of ventricular arrhythmias
- Case series of sudden cardiac death
- Assessment of current management and need using national routine data on ICD implantation
- National survey of ICD implantation centres

### ***Summary of findings***

The systematic review showed that no UK studies had been published on the incidence of ventricular arrhythmias; only U.S. studies undertaken in the 1990s based on routine data. The best estimate from these studies was an age-adjusted rate of about 200 per million population for ventricular arrhythmias requiring hospital admission. Incidence rates in studies reviewed were higher in males than females and increased with age. There were no published studies on the incidence of less severe ventricular arrhythmias not requiring hospitalisation.

Published prognostic studies suggested that case fatality rates were high for patients who were admitted to hospital with a life threatening ventricular arrhythmia. Long term survival rates varied greatly; both of patients with life threatening ventricular arrhythmias and those with NSVT. Prognosis was strongly associated with degree of underlying heart disease. In particular, patients with poor left ventricular function had the worst prognosis.

In the prospective cohort study, an incidence rate of 200 per million was estimated for all patients with ventricular arrhythmias who had survived the first day after their diagnosis. The incidence of life threatening ventricular arrhythmias was 62 per million population; about three fold lower than the best published estimate. Most patients presented with syncope, palpitations, chest pain or shortness of breath. Underlying heart disease was common and over half of the patients with life threatening ventricular arrhythmias had suffered a previous MI. The survival experience was good, with 88% of patients surviving to 12 months. Seventeen patients in this incident cohort study were managed with an ICD; an implantation rate of 42 per million population. Those patients with life threatening ventricular arrhythmias not managed with an ICD appeared to receive appropriate management given their individual health circumstances. The majority of patients with NSVT were not managed for this arrhythmia or investigated further.

The SCD study suggested that very few of these fatal cases presented with ventricular arrhythmias prior to their event. Therefore, the first presentation of the majority of patients presenting with a life threatening ventricular arrhythmia was as an SCD. However, two experts agreed that 49% of cases should have had further diagnostic testing during their lifetime. Most of these cases had suffered an MI and/or were diagnosed with heart failure but were not referred for heart rhythm monitoring.

An analysis of routinely collected national ICD data (1998-2000) suggested that ICD rates were increasing, particularly the implantation of new devices. Implantation was most common for males and middle aged persons and survival from a cardiac arrest was the most common presentation for an ICD. An assessment of English regional ICD implantation rates suggested that rates in some areas fell well below that of the national rate.

An assessment of the relationship between ICD use and need, using IHD mortality and deprivation data as two proxy measures of need suggested possible inequity of ICD utilisation within England. Results from the deprivation analysis strongly suggested that the inverse care law was operating; those areas where need was the highest also had the lowest rates of new ICD implantation.

Results from the national survey of ICD centres suggested that patient identification was the greatest barrier to ICD use; with perceived under referral of patients with indications for ICDs from clinicians in primary and secondary care. Future direction was seen as a shift towards providing ICDs in secondary care and changing indications for ICDs (the MADIT 2 study criteria: patients post MI with low LVEF). However, staff and funding shortages were perceived as problems that could prevent such a change.

### ***Interpretation of findings***

Variations in incidence estimates between studies are to be expected. The diagnosis of a ventricular arrhythmia is dependent on the patient having their heart rhythm monitored during their arrhythmia. For life threatening cases, this means reaching the patient swiftly (preventing an imminent sudden cardiac death). For non-sustained VT and self reverting sustained VT cases, it depends on referral patterns for diagnostic

testing, the frequency of the arrhythmia and the insensitivity of heart rhythm monitoring.

The diagnostic test for ventricular arrhythmias is an ECG. All types of ECG are equally capable of detecting a ventricular arrhythmia if an arrhythmia occurs whilst monitoring. The variation in test sensitivity is associated with the frequency of episodes and thus the duration of monitoring. A stand alone ECG is undertaken in minutes whereas an implantable heart recorder can detect heart rhythm over a period of 14 months (before battery depletion). If the diagnostic test is not undertaken at the exact moment an arrhythmia occurs it will not detect this abnormality.

Incidence also varies with case definition. The spectrum of disease for ventricular arrhythmias is vast and continuous; ranging from no symptoms (associated with a short reversible run of ventricular ectopic beats) to ventricular fibrillation and imminent SCD. In the prospective cohort study, a pragmatic case definition of four or more consecutive ventricular beats at a rate of 100 bpm was used. Presenting symptoms ranged from palpitations to cardiac arrests. Feasibility study one, undertaken prior to the cohort study, found that the inclusion of undiagnosed cases at SGH would have doubled the number of NSVT cases.

Using data from the SCD case series and routine IHD mortality data, the incidence of SCD presumed to be primarily caused by ventricular arrhythmias was estimated to be 557 per million population; about ten times higher than the incidence of life threatening ventricular arrhythmias (survivors one day after hospital admission) within the same area and time period. Most of the post-mortem SCD cases in the case series had no history of VT nor was there evidence of symptoms suggestive of ventricular arrhythmias in GP notes. Is it therefore, that most patients' first experience of symptoms is the death itself or that they had symptoms but did not present to the health service? Or, with about 40% having some form of underlying heart disease,

should these patients have been investigated further for ventricular arrhythmias at some point during their lifetime?

Data from hospital and GP notes of patients in the SCD case series suggested that very few patients presented with syncope or palpitations during their lifetime and only a small proportion of patients with symptoms were referred for heart rhythm monitoring.

The National Service Framework on CHD now includes a chapter on arrhythmias and SCD (published in 2005)<sup>98</sup>. The need for expert assessment of patients when an arrhythmia is suspected and that an appropriate and clinically effective care pathway is followed is acknowledged in this document. However, guidance is needed on the constitution of this care pathway. The NSF also proposes that all patients with symptoms suggestive of a ventricular tachycardia e.g. recurrent syncope associated with palpitations or recurrent unexplained falls, survivors of out of hospital cardiac arrest, a family history of SCD or documented ventricular tachycardia (including presumed ventricular tachycardia) should be assessed by a heart rhythm specialist<sup>98</sup>. However, the infrequency of most patients' symptoms makes diagnosis difficult.

### ***ICD provision***

Reassuringly, the cohort study suggested that all those patients eligible for an ICD were considered for one of these devices. This may have been due to the existence of a specialist ICD centre within the study catchment area. The assessment of national routinely collected ICD data suggested that supply varied by geographical area i.e. English region. This variation could be due to inaccessibility to ICD centres. A further prospective cohort study including areas where a specialist service was less accessible would be needed to address this supposition.

Many patients with NSVT in the cohort study were not investigated to establish the existence of any underlying heart disease. If they had been found to have suffered a previous MI they should have had an EPS and then possibly an ICD (for primary prevention of an SCD, as recommended by NICE in 2000). Conversely, results from the SCD case series suggested that very few patients who had a history of previous MI had been investigated for a ventricular arrhythmia. There appears to be a large mismatch between indications for an ICD for the primary prevention of a SCD and ICD provision. The most likely reason for this mismatch is the cost and service requirements associated with the further investigation of all patients who have suffered an MI and/or NSVT.

The period prevalence of symptoms associated with ventricular arrhythmias i.e. syncope and palpitations in patients not presenting to the health service cannot be determined without some form of population based health survey. However, given that these symptoms can be indicative of a number of causes, without health service contact and referral for diagnostic testing, it would be impossible to determine the magnitude of need for an ICD.

If emergency response to cardiac arrest was improved, more patients could survive to hospital admission and be considered for an ICD<sup>11,99</sup>. Response is improving, in line with the CHD National Service Framework Targets. However, the two major limitations to success are 1. the number of unwitnessed SCDs and 2. a poor survival rate in-hospital. In the SCD case series, 40% of events were unwitnessed.

International comparisons of ICD utilisation have shown that the UK has one of the lowest ICD implantation rates in industrialised countries. The national ICD rate of 17 per million population in 2000, fell far below the recommended 50 per million population. However, the rate of ICD use is increasing and the UK is likely to reach the 50 per million population target in 2006.

It has been suggested that the cost of these devices is the main barrier to increased diffusion of ICDs. In 2000, ICDs were about £20,000 with cost-effectiveness ranging from £20,250 to £87,000. The price of existing devices is falling, but more costly advanced ICDs with additional pacing capabilities are now available. With the advent of the NICE guidance in 2000, ICD utilisation in the UK increased dramatically (see chapter 1, figure 1.4). The addition of a further patient group in the 2005 NICE guidance is likely to have a similar effect.

For this additional patient group i.e. patients with a previous MI, left ventricular dysfunction and a specific QRS interval on ECG, there is no requirement for evidence of ventricular arrhythmias and thus no need for an EPS. Recently, there has been an increase in the number of Cardiologists<sup>35</sup>. This broadening need coupled with an increase in staffing could increase the impetus to shift the ICD service from tertiary into secondary care. An ICD service without the need for EPS could reduce the cost thereby increase the supply of these devices to patients. There is a need for modelling to determine the cost-effectiveness of such a change in service provision.

### **Conclusions**

The 'multi-faceted' approach adopted for this thesis has provided a way of comprehensively assessing the epidemiology of a disease, with emphasis on indications for a specific health care intervention. In a seminal article, published soon after the NHS reforms, Frankel considers the need to guide health care provision by extending the assessment of disease epidemiology into 'the realm of the population distribution of indications for treatment'<sup>100</sup>. This thesis has taken this direction in assessing the epidemiology of ventricular arrhythmias to inform need for ICDs.

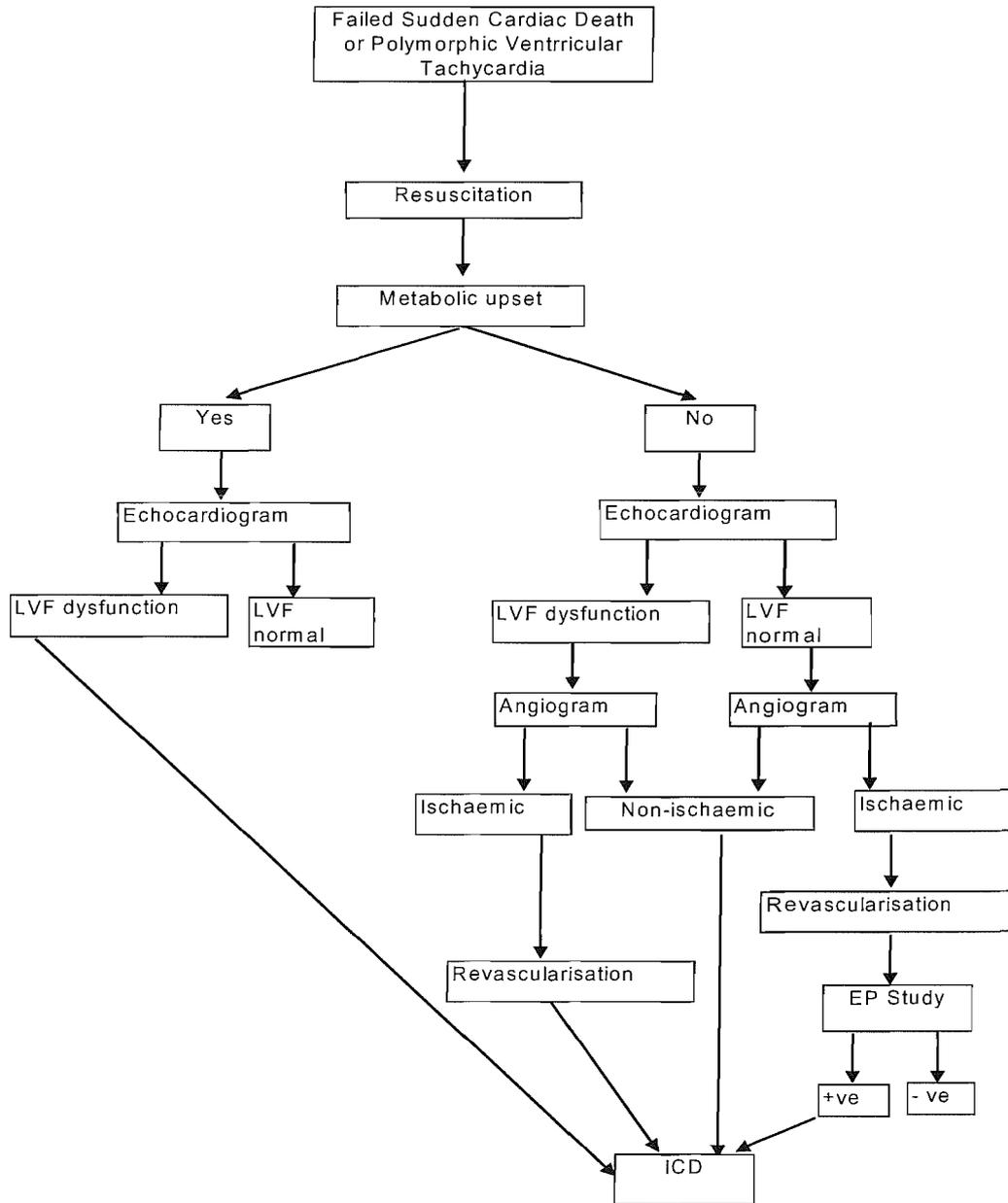
No one research method could accomplish this; each research method used in this thesis contributed some data towards assessing the epidemiology of ventricular arrhythmias to inform need for ICDs.

The difficulties in researching this area are fundamental ones. Firstly, is a ventricular arrhythmia a disease per se or an electrophysiological phenomenon which simply serves as a risk indicator? It is important to identify patients with life threatening ventricular arrhythmias and those at risk of developing one because of the high mortality risk and the ability to benefit from a cost-effective health intervention i.e. an ICD. However, the proven existence of non-sustained and self reverting sustained ventricular arrhythmias is dependent on the frequency of the arrhythmia and thoroughness of diagnostic investigation and degree of risk dependent on whether the patient suffers from an underlying heart problem<sup>86</sup>.

Secondly, the incidence of SCD presumed to be caused by ventricular arrhythmias is heavily dependent on (a) whether a post-mortem is undertaken and (2) the extent of the pathological examination. These factors are influenced by public opinion, religious beliefs and policy changes.

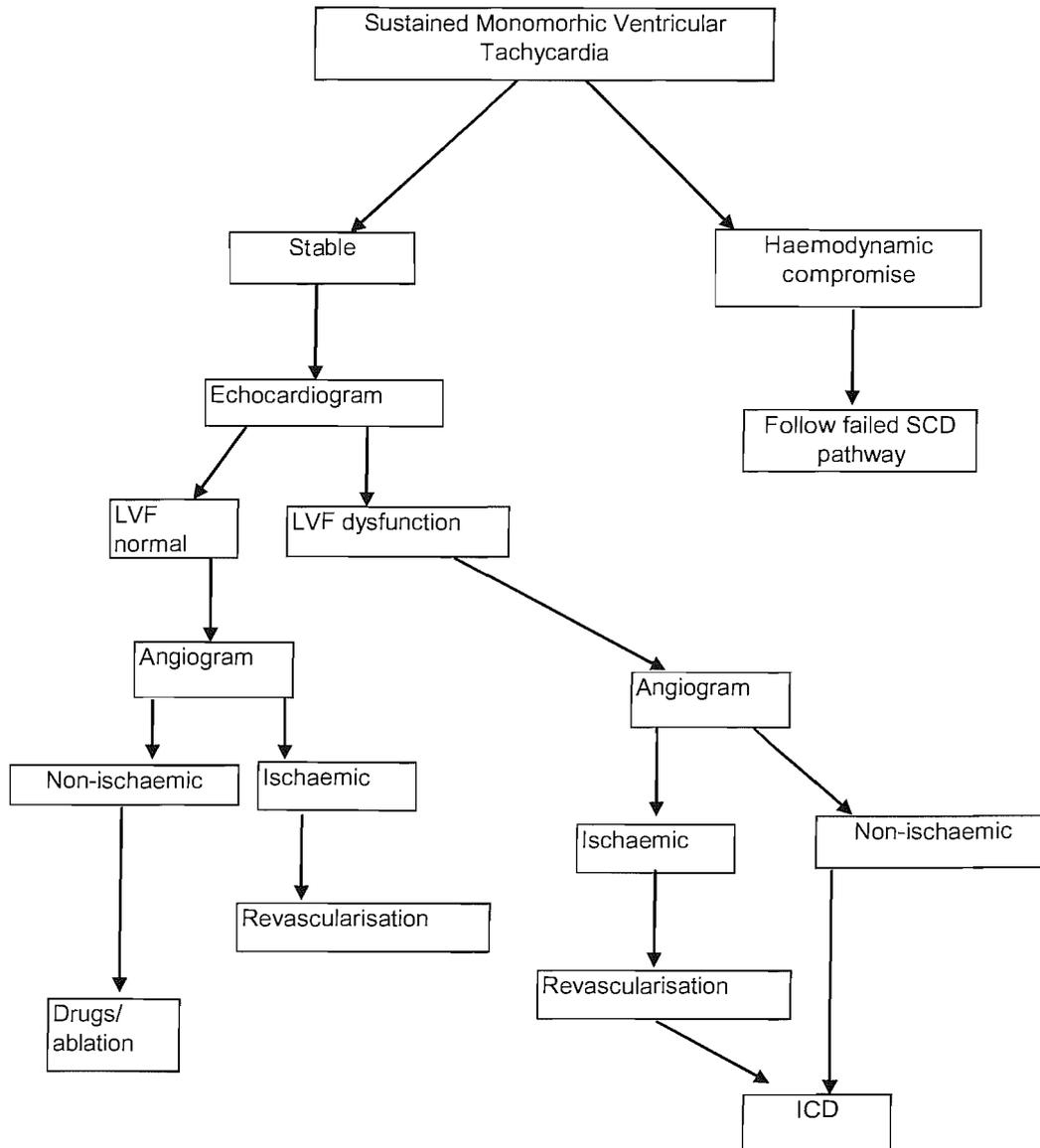
Thirdly, since this study was initiated, there has been a shift in the use of ICDs. In 2000, the NICE recommendations on ICDs were for patients with life threatening ventricular arrhythmias alone. Since that time, evidence has accumulated that ICDs provide a survival benefit to patients who have suffered an MI and a degree of heart failure, but do not necessarily suffer from ventricular arrhythmias. These patients make up a much larger group than those with life threatening ventricular arrhythmias. NICE has recently amended its guidance (2005) to include a small sub-group of these patients for which an ICD was deemed most cost-effective. As with other cardiac interventions, the epidemiology of indications for an ICD is driven by the cost-effectiveness of this health technology for rapidly expanding indications.

**Appendix 1 Management pathways: (A) Management pathway for failed SCD or polymorphic VT**



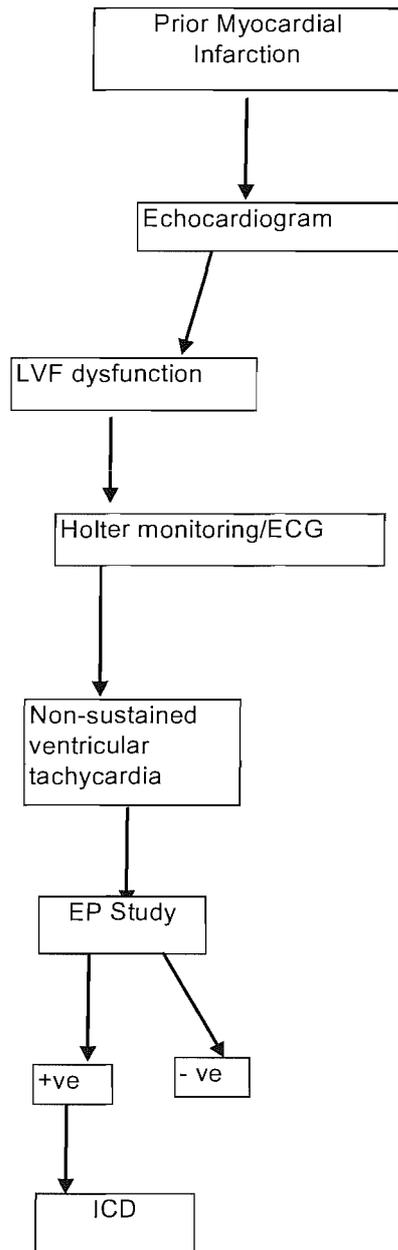
## Appendix 1 Management pathways

### (B) Management pathway for sustained monomorphic VT



## Appendix 1 Management pathways

### (C) Management pathway post MI



## Appendix 2 Search strategies

### Medline search strategy

- #1 explode 'Incidence-' / all subheadings in MIME,MJME
- #2 incidence
- #3 histor\*
- #4 course\*
- #5 progress\*
- #6 disease\*
- #7 natural\*
- #8 (epidemiol\*) or (aetiolog\*) or (etiolog\*)
- #9 etiolog\*
- #10 aetiolog\*
- #11 epidemiol\*
- #12 explode 'Cohort-Studies' / all subheadings in MIME,MJME
- #13 explode 'Time-Factors' / all subheadings in MIME,MJME
- #14 explode 'Risk-Factors' / all subheadings in MIME,MJME
- #15 ((natural\*) or (disease\*))near1((progress\*) or (course\*) or (histor\*))
- #16 explode 'Prognosis-' / all subheadings in MIME,MJME
- #17 prognosis
- #18 explode 'Survival-Analysis' / all subheadings in MIME,MJME
- #19 (explode 'Incidence-' / all subheadings in MIME,MJME) or (incidence) or (explode 'Risk-Factors' / all subheadings in MIME,MJME) or (explode 'Time-Factors' / all subheadings in MIME,MJME) or (explode 'Cohort-Studies' / all subheadings in MIME,MJME) or ((epidemiol\*) or (aetiolog\*) or (etiolog\*)) or (((natural\*) or (disease\*))near1((progress\*) or (course\*) or (histor\*))) or

(explode 'Prognosis-' / all subheadings in MIME,MJME) or (prognosis) or  
(explode 'Survival-Analysis' / all subheadings in MIME,MJME)

#20 explode 'Tachycardia-Ventricular' / all subheadings in MIME,MJME

#21 ventricular near1((tachycardia))

#22 arrhythmia\*

#23 explode 'Arrhythmia-' / all subheadings in MIME,MJME

#24 (explode 'Arrhythmia-' / all subheadings in MIME,MJME) or (arrhythmia\*)

#25 ventricular

#26 ((explode 'Arrhythmia-' / all subheadings in MIME,MJME) or  
(arrhythmia\*)) near ventricular

#27 explode 'Syncope-' / all subheadings in MIME,MJME

#28 syncop\*

#20 (explode 'Tachycardia-Ventricular' / all subheadings in MIME,MJME) or  
(ventricular near1(tachycardia)) or (((explode 'Arrhythmia-' / all subheadings in  
MIME,MJME) or (arrhythmia\*)) near ventricular) or (explode 'Syncope-' / all  
subheadings in MIME,MJME) or (syncop\*)

#21 ((explode 'Incidence-' / all subheadings in MIME,MJME) or (incidence) or  
(explode 'Risk-Factors' / all subheadings in MIME,MJME) or (explode 'Time-  
Factors' / all subheadings in MIME,MJME) or (explode 'Cohort-Studies' / all  
subheadings in MIME,MJME) or ((epidemiol\*) or (aetiolog\*) or (etiolog\*)) or  
(((natural\*) or (disease\*))near1((progress\*) or (course\*) or (histor\*))) or  
(explode 'Prognosis-' / all subheadings in MIME,MJME) or (prognosis) or  
(explode 'Survival-Analysis' / all subheadings in MIME,MJME)) and ((explode  
'Tachycardia-Ventricular' / all subheadings in MIME,MJME) or (ventricular  
near1((tachycardia)) or (((explode 'Arrhythmia-' / all subheadings in  
MIME,MJME) or (arrhythmia\*)) near ventricular) or (explode 'Syncope-' / all

subheadings in MIME,MJME) or (syncop\*)) and (LA=ENGLISH) and (AGE=ADULT)

### Embase search strategy

#1 incidence

#2 explode 'incidence-' / all subheadings

#3 ((natural\*) or (disease\*)) near1 ((progress\*) or (course\*) or (histor\*)) (65864 records)

#4 (epidemiol\*) or (aetiolog\*) or (etiolog\*) (1053487 records)

#5 prognosis

#6 explode 'prognosis-' / all subheadings

#7 explode 'cohort-analysis' / all subheadings

#8 cohort near1 stud\*

#9 explode 'risk-factor' / all subheadings

#10 explode 'survival-' / all subheadings

#11 (incidence) or (explode 'incidence-' / all subheadings) or (((natural\*) or (disease\*)) near1 ((progress\*) or (course\*) or (histor\*))) or ((epidemiol\*) or (aetiolog\*) or (etiolog\*)) or (prognosis) or (explode 'prognosis-' / all subheadings) or (explode 'cohort-analysis' / all subheadings) or (cohort near1 stud\*) or (explode 'risk-factor' / all subheadings) or (explode 'survival-' / all subheadings)

#12 explode 'heart-ventricle-tachycardia' / all subheadings

#13 explode 'heart-arrhythmia' / all subheadings

#14 ((explode 'heart-arrhythmia' / all subheadings) or arrhythmia\*) near ventricular

#15 explode 'syncope-' / all subheadings

#16 syncop\*

#17 ((incidence) or (explode 'incidence-' / all subheadings) or (((natural\*) or (disease\*)) near1 ((progress\*) or (course\*) or (histor\*))) or ((epidemiol\*) or (aetiolog\*) or (etiolog\*)) or (prognosis) or (explode 'prognosis-' / all subheadings) or (explode 'cohort-analysis' / all subheadings) or (cohort near1 stud\*) or (explode 'risk-factor' / all subheadings) or (explode 'survival-' / all subheadings)) and ((explode 'heart-ventricle-tachycardia' / all subheadings) or (((explode 'heart-arrhythmia' / all subheadings) or arrhythmia\*) near ventricular) or (explode 'syncope-' / all subheadings)) and (LA=ENGLISH)

#18 (nonhuman in der) not ((nonhuman in der) and (human in der))

#29 #17 not #18

## Appendix 3 Data abstraction forms

### Data extraction form for incidence studies

**Ref id no:**

**Authors & date:**

**Study design:**

**Geographical area of study:**

**Date and duration of study:**

**Study population (size and characteristics):**

Was the study population well described? Was it representative of the general population?

**Case finding methods (where/how):**

Was ascertainment of cases from the study population likely to be complete?

Inclusion/exclusion criteria:

Diagnostic test/s used:

Definition of diagnostic criteria:

**Was there a clear definition of the condition and measurements?**

**Were criteria for each final diagnosis explicit and credible?**

**Was the diagnostic work up comprehensive and consistently applied for a defined population?**

**Can it be determined that cases were truly incident?**

**Did the cases represent the full spectrum of those who present to health care with ventricular arrhythmias**

Overall number of cases & by age/sex etc.:

Rates presented (overall & by age/sec etc.) and confidence intervals:

**Does this study meet the inclusion criteria?**

**Data extraction form for prognostic studies**

**Ref id no:**

**Authors & date:**

**Study design:**

**Place of study:**

**Date and duration of study:**

**Number of cases:**

Were cases consecutive?

**Case definition:**

**Baseline characteristics:**

**Case finding methods (where/how):**

**Inclusion/exclusion criteria:**

**Diagnostic test/s used:**

**Definition of diagnostic criteria:**

Was there a clear definition of the condition and measurements?

Was the diagnostic work up comprehensive and consistently applied for a defined population?

Was there a representative and well-defined sample of patients at a similar point in the course of their disease?

Did the cases represent the full spectrum of those who present to health care with ventricular arrhythmias?

**Treatment subsequent to inclusion:**

**Duration of follow up:**

Was follow up sufficiently long and complete to assess prognosis?

**Number of deaths:**

**Number of recurrent ventricular arrhythmias?**

**Loss to follow up?**

**Survival analysis undertaken & results?**

Was the analysis correctly undertaken?

Was there adjustment for important prognostic factors?

Does this study meet the inclusion criteria?

**Appendix 4                      Details of the 32 prognostic studies in the systematic review**

<b>Authors, date and study location</b>	<b>Study design, date and length of follow up</b>	<b>Case definition and case finding methods</b>	<b>Inclusion/exclusion criteria</b>	<b>Diagnostic test/s used</b>	<b>Treatments subsequent to inclusion</b>
<b>All cases in each study had sustained VT or VF</b>					
Alexander M et al <sup>43</sup> , 2002. California USA	Retrospective cohort study. Patients admitted from 1992 to 1994 with 360 days follow up.	Primary diagnosis of either ventricular tachycardia (427.1) or ventricular fibrillation/flutter (427.41/42). Cases identified from data files of all discharges from Californian hospitals.	Patients with a prior admission for VT/VF in 1991 were excluded.	Not stated.	ICDs were implanted for 10% of black patients, 15% of Latino, 16% of Asian and 22% of White patients.
Andresen D et al <sup>67</sup> , 1992. Germany.	Prospective cohort study. Patients referred between 1984 and September 1990. Mean follow up was 21 +/- 16 months	Patients with a history of sustained VT who were noninducible on EPS. Patients referred to the department of Cardiology at Klinikum Steglitz, Free University of Berlin and the Klinikum Grosshadern, University of Munich. Causes and circumstances of deaths identified by telephoning relatives or family physicians. Death was defined as unexpected if it occurred after a witnessed sudden collapse or during sleep.	None stated.	EPS	No antiarrhythmic therapy during follow up. ICDs were not available. Each patient was treated with a beta-blocker on an individual basis.
Coughlin S et al <sup>45</sup> , 1994. Washington DC, U.S.	Prospective cohort study. Cases identified from July 1, 1990 through February 29 1992. Median follow up 13 months.	ICD 9 codes for dilated or unspecified cardiomyopathy 425.4-425.9. Ventricular arrhythmias were defined as sustained ventricular tachycardia or multifocal or unifocal premature ventricular complexes. Cases of dilated or unspecified cardiomyopathy were ascertained from discharge listings of 5 metropolitan Washington DC hospitals	Cases who were diagnosed prior to July 1 1989, who were younger than 18 years of age or who resided outside the Washington DC metropolitan area were excluded. Cases with a history of known coronary artery disease, congenital heart disease, significant valvular heart disease, heavy alcohol abuse were also excluded.	Not stated	Only presented for all IDC patients.

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
Hsu J et al <sup>46</sup> 2002. Northern California, U.S.A	Prospective cohort study. Patients recruited from January 1995 to April 1998. Follow up was for 24 months.	Patients who were discharged alive with a life threatening ventricular arrhythmia. These were patients with a primary diagnosis of cardiac arrest, ventricular tachycardia or ventricular fibrillation. Patients were identified through a search of automated records of those admitted or discharged with ICD-10 codes 427.41, 427.1, 427.5, 53.32, 37.97, 37.89.	Exclusion criteria were patients who: had an arrhythmia in the first 48 hours post-MI; non-sustained VT; aged < 18 years; non-English speaking; severe or moderate dementia; life expectancy of <6 months; acquired immunodeficiency syndrome; not discharged home; not Kaiser members or had a transient, reversible cause of arrhythmia.	Diagnostic tests not stated. Clinical charts were checked for evidence of VT, VF or cardiac arrest (with no rhythm recorded).	91 patients received amiodarone, 94 patients had an ICD implanted (26 also received amiodarone) and 79 patients received other treatments (beta-blockers, other antiarrhythmic drugs).
Leclercq J-F et al <sup>47</sup> , 1991. Paris, France	Retrospective cohort study. Patients referred between 1978 and 1988. Mean follow up was 61 +/- 40 months after first VT occurrence.	Patients with sustained monomorphic VT. Cases of VT were all patients referred to one institution. Deaths were identified by phone call to the patient or to his or her family or physicians. All cases of death were classified by interview with relatives, family or physicians.	Only patients with non-self-terminating VTs with a ventricular rate of > 120 beats/min were included.	ECG.	First choice of treatment was with class 1 antiarrhythmic drugs, (2) in case of recurrence of VT: amiodarone or beta-blockers, (3) in case of recurrence of VT: drug combinations or surgery. Surgery was attempted in 25 patients, an ICD was implanted in 12 patients (10 in group 1 and 2 in group 2)

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
McDonald K et al <sup>48</sup> , 2002 patients identified as Medicare beneficiaries (U.S.A)	Retrospective cohort study. VT/F patients identified from January 1985 to December 1995. Follow up was for 8 years. Patients who died before admission were identified from January 1990 to December 1994.	Patients discharged from hospital with a principal discharge diagnosis of ventricular tachycardia or ventricular fibrillation/cardiac arrest on the basis of ICD9 codes: 427.1, 427.4 and 427.5. Patients were identified using the inpatient hospitalisation file and discharged with the ICD9 codes listed. Another cohort was identified, using similar methods, of ventricular arrhythmia patients who died in the emergency department before hospital admission.	Excluded patients less than 65 years of age; residing or admitted to a hospital outside the U.S.A; enrolled in a health maintenance organisation; without continuous enrollment in Medicare part A or part B after their initial VT/F admission; admitted to a nonacute care hospital or to a federal hospital; with invalid mortality data and without Health Insurance or complete data.	Not stated.	In 1987, 3% of patients underwent EPS and 1% received an ICD. In 1991, 16% underwent EPS and 6% received an ICD. In 1995, EPS and ICD rates were 22% and 13% respectively. Patients with CHF were less likely to undergo these interventions.
Naccarella F et al <sup>49</sup> , 1992. Bologna, Italy.	Prospective cohort study. Patients identified from July 1979 to December 1989. Mean follow up of 78 months.	At least one episode of VT late after AMI (60 days or more after MI), episodes of VT/VF associated with different cardiac diseases, out of hospital cardiac arrest due to documented malignant ventricular arrhythmias (MVA) (VT and/or VF). Patients with MVA less than 60 days after AMI were evaluated separately. All patients were admitted to the cardiology department of the Maggiore hospital.	Study limited to patients receiving standard antiarrhythmic treatment.	All patients had non-invasive cardiac evaluation Cardiac catheterisation was performed in some patients to exclude indications for cardiac surgery.	Not stated.

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
O'Hara G et al <sup>50</sup> , 1992. Maastricht and Liege, the Netherlands.	Cohort study. Unclear whether prospective or retrospective. Date and duration not stated. Mean 34 months follow up (range 1 to 108).	Patients with an old MI admitted to the Academic Hospital of Maastricht or Liege for the evaluation of a spontaneous monomorphic VT or ventricular fibrillation. Sustained VT was defined as VT lasting more than 30 seconds or requiring pharmacologic or electrical intervention or both because of circulatory collapse.	All patients had suffered sustained monomorphic VT or VF late after acute MI and were admitted to the Academic Hospital of Maastricht or Liege within a period of 3 months after the arrhythmic event for evaluation of spontaneous occurrence of sustained monomorphic VT or VF.	left ventricular angiogram, coronary angiography, exercise testing and programmed electrical stimulation. Exercise tests were examined for evidence of sustained VT/VF.	Amiodarone for 53% of group 1 vs 56% of group 2, sotalol 35% of group 1 vs 26% of group 2 and propafenone for 12% of group 1 vs 16% of group 2.
Pinski S et al <sup>51</sup> , 1992. Cleveland, Ohio, USA.	Retrospective cohort study. Undertaken in 1988 and 1989. Mean follow up of 17 +/- 12 months.	First episode of ventricular tachycardia or ventricular fibrillation with diagnosis made on the basis of clinical and ECG criteria not associated with reversible causes. All patients discharged from the coronary care unit.	Inclusion criteria were (1) admission to the unit within 48 hours of a first episode of documented sustained VT or VF or development of such an episode during their stay in the unit; (2) occurrence of the episode more than 5 days after an acute MI or cardiac surgery and in the absence of circulatory shock; and (3) candidacy for EPS by current guidelines.	Not stated.	15 patients were discharged on amiodarone alone, 5 on combination of amiodarone & a class I drug. Eight had an ICD during initial admission and 3 more during follow up period. EPS was performed in 22 patients during initial hospital admission.

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
Rodriguez et al, 1992 <sup>52</sup> . Two patient groups: (1) Study group in Maastricht, the Netherlands and (2) Test group in Heidelberg, Germany	Retrospective study of two cohorts. Dates and duration not stated. Study group was followed up for 3.4 years and test group was followed up for 2.4 years.	The case definition was not stated. The test group were patients admitted to the University Hospital, Heidelberg. No other case finding information available.	Consecutive patients. All patients received antiarrhythmic drug therapy. No patient had arrhythmia surgery or an ICD.	The study group had ECG documented sustained monomorphic VT or VF. No information on the test group, but assume these were also ECG documented.	Treatment subsequent to inclusion All patients received antiarrhythmic drug therapy. No patient had arrhythmia surgery or an ICD. 7% of the study group and 21% of the test group were receiving oral sotalol.
Saxon L et al <sup>53</sup> , 1989. Chicago, U.S.	Retrospective cohort study. Patients included in study between 1982 and 1987. Mean follow up was 18 +/- 19 months for the cardiac arrest group, 23 +/- 19 months for the syncope group and 32 +/- 26 months for patients with palpitations.	Cardiac arrest, syncope defined as transient loss of consciousness and palpitations with induced or spontaneous sustained ventricular tachycardia or fibrillation. Patients were referred to the service at Rush-Presbyterian St Luke's Medical Centre for electrophysiologic evaluation of documented spontaneous and sustained VT or fibrillation who also had inducible sustained VT in the electrophysiologic laboratory.	Patients were excluded if their tachycardia occurred in the setting of an acute MI.	All patients had a detailed history and physical examination, a 12 lead ECG, laboratory analysis and a chest radiograph. Left ventricular ejection fractions were obtained by left ventriculography or by technetium 99m scintigraphy according to established methods. EPS were performed in an unsedated postabsorptive state.	73% of palpitation group, 90% of syncope patients and 66% of the cardiac arrest group received electrophysiologically guided drug therapy. 27% of palpitation patients, 0% of syncope and 7% of cardiac arrest patients underwent antitachycardia surgery. 0% of palpitations patients, 10% of syncope group and 27% of cardiac arrest group received ICDs.

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
Wiesfeld et al, <sup>54</sup> 1995. The Netherlands.	Prospective cohort study. Patients identified between January 1989 and January 1992. Mean follow up was 21 +/- 11 months.	Sustained VT was defined as VT with a rate above 100 beats per min and lasting for more than 30 seconds or requiring intervention within 30 secs for haemodynamic collapse. Sudden cardiac death was defined as death within 1 hour after onset of symptoms or during sleep, in the absence of increasing angina or overt heart failure. Patients admitted to the Groningen University Hospital with sustained VT or VF	Patients who had an acute MI within 48 hours of tachyarrhythmic event, patients with cardiomyopathy, significant obstructive valvular heart disease, congenital heart disease, long QT syndrome, inflammatory heart disease or electrolyte disturbances and patients with a proarrhythmic response to antiarrhythmic drugs were excluded.	12 lead ECG, standard blood tests, exercise testing, multigated blood pool scintigraphy, echocardiography and coronary angiography	Group A (14 patients) received anti-ischaemic therapy only (8 had PTCA, 3 CABG and 3 drugs). Group B (13 patients) anti-ischaemic and antiarrhythmic therapies and group C (55 patients) antiarrhythmic treatment (1 had ablation). Six patients had an ICD implanted.
<b>All cases had inducible VT or VF</b>					
Bhandari A et al <sup>55</sup> , 1989. California, USA.	Prospective cohort study. Patients were recruited from September 1983 to June 1985. Follow up ranged from 4 to 36 months (mean of 18 months)	Sustained VT was defined as lasting 30 seconds or longer or caused haemodynamic compromise and had to be terminated in less than 30 seconds. NSVT was defined as lasting 6 beats or more in less than 30 seconds. VF was defined as disorganised rapid ventricular activity requiring immediate defibrillation because of haemodynamic compromise. Patients aged 70 years or younger admitted to the intensive cardiac unit of the LAC-USC medical Centre with a diagnosis of MI were screened.	Inclusion criteria were clinically stable MI patients who didn't have Killip class III or IV congestive heart failure, moderate to severe angina pectoris or spontaneous sustained VT in the 48 hours after MI. Patients were excluded if they had end stage disease of another organ system or if they refused to participate in the study.	Programmed ventricular stimulation (EPS) undertaken at the right ventricular apex. If these arrhythmias were not induced, the same steps were repeated at the right ventricular outflow tract and then the left ventricular apex. This was performed within 7-18 (mean 11) days after the infarct.	Of those patients with sustained VT or VF on EPS: beta-blockers were administered to 4 patients for control of angina and/or hypertension, first 10 patients received prophylactic antiarrhythmic treatment and 6 patients underwent CABG, PTCA or both for left main coronary disease or for symptoms of intractable angina.

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
McCowan <sup>56</sup> 1991. Charleston, U.S.	Unclear whether prospective or retrospective, cohort or selected case series. All EP tests performed between October 1989 and September 1990. Follow up was 6.4 months +/- 3 months.	Malignant ventricular arrhythmias occurring outside the setting of an acute MI, drug toxic reaction, electrolyte imbalance or other reversible cause. Patients having inducible arrhythmias on EP testing. Patients referred to the cardiac arrhythmia service at Charleston area medical centre for evaluation of a documented cardiac rhythm disturbance or symptoms suggesting the presence of an arrhythmia	None stated.	All patients underwent echocardiography, signal averaged ECG or tilt table testing then all underwent EP testing. EP studies were performed in the fasting state and with antiarrhythmic drugs being held for 48 hours or 5 drug half lives. Two or three multipolar pacing catheters were used.	Performance of antiarrhythmic drugs was tested during EP study. Those patients failing acute and follow-up drug testing on conventional antiarrhythmic drugs were placed on amiodarone (25 patients) or received an ICD (17 patients) or both.
<b>Cases in each study had sustained VT or NSVT at baseline</b>					
Brodsky M et al <sup>57</sup> , 1993. California, U.S.	Retrospective case series (no information on whether cases were consecutive). Mean of 50 +/- 34 months (range 1 to 113 months). Follow up started on date of initial invasive EPS	Spontaneous symptomatic ventricular tachycardia with no apparent structural heart disease. Patients referred to an arrhythmia service for evaluation of spontaneous symptomatic VT. None of the patients had significant coronary artery disease as evidenced by coronary angiography in 31 patients and the results of history and physical and noninvasive tests in the other 6 patients.	Patients were excluded if they had symptomatic ischaemia, vasospastic coronary artery disease, previous MI, left ventricular ejection fraction <50%, congenital heart disease, significant valvular disease, hypertension, QTc > 460 msec, preexcitation, pulmonary disease, or any reversible disorder possibly responsible for the arrhythmia	EPS on all patients. All 37 patients were tested with a 12 lead ECG, signal-averaged ECG, 24 hour ambulatory ECG (VT noted for 29 patients), exercise treadmill testing (VT noted for 21 patients), and 2D, M-mode and Doppler echocardiogram. Coronary angiography and left ventriculogram were performed in 31 patients, right ventriculogram in 15 and myocardial biopsy in 14.	11 patients required an intervention for termination of the arrhythmia. All 37 patients were treated with antiarrhythmic drugs. An ICD was implanted in 3 patients.

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
Feleke E & Hulting J <sup>58</sup> 1989. Stockholm, Sweden.	Retrospective cohort study. Patients identified over 18 months - ending December 1978. Follow up was up to 6 years after discharge or date of death.	VT was defined as four or more consecutive ventricular beats with a rate above 120 per min. A run of VT (more than about 20 complexes) passing into VF was diagnosed as VT and VF. Acute MI was diagnosed according to standard criteria. All patients observed in the CCU over an 18 month period were surveyed. Cases were non-AMI patients with VT and age-sex matched AMI patients with and without VT	Arrhythmias were not studied during or immediately after resuscitation or during implantation of a temporary pacemaker	Automated monitoring system with ECG write -out. A computer system was constructed to detect and diagnose arrhythmias and artefacts, these were manually scrutinized for occurrence of VT. Some patients had VT before connection of the system and these episodes were included in the results.	Lignocaine was used as drug of first choice in VT. Many patients with short or single (asymptomatic)VT did not receive antiarrhythmics. Oral procainamide, quinidine and disopyramide were sometimes given against recurring VT but long-term prophylaxis after VT was not prescribed routinely
Hosoda S et al <sup>59</sup> , 1995, Japan.	Prospective cohort study. Patients admitted with MI between 1983 and 1988.	Six or more successive ventricular premature beats was considered VT. All MI patients who were discharged alive after treatment in the CCU and who were examined by coronary arteriography.	Excluded patients who died during hospitalisation	Not stated.	Not stated for VT patients alone.

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
Juul-Moller S et al <sup>60</sup> , 1991. Malmo, Sweden.	Prospective cohort study. Men invited for examination during 1982 and 1983. Mean follow up period was 53.1 months (range 3.6 to 63.5 months)	Men born in 1914 from Malmo in Sweden. See definition of diagnostic criteria for VT case definition. Subjects were randomly selected, a 50% sample of all men born in 1914 from Malmo Sweden. Cases were patients identified as having VT on continuous ECG recording.	Random sample of men born in 1914. No exclusion criteria. See diagnostic criteria for VT criteria	Continuous ambulatory recording using a conventional ECG tape recorder with two pairs of bipolar electrodes	Not stated.
Kapoor et al <sup>61</sup> , 1990, Pittsburgh, U.S.	Prospective cohort study. Patients recruited from April 1981 to February 1984. Mean follow up for all syncopal patients was 40 months. Follow up for VT cases alone not stated.	Syncope was defined as a sudden transient loss of consciousness not compatible with other listed diagnoses. VT was defined as: symptomatic, sustained or leading to hypotension on ECG monitoring. Patients were identified from (1) the emergency room through a daily review of ER room visits, (2) admissions to the inpatient service and (3) Outpatients.	Patients who required pharmacologic or electrical cardioversion at their initial presentation were not included.	History, physical and neurologic examination, baseline lab examination, 12 lead ECG, prolonged ECG monitoring of at least 24 hours either ambulatory or bedside, some patients had cerebral angiography and/or EPS	Not stated, only know that for 10 patients an EPS was undertaken to determine therapy

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
Kofflard M et al <sup>62</sup> , 1993, Rotterdam, the Netherlands.	Prospective cohort study undertaken from 1970 to 1990. Follow up for the whole group was 7 +/- 5 years. Follow up for the VT group was 8 +/- 5 years.	The diagnosis of hypertrophic cardiomyopathy was based on clinical parameters alone, after 1979 it was based on echocardiographic findings. Ventricular tachycardia was defined as 3 or more consecutive ventricular beats on Holter monitoring. Patients identified from the HC clinic at the Thoraxcentre of Academic Hospital 'Dijkzigt.	Patients with identifiable causes of left ventricular hypertrophy, such as valvular aortic stenosis and uncontrolled systemic hypertension were excluded	24 hour ambulatory electrocardiographic monitoring	During follow up, 32 patients underwent myotomy/myectomy. One patient underwent concomitant mitral valve replacement and 3 had a CABG. 4 patients had permanent pacemakers after surgery. No patient had an ICD implanted.
Maggioni et al <sup>39</sup> , 1993, Italy.	A prospective cohort study (for the purposes of this study) nested in an RCT of streptokinase vs t-PA with/out s.c. heparin in a factorial design. Study published in 1983. Follow up of 6 months.	Patients suffering an MI (see GISSI-2 study criteria for MI definition) admitted to the cardiac care unit within 6 hours of onset of symptoms and no clear contraindication to fibrinolytic treatment and/or heparin. For definition of VT see diagnostic criteria. Patients suffering an MI who had thrombolytic therapy and had a 24 hour ECG an average of 17 days (range 6-36 days) after randomisation	Only MI patients with no clear contraindications to thrombolytic treatments.	24 hour ambulatory ECG monitoring following a washout of antiarrhythmic and beta-blocking therapy whenever this was considered feasible by the attending physician.	After discharge, 25.6% of post-MI patients were treated with beta-blockers and 11.2% with antiarrhythmic drugs.

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
Spirito P et al <sup>63</sup> , 1994. Geneva, Bologna and Rome.	Not stated, but text on cases and time period suggests prospective cohort study	Diagnosis of HCOM was based on echocardiographic demonstration of hypertrophied and nondilated left ventricle in absence of other diseases that could produce comparable left ventricular hypertrophy. Ventricular tachycardia was defined as 3 or more premature ventricular depolarisations in succession. Sudden cardiac death was prospectively defined as instantaneous collapse with subsequent death in minutes. Patients with HCOM were evaluated in the outpatient or inpatient services of 3 hospitals.	No symptoms of heart failure or only mild symptoms (New York Heart Association functional class I or II) at the time of their initial ambulatory ECG recording and not taking cardioactive medications at the time of the ambulatory ECG recording. Patients with recurrent syncope or recent syncope were excluded (see p2745).	Continuous 24 to 48 hour ambulatory ECG recording	88 patients (20 with VT) were asymptomatic and not treated. Treatments for patients with VT were: beta-blockers for 9 patients, verapamil for 13 patients and 9 patients also received class I or III antiarrhythmic medications.
Stewart R et al <sup>64</sup> , 1990. London, England.	Retrospective cohort study. Patients recruited between 1978 and 1986. Mean period of observation was 43 months (range 1-105 months).	Patients with DCM i.e. dilatation and globally decreased contraction of one or both ventricles in the absence of an identifiable cause. VT was defined as $\geq 3$ consecutive wide complex beats without preceding P waves with a mean rate of $>120$ bpm. Significant arrhythmia was defined $> 250$ ventricular ectopic beats or VT on 24 hour ECG.. Patients with DCM seen at the Hammersmith Hospital.	DCM patients were excluded whose residence was outside the UK, not having 24 hours ECG or having NYHA class 4 symptoms and those lost to follow up (no data reported)	ECG recordings were performed a mean of 28.5 months (range 1-144 months) after the onset of symptoms while patients were ambulant and on their usual medications. ECG printouts were reviewed and arrhythmias recorded by one investigator blinded to outcome.	Treatment for the whole DCM group described: 40 patients received anti-arrhythmic therapy (5 specifically for ventricular arrhythmias)

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
Tanabe T et al <sup>65</sup> , 1989. Kanagawa, Japan	Case series. Not clear whether prospective or retrospective. Cases were identified between September 1976 and December 1987. mean 31 months follow up, range 5 to 81 months.	VT was defined as runs of > 3 consecutive ventricular premature contractions at a minimum rate of 120 bpm from Holter monitoring. Patients with VT who had been admitted to Tokai University Hospital. All had one or more runs of VT per day in the recordings obtained from Holter monitoring during the hospitalisation.	Patients with acute or recent MIs, unstable angina, deteriorating congestive heart failure, advanced atrioventricular block, electrolyte imbalance, hypoxia or digitalis intoxications were excluded.	Holter monitoring. Ejection fraction was recorded using radionuclide ventriculography.	Not stated.
Wilber et al <sup>66</sup> , 1990. Maywood, Illinois, U.S.	Cohort study. Probably prospective (given 4 monthly follow up phone calls). Patients referred to the service between October 1986 and December 1989. Mean follow up of 16.7 months.	Patients referred to the arrhythmia service with 1. The presence of nonsustained VT (3 or more consecutive beats; rate >120) on ambulatory monitoring in the absence of antiarrhythmic therapy, 2. chronic coronary artery disease without MI or cardiac surgery within the previous 30 days, 3. left ventricular ejection fraction of less than 40% and 4. no prior history of sustained ventricular arrhythmias, syncope or unexplained dizziness.	See case definition. There were no exclusion criteria.	Nonsustained VT was documented by quantitative 24-hour Holter monitoring (81 patients) or ambulatory telemetry monitoring. Coronary anatomy was documented by cardiac catheterisation. Assessment of left ventricular function was performed by contrast or radionuclide ventriculography. An EP study was performed on all patients.	In the 43 patients with inducible sustained arrhythmias, serial electropharmacological testing was undertaken. 20 patients were discharged on drug therapy and had their arrhythmia suppressed. 20 patients with inducible VT that was not suppressed received drug therapy.

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
<b>All cases in each study had NSVT</b>					
Algra et al <sup>4</sup> , 1993. Rotterdam, Netherlands.	Case-control study nested in a cohort study. Baseline data from all deaths and sample of all patients was taken retrospectively. Patients having 24 hour ECGs between 1 August 1980 and 31 December 1984. 2 years follow up.	Patients having 24 hour ECG for the evaluation of the following symptoms: palpitation, dizziness, syncope, angina (65%), the effect of antiarrhythmic therapy (8%), risk after MI (10%), or a search of a cardiac cause of transient ischaemic attacks or strokes (7%). All 6693 consecutive patients who had 24 hour ECG in one of four participating hospitals. Cause and circumstances of death were determined from the records of GPs and hospitals. Definition of SCD provided in 'follow up' section of methods.	None stated.	24 hour ECG	Not stated.
Andresen D et al, <sup>44</sup> 1992. Berlin, Germany.	Retrospective cohort/case series. Date and duration not stated. Follow up was 17.4 +/- 5 months (assuming this is mean follow up).	Patients presenting with nonsustained VT defined as at least 3 consecutive premature beats during routine 24 hour Holter monitoring. Case finding methods not stated.	No exclusion criteria specified.	24 hour Holter monitor.	Not stated.

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
De Maria R et al <sup>68</sup> 1992, Italy	Prospective cohort study. Patients were enrolled between January 1986 and March 1990. Mean follow up was 29 months (range 15 days to 68 months)	Idiopathic dilated cardiomyopathy (IDC) was confirmed invasively by demonstrating (1) absence of significant coronary artery disease, (2) absence of specific heart muscle disease or active myocarditis and (3) reduced left ventricular ejection fraction. NSVT was defined as 3 or more ventricular premature complexes in succession. Patients were identified from a Multicentre registry on the natural history of IDC.	Only included those patients with a clinical suspicion of IDC (see case definition)	12 lead ECG, M-mode and 2-dimensional echocardiography, 24 hour Holter monitoring and exercise stress testing.	Treatment subsequent to inclusion 45 patients (21%) were receiving maintenance antiarrhythmics; 31 were receiving amiodarone (7 of these patients had VT on Holter)
Hammill S et al <sup>69</sup> , 1990. Minnesota, U.S.	Prospective cohort study. December 1985 to July 1987. Follow up by ejection fraction. Mean follow up was 17.4 months for patients with an ejection fraction > 40% and 14 months for those < 40%.	Asymptomatic non-sustained VT, defined as from 3 beats to <30 seconds' duration.	Patients said they had not had palpitations, near syncope, syncope or previous cardiac arrest.	VT was documented during ambulatory or in-hospital monitoring in the absence of antiarrhythmic medications. Left ventricular ejection fraction was determined by contrast or radionuclide angiography or echocardiography. All patients had an EP test	Antiarrhythmic drug therapy was administered to all patients who had a positive EP study and some of the patients who had a negative study (treated empirically by referring physician). Treatment was with 1A, 1B or 1C anti-arrhythmics or amiodarone.

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
Kadish et al <sup>70</sup> , 1993. Michigan, U.S.	Retrospective cohort study. Date not stated but mean follow up of 19.6 months. Range 1 to 65 years.	Patients with asymptomatic nonsustained VT that underwent EP testing. Patients with nonspecific palpitations were not considered symptomatic. Nonsustained VT was defined as having a duration of 3 beats to 30 seconds.	Patients who had suffered a cardiac arrest or experienced sustained uniform VT were not entered into the study.	Non sustained VT was documented by ambulatory monitoring (240 patients) or telemetry recordings. Baseline electrophysiological testing.	Patients with inducible sustained monomorphic VT (52 patients) underwent a mean of 1.9 +/- 1.3 drug trials (range 1 to 5). No patient had an ICD or arrhythmia surgery.
Klein R et al <sup>71</sup> , 1989. New Mexico, U.S.	Case series. No information if prospective or retrospective. Date not stated but patients were followed up for a mean of 14 months (range 1-57)	Non-sustained VT of 5 beats or more during routine ambulatory ECG. Non-sustained VT was detected during routine evaluation of coronary artery disease in 35 patients and during evaluation of presyncope in 5 patients. No further details.	Patients were excluded from EP testing if 1. the tachycardia was polymorphic; 2. there was a documented episode of syncope; 3. the patients had a history of sustained VT or resuscitation for sudden death in absence of acute MI or 4. acute MI had occurred in the 2 weeks preceding the episode of non-sustained VT. No patient had decompensated congestive heart failure, electrolyte or metabolic abnormalities or long QT syndrome.	Coronary artery disease was documented by cardiac catheterisation in 34 patients (other 6 patients had a documented history of acute MI), left ventricular function was assessed by cardiac catheterisation, radionuclide or echocardiographic analysis. Non-sustained VT was documented on 24 hour ambulatory ECG Holter monitoring in 37 patients and during ambulatory telemetric monitoring in 3 patients.	16 of 22 patients in group 1 underwent acute drug testing, an effective drug was found for 12 of these patients, 11 of these patients discharged on this treatment. No treatment was recommended for the 18 patients with no inducible VT. But 4 of these patients were treated with mexitine, procainamide, quinidine and tocainide.

Authors, date and study location	Study design, date and length of follow up	Case definition and case finding methods	Inclusion/exclusion criteria	Diagnostic test/s used	Treatments subsequent to inclusion
Takahashi M et al <sup>72</sup> 1994. Japan	Cohort study. Unclear whether prospective or retrospective. Date and duration not stated.	Non-sustained VT was defined as a run of at least 3 consecutive beats at a rate more than 100/min, but spontaneously terminating within 30 seconds.	Patients who had experienced acute MI within 4 weeks, acute myocarditis (within 4 weeks after onset) or who had abnormal electrolytes were excluded.	Patients diagnosed with Holter monitor. All patients underwent 12-lead ECG, chest x-ray, echocardiography and treadmill examinations. Myocardial scintigraphy and cardiac catheterisation were also performed. EPS was performed to induce ventricular tachyarrhythmias.	Anti-arrhythmic drug efficacy was assessed in 6 patients with inducible NSVT. Induction was prevented by procainamide in 3 patients, disopyramide in 2 patients and by verapamil in 1 patient. 18 non-inducible patients continued to receive prescribed anti-arrhythmic treatment. 2 patients had electrical catheter ablation.



## Appendix 6 ICD centre survey letter and questionnaire

October 2002

Dear Colleague,

*Study Title A review of the evidence on the effects and costs of ICD therapy in different patient groups, and modelling of cost effectiveness and cost utility for these groups in a UK context.*

A national study on the effects and costs of ICD therapy detailed above has been commissioned by Health Technology Assessment (national R&D). We, together with Martin Buxton (Professor of Health Economics at Brunel University and a member of NICE) are lead investigators. As part of this study we are working closely with the national database and are keen to get further information on current service provision. We would be very grateful if you would fill in the short questionnaire on the service that you provide to patients receiving, or eligible for, ICD therapy. This will provide important data for the final report, and will inform future national planning of workforce and service provision. Your centre will not be identified in any report or publication, but your assistance will be acknowledged. We will let you know of results of the survey.

If you have any queries please contact Dr Julie Parkes.

Please return your completed questionnaire by Friday October 18<sup>th</sup>.

***Your help is gratefully appreciated***

With kind regards

Yours sincerely

Dr Andrew Grace  
Consultant Cardiologist  
Papworth Hospital  
Cambridge  
[jules@soton.ac.uk](mailto:jules@soton.ac.uk)

Dr Julie Parkes  
University of Southampton  
Lecturer Public Health Medicine  
**02380 798927 email**

**National Survey of service provision for Implantable cardioverter defibrillators (ICD)**

**Your replies will be treated in strict confidence**

Name

Hospital

What is the approximate size of the catchment population for your ICD practice?

100,000-300,000

300,001-500,000

500,001-1 million

>1 million

>2 million

>3 million

What was the number of new and replacment ICDs put in by your unit in each of the following years?

	1999		2000		2001	
	New	Replacem nt	New	Replacem nt	New	Replacem nt
<10						
10-19						
20-34						
35-49						
50-74						
75-100						
>100 (please specify)						

Please indicate which grade of staff are significantly involved in the care of patients who are eligible/ receive ICDs at your hospital. (Write approximate numbers of whole time equivalent(WTE) staff in the appropriate boxes).

Staff description	WTE
Consultant, Senior Lect or Professor	
Associate specialist or Staff grade	
SPR NHS	
SPR R&D	
Specialist nurse NHS funded	
Specialist nurse R&D funded	
Technical staff	
Other please specify	

4.a Do you have facilities to conduct electrophysiological study (EPS) Yes/No

If Yes

4b How many EPS studies per month in patients eligible for ICD (approximately)

\_\_\_\_\_

4c In how many cases of ICD implantation has EPS been conducted? (Please ring)

0%    0-4%    5-9%    10-24%    25-49%    50-74%    >75%    100%

5 Please indicate your response to each of the given statements describing possible barriers to care for patients eligible for ICD.

	Stongly agree	Agree	Unsure	Disagree	Strongly disagree
Patient identification/diagnosis					
Clinic waiting time for initial referral					
EPS waiting times					

Implantation waiting times					
Staffing capacity					
Staffing skillmix					
Funding for treatment					
Patient refusal					
Patient non attendance					
Other - please specify					

Please write any additional comments below

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6a Is there a waiting list for ICD implantation? Yes/No

If Yes

6b What is the current median waiting time for a device?

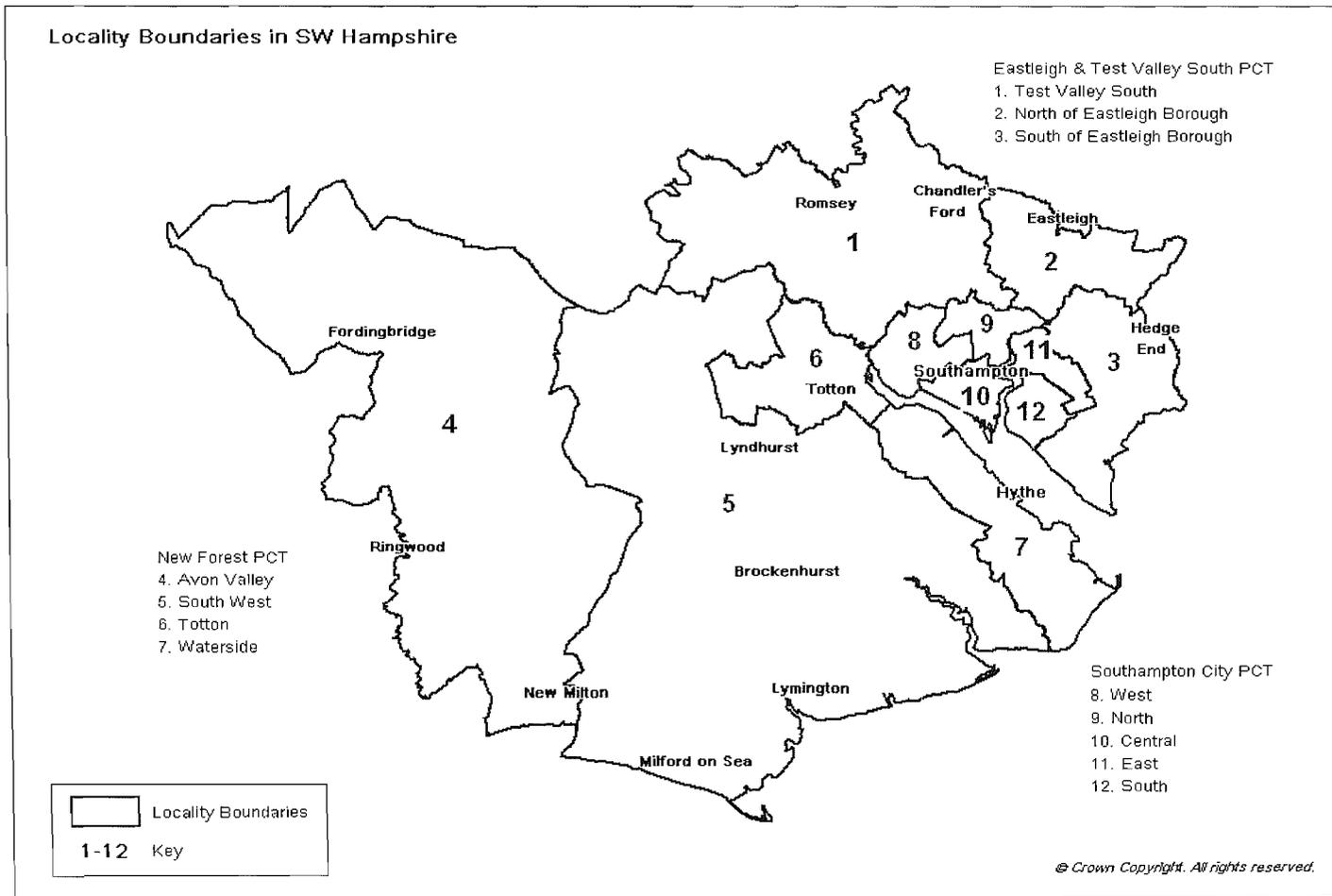
7. What percentage of your ICD data is routinely entered into the ICD national database? Please ring.

0-19% 20-39% 40-49% 50-59% 60-69% 70-79% 80-89% 90-99% 100%

8. How do you envisage practice for patients eligible for ICD changing at your unit over the next one/two years? (Please use extra sheet of paper if required)

Thank you very much for taking the time to fill in this questionnaire. Your contribution is very much valued.

Appendix 7 Map of the Southampton and South West Hampshire Health Authority area





## Appendix 9 Study letter and patient information sheet

«Title» «First\_Name» «Last\_Name»  
«Address\_Line\_1»  
«Address\_Line\_2»  
«City»  
«State»  
«ZIP\_Code»

Friday 28<sup>th</sup> February 2003

**Southampton Arrhythmia Study**  
Ethics submission no. 316/01

Dear «Title» «Last\_Name»,

My name is Debbie Chase, I am a researcher working at Southampton General Hospital. I am writing to ask if you would be willing to participate in a study. This study is about how common a particular type of heart rhythm is and what impact it has on your daily life.

You have been chosen for this study because you have recently had a test that showed this type of heart rhythm. This study is purely observational and wouldn't require any extra tests, treatments or hospital visits.

Please read the enclosed information sheet and if you are happy to take part please sign one of the enclosed consent forms and send this, along with your completed questionnaires, in the enclosed pre-paid envelope. Please keep the information sheet and the other consent form for your records.

I would be very grateful if you could reply by Monday 17<sup>th</sup> March.

Many thanks for your time,

Yours Sincerely,

Debbie Chase  
Research Fellow

28<sup>th</sup> October 2002

## **Southampton Arrhythmia Study**

Ethics submission no. 316/01

### PATIENT INFORMATION SHEET

Thank you for reading this information sheet.

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

#### **Why is this study being done?**

We are doing a study at Southampton NHS Trust Hospitals looking at how common ventricular arrhythmias are in the Southampton area. We also want to know how patients present with this condition and whether it has an impact on their daily life.

This study will help us improve our understanding of this condition.

#### **What is an arrhythmia?**

An arrhythmia is a change in the rhythm of your heartbeat. In most people, arrhythmias are minor and are not dangerous. A small number of people, however, have arrhythmias that are dangerous and require treatment. Your doctor will talk with you about whether you need treatment for any arrhythmias identified as occurring in you.

#### **Why have I been chosen?**

You have been chosen because you have recently had a test that showed an arrhythmia. The tests or treatments you require (if any) are not part of this study, and will be discussed separately with you by the doctors involved in your care.

#### **What does taking part involve?**

This study is purely 'observational'. That means we just want to see what happens to you and what tests and treatments you get. This study will not require any extra treatments, tests or hospital visits.



## **Appendix 10 Baseline questionnaire**

### **Southampton Ventricular Arrhythmias Study Ethics submission no. 316/01**

Thank you for taking the time to answer this questionnaire. Please answer each question by ticking the relevant box.

All the information that you give us will be treated in strict confidence, and in order to protect your privacy a confidential study number will be used instead of your name. Only the study investigator, Debbie Chase, will know patients names, and all the information will be kept in a locked filing cabinet which only the study investigator will be able to access.

There are three sections to this questionnaire. Section 1 asks about you, section 2 asks about your previous health and section 3 should only be filled out if you have ever suffered syncope/blackouts.

Please complete the following and return in the self addressed envelope to:

Debbie Chase,  
Research Fellow,  
Health Care Research Unit  
Southampton General Hospital  
Tremona Road  
Southampton  
SO16 6YD

1. Are you male  female

2. What is your age?  years old

3. What is your date of birth?

4. What is your marital status?

Married/couple  Divorced   
Separated  Single   
Widowed

5. What is your home situation?

I live alone   
I live with my spouse/partner   
I live with family member/s   
I live with non-family member/s

6. What is your ethnic group?

White  Black   
Mixed  Chinese   
Asian  Other

7. During the last 30 days, were you:

Working full-time   
Working part-time   
Unemployed, laid off or looking for work   
Retired   
Disabled   
Keeping house   
None of the above

Answer questions 8 through to 11 for the main job you were doing in the last 30 days, or if not working within these 30 days, your last main job.

8. Do (did) you work as an employee or are (were) you self-employed?

Employee   
Self-employed with employees   
Self-employed/freelance without employees

9. How many people work (worked) for your employer at the place where you work (worked)?

- 1 to 24   
25 or more

10. What is (was) the full title of your *main* job?

- For example, PRIMARY SCHOOL TEACHER, STATE REGISTERED NURSE, CAR MECHANIC, TELEVISION SERVICE ENGINEER, BENEFITS ASSISTANT
- Civil Servants, Local Government Officers – give job title not grade or pay band

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-----  
-----

11. Describe what you do (did) in your *main* job

-----  
-----  
-----

12. Do (did) you supervise any other employees?

- Yes   
No

13. Are you a car driver? Yes  No

14. What is your smoking history?

- Current smoker  Past smoker   
Never smoked

15. Have you suffered any 'blackouts' in the last year (i.e. episodes where you have passed out)?

- Yes  No

**Only answer questions 16 to 19 if you have answered 'Yes' to question 17.**

16. How many blackouts have you suffered in the last 12 months?

.....

17. Have you ever been admitted to hospital as a result of a blackout?  
Yes  No

18. If the answer to question 19 was yes, which hospital were you admitted to?

-----

19. Have you ever seen you GP about your blackout/s?  
Yes  No

20. Have you ever had a heart attack?  
Yes  No

21. Have you ever had angina?  
Yes  No

22. Have you ever had diabetes?  
Yes  No

23. Have you ever had any other heart trouble?  
Yes  No

24. If you have answered 'yes' to question 23 please specify

-----

25. Do you have a family history of heart disease?  
Yes  No

26. If you have answered 'yes' to question 25 please specify

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**HEALTH STATUS QUESTIONNAIRE (SF-36) UK**

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**Strictly private and confidential**

The following questions ask for your views about your health. How you feel about your health and, how you feel and how well you are able to do your usual activities. If you are unsure about how to answer any question, please give the best answer you can and make any comments in the space available after the final question.

Please go through each page of the questionnaire and answer all the questions.

**Participant ID:**            **1-3**

**Record:**                            **4**

**Please tick ONE box per question**

For  
Official  
Use  
Only

1. In general would you say your health is:

- Excellent
- Very good
- Good
- Fair
- Poor

2. Compared to one year ago, how would you rate your health in

general now?

- Much better than one year ago
- Somewhat better now than one year ago
- About the same
- Somewhat worse now than one year ago
- Much worse now than one year ago

### HEALTH AND DAILY ACTIVITIES

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

**Please tick ONE box per question:**

a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

- Yes limited a lot
- Yes limited a little
- No not limited at all

b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf.

- Yes limited a lot
- Yes limited a little
- No not limited at all

c. Lifting or carrying groceries.

- Yes limited a lot
- Yes limited a little
- No not limited at all

d. Climbing several flights of stairs.

- Yes limited a lot
- Yes limited a little
- No not limited at all

e. Climbing one flight of stairs.

- Yes limited a lot
- Yes limited a little
- No not limited at all

f. Bending, kneeling or stooping.

- Yes limited a lot
- Yes limited a little
- No not limited at all

g. Walking more than a mile.

- Yes limited a lot
- Yes limited a little
- No not limited at all

h. Walking half a mile

- Yes limited a lot
- Yes limited a little
- No not limited at all

i. Walking 100 yards.

- Yes limited a lot
- Yes limited a little
- No not limited at all

j. Bathing and dressing yourself.

- Yes limited a lot
- Yes limited a little
- No not limited all

4. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

**Please tick ONE box only per question**

a. Cut down on the amount of time you spent on work?

Yes

No

b. Accomplished less than you would like?

Yes

No

c. Were limited in the kind of work or other activities?

Yes

No

d. Had difficulty performing the work or other activities?

Yes

No

5. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling anxious or depressed?)

a. Cut down on the amount of time you spent on work?

Yes

No

b. Accomplished less than you would like?

Yes

No

c. Didn't do work or other activities as carefully as usual?

Yes

No

6. During the past 4 weeks to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Not at all  
Slightly  
Moderately  
Quite a bit  
Extremely

7. How much bodily pain have you had during the past 4 weeks?

None  
Very mild  
Mild  
Moderate  
Severe  
Very severe

8. During the past 4 weeks how much did pain interfere with your normal work (including work both outside the home and housework?)

Not at all  
 Slightly  
 Moderately  
 Quite a bit  
 Extremely

**YOUR FEELINGS**

9. These questions are about how you feel and how things have been with you during the past month (for each question please indicate the one answer that comes closest to the way you have been feeling.)

**Please tick ONE box per question**

a. Did you feel full of life?

All of the time  
 Most of the time  
 A good bit of the time  
 Some of the time  
 A little of the time  
 None of the time

b. Have you been a very nervous person?

All of the time  
 Most of the time  
 A good bit of the time  
 Some of the time  
 A little of the time  
 None of the time

c. Have you felt so down in the dumps that nothing could cheer you up?

All of the time  
 Most of the time  
 A good bit of the time  
 Some of the time  
 A little of the time  
 None of the time

d. Have you ever felt calm and peaceful?

All of the time  
 Most of the time  
 A good bit of the time  
 Some of the time  
 A little of the time  
 None of the time

e. Did you have a lot of energy?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

f. Have you ever felt downhearted and low?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

g. Did you feel worn out?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

h. Have you been a happy person?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

i. Did you feel tired?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

j. Has your health limited your social activities?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

**HEALTH IN GENERAL**

10. Please choose the answer that best describes how true or false each of the following statements is for you.

**Please tick ONE box only per question**

a. I seem to get ill more easily than other people.

- Definitely true
- Mostly true
- Not sure
- Mostly false
- Definitely false

b. I am as healthy as anybody I know.

- Definitely true
- Mostly true
- Not sure
- Mostly false
- Definitely false

c. I expect my health to get worse.

- Definitely true
- Mostly true
- Not sure
- Mostly false
- Definitely false

d. My health is excellent.

- Definitely true
- Mostly true
- Not sure
- Mostly false
- Definitely false

**Comments:**

**That is the end of the questionnaire**

**Thank you very much for your assistance**

**Appendix 12 Syncope Functional Status Questionnaire**

**SYNCOPE FUNCTIONAL STATUS QUESTIONNAIRE**

Please fill out the following questionnaire if you have ever suffered 'syncope' (blackouts). It is not necessary to fill out this questionnaire if you have never suffered from syncope.

Please answer the following 4 questions

**1. These episodes affect my life and daily routine by:**

Please TICK one box only for each question: YES, NO, or NOT-APPLICABLE (N/A)

	YES	NO	N/A
Interfering With My Life Or Routine			
Preventing Me Or Causing Me To Avoid Driving			
Reducing The Amount Of Walking I Do Each Day			
Interfering With My Use Of Public Transport			
Interfering With Performing Errands ie: Shopping			
Interfering With Physical Activities			
Affecting My Ability To Work At My Job			
Affecting Relationships With My Spouse/Partner			
Affecting Relationships With My Family			
Affecting Relationships With My Friends			
Affecting My Sexual Functioning			

2) How much do you worry about your episodes? On the scale below, circle the ONE number that fits you.

1	2	3	4	5	6	7	8
---	---	---	---	---	---	---	---

All I do is worry

I never worry

3) How much do you fear a typical episode coming on? On the scale below, circle the ONE number that fits you.

1	2	3	4	5	6	7	8
---	---	---	---	---	---	---	---

I am terrified

Neutral

I have no fear

4) How does worry about an episode affect your daily life? On the scale below, circle the ONE number that fits you.

1	2	3	4	5	6	7	8
---	---	---	---	---	---	---	---

All I do is worry  
so worry keeps me  
from my routine

I never worry  
so worry does  
not interfere

# Appendix 13 Cardiac death post mortem form (completed by Pathologists)

Hospital No.  
 Name  
 D.O.B  
 G.P.

Date of Death:  
 Date of Postmortem:  
 Post mortem No:  
 Consultant:  
 SHD/SpR:

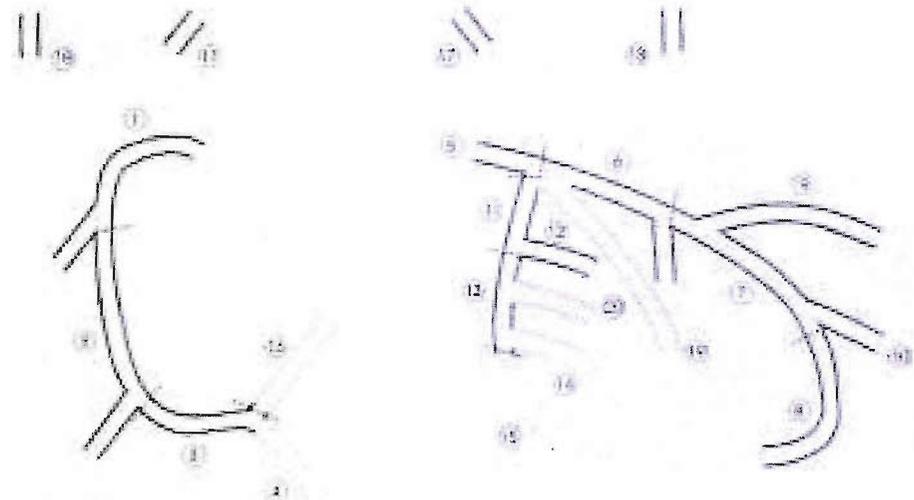
**History**

Sudden Death	Y/N	Nitrates	Y/N
Witnessed	Y/N	Diuretics	Y/N
Previous infarct	Y/N	Digoxin	Y/N
Previous CABG	Y/N	Beta Blockers	Y/N
Previous Angioplasty	Y/N	ACE inhibitors	Y/N
Hypertension	Y/N	Angiotensin RA	Y/N
Diabetes	Y/N	Ca Channel B	Y/N
Family History IHD	Y/N	Aspirin	Y/N
		Lipid Lowering	Y/N

Other information

**Coronary Anatomy**

Please indicate minimum diameter, old or recent occlusion as appropriate



**CA Segment Definition**

- |                               |                  |                                 |                             |
|-------------------------------|------------------|---------------------------------|-----------------------------|
| 1. RCA proximal               | 6. LAD proximal  | 11. Circumflex proximal         | 16. Posterolateral from RCA |
| 2. RCA mid                    | 7. LAD mid       | 12. Obtuse marginal (OM)        | 17. Venous graft            |
| 3. RCA distal                 | 8. LAD distal    | 13. Circumflex distal           | 18. Arterial graft          |
| 4. Right posterior descending | 9. 1st diagonal  | 14. Posterolateral from LAD     | 19. Intermediate            |
| 5. Main stem                  | 10. 2nd diagonal | 15. Postero-descending from LAD | 20. Additional OM           |

**Cardiac Findings**

other findings

Tricuspid V	N	AbN
Pulmonary V	N	AbN
Mitral V	N	AbN
Aortic V	N	AbN
Acute infarct	Y	N
Healed infarct	Y	N
Mural thrombus	Y	N
Cardiac rupture	Y	N

Heart weight  g  
 LV thickness  mm  
 RV thickness  mm

## Hospital Notes Questionnaire – all information as recorded in the hospital notes

1. Does the patient have a set of hospital notes?

Yes  No

2. If yes, what is the year of first entry?

3. Does the patient have a separate set of cardiac notes?

Yes  No

4. If yes, what is the year of first entry?

5. Has the patient ever suffered an MI?

Yes  No

6. If the answer to question 3 is yes, give details of number of MIs, when, where managed and treatment received

-----  
7. Has the patient ever suffered a cardiac arrest?

Yes  No

8. If the answer to question 3 is yes, give details of number of cardiac arrests, when, where managed and treatment received

-----

9. Has the patient ever had angina?

Yes  No

10. If the answer to question 7 was yes, when was it diagnosed and how was the angina managed?

-----

11. Has the patient ever been diagnosed with heart failure?

Yes  No

12. If the answer to question 9 was yes, when was it diagnosed and how was it managed?

-----

13. Has the patient ever been diagnosed with a ventricular arrhythmia?

Yes  No

14. If the answer to question 11 was yes, when was it diagnosed and how was it managed?

-----

15. Has the patient ever been diagnosed with any other type of arrhythmia?

Yes  No

16. If the answer to question 11 was yes, when was it diagnosed and how was it managed?

-----

17. Has the patient ever been diagnosed with diabetes?

Yes  No

18. If the answer to question 11 was yes, when was it diagnosed and how was it managed?

-----

19. Does the patient have hypertension?

Yes  No

20. If the answer to question 11 was yes, when was it diagnosed and how was it managed?

-----

21. Has the patient suffered any 'blackouts' in their lifetime (i.e. episodes where they have passed out)?

Yes  No

22. Has the patient presented to the health service with any of the following?

Syncope  Palpitations   
Chest pain  Shortness of breath   
Dizziness  Fall

23. If the answer to question 20 is yes, give details

Symptom	Where managed	How managed

24. Has the patient ever suffered from cerebrovascular disease?

Yes  No

25. If the answer to question 24 was yes, when was it diagnosed and how was it managed?

-----

26. Has the patient ever suffered from peripheral vascular disease?

Yes  No

27. If the answer to question 26 was yes, when was it diagnosed and how was it managed?

-----

28. Is the patient's smoking history recorded?

Yes  No

29. What is the patient's smoking history?

Smoker  Previous smoker then stopped

Never smoked  N/A

30. What previous investigations has the patient had?

	yes/no	date	where	result?
ECG – last				
Exercise test				
Echo				
24 hour tape				
Tilt test				
EEG				
Brain scan				
Reveal				
EP study				
Angiogram				
Other				

Relevant medical history:

	has (tick)	year	details
LV dysfunction (<40%/low ejection fraction) & test used			
PTCA			
CABG			
Ablation			
Other cardiac surgery			
Pacemaker			
Epilepsy			
Cardiomyopathy			
TIA/CVA			
Familial condition i.e. Long QT syndrome, Brugada syndrome, ARVD, HCOM			
Dementia			
Cancer			
Thyroid disease			
Falls			
Other – specify			

Drug history (at time of death):

	yes / no	date started	date stopped
Beta blockers			
Ca channel blockers			
Nitrate			
Diuretic			
Ace inhibitor			
Statin			
Aspirin/antiplatelet agent			
Amiodarone			
Digoxin			
Other anti-Arrhythmic			
Anti-epileptic			
Oral hypoglycaemics			
Insulin			
Other – specify			

Family medical history:

	Parent?	Sibling?	Child?
Syncope/palpitations			
Ischaemic Heart disease			
Epilepsy			
Sudden Death			
Other – specify			

31. Does the patient meet the NICE criteria for an ICD?

Yes  No

32. Is there evidence to suggest that this patient could have been considered for an ICD?

Yes  No

Further information

## Appendix 15 Judging appropriateness of cases for ICDs

### Degrees of Certainty

#### 1. Appropriate for ICD

Those cases where one could be most certain that patients should have been considered for an ICD are those meeting the NICE criteria for an ICD:

**Secondary prevention** i.e. for persons who present in the absence of a treatable cause, with:

- (4) Cardiac arrest due to either VT or VF,
- (5) Spontaneous sustained VT causing syncope or significant haemodynamic compromise,
- (6) Sustained VT without syncope/cardiac arrest, and who have an associated reduction in ejection fraction (less than 35%) but are no worse than class 3 of the New York Heart Association functional classification of heart failure.

**Primary prevention** for patients with:

- a history of previous MI and all of the following:
  - i) non-sustained VT on Holter monitoring,
  - ii) inducible VT on electrophysiological study
  - iii) left ventricular dysfunction with an ejection fraction less than 35% and no worse than class III of the New York Heart Association functional classification of heart failure
- a familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia and following repair of Tetralogy of Fallot.

**NICE are currently considering the inclusion of two further criteria:**

- *Patients with a prior MI (>30 days) with an ejection fraction of 30% and below (MADIT-2 criteria)*
- *Patients with non-ischaemic cardiomyopathy*

#### 2. Inappropriate for an ICD

- Reversible triggering factor for VT/VF can be identified e.g. VT in evolving AMI or electrolyte abnormalities
- Life expectancy less than 1 year (including severe heart failure – NYHA class IV drug-refractory congestive heart failure who are not candidates for cardiac transplantation)
- Patients not psychologically 'robust' enough for ICD (history of psychiatric disorders including uncontrolled depression and substance abuse)
- Frequent tachyarrhythmias that may trigger shock therapy, such as sustained VT not responsive to antitachycardia pacing or pharmacological therapy

**3. Grey area (should have been considered for further diagnostic testing or probably should have been considered for further diagnostic testing)**

For cases not considered to be at either end of this spectrum, a Consultant Cardiologist's decision is crucial in determining the level of certainty that each case could or could not be identified.

Note: Cases meeting non-UK guidance and recommendations for ICDs could fall into these categories.

**4. No evidence to justify further testing**

Cases with evidence of cardiac abnormalities but these would be insufficient and/or irrelevant to justify further testing (based on judgement).

**5. De Novo**

Cases with no evidence of cardiac abnormalities. These cases would not have been identified as being at risk of an SCD.

## Appendix 16 Example of a SCD case proforma

Post mortem number	1191
Gender	Male
Age of each case at date of death	82
Hospital notes: Has the patient ever suffered an MI?	No
Hospital notes: Details of MIs	N/A
GP notes: Has the patient ever suffered an MI?	No
GP notes: Details of MIs	N/A
Hospital notes: Previous cardiac arrest	No
Hospital notes: Details of cardiac arrests	N/A
GP notes: Previous cardiac arrest	No
GP notes: Details of cardiac arrests	N/A
Hospital notes: Diagnosed with a ventricular arrhythmia	No
Hospital notes: Type of ventricular arrhythmia	N/A
Hospital notes: Details of ventricular arrhythmia	N/A
GP notes: Diagnosed with a ventricular arrhythmia	No
GP notes: Type of ventricular arrhythmia	N/A
GP notes: Details of ventricular arrhythmia	N/A
Hospital notes: Diagnosed with other type of arrhythmia	Yes
Hospital notes: Details of other type of arrhythmia	atrial fibrillation
GP notes: Diagnosed with other type of arrhythmia	Yes
GP notes: Details of other type of arrhythmia	22/12/97 Atrial fibrillation
Hospital notes: History of heart failure	No
Hospital notes: Details of heart failure	N/A
GP notes: History of heart failure	Yes
GP notes: Details of heart failure	Congestive cardiac failure in letter 13/02/97
Hospital notes: Blackouts in the past	No
GP notes: Blackouts in the past	No
Hospital notes: Evidence ECG undertaken	No test undertaken
GP notes: Evidence ECG undertaken	No test undertaken
Hospital notes: Evidence exercise test done	No test undertaken
GP notes: Evidence exercise test done	No test undertaken
Hospital notes: Evidence echocardiogram done	No test undertaken
GP notes: Evidence echocardiogram done	No test undertaken
Hospital notes: Evidence Holter done	No test undertaken
GP notes: Evidence Holter done	No test undertaken
Hospital notes: Evidence EP study done	No test undertaken
GP notes: Evidence EP study done	No test undertaken
Hospital notes: Evidence angiogram done	No test undertaken
GP notes: Evidence angiogram done	No test undertaken
Hospital notes: Evidence of heart failure on angiogram and/or CXR	No test
GP notes: Evidence of heart failure from angiogram and CXR	No test
Hospital notes: PTCA in the past	No
GP notes: PTCA in the past	No
Hospital notes: CABG in the past	No
GP notes: CABG in the past	No
Hospital notes: Ablation in the past	No
GP notes: Ablation in the past	No
Hospital notes: Other cardiac surgery in the past	No
GP notes: Other cardiac surgery in the past	No
Hospital notes: Pacemaker implanted in the past	No

GP notes: Pacemaker implanted in the past	No
Hospital notes: Cardiomyopathy diagnosed in the past	No
Hospital notes: Cardiomyopathy details	N/A
GP notes: Cardiomyopathy diagnosed in the past	No
GP notes: Cardiomyopathy details	N/A
Hospital notes: Familial condition i.e. long QT syndrome, Brugada syndrome, ARVD or HCOM	No
GP notes: Familial condition i.e. long QT syndrome, Brugada syndrome, ARVD or HCOM	No
Hospital notes: History of dementia	No
GP notes: History of dementia	No
Hospital notes: Cancer history	Yes
GP notes: Cancer history	Yes
Hospital notes: Use of amiodarone	Yes
Hospital notes: Details of amiodarone use	None
GP notes: Use of amiodarone	No
GP notes: Details of amiodarone use	N/A
Hospital notes: Combinations of 2 or more diuretic, ace-inhibitor and beta-blocker Received 2 or more drugs	
GP notes: Combinations of 2 or more diuretic, ace-inhibitor and beta-blocker Received 2 or more drugs	

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