THE EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH
IN WESTERN AUSTRALIA

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BMed, MMed

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The thesis contains published work and/or work prepared for publication, all of which has been co-authored. Each co-author has agreed to the inclusion of the manuscript in this thesis. The bibliographical details of the work and where they appear in the thesis are outlined below.

Chapter 4 is an expanded version of this paper.


Chapter 5 is an expanded version of this manuscript.

We confirm that permission has been obtained from all co-authors to include these manuscripts in this thesis.

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Assistant Professor Siobhan Hickling  
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**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
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<tr>
<td>AM</td>
<td>Australian Modification</td>
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<tr>
<td>ARREST</td>
<td>Amsterdam Resuscitation Study</td>
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<tr>
<td>ASR</td>
<td>Age-Standardised Rate</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CM</td>
<td>Clinical Modification</td>
</tr>
<tr>
<td>CREDO-Kyoto</td>
<td>Coronary Revascularisation Demonstrating Outcome study in Kyoto</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>Defibrillator In Non-Ischaemic cardiomyopathy treatment Evaluation</td>
</tr>
<tr>
<td>FINGER</td>
<td>Finland-Germany myocardial infarction study</td>
</tr>
<tr>
<td>HMD</td>
<td>Hospital Morbidity Data</td>
</tr>
<tr>
<td>HMDS</td>
<td>Hospital Morbidity Data System</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischaemic Heart Disease</td>
</tr>
<tr>
<td>LIFE</td>
<td>Losartan Intervention For Endpoint reduction in hypertension</td>
</tr>
<tr>
<td>MONICA</td>
<td>Monitoring of trends and determinants in Cardiovascular disease</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>RR</td>
<td>Rate Ratio</td>
</tr>
<tr>
<td>SCD</td>
<td>Sudden Cardiac Death</td>
</tr>
<tr>
<td>TRACE</td>
<td>Trandolapril Cardiac Evaluation</td>
</tr>
<tr>
<td>WA</td>
<td>Western Australia</td>
</tr>
<tr>
<td>WADLS</td>
<td>Western Australian Data Linkage System</td>
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ABSTRACT

Introduction

Sudden cardiac death (SCD) refers to a sudden pulseless condition presumed due to a life-threatening ventricular arrhythmia or pulseless electrical activity occurring within a short period in individuals with or without a history of established heart disease. The magnitude of SCD remains considerable although overall cardiovascular mortality rates have been declining. The worldwide incidence rates of SCD have been estimated, however they vary widely due to inconsistent definitions used and varying methodologies employed to monitor and estimate SCD. Even with a well-accepted definition of SCD, estimates of SCD are still difficult as the circumstances surrounding a sudden death are frequently absent. Therefore, the epidemiology of SCD is still poorly understood globally, particularly in Australia. Historical community-based studies have shown a generally declining trend in SCD. There are limited international and no Australian studies detailing contemporary trends in the incidence rates of SCD at a population level. Substantial advancements in clinical management of the underlying cause of SCD (including drug therapy and device-based therapy) and prevention of SCD (including first responder defibrillator program) may have influenced the epidemiology of SCD. There are also few studies examining the clinical predictors of SCD particularly following a cardiovascular disease (CVD) event. Individuals with established CVD are a target study population for identification of predictors of SCD as they have a substantially greater risk of SCD than those without.

The primary aims of this thesis were to estimate the trends in SCD using routinely collected administrative deaths records and morbidity data and to explore predictors of SCD to determine the potential for its prevention in Western Australia (WA). The specific objectives to address the aims were:
1. To develop a method for SCD case ascertainment using the statutory mortality and morbidity data for the WA population;

2. To measure trends in incidence rates of SCD overall and by age, sex, and prior CVD hospitalisation history; and

3. To estimate incidence rates of SCD and identify clinical predictors of SCD following key CVD events.

Methods

The study objectives were investigated using high-quality person-linked administrative health data which included mortality and hospital morbidity data from January 1, 1985 to June 30, 2011. Continuous and categorical variables were presented as mean ± standard deviation and proportions (%) respectively. Difference in means of two independent groups such as sex was determined using an independent t-test. Differences in proportions of independent groups such as age groups were examined using a Pearson’s chi-squared test. Age-standardised rates (ASRs) were calculated using the direct method. Annual change in incidence rates was estimated using Poisson log-linear regression modelling. Unadjusted cumulative incidence was estimated by Kaplan-Meier survival curve. Predictors for SCD were identified from multivariable Cox regression modelling.

Results

A developed method for sudden cardiac death identification

A total of 9,567 SCD cases were identified through the developed multiple source method with four criteria using the linked administrative health data in WA from January 1, 1997 to December 31, 2010. The method was based on a combination of place, death within 24 hours, discharge diagnoses, underlying cause, associated cause and/or a post-mortem. Approximately 10% of cases were identified by more than one criterion. Criterion one and two captured one third of SCD cases who had
recorded having a fatal arrhythmia. Criterion three captured 40% of cases that died out-of-hospital or in-hospital within 24 hours of any-cause admission and had a post-mortem.

Magnitude of sudden cardiac death in the general population

Men accounted for two thirds of the total SCD cases identified. Men were nine years younger than women succumbing to SCD. Four in five cases occurred outside the hospital, with ischaemic heart disease the most common underlying cause of death. The majority of SCD cases occurred in those aged ≥35 years old, with one in three having no previous CVD hospitalisation in the 10 years prior to death. The crude SCD incidence rate was 34.6 per 100,000 person-years in the general WA population, with the ASR of 37.8 per 100,000 person-years. The average annual ASR for people aged 1-34 years was 1.1 per 100,000 person-years whereas that for people aged ≥35 years was 70.7 per 100,000 person-years. Men had higher annual ASRs of SCD than women.

Trends in sudden cardiac death

Overall declining trends in incidence rates of SCD were observed in men and women although limited improvement was found in 35-to-54-year-olds in a whole-population setting. The decreasing trends were evident in SCD cases with and without prior CVD hospitalisation history. Individuals with prior CVD hospitalisations had three times higher incidence rates of SCD than those without.

Magnitude of sudden cardiac death in high-risk populations

The magnitude of SCD was substantially high in potentially high-risk groups of individuals with four respective selected key CVD incident events of myocardial infarction, heart failure, atrial fibrillation, and stroke. The incidence rates of SCD were 26-fold, 22-fold, 7-fold, and 6-fold higher respectively in patients after incident hospitalised myocardial infarction, followed by heart failure, stroke, and atrial fibrillation compared to the general WA population.

Clinical predictors of sudden cardiac death in high-risk populations
Myocardial infarction, arrhythmias, heart failure, and chronic kidney disease were identified as common clinical predictors of SCD in patients after incident hospitalisation for myocardial infarction, heart failure, atrial fibrillation, and stroke. Early and late cardiac procedures (including percutaneous coronary intervention, coronary artery bypass grafting, and implantable cardioverter-defibrillator) were strong protective factors for SCD following incident myocardial infarction.

**Conclusions**

A multiple source method for SCD case ascertainment has been developed using high-quality person-linked administrative health data where the magnitude of SCD in WA estimated generally correspond to estimates from the literature. Declining trends in incidence rates of SCD are evident and independent of sex and prior hospitalisations despite limited improvements in young adults. The incidence of SCD is substantially higher in high-risk populations of selected key CVD incident events of myocardial infarction, heart failure, atrial fibrillation, and stroke, compared to the general WA population. Clinical predictors of SCD following these four key CVD incident events have been identified to provide clinicians with risk profiles for treatment consideration particularly for SCD prevention. These findings are highly important for enhancing our understanding of the epidemiology of SCD and considering the implication of previous benefit and future potential from both primary and secondary prevention for SCD.
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CHAPTER 1. GENERAL INTRODUCTION

1.1 Background

Sudden cardiac death (SCD) describes a critical state of unexpected natural sudden circulatory
collapse resulting from a cardiac cause in a person with or without a previous history of heart
disease.[1-3] Approximately 80% of collapse occurs outside the hospital or in the emergency room.[4] It is estimated that SCD accounts for approximately 80% of ischaemic heart disease (IHD) deaths, 50% of cardiovascular deaths, and 15% of deaths from all causes.[5, 6] Despite the overall decline in cardiovascular mortality largely due to primary and secondary prevention of IHD, the burden of SCD is unknown.[1, 7-9]

The estimates of the annual incidence rates of SCD vary widely, from 30 per 100,000 person-years to 150 per 100,000 person-years in the general population in North America, South America, Europe, and Asia.[10-14] It is difficult to compare and interpret the variation in these incidence rates because of inconsistent definitions of SCD and varying methodologies employed to estimate and monitor SCD. Even though a well-accepted definition is available, estimates of SCD are still challenging. Adjudicating a death as sudden is difficult as the circumstance of death or information on the fatal event is frequently unavailable. There is a lack of data sources for case ascertainment in most countries.[15] Hence the epidemiology of SCD is still poorly characterised worldwide, particularly in Australia.

Different methodologies, predominantly single versus multiple data sources, have been used for the surveillance of SCD. These data sources used include death certificates, hospital records, emergency medical response records, autopsy documents, and/or questionnaires.[1, 13, 16-18] Each of these data sources alone may not capture all the SCD cases due to their potentially inherent limitations thereby underestimating the SCD statistics.[10] A multiple source method of SCD case ascertainment
In Australia, the statutory Western Australia Data Linkage System provides a unique opportunity for multiple sources to fill the gap of investigating the epidemiology of SCD in Western Australia (WA).

A limited number of worldwide studies on the trends in SCD suggest a general decline in the incidence rates.[20-22] The declines in the incidence rates of SCD vary across studies and involve different time periods.[20-22] Importantly, the falls in the incidence rates of SCD coincide with declining age-adjusted mortality rates in cardiovascular disease (CVD) and IHD in more recent decades.[20-22] Although cardiovascular mortality rates have been falling in Australia since the late sixties, it is unclear whether a similar trend is observed for the incidence of SCD in WA.[23] The reason for the fall in the incidence rates of SCD is inconclusive although two historical community-based studies in the 1990s suggested the declining trends in SCD were attributable to the contributions of primary and secondary prevention of IHD.[20, 24] Currently, much progress has been made in clinical diagnosis and treatment of CVD and IHD or both, cardiovascular risk factors prevention and management, and acute care.[25] All these advancements may have impacted and changed the epidemiology of SCD. Therefore, it is timely to have a renewed understanding of the trends in SCD.

From a prevention perspective, our understanding of the predictors of SCD is important and may have improved as our knowledge of pathophysiology for SCD has advanced.[26] Whilst the major cardiovascular risk factors of SCD have been examined in a community-based study[27] or in a single sex study (men or women),[28-31] predictors of SCD in the Australian population have not been examined in detail. It is unclear whether the risk factors examined are still predictive of SCD with the changing trends in the prevalence of cardiovascular risk factors observed worldwide, including Australia.[22, 32, 33] The treatment of these risk factors has also progressed in the form of blood pressure-lowering therapy and lipid-lowering therapy.[34] Furthermore, individuals with a history of CVD have a five-fold higher risk of SCD than those without.[20, 35] Therefore, it is important to identify SCD predictors in individuals with a CVD event for prevention potential for SCD.
1.2 Study aim and objectives

The primary aim of this thesis was to examine and report on trends in SCD in a single representative Australian jurisdiction using routinely collected administrative deaths records and morbidity data and to explore predictors of SCD to determine the potential for SCD prevention.

The specific objectives to meet were:

Objective 1: To develop criteria for the identification of SCD cases using the statutory mortality and morbidity data collections in the WA population aged ≥1 year old from 1997 to 2010, and to examine the characteristics, incidence rates, and underlying causes of the identified SCD as ascertained using the method developed for case identification (Chapter 4).

Objective 2: To measure trends in incidence rates of SCD overall and by age and sex, and prior CVD hospitalisation history in individuals aged 35 to 84 years in WA from 1997 to 2010 and to determine whether the relative risk of SCD in individuals with and without prior CVD hospitalisation history has changed during this period (Chapter 5).

Objective 3: To estimate each the incidence rate of SCD following the incident key CVD events of myocardial infarction, heart failure, atrial fibrillation, and stroke, in people aged 35 to 84 years in WA between 2000 and 2009 and to identify independent predictors of SCD separately in these four incident key CVD events.

1.3 Structure of the thesis

The overall structure of this thesis follows the traditional format of Introduction, Methods, Results, and Discussion within each of the study chapters relating to objectives 1, 2 and 3. The results chapters in this thesis are comprised of expanded papers (some published, some yet to be published) as allowed under The University of Western Australia Doctor of Philosophy rule.[36] The literature review chapter precedes the study chapters and a general discussion chapter of the project findings is presented at the end.
Chapter 1 provides a brief background of the epidemiology of SCD to highlight the public health issue derived from SCD, outlines the aim and objectives, and describes the structure of the thesis.

Chapter 2 provides a literature review relevant to the studies undertaken within the scope of this thesis, covering the findings and challenges of SCD measurement, magnitude of SCD, trends in SCD, and predictors of SCD.

Chapter 3 provides a brief overview of the data sources used in this thesis and describes the preliminary analyses for the methodological decisions for the analyses in the thesis.

Chapter 4 is the first results chapter, addressing Objective 1. It describes a method for SCD identification using population-wide person-based administrative morbidity and mortality data. It also describes the magnitude of SCD in WA from 1997 to 2010.

Chapter 5 is the second results chapter, addressing Objective 2. It examines trends in the incidence rates of SCD overall and stratified by CVD hospitalisation history, gender and age groups in individuals aged 35-84 years from 1997 to 2010. It also determines the change in relative risk of SCD in individuals with and without prior CVD hospitalisation history during this period.

Chapter 6 is the third results chapter, addressing Objective 3. It estimates each the incidence rate of SCD following the incident key CVD events of myocardial infarction, heart failure, atrial fibrillation, and stroke, in people aged 35 to 84 years in WA between 2000 and 2009. It also identifies independent predictors of SCD separately in these four incident key CVD events.

Chapter 7 provides a summary of the main findings of the thesis, interprets the implication of the results, acknowledges the study limitations and strengths, and suggests future research direction.
CHAPTER 2. THE EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH

This chapter presents the background and justification for studying the trend and predictors of sudden cardiac death (SCD) in Australia. It covers what is known about the aetiology and pathophysiology of SCD as well as the various methodologies in the literature used to identify SCD cases including the data sources. The advantages and disadvantages of each of the data sources used for SCD research are discussed. Current epidemiology of SCD including trends in the incidence rates of SCD and the accompanying predictors of SCD are then summarised. Given the limited number of studies of SCD available, studies of trend and predictors on sudden unexpected cardiac death, sudden cardiovascular death, sudden arrhythmic cardiac death, out-of-hospital SCD, out-of-hospital cardiac arrest, or out-of-hospital ischaemic heart disease (IHD) death are also presented for some insights into this PhD project on SCD.

2.1 Measuring sudden cardiac death

This unpredictable fatal event is characterised by unspecified symptoms at onset, a short time from onset of symptoms to death, death usually occurring at home (80%), and frequent absence of any witnesses (40%).[37] These characteristics of SCD make it challenges for case ascertainment when applying the definition of SCD.

2.1.1 Definitions

Consensus on the definition of SCD from both clinical and public health perspectives is yet to be achieved. Clinically, SCD is defined as a sudden pulseless condition presumed due to a life-threatening ventricular arrhythmia or pulseless electrical activity that occurs within a short time (generally ≤1 hour) after the onset of symptoms in a previously stable individual without evidence of other co-existing fatal conditions.[2, 4] It is debatable how “sudden death” is assessed and how
cardiac involvement is ascertained since neither autopsy nor medical history can reliably determine whether an arrhythmia is the underlying cause of death. Such documentation of the abnormal heart rhythm is usually absent. This is particularly for unwitnessed deaths that account for approximately 40% of the cases where no information is likely to be available.[37]

The most accepted definition of SCD in public health is sudden unexpected death occurring within one hour of symptom onset if the event is witnessed, or within 24 hours of having been observed alive and symptom free if the event is unwitnessed.[38] Application of the definition in order to measure the magnitude of the problem is still challenging from a public health surveillance perspective for several reasons. Firstly, the duration of symptoms prior to death is not typically known and therefore not routinely reported in collected administrative health data. Secondly, there is lack of national SCD registries in most countries including Australia, making this definition less operational for obtaining circumstances surrounding death in this situation (such as time of death, onset of symptoms, and witnesses).

### 2.1.2 Aetiology and underlying pathophysiology of sudden cardiac death

The pathogenesis of SCD is complex and multifaceted and our knowledge of it continues to evolve. The aetiology behind SCD varies with age. In general, coronary atherosclerosis is the most common pathological findings at autopsies of SCD in older adults, whereas coronary artery anomalies (such as hypoplastic coronary arteries) and hypertrophic cardiomyopathy are contributors to fatal arrhythmias in children and younger adults.[39]

Coronary artery disease (CAD) is the most common clinical finding associated with SCD, accounting for approximately 70%-75% of SCD cases in people older than 35 years.[26] The pathophysiology of SCD may be reviewed from two aspects: vascular and myocardial pathophysiology. Firstly, vascular pathophysiology in CAD is frequently associated with coronary atherosclerosis. Coronary atherosclerosis is part of a dynamic process where plaques are formed by inflammatory changes in the
vessel wall in response to irritation or as part of the inbuilt healing process. As these plaques attach to
the damaged vessel wall, they are prone to fracture, fissuring, rupture, haemorrhage, occlusion, and
thrombosis.[40, 41] All these pathophysiological changes could eventually lead to a transient
ischaemic event which can trigger SCD.[41] Secondly, myocardial pathophysiology may be a static
process where scar substrates forms the anatomical basis of arrhythmogenic circuits, or a dynamic
process where normal cardiac muscle is met with transient ischaemic changes, interacting with
abnormal substrates from a previous coronary event resulting in arrhythmias.[41] It is not yet clear
whether myocardial changes alone can initiate arrhythmias or if vascular pathophysiology is a
necessary culprit.[41]

Cardiomyopathy represents the second largest group of cases in SCD and includes hypertrophic and
dilated cardiomyopathies.[26] Cardiomyopathy as the underlying disease state accounts for 10%-15%
of SCD cases.[26] It is the most common cause of SCD in adolescents and young adults.[42-45] It
has remained uncertain whether hypertrophy is mechanistically involved in the development of SCD
or merely an indicator of susceptibility to CAD or plaque rupture.[46] One study has shown that
hypertrophy modulated arrhythmia can result in SCD when there is electrical heterogeneity from
coronary artery scarring and subsequent remodelling.[47] Dilated cardiomyopathy correlates with the
presence of non-sustained ventricular tachycardia leading to SCD, presuming that it is based on
ventricular tachyarrhythmia.[48-50] The progress of these fatal arrhythmias is associated with
abnormal repolarisation in ventricular myocardium[51] and bundle-branch re-entry.[52]

Valvular heart disease is the third largest cause of SCD after CAD and cardiomyopathy, although it
accounts for only a small proportion of SCD cases overall.[53] The most common valvular heart
disease is aortic stenosis whilst a less common valvular disorder is aortic regurgitation.[54] A clear
mechanism for aortic stenosis or regurgitation in SCD has not yet been established. It could be that
aortic valve calcification extends into the conduction system causing ischaemia or atrioventricular
blocks resulting in ventricular arrhythmias.[55, 56] Mitral valve prolapse has also been linked with
SCD.[57] Prior studies have detailed a growing risk of SCD associated with specific anatomic lesions
in mitral valve prolapse, endocardial friction lesions, and thrombotic lesions in the angle between the posterior leaflet and the left atrial wall.[53, 54, 57]

The remaining SCD cases occur in those who have congenital cardiac structural anomalies or structurally normal but electrically abnormal hearts.[58] The underlying pathophysiologies are mixed and not always clear. They may be related to the development of rapid conduction to the ventricles over the accessory pathway and/or electrophysiological disturbances.[59] Young children with congenital conditions, such as tetralogy of Fallot, transposition of the great arteries, aortic stenosis, and pulmonary vascular obstruction, have a much higher risk of SCD.[60] Idiopathic arrhythmias are the cardiac cause of half of the deaths of children who die during exercise who have apparently normal hearts at autopsy.[61] Sudden cardiac death can also result from severe late complications of surgical repair of complex congenital cardiac lesions.[60]

Sudden infant death syndrome describes the unexpected death of neonates and infants under one year of age, whose cause of death remains unexplained after a comprehensive case investigation, including autopsy, examination of circumstances, and/or review of clinical history.[62] Sudden infant death syndrome is usually researched as a separate topic although there is yet no agreement among cardiologists as to whether it should be classified as SCD or not as a cardiac cause of this syndrome has yet to be established.[39] Therefore, deaths aged under one year old were excluded from all the analyses in this thesis.

2.1.3 Data collection sources

Obtaining data for SCD identification is difficult even when a standardised definition is used. This is because defining a death as sudden is generally retrospective and the circumstances surrounding the death are often absent. In theory, collecting long-term prospective mortality data at the population level is the best way to obtain reliable data for case ascertainment. However, these data are difficult to obtain. Therefore, a range of alternative methods have been used to obtain data for the purpose of
epidemiological studies of SCD such as death certificate-based surveillance, multiple sources of ascertainment (source including circumstances of death, medical records, next-of-kin interviews, emergency room resuscitation records, and/or available autopsy reports), and questionnaire based approach, which are described below.

Case ascertainment by retrospectively examining death certificates is a common method used to identify SCD as it provides objective documented death information and uniform data when standard disease codes are applied. International Classification of Diseases (ICD) codes for cardiac arrest, 427.5 (not specific to SCD) and I46 (I46.1 specific to SCD) are assigned only if resuscitation is undertaken.[63] These two codes are rarely assigned as the underlying cause of death because it reflects a mechanism of death rather than the underlying cause of death.[64] In addition, duration between the onset of symptoms and death is not typically recorded in death certificates. This method relying on the sole death certificate was reported to overestimate SCD rates by 200%-300%.[17]

Multiple sources of ascertainment have been proposed but used in only a few studies to overcome the limitations of each of the sources when considered individually.[17, 65] These data sources generally included hospital documents, post-mortem reports, and next-of-kin interviews. Hospital documents data can be obtained for witnessed cases and may also be available from emergency medical personnel or paramedics. But for unwitnessed cases, detailed clinical records are usually absent. Autopsy derived data can accurately reflect the aetiology of SCD, but the data cannot be a representative source for a population based epidemiology study. This is because autopsy rates have decreased substantially in many countries including Australia in recent decades.[66-70] Specifically, hospital autopsy rates declined from 21% in 1992 to 12% in 2003 to 8% in 2010 in Australia.[66, 71]

A questionnaire based approach is a more recent method to gather data on likely SCD when the conventional methods are not feasible or reliable in collecting mortality data, especially in developing countries.[72, 73] The inherent limitations of studies based on questionnaires or interviews are recall bias and selection bias. There is also a concern if the response rate is low.
2.1.4 Other studies related to sudden cardiac death

Studies on out-of-hospital death including out-of-hospital SCD, out-of-hospital IHD death, or out-of-hospital cardiac arrest may provide some indication regarding ascertainment of SCD, as these definitions share some characteristics of SCD. Around 80% of SCD cases occur outside of hospital.[4] In terms of aetiology and pathophysiology, IHD is the most common underlying cause of SCD.[4] Cardiac arrest is a critical state usually occurring within minutes before SCD.[74] When cardiac arrest occurs, if community-based interventions and life support systems are not available or fail, SCD subsequently occurs.[74] Research on cardiac arrest can provide some insights although it generally focuses on how to improve the survival rates of out-of-hospital cardiac arrest worldwide and currently the rates varied from 2% to 11%.[75] Not all cardiac arrests are classified as SCD as cardiac arrest can be caused by non-cardiac factors such as drug overdose.[76]

In addition, research on sudden arrhythmic cardiac death, sudden cardiovascular death, or sudden unexpected cardiac death may also offer some implications for SCD. Ventricular tachyarrhythmia was the presumed mechanism of SCD although the proportion of ventricular fibrillation decreases whilst that of asystole and pulseless electrical activity increases.[26, 77] Sudden cardiovascular death or sudden unexpected cardiac death is broadly related to SCD, including non-arrhythmic cardiac causes which are recognised as underlying disease states of SCD (such as congestive heart failure and embolic phenomena).[78]

2.2 Magnitude of sudden cardiac death

The incidence rate of SCD is difficult to ascertain due to the inconsistency in definitions and methods applied in different studies as discussed in Section 2.1. However, a number of studies have estimated the magnitude of SCD using different methodologies. Table 2.1 provides a summary of key worldwide studies for research on the magnitude of SCD from the 1960s. Most of them used community-based cohorts. Also included in Table 2.1 are some early studies that can be considered
proxies for SCD, including out-of-hospital IHD death, sudden arrhythmic cardiac death, sudden unexpected cardiac death, or cardiac arrest. However, studies limited to these diseases only might not reflect the complete magnitude of SCD. The SCD incidence rates varied from study to study, most probably due to different methodologies used to estimate SCD-single source versus multiple source data.

2.2.1 Measurement using single source data

Single source data can provide a crude estimate of SCD incidence. The administrative mortality dataset is the most common data source. A study of all the United States residents aged ≥35 years old measured the incidence rate of SCD using the mortality statistics data from 1989 to 1998.[79] In this study, cases were considered to be SCD if cardiac disease was the underlying cause of death and the deaths occurring out-of-hospital (including in the emergency room), or the individuals were “dead on arrival”. [79] The annual incidence rate of SCD was found to be around 300 per 100,000 person-years, accounting for 63% of all cardiac deaths.

Another frequently used data source is emergency services data (collected from the first responders, the emergency medical service registry, or the ambulance cardiac arrest registry). Several community-based surveillance studies in the United States using first-responder data showed the annual incidence rate of treated primary cardiac arrest ranged from 41 to 89 per 100,000 person-years,[80-83] with survival rates below 10%.[75] Three other studies reported the incidence rate of SCD using equivalent data sources-emergency medical service registry in Aurich, Germany,[18] the ambulance cardiac arrest registry in Perth[84, 85] and the corresponding registry in Sydney,[86] Australia. Between the three studies, the incidence rates of SCD were wide, ranging between 30 and 70 per 100,000 person-years. Although similar definitions were used and real differences in the incidence rates of SCD may exist among these populations, it is possible that reliance on a single data source might not give a true estimate. This would be particularly relevant for cases of SCD that go unwitnessed.
When autopsy data alone are used, the reported annual incidence rates of SCD again vary. In a Brazilian community study using Coroners’ Office autopsy reports, the incidence rate of SCD from 2006 to 2010 was found to be 30 per 100,000 person-years.[12] Another study in Epirus, Greece using post-mortem data reported the SCD incidence rate of 19 per 100,000 person-years from 1998 to 2008.[19] One possible explanation for these different incidence rates might be due to the proportion of the population who are autopsied.[70, 71, 87]

A questionnaire-based approach is devised to estimate the incidence rate of SCD when the emergency medical response systems may not be complete and other sources are unavailable for research. A study in Southern India devised the structured questionnaires and carried out the survey over the course of one year through medical trainees in eight medical colleges and teaching hospitals (including medical students, medical residents, and medical fellows) and their whole families.[88] Collected data covered cause of death and medical condition of the deceased in the last one or two days prior to the death.[88] This study estimated SCD was responsible for 10% of overall mortality in this population and SCD cases were generally young with an average age of 60 years.[88] However, recall bias and socially desirability bias by the family may have occurred. Selection bias was minimised through the use of stratified multistage cluster sampling to obtain data for a larger population of around 22,000 who were representative of the general population.[88] It is difficult to compare the findings from this questionnaire-based approach with those from other approaches due to a lack of validation data.

2.2.2 Measurement using multiple sources of data

Multiple sources available for research vary across studies and using multiple sources of data for case ascertainment may improve the quality of the SCD incidence rate estimation. The Paris Prospective Study using data from medical examinations, routine blood tests, hospital records, and death certificates showed SCD comprised 5.6% of total mortality and approximately one fifth of all
cardiovascular deaths.[89] The findings might have limited generalisation to females as this study examined a cohort of around 7,000 middle aged 43 to 52 years working males from 1960 to 1983.[89]

In an investigation in Maastricht, the Netherlands, multiple source data included General Practitioner’s reports and family interviews collected for unwitnessed cases, and ambulance personnel reports collected for witnessed cases.[90] This study reported the estimated annual incidence rate of out-of-hospital cardiac arrest to be around 89 per 100,000 person-years from 1991 to 1994 in a population aged 20-75 years.[90] Approximately half of the cases had no prior history of heart disease.[90] Most cases occurred at home (80%) and some were witnessed (60%).[90] Cardiac resuscitation was administered to half of the cases, with only 6% surviving and later being discharged from hospital.[90] Although the study focuses exclusively on out-of-hospital cardiac arrest, it may provide some indication of SCD as SCD occurs in a very short time after cardiac arrest if cardiac resuscitation is not available or fail.

More recently, SCD incidence rates reported from the United States, Ireland, and China were consistent using the approach of multiple data sources even though the data sources used were slightly different across the studies.[13, 17, 65] The multiple sources included circumstances of death, emergency room resuscitation records, medical records, relative and witness interviews, and/or available autopsy data.[13, 17, 65] The incidence rates of SCD observed in Multnomah County, the United States in 2002-2003, in a rural population of the West of Ireland in 2005, and in four regional populations in China to were at close range, from 42 to 53 per 100,000 person-years.[13, 17, 65]

In summary, varying methodologies by the single or multiple source data may have contributed to the challenges of determining the incidence rates of SCD and revealing the real rate differences. There is currently no gold standard methodology for SCD identification. Multiple source data where they are available are preferred to single source data when estimating the incidence rates of SCD because they may improve the quality of case ascertainment.
<table>
<thead>
<tr>
<th>Study</th>
<th>Terminology used in each study</th>
<th>Study period</th>
<th>Age included (years)</th>
<th>Data source</th>
<th>SCD statistics*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North America</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multnomah, United States[17]</td>
<td>SCD</td>
<td>2002-2003</td>
<td>All</td>
<td>Multiple sources: circumstances of death, medical records, and available autopsy data.</td>
<td>53/100,000</td>
</tr>
<tr>
<td>Seattle, United States[80]</td>
<td>Out-of-hospital cardiac arrest</td>
<td>2002</td>
<td>≥20</td>
<td>Single source: Seattle Fire Department’s emergency medical services system</td>
<td>61/100,000</td>
</tr>
<tr>
<td>United States[79]</td>
<td>SCD</td>
<td>1989-1998</td>
<td>≥35</td>
<td>Single source: death certificates</td>
<td>63% of cardiac deaths (rate not reported)</td>
</tr>
<tr>
<td>Edmonton, Canada[91]</td>
<td>Out-of-hospital cardiac arrest</td>
<td>1997-2002</td>
<td>All</td>
<td>Multiple sources: cardiac arrest care and emergency medical services data</td>
<td>56/100,000</td>
</tr>
<tr>
<td><strong>South America</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribeirão Preto, Brazil[12]</td>
<td>SCD</td>
<td>2006-2010</td>
<td>All</td>
<td>Single source: coroner’s office autopsy reports</td>
<td>30/100,000</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paris, France[89]</td>
<td>Sudden death</td>
<td>1967-1996</td>
<td>43-52</td>
<td>Multiple sources: medical examination, blood reports, hospital records, and death certificates</td>
<td>5.6% of total mortality (rate not reported)</td>
</tr>
<tr>
<td>West of Ireland (Galway, Mayo, and Roscommon)[65]</td>
<td>Out-of-hospital cardiac arrest</td>
<td>2005</td>
<td>All</td>
<td>Multiple sources: emergency room resuscitation records, medical records, and autopsy reports</td>
<td>51/100,000</td>
</tr>
<tr>
<td>Aurich, German[18]</td>
<td>SCD</td>
<td>2002-2009</td>
<td>All</td>
<td>Multiple sources: emergency medical records and death certificates</td>
<td>81/100,000</td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand (Amphurs, Baan Fang, Baan Phai, Nam Phong, Phra Yuen)[92]</td>
<td>Sudden unexplained death syndrome</td>
<td>1990</td>
<td>20-49</td>
<td>Multiple sources: mailed questionnaires and interview of relatives</td>
<td>38/100,000</td>
</tr>
<tr>
<td>Epirus, Greece[19]</td>
<td>SCD</td>
<td>1998-2008</td>
<td>1-80</td>
<td>Multiple sources: circumstances of death, medical records, autopsy, and available police and ambulance data.</td>
<td>19/100,000</td>
</tr>
<tr>
<td>China (Kelamayi, Yuxian, Beijing, Guangzhou)[13]</td>
<td>SCD</td>
<td>2005-2006</td>
<td>All</td>
<td>Multiple sources: medical records, death certificates, and interview of relatives and witnesses</td>
<td>42/100,000</td>
</tr>
<tr>
<td>India[88]</td>
<td>SCD</td>
<td>Not mentioned</td>
<td>All</td>
<td>Single source: staged questionnaire-based kindred-wide approach</td>
<td>10% of overall mortality (rate not reported)</td>
</tr>
<tr>
<td><strong>Australia</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Perth, Western Australia[84, 85]</td>
<td>Out-of-hospital cardiac arrest</td>
<td>1996-1999</td>
<td>≥16</td>
<td>Multiple sources: ambulance service database linked to Western Australia hospital morbidity and mortality data</td>
<td>33/100,000</td>
</tr>
<tr>
<td>Sydney, Australia[86]</td>
<td>Out-of-hospital cardiac arrest</td>
<td>2004-2005</td>
<td>All</td>
<td>Single source: ambulance service database</td>
<td>52/100,000</td>
</tr>
</tbody>
</table>

*When incidence rate of SCD was not reported, other indices/statistics were provided alternatively.
2.3 Trends in incidence rates of sudden cardiac death

There have been limited data studying trends in incidence rates of SCD. However, the available information is detailed in this section and summarised in Table 2.2. As there are only a small number of studies specifically measuring trends in SCD, studies on out-of-hospital SCD, out-of-hospital cardiac arrest, and sudden cardiovascular death were also reviewed.

2.3.1 Trends in incidence rates of sudden cardiac death

A limited number of studies have investigated trends in incidence rates of SCD, including two in North America, two in Europe, and one in Asia. In the United States, trends in incidence rates of SCD were studied between 1989 and 1998 using national mortality data, with SCD defined as deaths occurring outside of hospital or in the emergency room with the underlying cause of death being cardiac disease.[79] This study reported the declines in age-adjusted SCD rates of 11.7% for men and 5.8% for women over the 10 years.[79] This was further supported by the declining trends observed in a community-based study, the Framingham Heart Study.[20] This Framingham Heart Study used multiple data sources with SCD defined by a physician panel as an IHD death that occurred within one hour of the onset of symptoms and no other probable cause of death was suggested in the medical record.[20] This study reported long-term declines in SCD incidence rates for four time periods, 1950 to 1969, 1970 to 1979, 1980 to 1989, and 1990 to 1999.[20] The overall age- and gender-adjusted SCD rates declined by 49%, comparable to the decreases in IHD death (59%) and non-sudden IHD death (64%).[20] Declining trends were observed in men and women, in subjects with and without a prior history of IHD, and in smokers and non-smokers.[20]

Two other studies conducted in Europe also supported the decreasing trend in SCD incidence rates. The Northern Sweden MONItoring of trends and determinants in CArdiovascular disease (MONICA) study defined SCD as instantaneous death caused by heart disease that occurred within one hour of the onset of symptoms. Multiple data sources were used in this study for case ascertainment.[93] An
annual statistically significant decrease of 1.8% in the incidence rate of SCD was seen in men (95% CI 3.2% to 0.3%) but not in women (-1.0%, 95% CI -4.4% to 2.4%) from 1985 to 1999.[93] A small number of SCD cases observed in the younger age groups particularly in women were acknowledged.[93] Age restriction was imposed as the MONICA study recruited patients with acute myocardial infarction aged below 65 years of age.[93]

A study conducted in Rotterdam, the Netherlands reported a decreasing trend in SCD incidence rates in the middle to older age groups (≥45 years), where two subcohorts were observed in two periods using mortality data and medical records if available.[94] The annual decline in the age- and sex-adjusted incidence rate was 3.6% (95% CI 1.8% to 5.1%).[94] Decreasing trends in age-adjusted incidence rates were observed in both men and women.[94] An overall decreasing risk of SCD with a sex- and age-adjusted hazard ratio was 0.6 (95% CI 0.4 to 0.8).[94] More healthy individuals were found in the first subcohort in 1990-2000, which might not reflect the real estimates of decline in the incidence rates of SCD.

One study in Asia, the Circulatory Risk in Communities Study in Japan showed a slightly different trend compared to the previously described studies.[22] This study, which used multiple data sources, reported a decreasing trend in the period 1981-1995 but the trend was then unchanged from 1996 to 2005.[22] This study showed the incidence rates of SCD declined from 76.0 per 100,000 person-years in the period 1981-1985 to 36.8 per 100,000 person-years in the period 2001-2005.[22] Age-adjusted annual rate reductions, however, were not reported.[22] The decline in SCD incidence rates were in parallel with falls in the prevalence of hypertension and smoking from 1981 to 1995.[22] The incidence rates of SCD plateaued from 1996 to 2005 when the prevalence of hypertension was stable, the prevalence of diabetes grew, and the prevalence of smoking decreased.[22]

In summary, an obvious declining trend in the incidence rates for SCD was observed in the studies before the 1990s. Contemporary evidence suggests a continuing decline. However, it is not yet
conclusive due to the limited number of studies available. Further research is warranted to confirm the trends.

### 2.3.2 Other trends studies related to sudden cardiac death

As few studies on the trends in SCD were available, other studies on out-of-hospital cardiac arrest, sudden IHD death, and sudden cardiovascular death were reviewed for some insights. A study in Perth, Western Australia on out-of-hospital cardiac arrest was conducted using the data from the emergency medical service where resuscitation and advanced life support were provided in the Perth region, covering an area of over 5,300 km².[85] This study reported declining incidence rates of out-of-hospital cardiac arrest from 1997 to 2010, with 95% of the cases having presumed cardiac aetiology.[85]

The Atherosclerosis Risk in Communities (ARIC) study on sudden IHD death study in the United States, where residents aged 35-74 years in four communities from 1987 to 2004 were assessed.[95] This study showed a statistically significant decline in the incidence rates of sudden IHD death in men only, possibly attributable to better primary and secondary prevention.[95] However, it was also reported that there was a greater decrease in incidence rates in those with prior IHD (58%) than those without (31%).[95] The reasons for the greater reduction observed in those with established IHD rather than those without and no statistically significant change in women’s incidence rates were unclear, warranting further research.[95]

A Polish study of sudden cardiovascular death using government statistics was conducted from 2003 to 2008. Sudden cardiovascular death included SCD (ICD-10 code I46.1), sudden death, cause unknown (R96), and IHD deaths (I20-I25).[96] This study reported a significantly increasing trend in the incidence rates of sudden cardiovascular death in 14 out of 16 voivodeships (administrative subdivisions of Poland) and an obvious reduction in mortality rate attributed to IHD in almost all voivodeships.[96] The authors concluded that the mortality rates due to sudden cardiovascular death
were overestimated whereas the mortality rates due to IHD were underestimated because sudden
death with unknown cause was included.[96] As acknowledged by the authors, the discordant results
may be attributable to difficulties of determining the cause of death and a lack of coding guidelines on
the cause of death where there were regional disparities in the approach to coding cause of death.[96]

To summarise, the studies on trend in out-of-hospital cardiac arrest, sudden IHD death, and sudden
cardiovascular death suggested slightly different trends although most reported a declining trend.
Inconsistent results may be attributable to different outcome measures (out-of-hospital cardiac arrest,
sudden IHD death, and sudden cardiovascular death).
## Table 2.2. Summary of trends in incidence rates of sudden cardiac death

<table>
<thead>
<tr>
<th>Study</th>
<th>Terminology used in each study</th>
<th>Study period</th>
<th>Age included (years)</th>
<th>Data source</th>
<th>Annual change in mortality rate (%; 95% confidence interval)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham Heart Study[20]</td>
<td>SCD</td>
<td>1950-1999</td>
<td>28-62</td>
<td>Multiple sources: hospital records, primary medical doctor records, and next-of-kin interviews</td>
<td>-1.2%, (-0.6%, -1.7%) (males)† -1.2%, (-0.2%, -1.9%) (females)†</td>
</tr>
<tr>
<td>United States[79]</td>
<td>SCD</td>
<td>1989-1998</td>
<td>≥35</td>
<td>Single sources: death certificates</td>
<td>-1.2% (males)‡ -0.6% (females)‡</td>
</tr>
<tr>
<td>Northern Sweden[93]</td>
<td>SCD</td>
<td>1985-1999</td>
<td>35-64</td>
<td>Multiple sources: medical history, symptoms, electrocardiography, and cardiac enzymes</td>
<td>-1.8% (males)‡ -1.0% (females)‡</td>
</tr>
<tr>
<td>Japan[22]</td>
<td>SCD</td>
<td>1981-2005</td>
<td>30-84</td>
<td>Multiple sources: death certificates, medical records, ambulance records, and next of kin reports</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rotterdam, the Netherlands[94]</td>
<td>SCD</td>
<td>1990-2010</td>
<td>≥45</td>
<td>Multiple sources: death certificates and medical records</td>
<td>-3.6%, (-1.8%, -5.1%)†</td>
</tr>
<tr>
<td>Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, United States [95]</td>
<td>Sudden coronary heart disease deaths</td>
<td>1987-2004</td>
<td>35-74</td>
<td>Multiple sources: death certificates, information from next of kin, certifying and family physicians, and coroner or medical examiners</td>
<td>-3.2%, (-2.6%, -3.7%) (with history of IHD)† -1.7%, (-0.7%, -2.5%) (without history of IHD)†</td>
</tr>
<tr>
<td>Perth, Western Australia[85]</td>
<td>Out-of-hospital cardiac arrest</td>
<td>1997-2010</td>
<td>All</td>
<td>Single sources: emergency medical service</td>
<td>Not reported</td>
</tr>
<tr>
<td>Poland[96]</td>
<td>Sudden cardiovascular death</td>
<td>1997-2008</td>
<td>25-64</td>
<td>Single sources: official governmental statistical data</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*changes in incidence rates have been summarised as annual changes; where changes for the overall study period were reported, these data have been included in the Section 2.3.1.
†recalculated according to the findings reported from the literature.
‡95% confidence interval for changes in mortality rates was not reported.
§changes in mortality rates were reported as statistically significant.

SCD, sudden cardiac death.

### 2.3.3 Trends in age-specific rates of sudden cardiac death

Different trends in age-specific rates of SCD have been reported in a few population-based and community surveillance studies.[22, 79, 93] Different decreasing trends in SCD incidence rates have been shown in younger and older age groups, with the greatest declining trend in the middle age group (55-64 years).[22, 79, 93] However, not all studies involved all age groups. The Northern Sweden MONICA study restricted the upper age limit at 64 years.[93] The Circulatory Risk in Communities Study in Japanese communities included people up to 74 years and started from 30
years of age.[22] The United States state-wide study started from 35 years with no upper age limit.[79]

Younger adult age groups (35-44 years of age) have generally shown a small decline or no decline in SCD incidence rates over the past two to three decades and expressed different rate reductions in men and women. In a state-wide study of the United States adult population from 1989 to 1998, SCD incidence rates for 35-44-year-old men declined less than all other age groups whereas women had an increase of 21% in SCD incidence rates for the same age group.[79] Except for the age of 35-44 years, women’s decline in SCD incidence rates was much less than men’s.[79] The biggest rate reduction was found both in 55-64-year-old men and women.[79] The authors suggested that differences in risk factors, symptoms, and outcomes of CVD among men and women may account for the age and gender differences observed.[79] In contrast, the Northern Sweden MONICA study from 1985 to 1999 showed that statistically significant decreases in SCD incidence rates were small and only observed in the 55-64-year-old men possibly due to the small sample size and lack of statistical power of the study.[93] Contemporary studies are warranted to identify the age- and sex-specific trends in SCD.

2.4 Predictors for sudden cardiac death

Numerous predictors of SCD are poorly understood. Available evidence indicates the pathogenesis of SCD is complex and multifactorial. In this section, socio-demographic factors, traditional behavioural and biomedical risk factors, clinical predictors (including medical conditions of heart and circulatory system) are discussed. Cardiac procedures are also presented as they may modify the predictors of SCD and/or have a protective effect on SCD. Medical therapy is broadly reviewed as well as current attempts to alleviate occurrence of SCD in patients regarded as at-high risk.
2.4.1 Socio-demographic factors

Age, sex, and race are non-modifiable CVD risk factors which have been observed to increase the risk of SCD.[17, 97] A general increase in incidence rates of SCD with age has been observed regardless of sex or race,[17, 97] although a peak in incidence rates is observed in infancy and middle adulthood (ages 45-65 years).[17, 98, 99] Compared to men, women had a lower incidence rate of SCD at any age.[100] In middle-aged men, the risk of SCD was four times the risk in women of the same age.[100] However, this difference in risk of SCD between men and women narrows with increasing age.[101]

Sudden cardiac death appears to be more common in some races. African American adults were more likely to succumb to SCD compared to Caucasians.[97, 102] The reasons for this may be multifactorial and likely because African Americans have higher prevalence of traditional cardiac risk factors including hypertension, diabetes, and IHD.[103, 104] African American post-menopausal woman was independently associated with increased risk of SCD.[28] Together with genetic predisposing factors,[105] African Americans having less chances to access cardiac health care may have a substantial impact on the likelihood of SCD in this subgroup of African Americans.[106, 107] Furthermore, African Americans are known to have lower rates of receiving post-resuscitation care.[106, 107] In another state-wide study in the United States, the African American population was reported to have the highest age-adjusted rates for SCD, followed by white, American Indians/Alaska Native, and Asian/Pacific Islander populations.[79] The significant under-reporting of American Indian/Alaskan Native or Asian/Pacific Islander race or of Hispanic ethnicity on death certificates and census population may have led to underestimates of SCD in these groups.[79]

Economic disadvantage may contribute in part to the higher incidence rate of SCD in some races such as African Americans compared to Caucasians.[108] While the relative high risk of SCD in some races has been correlated with socioeconomic factors in a complex way, it is challenging to separate socioeconomic factors from a real genetic susceptibility in different races.[105, 107, 109]
Nonetheless, the association between socioeconomic disadvantage and increased risk of SCD has also been attributed to differences in access to primary care and emergency medical services.[110, 111]

### 2.4.2 Biomedical factors

A range of biomedical risk factors have been linked to SCD, including obesity, high blood pressure, high blood cholesterol, and diabetes. However, there is a disparity in evidence of the association between these biomedical risk factors and SCD. Diabetes is presented in section 2.4.4.4 under medical conditions.

The risk of SCD in obese patients is almost double that of age-matched controls.[112, 113] Ventricular tachycardia is thought to be the most common mechanism in obese people who succumb to SCD.[114, 115] There is a direct association between abdominal obesity and increased risk of SCD, and still an association between obesity and SCD after adjustment for potential mediators (such as hypertension, diabetes, lipid profile, previous IHD, heart failure, and left ventricular hypertrophy).[116] It appears that obese people have a range of risk factors for CVD which increase the risk of SCD. However, the association between body mass index (BMI) as a measure of obesity and SCD is not conclusive. The Nurse’s Health Study reported obese women (BMI ≥30 kg/m²) had a significantly increased risk of SCD[29] whereas the Women’s Health Initiative clinical trials and observational study did not show a significant association between BMI (BMI ≥30 kg/m²) and SCD.[28]

High blood pressure is an independent risk factor for SCD,[117] although high blood pressure often coexists with obesity and left ventricular hypertrophy.[112, 118, 119] In patients with high blood pressure who are not obese, normal cardiac output with high systemic vascular resistance results in left ventricular hypertrophy, increasing the risk of SCD.[120] Experimental and clinical studies have also shown that patients with high blood pressure and/or left ventricular hypertrophy are more likely
to develop life-threatening ventricular arrhythmias that result in SCD.[121, 122] Several community-based studies have confirmed high blood pressure as an independent predictor of SCD.[27, 30]

The evidence regarding the link between high blood cholesterol and SCD remains inconclusive. Early studies in the 1990s showed that in both American and Japanese cases of SCD, concentrations of cholesterol were significantly higher than in cases of non-SCD.[123, 124] More recently, both the Physician’s Health Study and the Nurse’s Health Study have shown that high blood cholesterol does not increase the risk of SCD.[29, 125] while some studies have shown that lowering cholesterol does not appear to be an effective way of reducing SCD.[126-128] However, a meta-analysis which included 10 randomised controlled trials enrolling 22,275 patients from 1966 to 2006 showed statin treatment reduced the risk of SCD by 19%.[129]

### 2.4.3 Behavioural factors

Behavioural factors linking to SCD include cigarette smoking, excessive alcohol intake, vigorous physical activity, and some dietary factors. A large and growing body of epidemiological studies have reported current cigarette smoking increased the SCD risk by at least 50%.[27-29, 130] Current smokers versus never smokers had a significantly increased association with the risk of SCD.[130] However, the Bezafibrate Infarction Prevention Trial indicated risk of SCD among smokers with established IHD did not increase with the number of cigarettes smoked per day.[130] By contrast, the Framingham study showed there was linear correlation between the number of cigarettes smoked per day and the SCD risk in men without a prior history of IHD.[131] Dose-response relationships were further confirmed by the Nurse’s Health Study that heavy current smoking (≥25 cigarettes per day) was a strong risk factor for SCD in women overall and those before versus after age 60 years.[29] In addition, cessation of smoking was shown to be associated with a lower incidence rate of SCD among individuals with or without recognised IHD.[131-134]
Different amount of alcohol consumption has a differential effect on the risk of SCD.[135-138] The effect of excessive alcohol intake (>30g/day) has been well established by increasing the risk of SCD by 100% in early studies in the 1980s.[135, 136] In contrast, the beneficial effect of light-to-moderate alcohol consumption (5.0-30.0g/day) has been studied.[30, 139, 140] Three large cohort investigations in men indicated light (5.0-15.0g/day) to modest (15.1-30g/day) consumption reduced the risk of SCD up to 80%.[30, 139, 140] Light-to-moderate alcohol (5.0-30.0g/day) consumption may be protective against serum lipid accumulation, plaque rupture, and inflammation, thus reducing the risk of SCD.[141] Long-term acute intake of alcohol may also influence the risk of SCD. A U-shaped relationship between light-to-moderate alcohol intake was observed in a four-year follow-up of the analysis from the Nurse’s Health Study which found that light-to-moderate (5.0-30.0g/day) alcohol drinkers had a 40% lower risk of SCD and higher intake (>30g/day) drinkers had no significant increase in risk.[142] The 10-year follow-up Women’s Health Initiative clinical trials and observational study later confirmed this finding.[143]

Physical activity has been found to have both favourable and harmful impacts on SCD risk.[144-146] The beneficial effects of regular moderate exercise on reduced risk of SCD may be related to electrophysiological effects through the sympathetic nervous system and increased cardiac electrical stability.[147] The negative impact of exercise on SCD may relate to the underlying cardiac disease and is worse in older individuals with established cardiac disease.[148] In children, adolescents, and young adults, congenital cardiac abnormalities may be the major cause of SCD whereas in older adults, atherosclerotic disease may be the underlying trigger.[149, 150] Three early studies conducted in the 1980s restricted to men of specific age groups (30-64 year,[151] 40-84 years,[152] 25-75 years[153]) examined the relationship between heavy physical activity and SCD.[151-153] These three studies indicated that people engaged in vigorous activity (such as calisthenics, running jogging, and rope jumping) had at least seven times of the risk of SCD (due to IHD) compared to those performing non-vigorous activity.[151-153] A community-based study conducted in the 1990s, which included adult men and women of all ages, and examined the relationship of a range of physical activities such as sleep, light, moderate and heavy activities, found the opposite, although the
definitions of the outcome were similar (sudden death due to IHD versus CAD).[150] This study showed most SCD (due to CAD) events (80%) occurred when people were taking part in light physical activity or were asleep.[150]

Some dietary factors have been found to protect against SCD whereas some others increased the risk of SCD. Fish consumption and nut intake appear to have a protective effect for SCD although studies on the underlying mechanism of their protection against SCD are scarce.[154] Two studies have reported a 50% reduced risk of SCD in people who consumed fish at least once per week,[155, 156] possibly because n-3 polyunsaturated fatty acids found primarily in fish may be antiarrhythmic and therefore protective against SCD.[154, 157] Another study showed consuming nuts two or more times per week reduced SCD risk by 147% in a cohort of 21,454 United States male physicians followed up for an average of 17 years.[158] Folic acid, phytochemicals, and other compounds found in nuts may be responsible for these protective effects.[159] By contrast, the Cardiovascular Health Study showed plasma trans fatty acids were associated with greater risk of SCD.[160] The Nurses’ Health Study reported higher dietary intake of trans fat was associated with an elevated risk of SCD among women with prior IHD only.[161] The association between trans fat and SCD is broadly suggested by a recent meta-analysis which included 41 prospective cohort studies from 1981 to 2014 which showed saturated facts had no association with all-cause mortality, CVD mortality, and IHD mortality, but total and industrial trans fats were associated with CVD mortality and IHD mortality.[162]

In summary, current data on the association between behavioural factors and SCD are not conclusive. Obtaining these data often require risk factor surveillance in a community or a primary care setting which are often not available from administrative health data.
2.4.4 Medical conditions

The risk of SCD increases with age as discussed in section 2.4.1 and SCD therefore becomes a major cause of mortality in elderly individuals who may have multiple pre-existing medical conditions. Medical conditions either at the myocardial or vascular level (such as myocardial infarction, heart failure, and peripheral artery disease) or conditions related to CVD (such as diabetes and chronic kidney disease) outline the extent of disease among individuals who have a higher clinical risk of succumbing to SCD. In this section, current evidence of SCD predictors is presented and the underlying mechanism is outlined.

2.4.4.1 Ischaemic heart disease

Ischaemic heart disease is associated with substantially increased risk of SCD.[28-31] The potential underlying mechanisms of SCD occurring in patients with IHD are: first, during or in the early phase after myocardial infarction (usually in the first 28 days), acute ischaemia and infarction precipitating polymorphic ventricular tachycardia or ventricular fibrillation lead to arrhythmic SCD.[26] Second, myocardial rupture, recurrent ischaemia, and extensive re-infarction cause non-arrhythmic SCD.[163] This phenomenon usually occurs between the first 28 days and six months after myocardial infarction.[164] Third, in the later phase (after the first 28 days to many years), ventricular remodelling, ischaemic cardiomyopathy, and the evolution of heart failure result in macro re-entrant ventricular tachycardia and/or pulseless electrical activity.[41, 165]

A range of observational studies have demonstrated pre-existing IHD or myocardial infarction to be a strong predictor of SCD.[28-31] The British Regional Heart Study which recruited 7,735 men aged 40 to 59 years old from 1978 to 1980 showed prior IHD was associated with a five-fold increased risk of SCD over eight-year of follow-up.[30] However, myocardial infarction as a significant component of IHD[41] is the main culprit in the SCD risk increase. This is supported by the Women’s Health Initiative clinical trials and observational study, which recruited 161,808 women aged 50-79 years old from 40 clinical sites across the United States from 1993 to 1998 and followed until 2009.[28] This
study showed previous myocardial infarction had a four times higher risk of SCD compared to those without this condition whereas prior IHD (excluding myocardial infarction) was not associated with SCD.\cite{28} Two other observational studies confirmed a marked increase in SCD risk was conferred by previous myocardial infarction although previous IHD (not including myocardial infarction) as a covariate was not examined in these two studies.\cite{29, 31}

2.4.4.2 Heart failure

The presence of heart failure causes a marked increase in SCD risk.\cite{28, 166, 167} The mechanisms of SCD in patients with heart failure are complex and generally developed in two stages. First, the process of cardiac remodelling in heart failure involves cellular changes in the myocardium, peripheral circulatory responses, and neurohormonal activation.\cite{168} All these responses provide the milieu for arrhythmogenesis.\cite{169} Second, changes from the former stage of cardiac remodelling lead to the stage of electrical remodelling in heart failure.\cite{168} In this stage, prolongation of the action potential and changes in calcium homeostasis cause polymorphic ventricular tachycardia.\cite{168} Active membrane and altered network properties may cause conduction delay and block and finally result in monomorphic ventricular tachycardia.\cite{170}

There is clear evidence that heart failure is a strong predictor of SCD.\cite{28, 166, 167} The Women’s Health Initiative clinical trials and observation study showed heart failure was associated with a 3.5-fold elevated risk of SCD in a large cohort of women aged 50 to 79 years in the United States.\cite{28} Two multinational randomised controlled trials of anticoagulation in established atrial fibrillation patients aged ≥65 years old showed heart failure increased the risk of SCD by approximately 2-fold.\cite{166, 167} However, the randomised controlled trial of prophylactic implantable cardioverter-defibrillator in myocardial infarction patients aged 18 to 80 years reported heart failure was not associated with the increased risk of SCD.\cite{171}
2.4.4.3 Arrhythmias

Arrhythmias considered as a candidate predictor in this thesis include ventricular tachycardia, ventricular fibrillation, and cardiac arrest. The mechanisms of SCD from arrhythmias are related to an abnormal underlying cardiac substrate, which causes electrical instability initiating fatal arrhythmias.[77] The pathophysiology involved in lethal arrhythmias appears that ventricular tachycardia develops into ventricular fibrillation and then to cardiac arrest.[172] Ischaemic heart disease is the common recognised structural heart disease providing the abnormal substrate.[4] Two forms are recognised in the triggering mechanisms in patients with IHD: acute myocardial ischaemia regardless of previous myocardial infarction; and silent myocardial ischaemia without clinical apparent myocardial infarction but with an anatomical evidence of scar from an old infarction.[173, 174] Although the mechanism of SCD induced by arrhythmias (including ventricular tachycardia, ventricular fibrillation, and cardiac arrest) is clear,[174, 175] few studies examine arrhythmias as a potential predictor of SCD.[30] The British Regional Heart Study reported arrhythmias were associated with a 2.5-fold increased risk of SCD in a cohort of men aged 40 to 59 years old from 1978 to 1980.[30]

2.4.4.4 Diabetes

There is inconsistent evidence from observational studies showing diabetes is associated with SCD although the mechanism for the association between diabetes and SCD has not been elucidated. Six possible mechanisms link diabetes and SCD and include: (i) cardiovascular autonomic neuropathy,[176-178] (ii) reduction in cardiac adenosine triphosphate sensitive potassium repolarizing currents,[179, 180] (iii) silent myocardial ischaemia for cardiac events,[181-183] (iv) attenuated ischaemic preconditioning effect,[184] (v) diabetic cardiomyopathy,[185-187] and (vi) alterations in the properties of L-type Ca\(^{2+}\) channels.[188] Other diverse pathophysiological changes linked with diabetes may also contribute to the increased risk of SCD. However, there is insufficient data to determine the contributions that any of these mechanisms play in elevated risk of SCD in patients with diabetes.
Observational studies reporting on the association between SCD and diabetes are summarised as follows. A recent meta-analysis of data from 14 observational studies reported on diabetes and risk of SCD from 1995 to 2013.[189] This study showed patients with diabetes had twice the risk of SCD compared to those without diabetes after adjusting for cardiovascular risk factors and/or electrocardiograph variables.[189] Community-based studies conducted in the United States and Japan showed medical history of diabetes was an independent predictor of SCD.[27-29] Further, impaired glucose tolerance has been shown to be associated with increased risk of developing SCD.[89, 190, 191] For example, the relative risk of SCD is 160% for individuals with impaired glucose tolerance but increases to 208% for patients with diabetes.[191]

By contrast, the CArdiovascular disease research using LInked Bespoke studies and Electronic health Records (CALIBER) programme recruited 1,921,260 individuals aged ≥30 years old in England between 1998, and 2010.[192] This study reported that type 2 diabetes was not associated with arrhythmias or SCD and indicated there may be interplay between IHD, diabetes and SCD.[192] In the British Regional Heart Study, diabetes was not found to be significantly associated with SCD after age adjustment and therefore was not tested in the multivariable model.[30]

### 2.4.4.5 Atrial fibrillation

There is inconsistent evidence of an independent association of atrial fibrillation with an increased risk of SCD. Two possible mechanisms may explain the association between atrial fibrillation and SCD: first, atrial tachycardia occurring in atrial fibrillation patients may induce rapid ventricular rates and directly cause ventricular refractoriness reduction, finally leading to ventricular tachycardia.[193, 194] Second, irregular rhythm of atrial fibrillation may trigger short-long-short ventricular sequences which may be proarrhythmic in its intrinsic nature.[195, 196]
The Women’s Health Initiative clinical trials and observational study, which recruited postmenopausal women aged 50 to 79 years in the United States from 1993 to 1998, demonstrated self-reported atrial fibrillation was not found to be significantly associated with increased risk of SCD.[28] However, some studies on myocardial infarction, heart failure, hypertensive patients or in the general population have shown that atrial fibrillation was significantly associated with an elevated risk of SCD. Specifically, the TRAndolapril Cardiac Evaluation (TRACE) study which recruited acute myocardial infarction patients from 1990 to 1992 in Denmark showed that the presence of atrial fibrillation (diagnosed by electrocardiogram) during the hospital stay of acute myocardial infarction increased the risk of SCD.[197] The TRACE study did not consider the prescription patterns of pharmacological treatment of IHD such as angiotensin converting enzyme inhibitors and beta blockers and introduction of invasive medical procedures which may have changed considerably the risk of SCD in the patients following myocardial infarction.[197] Consistent with the result of the TRACE study, a study which recruited acute myocardial infarction patients from three intensive care units in Italy between 1995 and 1998 showed that new onset (occurring within seven days of hospital stay) or permanent atrial fibrillation (diagnosed by electrocardiogram) increased the risk of SCD.[198]

The association between atrial fibrillation and SCD observed in heart failure patients appeared to relate to the extent of heart failure, classified by the New York Heart Association (NYHA) Functional Classification.[199] This classification categorises heart failure patients from class I to IV according to how much they are limited during physical activity and varying levels in shortness of breath and/or angina.[199] A study of 390 advanced heart failure patients (NYHA III or IV, the majority of whom were candidates for heart transplantation in the United States from 1983 to 1990) reported atrial fibrillation (diagnosed by electrocardiogram at enrolment) to be an independent marker for increased risk of SCD.[200] However, another study in 1,427 heart failure patients with NYHA II or III in the United States from 1980 to 1985 showed new onset or permanent atrial fibrillation (determined by retrospective review of electrocardiogram and hospital charts) was not associated with SCD.[201]
In lower-risk individuals including patients with hypertension and the general population, evidence has been presented to support the notion that atrial fibrillation was predictive of SCD. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study recruited 8,831 hypertensive patients and defined new onset atrial fibrillation as occurring during the follow-up period after enrolment and diagnosed by electrocardiogram, excluding those with history or presence of atrial fibrillation at enrolment.[202] This study showed new onset atrial fibrillation was independently associated with increased risk of SCD.[202] The Circulatory Risk in Communities Study recruited men and women aged 30-84 years in Japan between 1975 and 2005 and defined atrial fibrillation in annual cardiovascular risk surveys which was diagnosed by electrocardiogram.[27] This study showed atrial fibrillation (including new onset and permanent) had borderline association with SCD.[27]

However, the association between atrial fibrillation and SCD appears to be mediated or confounded by shared common determinants such as heart failure.[203, 204] A history of heart failure may partially explain the association between history of atrial fibrillation (determined by past records of patients as noted by a physician or electrocardiogram) and SCD as shown in the Oregon Sudden Unexpected Death Study.[203] In the multivariable analysis without adjustment for heart failure, atrial fibrillation was a significant marker of SCD whereas after adjusting for heart failure, this association was no longer significant.[203] These findings were further examined in the aggregation study of two population-based prospective cohorts (the Atherosclerosis Risk in Communities study and Cardiovascular Health Study).[204] New onset atrial fibrillation which was determined by electrocardiogram and hospital discharge records was significantly associated with SCD.[204] The significant association between atrial fibrillation and SCD was further confirmed by the analysis conducted in the cohort from the Atherosclerosis Risk in Communities study only.[204] Additional studies are required to confirm the association in a broader population as suggested by the authors because atrial fibrillation was also associated with an increased risk of non-SCD.[204]
Some evidence mentioned in this section suggests there is an association between atrial fibrillation and SCD. However, the source for the diagnosis of atrial fibrillation (self-report versus electrocardiogram records or discharge records), the type of atrial fibrillation (new onset versus permanent) involved in the study, and whether patients with history of atrial fibrillation were included may have influenced the observation on the association.

2.4.4.6 Chronic obstructive pulmonary disease

Emerging data indicate that chronic obstructive pulmonary disease is associated with elevated risk of SCD,[205-207] although the underlying mechanisms are not fully established to date in terms of the increased risk of SCD in patients with chronic obstructive pulmonary disease. First, chronic obstructive pulmonary disease may cause pathological changes in cardiac repolarisation leading to the abnormalities of QT or QTc interval and increase sympathetic tone.[207-211] All these changes are associated with cardiac electrical instability, thus causing cardiac arrhythmia.[208, 210, 212] Second, the pathogenic pathway of increasing SCD risk by systemic low-grade inflammation has been studied.[207, 213] Systemic low-grade inflammation is strongly associated with moderate to severe (but not mild) chronic obstructive pulmonary disease.[214]

Some evidence has shown that chronic obstructive pulmonary disease could be a critical predictor of SCD.[205-207] The Rotterdam study which recruited 14,926 general population aged ≥45 years since 1990 demonstrated chronic obstructive pulmonary disease was associated with a two-fold increased risk of SCD.[207] The risk increased in the 5 years after the diagnosis of chronic obstructive pulmonary disease.[207] This finding of the association between chronic obstructive pulmonary disease and SCD was confirmed by two other community-based studies.[205, 206] Specifically, the Oregon Sudden Unexpected Death Study which recruited 728 SCD cases and 548 controls with CAD from 2002 to 2013 reported chronic obstructive pulmonary disease conferred a similar SCD risk (odd ratio 2.2) compared to the Rotterdam study.[205] The AmsteRdm REsuscitation Study (ARREST) recruited 1,310 sudden cardiac arrest cases and 5,793 controls without sudden cardiac arrest from
2005 to 2008 showed obstructive pulmonary disease increased the risk of SCD by 40%.[206] In addition, the randomised controlled trial, the Valsartan in Acute Myocardial Infarction Trial (VALIANT) of valsartan, captopril or both which recruited 14,703 patients with myocardial infarction reported chronic obstructive pulmonary disease increased the risk of sudden death, non-cardiovascular death, and all-cause death.[215] Sudden death was considered as an endpoint in this trial including a wide range of underlying cause of death more than the cause of cardiac origin such as acute respiratory failure.[215]

2.4.4.7 Chronic kidney disease

There is inconclusive evidence on whether the risk of SCD in patients with chronic kidney disease increased independent of documented CVD. The underlying mechanism(s) of SCD in patients with chronic kidney disease are complex and unclear as there may be an interaction between a transient event and underlying substrate. The process of precipitating SCD in patients with chronic kidney disease is hypothesised as follows: (i) ischaemia, sympathetic activation, and inflammation as the pathophysiologic triggers,[216-218] (ii) structural remodelling induced by myocardial fibrosis, vascular calcification, and endothelial dysfunction,[219, 220] (iii) electrophysiologic remodelling, including slowing of conduction velocity and heterogeneous zones of repolarization,[221, 222] and (iv) dialytic triggers (electrolyte shifts and high blood pressure).[223, 224]

The heart and estrogen/progestin replacement study which recruited post-menopausal women with IHD in the United States suggested individuals with moderate levels of estimated glomerular filtration rate had a higher risk of SCD as compared with those with normal kidney function.[31] This finding was supported by another observational study which recruited patients who underwent cardiac catheterization at a single academic institution in the United States.[225] The risk for SCD increased 11% by each 10 ml/min decrement in estimated glomerular filtration rates.[225] Although few studies available demonstrated chronic kidney disease as an independent risk factor of SCD, many data indicated patients with chronic kidney disease have higher mortality rates even after adjustment.
for common comorbidities such as age, diabetes, and prior CVD.[226-228] Some other studies suggested chronic kidney disease may act as a risk multiplier in patients who were hospitalised with CVD including patients with myocardial infarction and those with heart failure.[229-232]

### 2.4.4.8 Peripheral artery disease

A limited number of data available suggest peripheral artery disease is an independent predictor of SCD.[167, 233] The mechanism linking peripheral artery disease and SCD remains poorly understood and may not be direct. The potential mechanism is likely to be associated with the underlying ischaemia of thrombotic origin[234] and inflammation.[235] Clinical practice has demonstrated patients with peripheral artery disease have a very high cardiovascular risk which was higher than that in patients with CAD or stroke in some studies.[236-239] Peripheral artery disease was more strongly predictive of cardiovascular death and all-cause death than prior myocardial infarction.[240] Notably, unlike CAD and stroke, traditional risk factors and prior cardiac or cerebral ischaemic events have less impact on the elevated cardiovascular risk conferred by peripheral artery disease.[241-245] Therefore, peripheral artery disease is suggested to be a predictive indicator.[243, 246, 247]

Evidence was obtained from the pooled cohort study of individual data from four clinical trials where 48,286 post non-ST-segment elevation acute coronary syndrome patients were included, showing history of peripheral artery disease to be an independent marker of SCD.[233] The association between prior peripheral artery disease and the increased risk of SCD was confirmed by the multinational randomised controlled trial of anticoagulation in established atrial fibrillation patients aged ≥65 years old.[167] In contrast, there was an increased risk of all-cause mortality or cardiovascular mortality but not specific to SCD observed in patients with acute coronary syndrome with a concomitant peripheral artery disease[248] and in older adults with systolic hypertension.[249] Some other studies showed peripheral artery disease altered heart rate variability[250] suggesting
patients with peripheral artery disease were at risk for advancing life-threatening ventricular arrhythmias based on the 2006 guidelines for the prevention of SCD.[8]

### 2.4.4.9 Stroke

A limited number of studies have examined whether there is a concurrence of relationship between SCD and acute stroke and whether a cause-effect relationship exists. Some mechanism(s) have been proposed in linking stroke and SCD although they have not been fully characterised. Five possible mechanisms include: (i) cardiac damage as a result of the underlying or undetected coronary disease in stroke patients;[251, 252] (ii) autonomic dysfunction after acute stroke causing elevated sympathetic tone;[253-255] (iii) neurogenic cardiac damage by cardiac myofibrillar degeneration and contraction band necrosis in cardiac nerves;[256, 257] (iv) electrical stimulation of insular cortex in insular stroke;[258-260] and (v) elevated cardiac enzymes (such as creatine kinase, creatine kinase-MB, and myoglobin) after acute stroke.[261, 262] All these changes either serve as substrate for ventricular arrhythmia, or involve the cardiac conduction system thus possibly increasing vulnerability of arrhythmogenesis.[263]

A large meta-analysis which included 39 studies with a total of 66,000 patients with a mean follow-up of 3.5 years demonstrated patients with transient ischaemic attack and ischaemic stroke had a higher risk of non-stroke vascular death.[264] In patients with stroke, there was a high prevalence of cardiac disease and risk factors of IHD.[265, 266] These underlying cardiovascular comorbidities increased the risk of cardiac morbidity and mortality after stroke.[267, 268] Further, abnormal electrocardiograms and cardiac arrhythmias were observed in 50%-70% of patients after acute stroke including ischaemic and haemorrhagic strokes.[269, 270] The patterns of abnormalities were from abnormal T waves to fatal arrhythmias such as ventricular fibrillation that caused SCD.[267, 268]

In a summary, the association between SCD and myocardial infarction or SCD and heart failure is established whereas the association between SCD and atrial fibrillation or SCD and diabetes is
inconclusive, warranting additional studies to confirm the relationship. Contemporary studies are few on examining the association between SCD and chronic kidney disease, SCD and chronic obstructive pulmonary disease, SCD and peripheral artery disease, or SCD and stroke although there are potential mechanisms to indicate their association, thereby requiring more research.

2.4.5 Implantable cardioverter defibrillator therapy

Implantable cardioverter defibrillator therapy is designed to reduce all-cause mortality and prevent SCD in patients with left ventricular dysfunction.[271] It works by keeping track of the heart rate and rhythm. Upon detection of abnormal heart rhythm, an electrical shock will be delivered to restore normal heartbeat.[272] The mortality benefit has been observed in heart failure patients (SCD-HeFT trial),[273] in patients with reduced left ventricular systolic dysfunction (Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II)),[274] and in patients with non-ischaemic dilated cardiomyopathy (DEFibrillator In Non-Ischaemic cardiomyopathy treatment Evaluation (DEFINITE) trial). [275] Specifically, in SCD-HeFT trial where patients received an implantable cardioverter defibrillator, the risk of all-cause death decreased one-fourth and arrhythmic SCD decreased by 60%.[276] This finding concurred with the result from MADIT-II.[274, 277] The DEFINITE trial also reported a significant decline in the risk of arrhythmic SCD but a non-significant reduction in the risk of all-cause death.[275] Given this device is highly effective at intervening SCD caused by ventricular arrhythmias, it may have altered the risk profiles of SCD in patients with left ventricular systolic dysfunction and heart failure. Further research on predictors of SCD should consider the impact of the implantable cardioverter defibrillator therapy.

2.4.6 Coronary revascularisation

There is cumulating evidence that coronary revascularisation (percutaneous coronary intervention or coronary artery bypass graft surgery) can considerably reduce the risk of SCD in patients with underlying IHD.[278, 279] The mechanism(s) of this procedure on SCD risk reduction is possibly
from attenuating the extent of jeopardised/ischaemic myocardium, improving left ventricular ejection fraction, and stimulating cardiac reverse remodelling.[280] The randomised controlled trial in Switzerland recruited 201 patients with one or two vessel blockages aged 26 to 75 years old from 1991 to 1997.[279] This trial reported a decline of incidence rates of SCD from 0.6% to 0.1% per year in the percutaneous coronary intervention group compared to the medical management group (from 0.6% to 1% per year) over a mean follow-up of 10 years.[279] The Bypass Angioplasty Revascularisation Investigation randomised trial and registry recruited 3,610 patients of all ages with clinically severe angina or angiographically documented CAD involving two or three vessels blockages, from 19 clinical sites in the United States and Canada between 1988 and 1991.[278] This trial demonstrated patients who underwent coronary artery bypass graft surgery had a 40% lower risk of SCD compared to those without undergoing this surgery but with percutaneous coronary intervention surgery instead over an average follow-up of eight years. [278]

The encouraging findings were confirmed by three observational studies.[281-283] The FINland-GERmany myocardial infarction study (FINGER), the community study in Olmsted County, and the study in FuWai Hospital in China reported coronary revascularisation procedure reduced the risk of SCD by 52% to 75%.[281-283] In these three studies the beneficial effects of coronary revascularisation procedure was from either percutaneous coronary intervention or coronary artery bypass graft surgery or both.[281-283]

In contrast, two other studies showed no effect of coronary revascularisation.[284, 285] The post-hoc analysis of SCD included 9,756 patients aged <75 years of age who survived first elective percutaneous coronary intervention (n=6,846) and coronary artery bypass graft surgery (n=2,910) from 2000 and 2002.[285] This analysis conducted from the long-term follow-up result of the coronary revascularisation demonstrating outcome study in Kyoto (CREDO-Kyotowhich) showed the coronary revascularisation procedure was not associated with the risk of SCD over a four-year period.[285] The Beta-Blocker Evaluation of Survival Trial recruited 2,708 patients aged ≥18 years old with advanced systolic heart failure from 90 clinical sites in the United States from 1995 to
This trial reported the coronary artery bypass graft surgery had no association with a reduced risk of SCD. Although the evidence of coronary revascularisation procedure on SCD appears inconclusive, the epidemiology of SCD may have changed.

### 2.4.7 Pharmacological therapy

Pharmacological treatment for SCD prevention involves anti-arrhythmic agents (such as amiodarone) in high-risk patients and “non-antiarrhythmic drugs” (such as angiotensin-converting-enzyme inhibitors, and statins) in patients with relatively low-risk profiles of SCD. Antiarrhythmic drugs are commonly classified into four groups although the classification is oversimplified as several antiarrhythmic drugs have more than one class effect. Class I drugs (sodium channel-blocking drugs, such as encainide) are not recommended to prevent SCD as they may boost the risk of SCD and all-cause mortality. Class II drugs (beta blockers) remain among the very few antiarrhythmic drugs showing multiple effects in the prevention of SCD in ischaemic heart disease and heart failure including anti-ischaemic effect and improvement in left ventricular structure and function. Class III drugs (prolong the refractory period) such as amiodarone have a varying effect on SCD, with some studies showing benefit while some showing harm. Class IV drugs (calcium channel blockers such as amlodipine) may indirectly prevent SCD in acute myocardial infarction patients. Albeit these raw classifications, the treatment effect of anti-arrhythmic agents for long-term primary and secondary prevention of SCD is highly variable and problematic due to life-threatening proarrhythmias and severe side effects.

On the other hand, an increasing number of studies indicate “non-antiarrhythmic drugs” tend to have a favourable effect on reducing SCD rates and provide overall survival benefits. Angiotensin-converting-enzyme inhibitors have revealed an anti-arrhythmic effects which are mediated by several mechanisms and a pivotal role for enhancing patients’ outcome and improving left ventricular dysfunction, thus playing a favourable part on reducing SCD risk. Compared to angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers have shown similar overall
mortality rates and a decline in SCD.[297, 298] As another important antiarrhythmic drug, statins have mortality benefits which are mostly paralleled with reduced SCD.[129] Anti-ischaemic instead of a primary anti-arrhythmia effect was suggested as the possible mechanism of SCD decline with statins.[299] The epidemiology of SCD may have altered given the widespread use of drug therapies in patients with structural heart disease such as myocardial infarction and heart failure, who have propensity to SCD.[300]

2.5 Conclusion

Prevention of SCD is a major public health issue yet there is limited epidemiological research on defining the burden of SCD and setting up preventive approaches by confirming the predictors particularly in Australia. The first step in preventing SCD is an accurate estimation of the burden of SCD. Declining trends in the incidence rates of SCD have been observed in a number of studies, but the rates of reductions are not consistent across the studies. Different study populations and study periods as well as using differing definitions and data sources to ascertain cases present significant challenges in measuring incidence rates of SCD, and the interpretation and translation of the research findings into preventive practices. Although some studies have utilised multiple data sources for case identification and estimated SCD rates based on the general population, there still remains significant gaps in the understanding as to the magnitude of SCD at a population level. Without a better understanding of the clinical predictors of SCD, the development of strategies to prevent SCD remains difficult. Therefore, this thesis aims to address these knowledge gaps by developing a method for identifying SCD from routine administrative health data, and using it to examine trends in SCD and clinical predictors of SCD to determine the potential for its prevention.
CHAPTER 3. DATA SOURCES AND METHODOLOGY

High-quality person-linked administrative health data were available for this epidemiological study of sudden cardiac death (SCD) in Western Australia (WA). A better understanding of the data sources and acknowledging the limitation of the dataset are fundamental to maximise the potential of findings of this work and for producing accurate and appropriate interpretations of the results.

This chapter, therefore, provides an overview of the data sources and outlines the general methods applied to the studies in the thesis. More specific information about each of the studies is detailed in the methods section (Chapters 4 to 6) and is not described in detail in this chapter. However, preliminary analyses were included which informed the methodology. The main parts in this chapter include an outline of the official registration of death and collection of hospital morbidity in WA, the dataset used for the studies in the thesis; challenges of SCD case identification; and general methods using the linked administrative health data to identify incident events, comorbidities, and candidate predictors.

3.1 Data Sources

3.1.1 Death registration

Death registration in WA started in 1841, with deaths from 1969 onwards provided in an electronic format suitable for the Western Australian Data Linkage System (WADLS). Death registration varies according to whether or not the death needs reporting to the coroner. If death occurs in a setting of being sudden, unexpected or as a consequence of violence or unnatural causes, the attending physician, paramedics, or police are required to report the death to the coroner under the Coroners Act 1996 (WA).[301] The police are then asked to attend and secure the scene of death. Subsequently, the deceased is transferred to the central State Mortuary at the Queen Elizabeth II Medical Centre, in metropolitan Perth, the capital city of Western Australia. A post-mortem examination is usually
required by the coroner, after which the family is informed as to the findings of coronial enquiry. Although the next of kin can lodge an objection to a post-mortem examination, under the provisions of the Act, the State coroner may overrule this objection especially in suspicious circumstances.[301] The death is provisionally registered without a cause of death and called an “incomplete” death registration. After the coronial investigation, the coroner will advise the Registrar of the cause of death which is then added to the death registration thereby removing the provisional label of “incomplete”.

Approximately 15% of deaths in WA are referred to the coroner for investigation and a determination on the cause of death (personal communication with Registrar General-Registry of Births, Deaths and Marriages, October 15, 2013).[302] The coroner gathers a range of data sources to determine the cause of death in particular, the pathologist’s post-mortem report. An estimated 95% of all coroner cases are subject to a post-mortem examination (personal communication with Principal Registrar-Office of the State coroner, October 14, 2013).[302] The proportions can vary according to resourcing of the coroner’s office and major disasters with large loss of life. Some coronial investigations may therefore take a long time.[303] The Australian Bureau of Statistics (ABS) performs a great number of queries to identify and minimise the number of cases with incomplete information for coding purposes.[303] External causes of death can be coded for the cases with incomplete information according to the International Classification of Disease (ICD)-10 coding rules particularly when the mortality statistics need to be finalised and released.[303]

Under the Coroners Act 1996 (WA), a reportable death may be exempted if the presenting physician or medical practitioner is familiar with the deceased’s medical history and agrees to the “Medical Certificate of Cause of Death”, which is the official registration of death form.[301, 304] If the doctor is unable to fill out the death certificate, he or she needs to advise the coroner or coroner’s delegate to determine the cause of death.[305] As a result, a post-mortem examination may be advised and conducted. However, next of kin can object to a post-mortem suggested by the coroner in this scenario and the post-mortem may be waived.[306]
When the Death Certificate is filled out by the attending medical doctor, the deceased will be sent to funeral home in preparation for burial or cremation. Before burial or cremation, the funeral director will contact medical referees to peruse the death certificate. If there is any evidence that the death is reportable under the Coroners Act 1996 (WA), the medical referees are obliged to inform the funeral director and the case is referred to the coroner for further investigation. Under the Births, Deaths and Marriages Registration Act, the funeral director is responsible for lodging and registering the deceased’s details on the death certificate.

3.1.2 Mortality dataset

All death registration information recorded on the death certificate and stored in the WA Death Registry is sent to the ABS. The ABS is responsible for producing cause of death statistics nationally (including causes of death coding and the validation process) and releasing the mortality data for research. There is generally a two-year time lag in the causes of death being made available due to lags in registration of death and the provision of that information to the ABS (including processing or data transfer).

Currently, the national mortality dataset covers multiple causes of death referring to all morbid conditions and diseases recorded on the death certificate, involving the morbid train of events contributing to the death event. Multiple causes include the underlying cause, the intermediate cause, or any intervening causes, and those conditions attributable to death but not related to the disease or condition responsible for death. The definition of underlying cause of death is the disease or condition which is responsible for the death and attributable to a chain of morbid episodes. Prior to 1997, the ABS mortality data only included a single underlying cause of death.

There are up to 48 multiple causes of death fields in national mortality dataset that are accessible for documentation. Specifically, up to eight out of these fields describe disease(s) or condition(s) directly
leading to death and up to 32 of these fields delineate a series of antecedent causes. This latter coding refers to the conditions that are considered as being antecedent not only in an aetiological or pathological sense, but also the conditions which are relevant to the underlying cause by damage of tissues or impairment of function over a long period of time.\[310]\ The remaining eight fields represent other significant conditions contributing to the death but which do not relate to the underlying cause.

The mortality dataset also includes a field indicating whether a post-mortem was conducted or not. There are four values in this field to show the post-mortem status of the death, including “carried out, to be carried out, no post-mortem, not stated”. “Carried out” means the post-mortem examination has been conducted. All other determinations mean the post-mortem examination has not been conducted at the time of obtaining the data.

### 3.1.3 Hospital Morbidity Data System

The Hospital Morbidity Data System (HMDS) accumulates information on all patients from admission to separation (date of discharge from hospital) in WA from the 1970s onwards. The Hospital Inpatient Summary Form (HA22) has been designed for data collection from acute public, private, and non-affiliated day hospitals which are required by the Health Department of WA to provide all inpatient data.\[311]\ The dataset contains information on patient identification, socio-demographics, service and administrative details, and clinical discharge diagnoses.\[312]\ The clinical discharge diagnoses are coded by clinical coders in hospital systems according to the standardised clinical coding process and periodic directives, but only the principal diagnosis field and up to 20 additional diagnosis (commonly termed secondary diagnosis) fields are available to researchers. The principal diagnosis field reveals the main complaint for which patients have been admitted for medical care. The remaining 20 diagnosis fields reflect coexisting condition(s) or conditions originating during the event of admitted clinical care and there is no known order of priority of assigning the secondary diagnoses. Diagnostic and therapeutic procedure fields record up to 11
procedures taken from the time of admission to the time of separation, comprising the principal procedure and any other procedures during the hospital admission. Both discharge diagnoses and procedures are coded by clinical coders using the relevant ICD versions and codes pertinent at the time. The ICD versions and coding applied within Australia during the period of the study are described in Section 3.1.5.

### 3.1.4 Western Australian Data Linkage System

Both the hospital morbidity and mortality datasets mentioned previously are contained and linked by the WADLS. The WADLS is a structure for the creation, storage, update and retrieval of links between health and welfare-related data for each person’s life whilst residing in WA.[313] The data linkages are achieved among over 30 population-based administrative and research health data collections in WA by the creation of a dynamic master linkage key file.[314] This linkage key file includes 3.8 million chains (average 5.2 links per chain) for potential linkages.[314] Each chain indicates all of the recognised events in the life of an individual, but does not include any accompanying clinical information. The WA Data Linkage Unit in the WA Department of Health officially stores the linkage key file. Access to the WA linked data requires the approval from the relevant data custodians to ensure the data requested is suitable for the purpose of the research and the approval from the relevant Human Research Ethics Committee(s). Having achieved these approvals, linkage staff in the WA Data Linkage Unit conducted the linkage among identified datasets provided by the data custodians to ensure the protection of patient confidentiality and security of linked data.

The WADLS contains eight core datasets: birth, death, and marriage registrations, public and private hospital separations (recorded by the HMDS), mental health encounter data, WA cancer registry, midwives confinement notification, and WA electoral roll registrations. Each dataset is updated regularly according to the process of the original data collection and preparation.
Three core steps are required in order to link data [315]: (i) narrowing potential matches of records by blocking the files of records; (ii) matching the potential linkage pairs of records to determine whether or not they relate to the same person; (iii) linking matched records into a composite record for each individual. The matching step can be impacted by the methods used which can be broadly classified as: clerical review, deterministic, fuzzy, and probabilistic matching.[316] The clerical review includes the manual comparison of records to determine matching status. This method is considered as the criterion standard but is time-consuming and costly,[316] so it is reserved for random samples of subsets to verify accurate and reliable records linking. Deterministic matching relies on the two datasets owning a unique identifier (such as insurance or medical record number), usually yielding up to 85% true matching. The issue with this method is that any error in the identifier will lead to either a missed or wrong match.[315, 316] Fuzzy matching can utilise partial identifiers (such as name, sex, date of birth, and residential address), which are not unique to the person but effectively narrow down the records for matching. Up to 90% of true matches can be found using this method. Probabilistic matching produces a probability of two records for their similarity which are then categorised as probable or improbable links, identifying up to 99% of true matches with only 1-2% of false positive matches.[317] This approach reaches a higher proportion of correct matching than other methods because it can accommodate the inherent variation and error within the datasets.[315, 317]

Currently the linkage of administrative health datasets (including the morbidity and mortality datasets used in the present study) utilises the method of probabilistic matching based on key identifiers including medical record number, name, sex, date of birth, and residential address via AUTOMATCH software.[317, 318] The accuracy of the links produced by the WADLS has been assessed in audits and validity studies.[313] The proportions of invalid and missed links both approximate to 0.1% of matches.[313]
3.1.5 International Classification of Disease coding

International Classification of Diseases is the international standard diagnostic classification utilised to classify diseases and other health problems recorded on various types of death records and health records involving the hospital morbidities, comorbidities or complications that require extended length of hospitalisation or more nursing care. As mentioned briefly above, the ICD versions are utilised by the ABS to code the cause of death in the mortality data and by the clinical coders to code the clinical discharge diagnoses and procedures in the hospital morbidity data (HMD). Specifically, the ICD-9 version was used in Australia between 1979 and 1987.[319] The revised ICD-9 versions with Clinical Modification (CM) was used from 1988 to June 30, 1999[64] and the Australian versions of ICD-10 was utilised from July 1, 1999 onward.[320] International Classification of Procedures in Medicine was used to record procedures in the ICD-9 era (January 1, 1979 to December 31, 1987). After that time, coding of procedures is incorporated into each ICD version or revision.

The quality of coding practice for death and hospitalisation records also impacts on the validity of this thesis. A study on national mortality codes for identifying adjudicated cardiovascular deaths reported the reliability of cause of death at 74% sensitivity and 97% specificity for IHD.[321] A validation study in WA comparing cases coded as myocardial infarction (ICD-9-CM 410; ICD-10-Australian Modification (AM) I21, I22) in the HMD to the American Heart Association criteria shows the sensitivity of myocardial infarction identified by the HMD to be an estimated 80%.[322]

As well as IHD, there are studies validating the morbidity codes in the HMD for diabetes, heart failure, stroke, and atrial fibrillation.[323-326] A study in WA shows a higher accuracy of identifying diabetes in HMD at approximately 90% sensitivity and specificity in patients with IHD when applying an extended lookback period.[323] Another study in WA shows a positive predictive value of 99.5% for heart failure as a primary discharge diagnosis in the HMD when compared to the medical chart diagnosis.[324] An Australian Institute of Health and Welfare study shows the coding of stroke in the HMD at 92% sensitivity and 85% of positive predictive value when both primary
diagnosis and secondary diagnosis fields are applied.[325] In a random sample of the WA linked morbidity and mortality data, the coding for atrial fibrillation has been validated with a positive predictive value of 84.6% when compared to a confirmatory electrocardiograph in the medical record and 98.9% adding a written record of atrial fibrillation in the medical notes.[326] Potential misclassification of diagnostic and cause of death coding cannot be excluded. Notwithstanding, the linked dataset for the present study is presumed to be of high-quality because it is regularly audited and validated for quality internally.[313]

3.1.6 Study setting and population

The resident population in WA was 2.2 million in 2010, with 75% living in the capital city, Perth.[327] More than half of the adult population were ≥35 years of age and the general population in WA by age groups were shown in Table 3.1.[327] Net overseas and interstate migration rates were low and estimated at 1.3% and 0.1% respectively in WA.[328] The total WA population growth was 2.2% and natural increase was 0.8% thereby being considered as stable.[328]

Table 3.1. Number and proportion of the general population in Western Australia by age groups in 2010

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Number</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>588,266</td>
<td>26.3</td>
</tr>
<tr>
<td>20-34</td>
<td>483,073</td>
<td>21.6</td>
</tr>
<tr>
<td>35-49</td>
<td>488,153</td>
<td>21.8</td>
</tr>
<tr>
<td>50-64</td>
<td>404,738</td>
<td>18.1</td>
</tr>
<tr>
<td>65-84</td>
<td>240,687</td>
<td>10.7</td>
</tr>
<tr>
<td>85 and over</td>
<td>34,268</td>
<td>1.5</td>
</tr>
<tr>
<td>Total</td>
<td>2,239,185</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Western Australia is representative of the Australian population in key socio-demographic and health economics indicators although the geography of WA differs from that of other states.[329] This is observed in a comparison study that WA was among the three closest jurisdictions to the national jurisdictional average for the majority of indicators in the census years 1991-2006.[329] These indicators were age, sex, Indigenous status, rural and remote population, out-of-state migration, available hospital beds, health expenditure, and Medicare benefits paid.[329]
3.1.7 Study dataset for this thesis

The individual-linked mortality and morbidity dataset for this thesis was part of a National Health and Medical Research Council funded project (#572558) entitled “The real and changing atherothrombotic disease burden and secondary prevention” which aimed to examine the epidemiology of atherothrombotic disease (including coronary, cerebral, and peripheral arterial territories). The study dataset consisted of linked data from two core data of the WADLS, that is, the HMDS and death registrations, which are detailed in Section 3.1.2 and 3.1.3. The de-identified linked dataset was extracted by the Data Linkage Branch. The initial study dataset included the recording of hospital and mortality data from 1985 to 2007; an update of the dataset subsequently extended the period to 2010; and an additional update of the mortality data to 30 June 2011.

Extraction of the study dataset was based on the records of mortality and hospital morbidity data using the relevant ICD version and/or revision. The dataset covers records for all individuals who died from and/or were ever hospitalised for CVD (ICD-9/ICD-9 CM 390 to 459; ICD-10-AM I00 to I99) or diabetes (ICD-9/ICD-9 CM 250; ICD-10-AM E10-E14) in WA from January 1, 1985 to June 30, 2011. For death records, these codes were selected where any of these codes were recorded in the multiple causes of death fields. For hospitalisation records, the codes were selected where any of these codes were recorded in any discharge diagnosis field in the HMDS. A terminal event occurring in the emergency room cannot be recognised through this dataset, thereby being considered as out-of-hospital death. Variables within the extracted dataset available for this study include patient identification, socio-demographics, service and administrative details, and clinical discharge diagnoses, and diagnostic and therapeutic procedures.
3.2 Challenges of sudden cardiac death case identification

The widely-accepted definition of SCD is unexpected natural death, if the onset of symptoms is witnessed within 1 hour, or if the onset of symptoms is unwitnessed but individuals are observed alive and well within 24 hours prior to death.[330] However, it is hard to apply this definition due to issues in deciding the precise timing from symptom onset to cardiac collapse and the fact that many SCD cases are unwitnessed.[17, 65] As argued by epidemiologists, epidemiological studies on SCD require a more flexible definition of SCD, focusing on the general population rather than individual cases.[330] Moreover, many countries such as Australia lack a national registry for SCD by which to monitor this fatal event.

Sudden cardiac death cases can be directly identified through the ICD as detailed in section 3.1.5. However, a specific ICD code for SCD (I46.1) was not available until ICD-10.[320] The most relevant code for SCD prior to its introduction in ICD-10 was the code for cardiac arrest (427.5). According to ICD-9 CM coding guidelines, the code for cardiac arrest should not to be assigned for a patient who dies during an inpatient stay, because cardiac arrest reflects the “mode of dying” rather than the underlying cause of death.[331] Even though a unique code (I46.1) for SCD has been available to nosologists since July 1, 1999, SCD is overwhelmingly under-reported in our local mortality dataset with only 3 cases being assigned this code as the underlying cause of death in WA during the period 1999 to 2010. This is because the code I46.1 is assigned only if resuscitation is undertaken and is rarely assigned as the underlying cause of death according to the coding guideline[64].

A different approach to maximise the unique research capability of the available data to identify cases of SCD thus is essential first step to the capturing its epidemiology in the population of WA between 1997 and 2010. The following Chapter 4 will provide the rationale and development of criteria used to define SCD for the thesis.
3.3 Use of the linked dataset to identify comorbidities, incident events, and candidate predictors

This section outlines preliminary analyses used to inform the methods including examination of the ICD codes, comparison of principal versus any discharge diagnoses and the length of lookback periods, and issues affecting the identification of comorbidity data and candidate predictors.

3.3.1 Examination of International Classification of Disease codes

Identification of SCD case, comorbidities of SCD cases prior to death, incident events, and candidate predictors were identified using the ICD codes which are provided in each corresponding chapter (Chapter 4 to 6). Some validation data on the ICD coding have demonstrated moderate to high levels of accuracy in the HMD which were presented in Section 3.1.5. The ICD codes used to identify heart failure and stroke were specifically confirmed by the following preliminary analyses for the thesis. There are a major code and additional codes for heart failure and incongruent codes for stroke among different revisions of ICD-9-CM.

A preliminary analysis was conducted in individuals who were hospitalised for heart failure from 1985 to 2010 and identified from the principal diagnosis field and other diagnosis fields (including principal and secondary diagnoses). The exclusive ICD code for most commonly used to identify heart failure is ICD-9 428/ICD-10-AM I50. Other codes indicate complications of heart failure such as hypertensive heart disease or hypertensive heart and chronic kidney disease or rheumatic heart disease.[64, 320] The comparison was made of the number of patients hospitalised for heart failure identified by the main heart failure code (ICD-9/ICD-9-CM 428, ICD-10-AM I50) versus this code plus other related conditions such as heart failure complicated with hypertensive heart disease, cardiomyopathy, and rheumatic heart failure (ICD-9/ICD-9-CM 428, 402.01, 402.11, 402.91, 404.1, 404.3, 425, 518.4, 514, 391.8, and 398.91, ICD-10-AM I50, I11.0, I13.0, I13.2, I42, J81, I01.8, I02.0).[324] Although there are <10% more patients identified using the main code plus additional
codes (Figure 3.1), only the main code for heart failure (ICD-9/ICD-9-CM 428, ICD-10-AM I50) was utilised as this was the more conservative perspective and is most commonly used in other studies. In the thesis, all diagnosis fields and a look-back period which are discussed in Section 3.3.3 below were applied to identify heart failure as a comorbidity maximising the ability of heart failure. For example, <1% more of incident myocardial infarction patients were identified to have the comorbidity of heart failure in the preceding 15 years using the broader group of codes compared to the main code only.
Figure 3.1. Number of patients hospitalised for heart failure identified by the major code (A) and the additional codes (B)

The diagnostic codes for stroke are known to not be completely congruent among the different revisions of ICD-9-CM. The main change in the ICD-9 era occurred were a fifth digit extension of codes 433 (conditions due to disease of precerebral arteries) and 434 (conditions due to disease of
cerebral arteries) available after July 1, 1995. The change to codes 433 and 434 was more specific to indicate the presence of associated cerebral infarction (codes 433.x1 and 434.x1) (Table 3.2). A preliminary analysis was conducted in individuals who were hospitalised for stroke from 1985 to 2010 and were identified from the principal diagnosis field and any diagnosis fields. The comparison was made of the number of patients hospitalised for stroke identified by three definitions. Definition 1: codes 430, 431, 433.x1, 434.x1, 436, I60, I61, I63, I64 were used to identify stroke (codes 433.x1, 434.x1 only available after July 1, 1995). Definition 2: codes 430, 431, 433, 434, 436 were used before the date of July 1, 1995, and codes 430, 431, 433.x1,434.x1, 436 codes were used from July 1,1995 to June 30, 1999, and codes I60, I61, I63, I64 were used after the date of July 1, 1999. Definition 3: codes 430, 431, 433,434, 436 were used before the date of July 1, 1999, and codes I60, I61, I63, I64 were used after the date of July 1, 1999.

Table 3.2. Mapping International Classification of Diseases codes for stroke

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>430, 431, 433, 434, 436</td>
<td>430, 431, 433, 434, 436</td>
<td>430, 431, 434.x1, 434.x1, 436</td>
<td>I60, I61, I63, I64</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3.2 show the counts in three definitions (A to C) of stroke identified by the principal and any discharge diagnoses. The number of patients hospitalised for stroke were less by definition 1; a little more by definition 2; and appreciably more by definition 3. The discrepancy was due to incongruent codes among different revisions of ICD-9-CM and the unavailability of a fifth digit specific code before July 1, 1995. After the comparison, definition 2 of stroke was preferred for all the analyses in the thesis.
3.3.2 Comparison of principal versus any discharge diagnoses

Patients hospitalised for myocardial infarction (ICD-9/ICD-9-CM 410, ICD-10-AM I21, I22), heart failure (ICD-9/ICD-9-CM 428, ICD-10-AM I50), atrial fibrillation (ICD-9/ICD-9-CM 427.3, ICD-10-AM I48), and stroke (ICD-9/ICD-9-CM 430, 431, 433, 434 (433.x1,434.x1), 436, ICD-10-AM I60, I61, I63, I64) were examined in Chapter 6 and identified through the hospital discharge diagnoses. The principal diagnosis reflects the main complaint for patients admitting to hospital for medical care whereas the secondary diagnoses reflect coexisting conditions during the event of admitted clinical care. As the main complaint for admitting to hospital suggests different clinical importance compared to the coexisting conditions, a preliminary analysis was conducted to compare the number of patients hospitalised for myocardial infarction, heart failure, atrial fibrillation, and stroke and identified by the principal and any discharge diagnoses as showed in Figure 3.3. The number of patients hospitalised for myocardial infarction, heart failure, atrial fibrillation, and stroke who were identified by the principal discharge diagnosis were lower than those identified by any discharge diagnoses. However,
trends in the number of patients hospitalised for myocardial infarction, heart failure, atrial fibrillation, and stroke identified by the principal discharge diagnosis were slightly went up or steady especially after 2000. The principal discharge diagnosis was preferred to use in the study cohorts identification in Chapter 6 as this enabled the study cohort to have the same main complaint for admitting to hospital.
Figure 3.3. Number of patients hospitalised for myocardial infarction (A), heart failure (B), atrial fibrillation (C), and stroke (D) identified by the principal and any discharge diagnoses

3.3.3 Comparison of 10- and 15-year lookback periods

Identification of incident or “first-ever” events from the linked data for the study cohorts depends on applying a lookback period to determine the prior hospitalisation history of disease. In the lookback
period, if there is no hospitalisation for the condition under investigation, it is considered an incident event. Otherwise, it is a recurrent event. A prevalent event includes an incident or recurrent event occurring in the designated study period. Different lengths of lookback periods are reported and compared to identify incident events as follows: different lookback periods have been used to identify prior hospitalisations for stroke in the HMD suggesting longer lookback period is better to capture the prior history.[332] Similarly longer lookback period is recommended to capture incident events of myocardial infarction.[333] The recurrent myocardial infarction events are less than 1% when $\geq 10$-year lookback period is applied.[332] The 10- and 15-year lookback periods have been applied to exclude recurrent acute coronary syndrome and hospitalised atherothrombosis events.[334, 335]

A preliminary analysis was conducted to compare the number of incident events identified by the 10-year and 15-year lookback periods and only the principal discharge diagnosis was investigated (as compared in Section 3.3.2). Figure 3.4 show generally upward trends parallel in the number of incident events identified by both lookback periods. There are marginal differences in the number of incident events of myocardial infarction, heart failure, atrial fibrillation, and stroke in the use of a 10-year versus 15-year lookback period (average annual difference of 2.7%, 2.9%, 2.1%, 1.5% respectively). To maximise our ability to eliminate potential recurrent events, a fixed 15-year lookback period was applied to identify the incident study cohorts in Chapter 6.
Figure 3.4. Number of incident events of myocardial infarction (A), heart failure (B), atrial fibrillation (C), and stroke (D) identified using a 10-year lookback and 15-year lookback
3.3.4 Comorbidity data for sudden cardiac death cases

Comorbidity variables for SCD cases were defined using their hospitalisation history in the lookback period and from the associated cause(s) of death as listed on death records. Conditions recorded on the most recent admission within 28 days of SCD only were not classed as comorbidities and were observed specially to reflect the health status close to the fatal event. A fixed 10-year lookback period from the date of SCD minus the 28 days was preferred to ascertain the comorbidities for SCD cases who had the hospitalisation history. The use of the associated cause(s) of death to explore the comorbidities for the SCD cases was particularly imperative to those without prior hospitalisation history for the comorbidity under investigation.

The quality of the comorbidity variables for the SCD cases identified from the linked data using all discharge diagnosis fields and the associated cause(s) of death could be impacted by three issues. Firstly, whether medical notes and discharge reports are correctly documented and the information is coded correctly by the clinical coders using the ICD codes. Secondly, beyond the principal diagnosis, secondary diagnoses in discharge summaries may not be completely coded because of the coding guidelines.[320, 331] Some validation data have shown acceptable levels of accuracy in the HMD for comorbidities under investigation (Section 3.1.5). However, some potential cardiac conditions or factors are available and coded in the HMD but were not examined in the thesis as the accuracy and internal consistency of these conditions or factors is known to be poor or uncertain, including cigarette smoking, alcohol-related hospital admission, hyperlipidemia, and obesity.[336, 337] Thirdly, whether morbid conditions and diseases are correctly recorded on the death certificate, including the morbid train of events contributing to the death event and the information on the death certificate are coded correctly.[338] Cause of death coding is standard as the majority of cause of death coding is undertaken through an automated coding process by the ABS.[338] The ABS mitigates the risk through rigorous coder training for manually coding complex or difficult cases, and extensive data quality checks.[338]
The ICD codes cover comprehensive circumstances for one clinical disease or condition. In cases where more specificity is needed, the sub-classification (4th and 5th digit level) is used to document the aetiology (cause), site, or manifestation of the disease or condition. For example, it is common for chronic IHD (I25) to be coded in secondary diagnosis fields to indicate the aetiology where the principal diagnosis is an acute presentation of myocardial infarction (I21). If death occurs, chronic IHD (I25) is also usually coded in associated cause(s) of death fields to elucidate the circumstance where myocardial infarction (I21) is the underlying cause of death. In order to accurately capture prior condition of IHD, in this thesis, IHD was not counted as a secondary code when recorded at the incident admission. When IHD recorded as the underlying cause of death, it was not counted as an associated cause code.

In addition, indirect measurement of variables for socioeconomic advantage and disadvantage status (Socio-Economic Indexes for Areas) are accessible in the linked dataset. The indexes are categorised into quintiles by the ABS through measuring the income, education attainment, unemployment, and motor vehicle ownership. However, there is low internal consistency across the methodologies used in measuring the variables of socio-economic advantage and disadvantage status resulting in a greater inconsistency when grouping these variables into the indexes.[339, 340] Therefore, these variables were not used in all the analyses of this thesis.

3.3.5 Data for candidate predictors of sudden cardiac death

Data for candidate predictors of SCD under investigation in the thesis (Chapter 6) were identified from their hospitalisation history using a lookback period. A fixed 15-year lookback period was used which is equivalent to that used for identifying the incident event. The accuracy of the candidate predictor of SCD identified from the linked data using all discharge diagnosis fields is impacted by the same three aspects as the comorbidities identification which were discussed in Section 3.3.4. Conditions recorded on the secondary diagnosis fields on the incident admission only were also included as candidate predictors as this practice maximises our ability of identifying the medical
conditions which can predict the outcome of SCD after the incident event. Further details of the methods used for identifying the candidate predictors of SCD were provided in chapter 6.

3.4 Statistics software

Statistical analyses were performed using SAS software version 9.3 (Chapter 4) and 9.4 (Chapter 5 and 6) (Cary, NC). The specific statistical analysis tests used are detailed in the statistical methods sections in Chapter 4 to 6.

3.5 Ethics Approval

The current study was approved by The University of Western Australia Human Research Ethics Committee (#RA/4/1/1491) and the Department of Health Human Research Ethics Committee (#2014/55). Non identifiable data for the study were extracted by the WA Data Linkage in the WA Department of Health. To facilitate the protection of patient privacy, data analyses were undertaken in the designated computer and network that are password and firewall protected from outside access. All these facilitate the protection of patient privacy.
CHAPTER 4. SUDDEN CARDIAC DEATH: CHARACTERISTICS, INCIDENCE RATES, AND UNDERLYING CAUSE

This chapter is based on the published paper:

4.1 Introduction

Cardiovascular disease death is the leading cause of mortality worldwide, reaching 17,000,000 deaths each year.[342] More than half of deaths from CVD are estimated to be sudden,[343] underscoring SCD as a public health issue. Substantial variations exist in SCD incidence rates, ranging from 40 per 100,000 person-years to 200 per 100,000 person-years in Northern America, Europe, and Asia.[13, 16, 65, 344] Different methodologies including single versus multiple data sources of cases ascertainment are one of the reasons for these disparities. Death certificates, medical records, or emergency room resuscitation records have been used as a single source for SCD ascertainment.[16, 79, 344] However, it is challenging to adjudicate a death as sudden by a single source method.[17] To improve the limitation of the method relying solely on a single data source, a multiple source method of ascertainment has been used in a few studies to increase the capture of SCD cases.[17, 65] Information from death certificates, medical records, emergency room resuscitation records, and/or autopsy records can be integrated for SCD surveillance by a multiple source method.[17, 65]

Various age ranges in different study populations may also impact the varying incidence rates of SCD.[39] The incidence rates of SCD are observed to be significant in people aged $\geq 35$ years old, reaching one to two per 1,000 person-years.[41, 79] The incidence rate of SCD in this age group is
contributed to by high incidence rates between the ages of 40 to 65 years.[345] One United States study reported the incidence rate of SCD to be 162.1 per 100,000 per person-years in adults aged ≥35 years old whereas the Northern Ireland study reported it as 103.8 per 100,000 per person-years in individuals of all ages.[79, 344] At the other end of the age spectrum in adolescents and young adults (below 35 years), the incidence rate of SCD was around one-hundredth that of the population aged ≥35 years old (one per 100,000 per person-years).[42, 346] A higher incidence rate of SCD was found in the adolescent group than young adults, suggesting a slightly inverse age relationship in those ≤35 years.[347]

In addition, differential underlying pathophysiology of SCD in two broader age groups (≥35 versus <35 years old) may contribute to the observed different incidence rates of SCD.[39] Ischaemic heart disease (IHD) is the most common cardiac pathology underlying SCD in adults aged ≥35 years old, accounting for approximately 80% of all SCD cases.[41] In contrast, IHD explains a much smaller proportion of SCD in children and young adults aged <35 years old, with hypertrophic cardiomyopathy, myocarditis, long QT syndromes, arrhythmogenic right ventricular cardiomyopathy, Brugada syndrome, and coronary artery anomalies accounting for significant proportions.[348]

In Australia, limited studies on the epidemiology of SCD have been conducted, possibly due to lack of a comprehensive data source. Even though the mortality data based on the death certificate is the most common used data source, the specific ICD code for SCD was not available until the implementation of ICD 10, from July 1, 1999.[63] Prior to this, only a relevant code of cardiac arrest (code 427.5) was codeable.[331] However, this code was not to be assigned for the deceased because this does not reflect the underlying cause of death according to the ICD-9-CM coding guidelines.[64] Sudden cardiac death is substantially under-reported when a unique code (I46.1) for SCD was accessible, possibly partly because it was directed that this code only be implemented if resuscitation has been attempted.[63] This was based on the preliminary examination of the routinely collected administrative morbidity and mortality data in WA, with only three SCD cases being assigned this code as the underlying cause of death. As a result, there is an essential first step to establish a method
for SCD identification here in Australia and then enhance our understanding by conducting epidemiological research of this terminal event.

Despite limited studies on SCD in Australia, studies on out-of-hospital SCD, out-of-hospital cardiac arrest, and sudden unexplained death may provide proxies for SCD and therefore are reviewed. An early Australian study estimated the out-of-hospital SCD rate to be 40 per 100 000 person-years in individuals aged 25-94 years from 1985 to 1989 in a small sample size (215 patients).[349] Later, two Australian and New Zealand studies reported relatively low rates of SCD in 1-35 year-olds between 1994 and 2002 (1.1 per 100,000 person-years) and 0-40 year-olds from 2006 to 2007 (2.0 per 100,000 person-years) respectively.[62, 350] More recently, a WA study reported the out-of-hospital cardiac arrest rate to be 60.2 per 100 000 person-years from 1997 to 2010.[85] Two-thirds of SCD occur in men, with three to four-fold higher incidence rate of SCD when compared to women of the same age.[65, 79, 344] As a consequence, there is a need to examine SCD by age groups and sex.

4.2 Study Objectives

1. To develop criteria for the identification of SCD cases using published evidence derived from the statutory morbidity and mortality data collections in the WA population aged \( \geq 1 \) year old from 1997 to 2010.

2. To examine the characteristics, incidence rates, and underlying cause of the identified SCD as identified using the method for case identification developed in Objective 1.

4.3 Methods

4.3.1 Dataset and study population

A person-linked mortality and morbidity dataset was used to develop the criteria for SCD identification and describe the characteristics and underlying cause of SCD cases. Details of the dataset are shown in Chapter 3. International Classification of Diseases 9 from 1979, ICD-9 CM,
from 1988, and ICD-10 AM, from July 1, 1999 were used to identify SCD, hospitalisation history, and underlying cause of SCD (ICD versions and codes are presented in Chapter 3).

4.3.2 Rationale for criteria development

The rationale of developing criteria for SCD identification is based on lack of consistent identification criteria as evident from published accounts of SCD. Firstly, when unwitnessed out-of-hospital cardiac deaths are found to be SCD, it accounted for 22% to 65% of the total number of identified SCD.[90, 91, 351] Secondly, a small proportion of SCD cases (20% to 25%) occur in-hospital within 24 hours of admission, with or without attempted resuscitation.[352] Thirdly, by definition, the underlying cause of death in SCD cases is cardiac disease, with 80% of SCD cases having IHD recorded as the primary cause of death and 10-15% of cases having cardiomyopathy.[4] Fourth, the risk of SCD is highest within the first 28 days of myocardial infarction, the acute period within which the heart is vulnerable to lethal arrhythmic attacks.[282, 353, 354] Fifth, half of SCD cases are the first manifestation of CVD.[29, 355, 356] Sixth, a coronial enquiry and/or a post-mortem examination provide an indication of the circumstance of SCD and the unexpected nature of SCD.[168] It is noted that the hospital autopsy rates have been declining worldwide from 40% to less than 1% since the 1960s.[66-68] The decreasing autopsy rates varied across countries, with the hospital autopsy rates declining from 21% in 1992 to 8% in 2010 in Australia.[66-68, 70, 71] All the evidence alone cannot conclusively diagnose an SCD. Therefore, place, time, discharge diagnosis, underlying and associated cause (s), and/or post-mortem status were integrated in this study to capture potential SCD cases.

4.3.3 Criteria development for sudden cardiac death

Four criteria were devised to identify SCD. Each criterion comprised two or three components including place, death within 24 hours, discharge diagnoses, underlying cause, associated cause and/or a post-mortem. Specific variables of place and time were not available in the linked mortality and morbidity dataset. Therefore, the components of place and death within 24 hours were estimated
from other variables within the dataset. Specifically, if the difference between the date of hospital discharge and the date of death was more than one day, death was considered as ‘out-of-hospital death’. If the difference between the date of hospital admission and the date of death was less than one day (inclusive), death was considered as ‘in-hospital death within 24 hours of admission’.

Underlying cause of death facilitated the primary cause determination for SCD. Associated causes of death and hospital discharge diagnoses can be supplement resources to describe the circumstances of death. The post-mortem status indicated the unexpected nature of fatal events.

To inform SCD, the term SCD-related disease was created and used to describe a range of disease or conditions associated with SCD. Each of these conditions involved in SCD-related disease has been implicated in complex pathophysiological mechanisms of SCD.[39] These conditions included: myocardial infarction, other IHD (including angina pectoris and chronic IHD), cardiomyopathy, arrhythmias, heart failure, myocarditis, endocarditis, pericarditis, valvular heart disease, pulmonary heart disease, rheumatic heart disease, and congenital heart disease. These conditions were identified from the underlying cause of death field in the mortality dataset using ICD codes (Table 4.1).
Table 4.1. International Classification of Diseases used to identify sudden cardiac death related disease

<table>
<thead>
<tr>
<th>SCD-related disease</th>
<th>ICD 9/ICD-9-CM code</th>
<th>ICD-10-AM code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic heart disease</td>
<td>390-393, 398</td>
<td>100-102, 109</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>410</td>
<td>121, 122</td>
</tr>
<tr>
<td>Other ischaemic heart disease†</td>
<td>411-414</td>
<td>120, 123-125</td>
</tr>
<tr>
<td>Pulmonary heart disease</td>
<td>415-417</td>
<td>126-128</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>420, 421, 423</td>
<td>130, 131</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>422</td>
<td>140</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>424, 426</td>
<td>133</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>425</td>
<td>142</td>
</tr>
<tr>
<td>Conduction disorder</td>
<td>426</td>
<td>144-145</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>427.1</td>
<td>147.2</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>427.4</td>
<td>149.0</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>427.5</td>
<td>146</td>
</tr>
<tr>
<td>Other dysrhythmias</td>
<td>427.0, 427.2-427.5, 427.8-</td>
<td>147.0-147.1, 147.9, 149.1-149.5, 149.8, 149.9, 149.8, 149.9, 149.9</td>
</tr>
<tr>
<td>Heart failure</td>
<td>428</td>
<td>150</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>394-397, 424.0-424.3</td>
<td>105-108, 134-139</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>745-746</td>
<td>Q20-Q24</td>
</tr>
</tbody>
</table>

† includes angina pectoris, other acute and chronic ischaemic heart disease.
CM, Clinical Modification; AM, Australian Modification; SCD, sudden cardiac death.

Four criteria were developed as follows. Criterion 1 captured individuals who died out-of-hospital or died in-hospital within 24 hours of any-cause hospital admission, and had an SCD-related disease as the underlying cause of death and an associated cause of death of ventricular fibrillation, ventricular tachycardia, or cardiac arrest. Criterion 2 captured individuals who died in-hospital within 24 hours of admission for ventricular fibrillation, ventricular tachycardia, or cardiac arrest, and had an SCD-related disease as the underlying cause of death. Criterion 3 captured individuals who died out-of-hospital or died in-hospital within 24 hours of any-cause admission, and had an SCD-related disease as the underlying cause of death and a post-mortem. Criterion 4 captured individuals who died out-of-hospital or died in-hospital within 28 days from the date of hospitalisation for acute myocardial infarction, and had an SCD-related disease as the underlying cause of death (Table 4.2).
Table 4.2. Criteria for sudden cardiac death identification

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Circumstances (place, time, diagnosis)</th>
<th>Underlying cause (from mortality data)</th>
<th>Additional information (from mortality data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion 1</td>
<td>Died out-of-hospital OR died in-hospital ≤ 24 hours of any-cause admission</td>
<td>Underlying COD was a SCD-related disease*</td>
<td>Associated COD† was VF, VT or cardiac arrest</td>
</tr>
<tr>
<td>Criterion 2</td>
<td>Died in-hospital ≤ 24 hours after admission for VF, VT or cardiac arrest recorded in any diagnosis field</td>
<td>Underlying COD was a SCD-related disease*</td>
<td></td>
</tr>
<tr>
<td>Criterion 3</td>
<td>Died out-of-hospital OR died in-hospital ≤ 24 hours of any-cause admission</td>
<td>Underlying COD was a SCD-related disease*</td>
<td>Indication that whether a post-mortem was conducted</td>
</tr>
<tr>
<td>Criterion 4</td>
<td>Died out-of-hospital OR died in-hospital, both following an admission for MI as principal diagnosis within last 28 days</td>
<td>Underlying COD was a SCD-related disease*</td>
<td></td>
</tr>
</tbody>
</table>

*SCD-related disease included ischaemic heart disease, cardiomyopathy, arrhythmias, heart failure, myocarditis, endocarditis, pericarditis, valvular heart disease, pulmonary heart disease, rheumatic heart disease, and congenital heart disease.

†Associated COD included direct and antecedent cause(s) as recorded in the death certificate.

COD, cause of death; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia; MI, myocardial infarction

Within each criterion, there was no priority given to any of the components. In other words, cases should meet each of the components of circumstances, underlying cause, and/or additional information demonstrated in each criterion. Between four criteria, cases were identified consecutively and in order from criterion 1 to 4. It is possible for cases to meet the requirements of more than one criterion. However, they were only ever counted once if identified by more than one criterion. For example, if one case was captured by criterion 1, the case was excluded possible identification in the remaining three criteria.

A common cause of sudden unexpected death occurring in an infant under one year of age is called the sudden infant death syndrome. The exactly primary cause of sudden infant death syndrome commonly remains unexplained after a complete post-mortem examination and a detailed case investigation. A cardiac cause of this syndrome has not yet been established. Therefore, cases aged <1 year were excluded in this study.
4.3.4 Identification of cardiovascular disease hospitalisation history for sudden cardiac death cases

Because a CVD hospitalisation history is more common in SCD cases aged ≥35 years old, hospitalisation history of CVD (ICD 9/ ICD-9-CM 390–459, ICD-10-AM I00-I99) was only identified for those aged ≥35 years old. If the SCD cases died out-of-hospital, CVD hospitalisation history was identified from any diagnosis field using a fixed 10-year lookback. If the SCD cases died in-hospital, CVD hospitalisation history was identified from any diagnosis fields in the preceding 10 years and the secondary diagnosis fields on the admission where they died in hospital.

4.3.5 Statistical analysis

Continuous and categorical variables were presented as mean ±standard deviation and proportions (%) respectively. Difference in mean age by sex was determined using an independent t-test. Differences in proportions by age groups and by post-mortem status were examined using a Pearson’s chi-squared test.

The annual crude incidence rate of SCD was calculated using the total number of SCD cases for each calendar year divided by the corresponding annual total WA population aged over one year from 1997 to 2010.[327] Age-standardised rates (ASRs) of SCD were calculated using the direct method, with the number of SCD cases for that year as the numerator and the WA population for that year as the denominator.[357] Rates were standardised using the WA population with the 2006 census as the standard population.[327]

In order to compare the observed rates in this WA study with published ASRs, the ASRs of this WA study were recalculated using the published standard population, age groups, and calendar years for each of the corresponding reported studies.[13, 16, 79, 344] As limited studies reported the ASRs,
some studies which only reported crude rates were also included and the crude rates observed in this WA study for the same calendar year and ages were recalculated for comparison.

**Sensitivity analysis**

To demonstrate the contribution of the components in the criteria for SCD identification, a revised criterion was used to identify SCD. By this revised criterion, SCD cases were identified as occurring out-of-hospital (including in the emergency room) and using only the underlying cause of death where it was a SCD-related disease.

It is complicated to identify a death as SCD if the deceased has previous hospitalisation history of heart failure, valvular heart disease, or implantable cardiac defibrillator as non-SCD might occur.[358]

To estimate the extent of potential misclassification of non-SCDs, the ASRs were recalculated after excluding SCD cases with previous hospitalisation history of heart failure, valvular heart disease, or implantable cardiac defibrillator in those ≥35 years of age.

**4.4 Results**

The number and characteristics of SCD cases identified by the developed criteria, and the incidence rates and underlying cause of death for identified SCD cases are presented in this section.

**4.4.1 Number and distribution of sudden cardiac death cases**

A total of 9,567 SCD cases were identified in WA from 1 January 1997 to 31 December 2010, of which 5,943 (62.1%) were men. Approximately 10% of cases can be identified by more than one criterion. Figure 4.1 shows that Criterion 1 and 2 captured one-third of SCD cases who had a fatal arrhythmia recorded as a cause of death. Criterion 3 captured 40% of cases that died outside-of-hospital or in-hospital within 24 hours of any-cause admission and had a post-mortem. Nearly 80% of cases occurred outside the hospital. Most SCD cases (98%) occurred in those aged ≥35 years old,
with one in three having no prior CVD hospitalisation in the 10 years before death. Age (mean ± standard deviation) was significantly different between men and women (68.8 ± 15.1 versus 77.9 ± 14.6 years, respectively; \( P < 0.0001 \)). Figure 4.2 shows that below the age of 85 years, a higher proportion of SCD cases were men. In comparison, in the ≥85 year age group, women comprised a higher proportion than men.

![Figure 4.1. Number of sudden cardiac deaths identified by the four criteria](image)

*The grey shadow represents the proportion of cases that were identified by more than one criterion.
Criterion 1: died out-of-hospital OR died in-hospital ≤ 24 hours of any-cause admission AND died of sudden cardiac death (SCD)-related disease AND with ventricular fibrillation, ventricular tachycardia or cardiac arrest as associated cause of death.
Criterion 2: died in-hospital ≤ 24 h of admission for ventricular fibrillation, ventricular tachycardia or cardiac arrest recorded in any diagnostic field AND died of SCD-related disease.
Criterion 3: died out-of-hospital OR died in-hospital ≤ 24 hours of any-cause admission AND died of SCD-related disease AND with indications that a post-mortem was conducted.
Criterion 4: died out-of-hospital OR died in-hospital following an admission for myocardial infarction as principal diagnosis within last 28 days AND died of SCD related disease.
Figure 4.2. Age and gender distribution of proportions of all sudden cardiac death cases identified in Western Australia from 1997 to 2010

4.4.2 Sudden cardiac death incidence rates

The crude SCD incidence rate of SCD was 34.6 per 100,000 person-years for the WA population from 1997 to 2010, with an ASR of 37.8 per 100,000 person-years (95% confidence interval (CI) 34.2 per 100,000 person-years to 39.4 per 100,000 person-years). The mean annual ASR of SCD for men was 51.5 per 100,000 person-years (95% CI 46.9 per 100,000 person-years to 56.1 per 100,000 person-years) whereas for women it was 24.1 per 100,000 person-years (95% CI 21.3 per 100,000 person-years to 26.8 per 100,000 person-years). The average annual ASRs for people aged 1-34 years and those aged ≥35 years were 1.1 per 100,000 person-years (95% CI 0.5 per 100,000 person-years to 1.8 per 100,000 person-years) and 70.7 per 100,000 person-years respectively (95% CI 64.0 per 100,000 person-years to 73.8 per 100,000 person-years). Figure 4.3 demonstrates that the age-specific rates of SCD were higher in men compared to women.
The sensitivity analysis of examining a revised criterion for SCD capture showed that the crude rate of out-of-hospital SCD was estimated to be substantially higher when the case identification only relied on underlying cause of death (100.6 per 100,000 person-years versus 34.6 per 100,000 person-years). The second sensitivity analysis of examining whether or not the ASR was similar when SCD cases with prior heart failure, valvular heart disease, or implantable cardiac defibrillator excluded demonstrated that the ASR of SCD reduced to 62.9 per 100,000 person-years in cases aged ≥35 years, with prior hospitalisations for heart failure (n = 769), valvular heart disease (n = 230), implantable cardiac defibrillator (n = 39), or any combination of the three aforementioned (n = 36) excluded.

### 4.4.3 Underlying cause of sudden cardiac death

Table 4.3 shows the distribution of the documented underlying cause of death for SCD, with 87% of cases having IHD recorded as the underlying cause of death. Ischaemic heart disease was the most common underlying cause of death in both the 1-34 year-olds and ≥35 year-olds, followed by arrhythmias in the 1-34 year-olds and heart failure in the ≥35 year-olds.
Table 4.3. Distribution of underlying cause of death among sudden cardiac death cases by broad age group

<table>
<thead>
<tr>
<th>Underlying cause of death^</th>
<th>1-34 year-olds</th>
<th>≥35 year-olds</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=155</td>
<td>n=9,412</td>
<td>n=9,567</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13.5</td>
<td>43.5***</td>
<td>43.0</td>
</tr>
<tr>
<td>Other ischaemic heart disease^b</td>
<td>29.7</td>
<td>44.4**</td>
<td>44.2</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>3.9</td>
<td>2.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.6</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>1.3</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1.9</td>
<td>0.04***</td>
<td>0.1</td>
</tr>
<tr>
<td>Unspecified cardiomyopathy^c</td>
<td>11.0</td>
<td>1.7***</td>
<td>1.8</td>
</tr>
<tr>
<td>Ventricular fibrillation, ventricular tachycardia, or cardiac arrest</td>
<td>1.3</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Arrhythmias, other^d</td>
<td>9.7</td>
<td>1.2***</td>
<td>1.2</td>
</tr>
<tr>
<td>Conduction disorders</td>
<td>0</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Pulmonary heart disease</td>
<td>5.8</td>
<td>1.5**</td>
<td>1.6</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>5.2</td>
<td>0.4***</td>
<td>0.5</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>4.5</td>
<td>0.2***</td>
<td>0.2</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>7.1</td>
<td>0.1***</td>
<td>0.2</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>2.6</td>
<td>0.4*</td>
<td>0.4</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1.9</td>
<td>0.3**</td>
<td>0.3</td>
</tr>
</tbody>
</table>

^P < 0.05, **P < 0.001, ***P < 0.0001 compared with SCD cases aged 1–34 years (chi-squared test).
^AFrom the International Classification of Diseases versions 9 and 10.
^BIncludes angina pectoris and chronic ischaemic heart disease.
^CIncludes other restrictive and non-obstructive hypertrophic cardiomyopathy.
^DIncludes paroxysmal tachycardia, atrial fibrillation and flutter, and unspecified cardiac arrhythmias.

Table 4.4 shows IHD was the most common underlying cause of death in the post-mortem group and non-post-mortem group. Specifically, other IHD was the most common underlying cause of death in the post-mortem group while myocardial infarction in the non-post-mortem group.
Table 4.4. Distribution of underlying cause of death among sudden cardiac death cases according to whether a post-mortem was undertaken or not

<table>
<thead>
<tr>
<th>Underlying cause of death</th>
<th>Post-mortem n=4,044</th>
<th>Non-post-mortem n=5,523</th>
<th>All n=9,567</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>21.6</td>
<td>58.7***</td>
<td>43.0</td>
</tr>
<tr>
<td>Other ischaemic heart disease</td>
<td>65.6</td>
<td>28.5***</td>
<td>44.2</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>2.6</td>
<td>2.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.8</td>
<td>2.7***</td>
<td>1.9</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>0.7</td>
<td>0.4*</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Unspecified cardiomyopathy</td>
<td>2.5</td>
<td>1.3***</td>
<td>1.8</td>
</tr>
<tr>
<td>Ventricular fibrillation, ventricular tachycardia, or cardiac arrest</td>
<td>0.2</td>
<td>2.2***</td>
<td>1.4</td>
</tr>
<tr>
<td>Arrhythmias, other</td>
<td>0.9</td>
<td>1.5*</td>
<td>1.2</td>
</tr>
<tr>
<td>Conduction disorders</td>
<td>0.05</td>
<td>0.3*</td>
<td>0.2</td>
</tr>
<tr>
<td>Pulmonary heart disease</td>
<td>2.8</td>
<td>0.7***</td>
<td>1.6</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>0.3</td>
<td>0.6*</td>
<td>0.5</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>0.1</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>0.4</td>
<td>0.1**</td>
<td>0.2</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.6</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>0.7</td>
<td>0.1***</td>
<td>0.3</td>
</tr>
</tbody>
</table>

\*P < 0.05, \**P < 0.001, \***P < 0.0001 compared with SCD cases who had a post-mortem (chi-squared test).

AFrom the International Classification of Diseases versions 9 and 10.

BIncludes angina pectoris and chronic ischaemic heart disease.

CIncludes other restrictive and non-obstructive hypertrophic cardiomyopathy.

DIncludes paroxysmal tachycardia, atrial fibrillation and flutter, and unspecified cardiac arrhythmias.

4.5 Discussion

A method for the identification of SCD was established based on published evidence using the person-linked administrative morbidity and mortality data. The magnitude of SCD was subsequently estimated in a WA population of around 2 million between 1997 and 2010. The ASR of SCD was low (37.8 per 100,000 person-years), with IHD primarily recorded as the main underlying cause of death. Men had mostly higher ASRs of SCD than women. Notably, two in three SCD cases over 34 years of age had a CVD hospitalisation history in the previous 10 years before death, underscoring the potential for prevention at both the individual and public health levels.

4.5.1 Comparison with other studies

Compared to preceding studies using different methodologies, the present study in WA demonstrated a relatively low incidence rate of SCD, as shown in Table 4.5. A single source method was used in studies in the United States, the Netherlands, and England and Wales whereas a multiple sources method was used in studies in Belfast (Northern Ireland), Kelamayi, Yuxian, Beijing, and Guangzhou.
(China), Multnomah County (Oregon, the United States), Galway, Mayo, and Roscommon (West Ireland), and Sydney (Australia). Besides different methodologies, age and sex differences among studies make it complicated to compare the crude rates of SCD. Nevertheless, differences remain, in spite of recalculating the ASR from the current study using the approaches comparable to the studies in the literature. The estimated ASR in WA is around one-third of the rate in the United States and half that in the Netherlands, but is approximately 1.4-fold higher than that of Northern Ireland and China. Different study periods might play a role in the observed differences in incidence rates as well. Except for the difference of age and sex distribution, other possible reasons for the distinct incidence rates of SCD across studies are explored further in the following sections.
Table 4.5. Estimated rates of sudden cardiac death in various populations and the comparable Western Australia rate

<table>
<thead>
<tr>
<th>Setting</th>
<th>Study data collection</th>
<th>Population&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Age included (years)</th>
<th>Study source</th>
<th>Average Annual rate (per 100,000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reported rate</td>
</tr>
<tr>
<td>Current study</td>
<td>1997-2010</td>
<td>2,023,662</td>
<td>≥1</td>
<td>Linked data from hospital morbidity data collection and mortality register</td>
<td>37.8</td>
</tr>
<tr>
<td>United States[79]</td>
<td>1989-1998</td>
<td>140,360,000</td>
<td>≥35</td>
<td>National mortality data</td>
<td>162.1</td>
</tr>
<tr>
<td>Belfast, Northern Ireland[344]</td>
<td>2003-2004</td>
<td>1,704,924</td>
<td>All</td>
<td>Emergency medical services and necropsy reports</td>
<td>88.0</td>
</tr>
<tr>
<td>The Netherlands[16]</td>
<td>1995-2001</td>
<td>11,991,000</td>
<td>≥18</td>
<td>Medical records</td>
<td>103.8</td>
</tr>
<tr>
<td>Current study</td>
<td>1997-2010</td>
<td>2,023,662</td>
<td>≥1</td>
<td>Linked data from hospital morbidity data collection and mortality register</td>
<td>34.6</td>
</tr>
<tr>
<td>Multnomah County, Oregon[359]</td>
<td>2002-2005</td>
<td>660,486</td>
<td>All</td>
<td>Medical records, clinical data, and available autopsy examination</td>
<td>58.0</td>
</tr>
<tr>
<td>Galway, Mayo, and Roscommon, West Ireland[65]</td>
<td>2005</td>
<td>380,057</td>
<td>All</td>
<td>Emergency room resuscitation records, autopsies</td>
<td>51.2</td>
</tr>
<tr>
<td>England and Wales[42]</td>
<td>2002-2005</td>
<td>3,997,664</td>
<td>1-34</td>
<td>Office of National Statistics mortality data</td>
<td>1.8</td>
</tr>
<tr>
<td>Sydney, Australia[62]</td>
<td>1994-2002</td>
<td>3,140,645</td>
<td>1-35</td>
<td>Demographic, clinical, and autopsy data</td>
<td>1.1&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>£</sup>standard population and/or study population described in each corresponding study for rate calculation as the denominator;
<sup>§</sup>comparable Western Australia age-standardised rates were calculated using the standard population, age groups, and calendar years from each corresponding study;
<sup>†</sup>only calculated for our study period of 1997-2010;
<sup>‡</sup>Western Australia crude rates were calculated using the Western Australia population under the same study duration and age range from each corresponding study;
<sup>§</sup>calculated and estimated according to the literature.
4.5.2 Variation in case identification

Different methodologies (single versus multiple data sources) for case ascertainment explain some variation in the reported rates of SCD worldwide. A ‘death certificate’ method is the most common single source approach for case ascertainment. This approach provides the basis for objective mortality information where standard disease coding guidelines are in place. A validation study in the United States was conducted to compare the incidence rate of SCD derived from the ‘death certificate’ method with a multiple source method (153 per 100,000 person-years versus 53 per 100,000 person-years respectively).[17] The incidence rate of SCD identified by the ‘death certificate’ method was around 300% greater than that by the multiple source method (including circumstances of death, medical records, and available autopsy reports).[17]

Following the practice of the validation study indicated previously, the sensitivity analysis in the current study was conducted to compare the incidence rate of SCD from where only the underlying cause of death was used, with that derived from the four criteria developed using the linked mortality and morbidity data (100.6 per 100,000 person-years versus 34.6 per 100,000 person-years). As a result, a 166% higher rate of SCD was observed for cases identified by only the underlying cause of death than the four criteria. This lends further indirect support that Australia may have a lower rate of SCD than other developed countries as has been shown for out-of-hospital cardiac arrest.[75]

The incidence rates of SCD observed in this study are lower than in those studies using the most comparable data sources (national mortality statistics).[42, 79] Disparities in the coding practices for cause of death and hospital discharge diagnosis may also be responsible for this apparent difference in incidence rates.[360-362] Various rates of autopsy may partly explain different SCD rates among studies although autopsy rates have declined nationally and internationally.[66-68]

By using multiple criteria for identification, SCD case ascertainment may be enhanced in this study because it is based on current knowledge of pathophysiological mechanisms of SCD.[42, 62, 163]
Life-threatening conditions including arrhythmias are an important pathophysiological mechanism precipitating SCD,[62, 163] and therefore integral to capturing cases. Documented life-threatening conditions alone would provide a low estimate of SCD as unwitnessed cases are less likely to have any records of life-threatening conditions.[65, 363] The highest risk of SCD is observed in the first 28 days of myocardial infarction[282, 353, 354] thereby the inclusion of patients dying within 28 days of myocardial infarction hospitalisation. In addition, a post-mortem provides an indication of the death being unexpected and unexplained, [301] thus giving credence to including this into the criterion to identify cases.

### 4.5.3 Variation in risk profiles

Various risk profiles among different study populations may be another reason for the observed differences in the incidence rates of SCD between studies. Conventional risk factors contribute to three fourths of the CVD epidemic worldwide,[364] although different associations of risk factors for SCD exist among different populations. [365] For example, hypertension conferred a 1.5-fold greater hazard of SCD in the Women’s Health Initiative clinical trial whereas it conferred a 2.5-fold higher risk of SCD in the Nurses’ Health Study.[27, 28] Both studies were adjusted for multiple variables.[27, 28] Environmental and societal factors such as lifestyle, dietary habits, and genetic influences [365] may also play a role in SCD risk. It is noted that SCD occurs earlier in men, which is found in both the present and previous studies.[65, 163] The findings suggest men may have specific risk factors that predispose to SCD such as diabetes [101] deserving further investigation. Further research exploring the factors contributing to the variations in the incidence rates of SCD would provide insights into both the mechanism and the potential for prevention.

### 4.5.4 Variation in underlying cause of death

Consistent with earlier studies,[65, 79] IHD was the most common underlying cause of death, with myocardial infarction alone documented for around half and other IHD (such as chronic IHD) for 44% of all cause of death. Importantly, many of these cases with the underlying cause of death of other
IHD had a post-mortem, implying the challenges of determining cause of death certified by a doctor when other IHD was the underlying culprit. This is supported by studies that 40 to 70% of SCD cases had a post-mortem performed, half of whom had no previous medical history and had healed or fibrotic myocardial infarction, and coronary artery thrombus that was asymptomatic.[344, 346]

Akin to prior studies,[62] hypertrophic cardiomyopathy was a less frequent cause of SCD in the younger groups compared to other types of cardiomyopathy although the significance for the difference was not tested given the numbers identified for hypertrophic cardiomyopathy in the younger groups were numerically low. However, hypertrophic cardiomyopathy was a considerably more frequent than in the cases ≥35 years of age. Rheumatic heart disease and pulmonary heart disease were likewise more common in the 1-34 year age group. The classification of ‘ventricular fibrillation, ventricular tachycardia, cardiac arrest, and other dysrhythmias’ was not indicating a specific underlying disease state thereby being under-coded according to the ICD coding guidelines.[64, 320] However, underlying disease state might not be found for the 1-34 year-olds[58] and the ‘ventricular fibrillation, ventricular tachycardia, cardiac arrest, and other dysrhythmias’ are the common electrical sequence of events in SCD.[4, 37] A significantly higher proportion of the coding for ‘ventricular fibrillation, ventricular tachycardia, cardiac arrest, and other dysrhythmias’ in the younger group appears to support this.[62]

4.5.5 Study strengths and limitations

Population-wide estimation of SCD was derived by developing four criteria based on the currently available evidence using high-quality person-linked administrative mortality and morbidity data. Several limitations of the present study, however, merit attention. Albeit the four criteria developed from different perspectives to capture SCD, there still could be some SCD cases missing out using these four criteria, for example, individuals who die in hospital greater than 24 hours after admission but without a history of acute myocardial infarction within previous 28 days. If “SCD-related disease” as one of the diagnosis elements in the criteria was documented in the associated causes of death
rather than underlying cause of death, the case may be missed although the chance of this is believed to be low. It was not possible to access individual medical records, death certificates, and autopsy reports. Potential misclassification of diagnostic and cause of death coding cannot be excluded. There could be some SCD cases missing given the reported 74% of sensitivity for IHD according to a previous study on the reliability of cause of death data.[321] Yet the reported 97% of specificity for IHD facilitates the identification of “true SCD” cases with IHD as the underlying cause of death thus ensuring the quality of case identification as 87% of SCD cases in this study had IHD recorded as the underlying cause of death. The introduction of troponin testing for myocardial infarction diagnosis over the 14-year study period may also have led to earlier investigation and therapy,[366] thereby indirectly influencing the number of cases that were captured and defined as SCD.

4.6 Conclusions

Statutory administrative mortality and morbidity data can be used to estimate age-standardised and age-specific rates of SCD to provide a new approach for monitoring SCD where such collections exist. The magnitude of SCD was estimated and found to be appreciable in the WA population although the incidence rate of SCD was relatively lower than a limited number of studies available. Two thirds of SCD cases aged ≥35 years old had a CVD hospitalisation history in the preceding 10 years, highlighting the potential for primary and secondary prevention of SCD.
CHAPTER 5. POPULATION-LEVEL TRENDS IN SUDDEN CARDIAC DEATH

This chapter is based on the following manuscript:


This chapter provides an expanded discourse on the manuscript, and includes description of trends in incidence rates of SCD from 1997 to 2010 stratified by CVD hospitalisation history, gender, and age groups.

5.1 Introduction

The previous chapter reported a relatively low incidence rate of sudden cardiac death (SCD) in the Western Australia (WA) population compared to other studies in Australia and internationally. Different methodologies and various risk profiles (cardiovascular versus environmental and societal risk factors) in different study populations may have contributed to the differences observed which were discussed in Chapter 4. Different study periods across the studies when the primary and secondary prevention of SCD progressed as time passed by may have influenced the incidence rates of SCD. One epidemiological way of assessing whether SCD prevention has advanced or not is to examine the trends in incidence rates of SCD.

Apparent declining trends in incidence rates of SCD have been reported in the 1990s, with annual incidence rates decreasing by 1.2% to 1.8% in men and 0.6% to 1.2% in women.[20, 79, 93] Yet limited contemporary evidence exists. A study in the Netherlands suggested a sustained fall from 1990 to 2010, with annual incidence rates declining by 1.9% in men and 2.1% in women.[94] A Japanese study showed a downward trend in SCD incidence rates until 1996 which thereafter
plateaued to 2005.[22] The magnitude of reduction in the annual incidence rates was not reported in
the Japanese study.[22] The declining trends in SCD incidence rates in these studies suggest
beneficial contributions of SCD prevention in the 2000s, but this indication appears inconclusive due
to limited studies available.

The terms “primary” and “secondary” prevention used on the topic of SCD are inconsistent and
different from the conventional epidemiological definition of primary and secondary prevention for a
disease.[25, 367] Traditional epidemiology defines primary and secondary prevention of a disease as
prevention ahead of disease and prevention during disease respectively.[368] In essence, SCD is an
irreversible fatal event. Any preventive strategy for SCD is considered “primary” according to the
conventional epidemiological definition, such as implantation of implantable cardioverter-defibrillator
for ventricular arrhythmias and early defibrillation by automated external defibrillators.[367] As a
major component of cardiovascular disease (CVD), ischaemic heart disease (IHD) is the most
common underlying cause of SCD, accounting for approximately 80% of all SCD cases as reported in
Chapter 4 and elsewhere.[5] Another 20% of SCD cases have been found to have cardiomyopathy,
valvular heart disease, or other CVD recorded as the underlying cause of death.[26] The
improvement in SCD prevention may be mostly related to the primary and secondary prevention of
CVD.[25] Therefore, the concept of primary and secondary prevention of SCD was applied in this
chapter by absence or presence of CVD hospitalisation history referring to primary and secondary
prevention of underlying CVD respectively.

To better understand primary and secondary prevention of underlying CVD on SCD, SCD cases were
stratified by presence or absence of CVD hospitalisation history. The trends in incidence rates of
SCD without and with CVD hospitalisation history suggest the primary and secondary prevention of
SCD respectively. A few studies have explored such an effect by stratifying SCD cases based on the
CVD hospitalisation.[20, 24] The Framingham Heart Study reported downward trends in SCD from
1950 to 1999, with annual incidence rates decreasing by 1.0% in individuals without prior history of
IHD or heart failure and by 1.4% in those with prior history of IHD or heart failure.[20] Another
A community study in Olmsted County also showed declining trends in SCD both in those without and with prior IHD, with annual incidence rates decreasing by 0.9% and 2.3% respectively from 1979 to 1998.[24] The declining trends observed in the incidence rates of SCD coincided with declines in mean systolic blood pressure and total serum cholesterol and the proportion of current smoking, in contrast to the increase in mean body mass index and the proportion of diabetes.[20] Greater use of beta-adrenergic blockers, angiotensin-converting-enzyme inhibitors, statin therapy, antiplatelet, thrombolytic treatment, and coronary revascularisation were estimated to have contributed to reductions in IHD mortality based on published literature.[369, 370] All these findings suggest improvements in primary and secondary prevention of SCD.

In the 2000s, the increase in proportions of overweight, obesity, and diabetes persisted without marked changes in total serum cholesterol.[371] However, decreasing trends in proportions of hypertension and current smoking were still observed in Australia and worldwide.[22, 32] Widespread use of beta-adrenergic blockers, angiotensin-converting enzyme inhibitors, statin therapy, and percutaneous coronary intervention procedure were found to improve survival after acute myocardial infarction, IHD, or heart failure.[129, 296, 372-376] This chapter investigates the trends in the incidence rates of SCD overall and also by CVD hospitalisation history, gender and age groups within Australia. As the magnitude of SCD was found to be different across gender and age groups in Chapter 4, the trends in incidence rates of SCD by gender and age groups were also analysed in this chapter.

5.2 Study objectives

1. To examine trends in incidence rates of SCD in the WA population aged 35-84 years old from 1997 to 2010, stratified by CVD hospitalisation history, gender, and age groups.

2. To determine whether the relative risk of SCD in individuals with and without prior CVD hospitalisation history has changed during this period.
5.3 Methods

5.3.1 Study cohort

The study cohort of SCD cases was identified from the established method with four criteria based on the published evidence using the person-linked administrative mortality and morbidity data from 1997 to 2010 (Chapter 4). Specifically, criterion 1 captured individuals who died out of hospital or died in hospital within 24 hours of any-cause admission, and had an SCD-related disease as the underlying cause of death and an associated cause of death of ventricular fibrillation, ventricular tachycardia, or cardiac arrest. Criterion 2 captured individuals who died in hospital within 24 hours of admission for ventricular fibrillation, ventricular tachycardia, or cardiac arrest, and had an SCD-related disease as the underlying cause of death. Criterion 3 captured individuals who died out of hospital or died in hospital within 24 hours of any-cause admission, and had an SCD-related disease as the underlying cause of death and a post-mortem (>50% of cases). Criterion 4 captured individuals who died in or out of hospital within 28 days from the date of hospitalisation for acute myocardial infarction, and had an SCD-related disease as the underlying cause of death.

Lower and upper age limits were imposed as different underlying pathophysiology was in two age groups, with IHD as the most common cardiac pathology underlying SCD in adults aged ≥35 years old versus cardiomyopathy in those <35 years old. A low SCD incidence rate was in individuals aged <35 years and declining sensitivity for myocardial infarction from hospital morbidity data in the very elderly. Therefore, individuals aged <35 years or >84 years old were excluded. A sensitivity analysis was conducted to determine whether or not a similar trend was observed when no age limit was imposed. The ICD 9 from 1979, ICD-9-CM, from 1988, and ICD-10-AM, from July 1, 1999 were used to identify cardiovascular disease and comorbidity hospitalisation history (ICD manuals, coding practice and codes used were detailed in chapter 3).
To better understand observed SCD as the component of CVD death, CVD death was also analysed. Cardiovascular disease death was defined as death from any cardiovascular cause according to the underlying cause of death in the linked mortality and morbidity data (ICD-9-CM 390–459, ICD-10-AM I00-I99).

**5.3.2 Cardiovascular disease and comorbidity identification**

Cardiovascular disease and comorbidity hospitalisation history available from 21 diagnosis fields and prior procedures available from 11 fields were identified using a fixed 10-year lookback from the date of SCD excluding the 28 days prior to the most recent hospitalisation. Recent hospitalisation for SCD-related disease within 28 days of SCD was identified to reflect the health status shortly before death. Comorbidity was also identified from the 48 associated causes of death fields. This was particularly relevant to exploring comorbidity where cases of SCD had no hospitalisation history. To highlight different sources for identification of comorbidities, comorbidities are presented separately for individuals with hospitalisation history versus those without, and separately from the hospital morbidity and/or mortality data. The underlying cause of death field was not used to identify comorbidity as it was integral to defining SCD cases.

The ICD codes were used to identify comorbidities including IHD, myocardial infarction, atrial fibrillation, heart failure, hypertension, diabetes, chronic kidney disease (based on the Australian Institute of Health and Welfare definition)[377] (Table 5.1). Prior procedures included coronary revascularisation (percutaneous coronary intervention and coronary artery bypass grafting) and implantable cardioverter defibrillator. Percutaneous coronary intervention and coronary artery bypass grafting were identified under the corresponding procedure codes. Implantable cardioverter defibrillator was identified by the procedure codes for the insertion of an implantable cardioverter defibrillator and the contemporary code for insertion of the elements (leads/electrodes and patches) (Table 5.1). [378]
Table 5.1. International Classification of Diseases used to identify cardiovascular disease and comorbidity hospitalisation, and cardiac procedures in sudden cardiac death cases

<table>
<thead>
<tr>
<th>Category</th>
<th>ICD 9/ICD-9-CM codes</th>
<th>ICD-10-AM codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>390-459</td>
<td>100-199</td>
</tr>
<tr>
<td>Ischaemic heart disease*</td>
<td>410-414</td>
<td>120-125</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>410</td>
<td>I21, I22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>401-405</td>
<td>110-115</td>
</tr>
<tr>
<td>Heart failure</td>
<td>428</td>
<td>150</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>427.3</td>
<td>148</td>
</tr>
<tr>
<td>Diabetes</td>
<td>250</td>
<td>E10-E14</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>AIHW definition [377]</td>
<td>AIHW definition [377]</td>
</tr>
<tr>
<td>Coronary revascularisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon angioplasty</td>
<td>36.01, 36.02, 36.05, 5-363</td>
<td>35304-00, 35305-00, 38303-00, 38306-02</td>
</tr>
<tr>
<td>Percutaneous transluminal coronary angioplasty with stents</td>
<td>36.06, 36.07</td>
<td>35338-00, 35338-01, 35344-00, 35344-01, 38312-00, 38312-01, 38318-00, 38318-01, 38310-00, 38310-01, 38310-02, 38306-00, 38306-01, 38306-02</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>36.1, 5-361</td>
<td>38497-00, 38497-01, 38497-02, 38497-03, 38497-04, 38497-05, 38497-06, 38497-07, 38500-00, 38500-01, 38500-02, 38500-03, 38500-04, 38500-05, 38503-00, 38503-01, 38503-02, 38503-03, 38503-04, 38503-05, 90201-00, 90201-01, 90201-02, 90201-03</td>
</tr>
<tr>
<td>Implantable cardioverter defibrillator</td>
<td>37.94, 37.96, 37.98</td>
<td>38524-00, 38393-00, 38524-03, 90203-10, 38456-29, 38390-03, 38368-03, 38350-03, 38393-01, 38521-04, 38524-02, 90203-06</td>
</tr>
</tbody>
</table>

*includes myocardial infarction, stable and unstable angina, and chronic ischaemic heart disease.

AIHW, Australian Institute of Health and Welfare

### 5.3.3 Statistical analysis

Baseline characteristics and comorbidities of SCD cases are presented separately for men and women as mean ± standard deviation for continuous variables and frequencies (%) for categorical variables. Differences in continuous variables and categorical variables were evaluated using a t-test and chi-squared test respectively.

Annual rates of SCD were calculated using SCD counts as the numerator and the WA population for each year as the denominator.[327] For SCD incidence rates stratified by CVD hospitalisation history, annual counts of SCD cases with and without CVD hospitalisation history were used as the numerators and the prevalent CVD population and CVD-free population as the denominators respectively. To identify the CVD prevalent population in WA, individuals with any CVD hospitalisation history in the 10-years prior to 30th June in each calendar year who were alive at this
date, were identified. The CVD-free population was calculated as the prevalent CVD population subtracted from the entire WA population at 30th June for each study year. Rates were standardised by the direct method using the age distribution (5-year age groups) of the WA population in 2010.[327, 357]

As SCD identification during the middle of the study period (Table 5.2) was impacted by a lower number of post-mortem examinations conducted in WA,[302] the counts of SCD cases were adjusted in each 5-year age group and calendar years of 2002-2006, for each gender. The adjustment process had several steps and is detailed as follows. Firstly, the SCD identification was modified by removing the indicator of a post-mortem conducted (termed modified SCD definition). The absolute difference in counts was calculated between the modified and non-modified SCD identification. A Poisson log-linear regression model including 5-year age group (categorical variable), calendar year (continuous variable), and age group × calendar year, was then fitted for the absolute difference in counts to data from the unaffected years (1997 to 2001 and 2007 to 2010), and the fitted model used to predict values for the difference in counts for 2002 to 2006. Finally, these predicted differences in counts for 2002 to 2006 were subtracted from the counts using the modified SCD definition to obtain the adjusted counts for 2002 to 2006. All analyses presented in this chapter used observed counts for 1997-2001 and 2007-2010 and the adjusted counts for 2002-2006. Trends in the age-standardised SCD incidence rates before and after this adjustment are shown in Figure 5.1. Both deviance and chi-squared statistics shown in the Poisson regression model outputs suggested that no evidence of over-dispersion was found.
Table 5.2. Observed number of sudden cardiac deaths and age-standardised rates (per 100,000 individuals) by sex and age groups, aged 35-84 years, Western Australia, 1997-2010

<table>
<thead>
<tr>
<th>Calendar year</th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th>Total</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35-54 years</td>
<td>55-69 years</td>
<td>70-84 years</td>
<td>35-54 years</td>
<td>55-69 years</td>
<td>70-84 years</td>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>ASR</td>
<td>N</td>
<td>ASR</td>
<td>N</td>
<td>ASR</td>
<td>N</td>
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<td>103.2</td>
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<td>123</td>
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<td>14.3</td>
<td>84</td>
<td>119.2</td>
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<tr>
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<td>119.7</td>
</tr>
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<td>18</td>
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<td>147.9</td>
<td>&lt;5</td>
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<td>12.5</td>
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<td>49</td>
<td>16.5</td>
<td>79</td>
<td>54.5</td>
<td>118</td>
<td>191.1</td>
<td>14</td>
<td>4.8</td>
<td>30</td>
<td>21.3</td>
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<td>115.7</td>
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<tr>
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<td>24.1</td>
<td>112</td>
<td>74.3</td>
<td>165</td>
<td>260.9</td>
<td>21</td>
<td>7.0</td>
<td>31</td>
<td>21.2</td>
<td>81</td>
<td>104.1</td>
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<td>106</td>
<td>34.2</td>
<td>175</td>
<td>111.5</td>
<td>193</td>
<td>296.6</td>
<td>33</td>
<td>10.8</td>
<td>42</td>
<td>27.5</td>
<td>112</td>
<td>142.9</td>
</tr>
<tr>
<td>2008</td>
<td>104</td>
<td>32.8</td>
<td>165</td>
<td>101.4</td>
<td>180</td>
<td>269.0</td>
<td>30</td>
<td>9.6</td>
<td>37</td>
<td>23.5</td>
<td>90</td>
<td>111.2</td>
</tr>
<tr>
<td>2009</td>
<td>94</td>
<td>29.0</td>
<td>165</td>
<td>98.3</td>
<td>198</td>
<td>289.1</td>
<td>16</td>
<td>5.0</td>
<td>43</td>
<td>26.0</td>
<td>108</td>
<td>130.7</td>
</tr>
<tr>
<td>2010</td>
<td>88</td>
<td>26.6</td>
<td>150</td>
<td>85.3</td>
<td>174</td>
<td>244.5</td>
<td>32</td>
<td>9.8</td>
<td>36</td>
<td>21.2</td>
<td>91</td>
<td>108.3</td>
</tr>
</tbody>
</table>

N, number; ASR, age-standardised rate.
Figure 5.1. Trends in age-standardised sudden cardiac death rates before and after adjustment to observed events for 2002 to 2006, in 35-84-year-olds, Western Australia, 1997-2010

The estimated annual change in SCD incidence rates and CVD mortality rates (in percent) for the whole period was calculated from the exponential of the $\beta$-coefficient for calendar year from the age-adjusted Poisson log-linear regression models, separately for men and women. The trend results were tested by testing change in rates between the period 1997-2001 and 2007-2010 (excluding the period 2002-2006) overall, by gender, by age groups.

The age-adjusted rate ratio (RR) comparing the SCD rate in men versus women was calculated and presented for the calendar years 1997 and 2010. A Poisson regression model that included 5-year age group, sex, calendar year, and an interaction term sex $\times$ calendar year was used to test whether the RR comparing men versus women changed over the study period. The age-adjusted RR was also tested by comparing those with and without a CVD hospitalisation history in 1997-2001 versus 2007-2010 to test whether the change in RR was impacted by the period of 2002-2006. Accordingly a similar Poisson regression model that included 5-year age group, categorical calendar period, CVD
hospitalisation history and an interaction term CVD hospitalisation history × categorical calendar period was used.

5.4 Results

5.4.1 Case characteristics

A total of 7,160 SCD cases aged 35-84 years were included between 1997 and 2010, with 1600, 700, 3465, and 1395 cases identified from criterion 1, 2, 3, and 4 respectively. Men comprised two-thirds of cases and had a lower mean age at death than women (66.2 versus 71.4 years, $P<0.05$) (Table 5.3). The most common underlying cause of death was IHD (87% of cases) in both men and women. Approximately half of SCD cases underwent a post-mortem, with a higher proportion in men. Women had a higher proportion of recent hospitalisation for SCD-related disease, mainly for IHD, compared with men. There were 61% of women with CVD hospitalisation history, compared with 53% in men.
Table 5.3. Characteristics of sudden cardiac death cases in Western Australia, aged 35-84 years, 1997-2010

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men (n=4,957, 69.2%)</th>
<th>Women (n=2,203, 30.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (standard deviation)</td>
<td>66.2 (12.2)†</td>
<td>71.4 (11.5)</td>
</tr>
<tr>
<td>Indigenous status, %</td>
<td>4.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Underlying cause of death, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>myocardial infarction</td>
<td>38.4†</td>
<td>46.9</td>
</tr>
<tr>
<td>other ischaemic heart disease‡</td>
<td>51.9†</td>
<td>38.3</td>
</tr>
<tr>
<td>valvular heart disease</td>
<td>2.0*</td>
<td>2.8</td>
</tr>
<tr>
<td>cardiomyopathy</td>
<td>3.1*</td>
<td>1.9</td>
</tr>
<tr>
<td>ventricular fibrillation, ventricular tachycardia or cardiac arrest</td>
<td>0.7*</td>
<td>1.2</td>
</tr>
<tr>
<td>others§</td>
<td>4.0†</td>
<td>8.9</td>
</tr>
<tr>
<td>Post-mortem conducted, %</td>
<td>56.5†</td>
<td>39.3</td>
</tr>
<tr>
<td>Recent hospitalization prior to death, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sudden cardiac death-related disease</td>
<td>33.9†</td>
<td>48.4</td>
</tr>
<tr>
<td>ischaemic heart disease</td>
<td>27.6†</td>
<td>40.1</td>
</tr>
<tr>
<td>myocardial infarction</td>
<td>23.3†</td>
<td>35.8</td>
</tr>
<tr>
<td>ventricular fibrillation, ventricular tachycardia or cardiac arrest</td>
<td>17.4†</td>
<td>22.3</td>
</tr>
<tr>
<td>Cardiovascular disease hospitalisation history, %</td>
<td>53.3†</td>
<td>61.2</td>
</tr>
<tr>
<td>Other hospitalisation history, %</td>
<td>32.9</td>
<td>31.5</td>
</tr>
<tr>
<td>No hospitalisation history, %</td>
<td>13.8†</td>
<td>7.3</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillators, %</td>
<td>0.8*</td>
<td>0.1</td>
</tr>
<tr>
<td>Coronary revascularisation, %</td>
<td>8.6*</td>
<td>6.5</td>
</tr>
</tbody>
</table>

*P<0.05; †P<0.0001 (P-value from Pearson’s chi-squared tests for difference between men and women).
‡includes angina pectoris and chronic ischaemic heart disease.
§includes myocarditis, endocarditis, pericarditis, pulmonary heart disease, rheumatic heart disease, congenital heart disease, and heart failure.
||includes percutaneous coronary intervention and coronary artery bypass grafting.

The most common comorbidity identified from morbidity data was IHD (half had myocardial infarction) followed by hypertension and heart failure. (Table 5.4) The three most common comorbidities were likewise IHD, hypertension, and heart failure when the aggregation of both morbidity and mortality data was used. Women had a higher proportion of atrial fibrillation, hypertension, diabetes mellitus, and chronic kidney disease than men (all P<0.05). (Table 5.4) However, a lower proportion of women underwent coronary revascularisation than men (P<0.05). (Table 5.3) In cases with no prior hospitalisations, heart failure was the most common comorbidity (9.4%), recorded at death.
Table 5.4. Comorbidities of sudden cardiac death cases based on hospitalisation and mortality data in Western Australia, aged 35-84 years, 1997-2010

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>With hospitalisation history, % (n=6,315)</th>
<th>No hospitalisation history, % (n=845)</th>
<th>Entire cohort(^\ddagger), % (n=7,160)</th>
<th>Men, % (n=4,957)</th>
<th>Women, % (n=2,203)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospital Morbidity Data Morbidity Data or Mortality Data</td>
<td>Mortality Data</td>
<td>Hospital Morbidity Data or Mortality Data</td>
<td>Hospital Morbidity Data or Mortality Data</td>
<td>Hospital Morbidity Data or Mortality Data</td>
</tr>
<tr>
<td>Ischaemic heart disease(^\ddagger)</td>
<td>34.8</td>
<td>37.3</td>
<td>2.0</td>
<td>33.4</td>
<td>33.0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16.9</td>
<td>17.9</td>
<td>0.5</td>
<td>15.9</td>
<td>15.4</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14.9</td>
<td>18.2</td>
<td>0.5</td>
<td>16.1</td>
<td>15.0(^*)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>16.6</td>
<td>31.6</td>
<td>9.4</td>
<td>29.0</td>
<td>26.7(^\dagger)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32.8</td>
<td>44.9</td>
<td>6.6</td>
<td>40.4</td>
<td>36.7(^\dagger)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14.2</td>
<td>23.4</td>
<td>3.0</td>
<td>20.9</td>
<td>19.3(^\dagger)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>11.7</td>
<td>19.4</td>
<td>0.4</td>
<td>17.2</td>
<td>16.3(^*)</td>
</tr>
</tbody>
</table>

\(^\ddagger\)P<0.05; \(^\dagger\)P<0.0001 (P-value from Pearson’s chi-squared tests for difference between men and women).
\(^\ddagger\)includes all sudden cardiac death cases with and without hospitalisation history.
\(^\ddagger\)includes myocardial infarction, angina pectoris, and chronic ischaemic heart disease.
5.4.2 Trends in age-standardised rates

Figure 5.2 and Table 5.5 show the trends in age-standardised rates of SCD by sex. The average annual fall in age-standardised rates of SCD was greater in women (-4.0%/year, 95% confidence interval (CI) -5.0 to -3.0) than in men (-2.3%/year, 95% CI -2.9 to -1.7, interaction \( P=0.0039 \)). The age-adjusted risk of SCD comparing the period 2007-2010 to 1997-2001 was 0.83 (95% CI 0.78 to 0.89) in men and 0.69 (95% CI 0.63 to 0.76) in women. The sensitivity analyses to determine whether or not the age limits imposed affected the observed trend suggest a great decline in SCD incidence rates in women than men if no age limit was imposed, although trends were not statistically significantly different (-2.2%/year, 95% CI -2.8 to -1.7 in men; -2.9%/year, 95% CI -3.6 to -2.1 in women, \( P=0.05 \) for the interaction term sex×calendar year). A consistent declining trend in CVD mortality rates was observed from 1997 to 2010 (-4.9%/year, 95% CI -5.3 to -4.6 in men and -5.5%/year, 95% CI -5.9 to -5.1 in women).

Figure 5.2. Trends in age-standardised rates of sudden cardiac death (SCD) and cardiovascular disease (CVD) death in 35-84 year olds, Western Australia, 1997-2010
<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Deaths*, n</th>
<th>Person-Years</th>
<th>Average ASR (per 100 000)</th>
<th>Annual % Change (95% CI)</th>
<th>Period % Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Ages (years)</td>
<td>35-84</td>
<td>6,879,023</td>
<td>90.0</td>
<td>-2.3</td>
<td>-16.8</td>
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<td></td>
<td>2390</td>
<td>6,939,390</td>
<td>34.0</td>
<td>-4.0</td>
<td>-30.9</td>
</tr>
<tr>
<td></td>
<td>2.4</td>
<td>(2.2 to 2.6)</td>
<td>(2.7 to 3.3)</td>
<td>0.0039</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55-69</td>
<td>1,907,951</td>
<td>106.4</td>
<td>-2.7</td>
<td>-19.6</td>
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<tr>
<td></td>
<td>569</td>
<td>1,853,912</td>
<td>31.6</td>
<td>-4.8</td>
<td>-35.9</td>
</tr>
<tr>
<td></td>
<td>5.1</td>
<td>(3.9 to 6.7)</td>
<td>(2.6 to 4.0)</td>
<td>0.0316</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70-84</td>
<td>845,175</td>
<td>311.7</td>
<td>-3.4</td>
<td>-25.5</td>
</tr>
<tr>
<td></td>
<td>1527</td>
<td>1,010,775</td>
<td>152.6</td>
<td>-5.2</td>
<td>-38.7</td>
</tr>
<tr>
<td></td>
<td>1.9</td>
<td>(1.6 to 2.1)</td>
<td>(2.1 to 2.7)</td>
<td>0.0245</td>
<td></td>
</tr>
</tbody>
</table>

*Death numbers based on the adjustment for the years 2002 to 2006.
†Period % changes calculated from comparing the rate change for 2007-2010 versus 1997-2001, estimated from Poisson regression models including 5-year age group and categorical calendar period.
‡Annual age-adjusted rate ratios in men versus women.
§P-value for the trend in annual age-adjusted rate ratios in men versus women from 1997 to 2010, estimated from Poisson regression models including 5-year age group, sex, calendar year, and sex × calendar year.
ASR, age-standardized rate; CI, confidence interval; RR, rate ratio.
5.4.3 Trends in age-specific rates

Figure 5.3 and Table 5.5 show the trends in age-specific rates of SCD by gender. The interaction term for age group by calendar year was highly significant in men and women \((P < 0.0001\) for the interaction term age group\(\times\)calendar year, separately in men and women). Significant downward trends were observed for age groups 55-69 and 70-84 in both men and women. Upward trends were observed in the 35-54 age group but this was only significant in women \((4.4\%/\text{year}; 95\% \text{ CI} 1.4 \text{ to } 7.5)\). Because the rate in the first year of the study period for women aged 35-54 years was noticeably lower than other years \((2.5 \text{ per 100,000 person-years})\), the trend was also analysed in this age group with the calendar year \((1997)\) excluded. This changed the result from an upward trend to a non-significant downward trend \((-1.5\%/\text{year}, 95\% \text{ CI} -3.2 \text{ to } 0.3)\).
Figure 5.3. Trends in age-specific rates of sudden cardiac death in men (A) and women (B) aged 35-84 years, Western Australia, 1997 to 2010
The age-adjusted RRs comparing men versus women increased slightly from 2.4 in 1997 to 3.0 in 2010 ($P=0.0039$ for trend). However, the trends in age-adjusted RRs comparing men versus women varied across the age groups (Table 5.5). The age-adjusted RRs show a significant upward trend in the 70 to 84-year age group (from 1.9 in 1997 to 2.3 in 2010, $P=0.0245$), an increasing but not significant trend in the 55 to 69-year age group ($P=0.0573$), and a significant downward trend in the 35 to 54-year age group (from 5.1 in 1997 to 3.2 in 2010, $P=0.0316$).

### 5.4.4 Trends in age-standardised rates according to previous CVD hospitalisation history

Figure 5.4 shows there was a similar declining trend in age-standardised rates of SCD with CVD hospitalisation history for men (-2.5%/year, 95% CI -3.5 to -1.6) and women (-3.6%/year, 95% CI -5.0 to -2.2) and without CVD hospitalisation history for men (-2.1%/year, 95% CI -3.0 to -1.3) and women (-4.2%/year, 95% CI -5.5 to -2.9). Age-adjusted RRs comparing those with versus without CVD hospitalisation history were 1.3 (95% CI, 1.2 to 1.4) in men and 1.4 (95% CI, 1.3 to 1.5) in women for the overall study period. These RRs did not change from 1997-2001 to 2007-2010 (CVD hospitalisation history × categorical calendar period, interaction $P>0.05$ for men and women).
Figure 5.4. Trends in age-standardised rates of sudden cardiac death in individuals (A) with prior cardiovascular disease hospitalisation history and (B) without prior cardiovascular disease hospitalisation history, aged 35-84 years, Western Australia, 1997-2010
5.5 Discussion

This population-wide study shows a significant fall in incidence rates of SCD from 1997 to 2010, declining by 17% in men and 31% in women. Overall trends in SCD were driven by declining rates in those aged 55 to 84 years whereas young individuals aged 35 to 54 years showed limited improvement, albeit from a very low level particularly in women. The overall age-adjusted RRs of SCD comparing men versus women increased significantly over the study period. A declining trend was also observed in cases with and without CVD hospitalisation history.

5.5.1 Comparison with other studies

The downward trend in SCD incidence rates observed in this study derived from linked administrative data is mostly consistent with other reports.[20, 22, 79, 93, 94] However, cross study comparisons are problematic given different data sources and approaches to assessing and measuring SCD. The study of fatal CVD rates over the same period suggests the observed decline in SCD incidence rates is real and thus potentially preventable.

5.5.2 Primary prevention of underlying cardiovascular disease

To better understand the potential for prevention of SCD, CVD hospitalisation history was used as a proxy for manifest IHD and other CVD. The findings of this study identified cases with no prior CVD history as indicated by no history of hospitalisation for CVD, which is similar to the cohort observed in the historical Framingham Heart Study where no prior history of IHD or heart failure was included together to identify the cohort with no previous heart disease.[20] Both studies showed a significant reduction in SCD incidence rates, but the annual incidence rates decreasing by approximately 3% observed in the WA study, higher than the 1.0% observed in the Framingham Heart Study.[20] The reduction for these studies could be due to primary prevention of cardiovascular risk factors has improved and is influencing rates in the 2000s.[379]
Steadily declining prevalence of tobacco smoking was observed in men and women for at least three decades due to strong prevention approaches such as smoke-free laws and exposure to mass media campaigns.[379] Use of a high sensitive cardiac troponin assay for myocardial infarction diagnosis since the late 1990s facilitated early diagnosis of acute myocardial infarction.[380, 381] After uptake of troponin testing, increasing rates of hospitalisation for less severity of myocardial infarction increased the likelihood of early intervention thus improving the prognosis of myocardial infarction,[382, 383] which may have contributed to the decline of SCD incidence rates.

### 5.5.3 Secondary prevention of underlying cardiovascular disease

The decline in SCD incidence rates in individuals with prior CVD suggests the effects of secondary prevention were at work. Approximately 50%, 70%, and 80% of acute coronary syndrome survivors in WA were dispensed beta blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins respectively in 2008.[373] Survival benefit may have favourably impacted on the risk of SCD as shown in a WA population-based cohort study of 9,580 first hospitalised myocardial infarction individuals. This study showed a 42% reduction in the hazard of all-cause mortality in those who were dispensed a combination of beta blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins during the period 1995-2006.[384]

As individuals with heart failure have six to nine times increased risk of SCD compared to the general population,[385] effective evidence-based management of heart failure could benefit the SCD prevention.[374] Stable prescription rates at hospital discharge of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and increasing prescription rates of beta blockers were observed in a WA study of first heart failure patients between 1996 and 2006.[375] A reduction of 29% to 32% in all-cause mortality appears to support current declines observed in incidence rates of SCD.[375]
Acute coronary revascularisation procedures in the ST segment elevation myocardial infarction patient population have improved SCD and all-cause mortality after acute myocardial infarction.[281, 386, 387] Separate effects of coronary artery bypass grafting and percutaneous coronary intervention on the risk of SCD were not reported.

All these favourable clinical management and prevention therapies indicated above may all work together and be implicated in current downward trends in SCD in WA. This is indirectly supported by the finding of this study that currently only one third of SCD cases have comorbidities of IHD or heart failure in the preceding 10 years, compared to one half of SCD cases reported in the 1990s.[20]

5.5.4 Primary prevention of sudden cardiac death

Notably, <1% of SCD cases were assessed to have an implantable cardioverter-defibrillator implanted prior to death. Use of implantable cardioverter-defibrillator therapy in the WA population has increased from 0.8 in 100,000 in 1995 to 14.9 in 100,000 in 2009,[378] likely contributing to the declining SCD incidence rates observed in this study. A decreasing proportion of ventricular arrhythmias in SCD cases was observed (from 3.1% to 2.2%, \( P=0.0062 \) for trend, data not shown) over time as shown in other studies.[388] This is probably due to the increased use of implantable cardioverter-defibrillator therapy, advances in preventive and therapeutic interventions for IHD, and the ageing population.[389] These changes in mechanisms underlying SCD suggest that implantable cardioverter-defibrillators may not be relied upon for future reductions in SCD.

Progress in early access to defibrillation by automated external defibrillators and development of community-based first responder programs[390] may also have contributed to the observed decline in the incidence rates of SCD. In Australia, a public access defibrillation project demonstrated an 86% survival rate for sudden cardiac arrest from first response to ambulance handover,[390] although this project was launched in WA in 2004 and still a low number of automated external defibrillators were
accessible and limited to major public arenas during the study period.[391] The benefit of this project over the longer term on reducing SCD incidence rates merits further investigation.

5.5.5 Gender differences

A larger annual decline of SCD incidence rates was observed in women. This may be due to better survival rate after sudden cardiac arrest in women compared to men.[392] Currently there is no clear explanation for this gender disparity although improved survival from co-existing chronic conditions may be one reason. This study reported that of the SCD cases in older women, there was a higher proportion of hospitalisation for SCD-related disease and comorbidities. This suggests that the treatment of these related chronic conditions may have contributed to a greater survival rate in these women, and hence, reflected in the decline in the death rates as a result of SCD. Further research on the determinants of SCD is warranted to clarify the role of sex and chronic conditions.

Importantly, discordant age-adjusted RRs comparing men versus women across age groups were observed, with a decreasing gender disparity in 35-54-year-olds but a widening gap between men and women in 70-84-year-olds. These age group differences may be attributed to a greater IHD risk occurring in post-menopausal women,[330] and marginal improvement in the risk in young women, as observed in this study. This finding coupled with a rise in acute coronary syndromes incidence observed in the young age group in WA,[334] emphasises the need for public health initiatives to target women and young adults who may ignore early symptoms and signs of CVD.[101, 393, 394]

5.5.6 Rationale of counts adjustment for sudden cardiac death

A sudden decline in the number of autopsy examinations in WA impacted the SCD identification with the indicator of a post-mortem being integrated into a method of four criteria for SCD ascertainment developed in Chapter 4. The low number of post-mortem examinations observed in this study corresponded to two regional disasters with high death toll which occurred in 2002 and 2004 which led to under-resourcing and affected the post-mortem practice in the period 2002-2006 in WA.[302]
The impact of the low number of post-mortem examinations was examined and confirmed by the preliminary analyses shown in supplementary Figure S5.1. There were linear trends in the incidence rates of SCD where cases were identified by the criteria for SCD identification with the criterion with the indicator of a post-mortem excluded. A method of modelling the incidence rates of SCD using the observed and predicted SCD cases was developed to obtain a linear trend,[395] although the ability to measure the real trend in incidence rates of SCD in the middle period 2002-2006 was limited. The sensitivity analyses support the justification for case counts adjustment for 2002-2006 by comparing the trends in incidence rates of SCD in two periods (2007-2010 versus 1997-2001).

5.5.7 Study strengths and limitations

There are several strengths of this study. We applied the widely accepted definition and contemporary pathophysiology of SCD and using a 10-year examination of an individual’s administrative records of hospitalisation and death derived estimates for the rates of SCD in over one million adults. Stratifying our findings by a history of CVD is novel. In addition to multiple causes of death data, place of death, hospital discharge diagnoses, and indications that a post-mortem evaluation was undertaken have been used to provide more details for case identification. More than half of all cases had undergone a post-mortem, supporting the unexpected death that underpins our findings.[301] Concomitant trends in total cardiovascular death have been provided.

Some limitations of this study are acknowledged. In this retrospective observational study, approximately 80% of SCD cases occurred outside of hospital, which may limit correct identification and recording of SCD aetiology. Multiple data sources available were utilised to capture cases. Changes in coding standards over time may affect the counts of comorbidities, but this could be countered by using a 10-year lookback period to identify these conditions. For example, a WA study showed use of a 10-year lookback period to identify diabetes in an IHD population from ICD-10 codes, with increasing sensitivity from 82% to 90% and negative predictive value from 91% to 95% of diabetes when compared to no lookback period applied.[323] Similar levels of concordance were
observed by the ICD 9 codes when the 10-year lookback period was used.[323] Information on comorbidities was obtained from hospital and mortality data, potentially improving capture of these conditions as well.

Cases that truly did not have any history of CVD cannot be determined as less severe patients of CVD might be diagnosed and treated in the community. For example, population-based cohort studies have shown that a large proportion (59%) of newly diagnosed heart failure in a community require hospitalisation within two-years of diagnosis[396] and over 80% of incident cases of heart failure require hospital admission.[397] Around 80% of diabetes patients diagnosed in a community primary care have a hospitalisation history of CVD and CVD-related disease such as diabetes and chronic kidney disease within 10 years.[398]

Death certificates, original medical notes, and autopsy records were not able to be accessed. More than half of all cases had undergone a post-mortem, supporting the unexpected cause of death that underpinned the findings.[301] This is also supported by a previous study reporting the reliability of the mortality data at 74% sensitivity and 97% specificity for IHD.[321]

5.6 Conclusions

This population-based study highlights a 14-year decline in SCD incidence rates since 1997. These trends were evident in cases of SCD with and without prior CVD hospitalisation, suggesting past benefit and future potential from both primary and secondary prevention interventions. These trends were underpinned by declining SCD incidence rates in older age groups, with marginal improvement in younger individuals.
5.7 Supporting information

Supplementary Figure S5.1. Incidence rates of sudden cardiac death identified by four respective criteria separately in men and women

*Criterion 1: died out-of-hospital OR died in-hospital ≤ 24 hours of any-cause admission AND died of sudden cardiac death-related disease AND with ventricular fibrillation, ventricular tachycardia, or cardiac arrest occurred.

*Criterion 2: died in-hospital ≤ 24 h of admission for ventricular fibrillation, ventricular tachycardia, or cardiac arrest recorded in any diagnostic field AND died of sudden cardiac death-related disease.
Criterion 3: died out-of-hospital OR died in-hospital ≤ 24 hours of any-cause admission AND died of sudden cardiac death-related disease AND with indications of whether a post-mortem was conducted.

Criterion 4: died out-of-hospital OR died in-hospital following an admission for myocardial infarction as principal diagnosis within last 28 days AND died of sudden cardiac death related disease.
CHAPTER 6. INCIDENCE AND PREDICTORS OF SUDDEN CARDIAC DEATH AFTER AN INCIDENT CARDIOVASCULAR EVENT

6.1 Introduction

In recent decades there have been considerable advances in identifying predictors that elevate the hazard of sudden cardiac death (SCD).[330] These predictors include clinical predictors (medical conditions of heart and circulatory system), coronary procedures, and more traditional behavioural and biomedical risk factors as discussed in Chapter 2. Some of these predictors may have a direct relationship to SCD.[30, 330] Some others may be interrelated and play an intermediate role in the mechanisms underlying the aetiologies of SCD.[30, 330]

The declining trend in incidence rates of SCD in the Western Australian (WA) population coincide with declining mortality from cardiovascular disease (CVD) in the same population as shown in Chapter 5, congruent with other studies.[385] Primary prevention for CVD has likely contributed to declining trends both in SCD and CVD death, including declining prevalence of CVD risk factors such as tobacco smoking.[379] Active treatment of acute coronary syndrome or heart failure by increasing dispensing of medications such as beta blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins has contributed to improved survival.[374, 375, 384, 399]

In addition, progress on management and interventions aimed at predictors of fatal ischaemic heart disease (IHD) or CVD may have contributed to the declines in SCD, probably due to some overlap between predictors of SCD, IHD, and CVD death such as diabetes and chronic kidney disease.[385] Identification of SCD predictors particularly the clinical predictors for example diabetes and chronic kidney disease in the CVD population is of particular interest as individuals with a CVD
hospitalisation history have a three-fold higher incidence rate of SCD compared to those without (shown in Chapter 5).

This chapter focuses on the following four major cardiovascular events: myocardial infarction, heart failure, atrial fibrillation, and stroke. Myocardial infarction, heart failure, and stroke are common reasons for hospitalisation for CVD.[32] Atrial fibrillation is one of the most commonly managed cardiac problems by general practitioners and there is increasing incidence of hospitalisation for atrial fibrillation worldwide.[32, 326, 400] Myocardial infarction, heart failure, atrial fibrillation, and stroke annually affect around 55,000 to 780,000 Australians whereas they impact approximately 735,000 to 6,000,000 individuals in the United States each year.[32, 326, 401-405] The magnitude and predictors of SCD following each of these four events are reviewed separately in the following sections.

6.1.1 Magnitude and predictors of sudden cardiac death after myocardial infarction

Myocardial infarction remains a common life-threatening event. Individuals with a history of myocardial infarction have a four to six times higher risk of SCD compared to the general population.[385, 406, 407] Some randomised controlled trials and observational studies have assessed the outcome of SCD after myocardial infarction from the first month to many years.[171, 282, 408] The community study in Olmsted County of 2,997 post-myocardial infarction patients aged >25 years reported cumulative incidence of SCD of 1.2%, 3.0%, and 5.0% in the first month, 1 year, and 3 years respectively.[282] A randomised controlled trial of treatment with valsartan, captopril, or both in 14,609 post-myocardial infarction patients of all ages showed the cumulative incidence of SCD was more marked in those with left ventricular ejection fraction ≤30% than those >40% of left ventricular ejection fraction (13.0% and 6.0% respectively at 3 years).[353] Another randomised controlled trial of implantable cardioverter-defibrillator in 674 post-myocardial infarction patients aged 18 to 80 years old reported a higher cumulative incidence (8% at 3 years) of
Arrhythmic death in patients after myocardial infarction without undergoing an implantable cardioverter-defibrillator than those who had an implantable cardioverter-defibrillator (4.0% at 3 years, \(P=0.009\).[171] Whilst the risk of SCD after myocardial infarction persists, the magnitude of SCD in this patient population is likely to have declined during the 2000s.[171, 409, 410] The possible change is because of advances in coronary artery reperfusion and pharmacotherapy for myocardial infarction such as angiotensin-converting-enzyme inhibitors, and the increased application of both, in particular for presentation with ST segment elevation myocardial infarction.[171, 409-411] Clinical practice guidelines on the management of myocardial infarction have continued to advance for the population with myocardial infarction.[171, 409-411]

To understand the impact of chronic conditions on the prognosis of myocardial infarction is important, particular for SCD which is a lethal complication of myocardial infarction. Although one way to recognise this impact is to examine whether these chronic conditions can predict SCD, a limited number of studies are available. However, several observational studies have examined the protective factors of SCD after myocardial infarction.[281-283] A two-centre prospective study (FINland-GERmany myocardial infarction study) of 2,130 post-myocardial infarction patients aged \(\leq 75\) years old showed treatment with coronary revascularisation therapy, beta blockers, aspirin, statins, and angiotensin-converting enzyme inhibitors were protective factors for SCD in post-myocardial infarction patients surviving to hospital discharge during a mean follow-up of three years.[281]

A single-centre study of 1,018 40-day survivors of acute myocardial infarction or patients with old myocardial infarction in the FuWai Hospital in China confirmed coronary revascularisation therapy was a strong protective factor of SCD during a mean follow-up of three years.[283] In addition, age and ejection fraction \(\leq 25\)\% were found to be risk markers of SCD.[283]

The community study in Olmsted County as mentioned previously confirmed revascularisation therapy was a strong protective factor of SCD in post-myocardial infarction patients surviving to discharge during a median follow-up of five years.[282] Recurrent heart failure and Charlson
comorbidities score of three or more were found to be the risk markers of SCD.[282] This study did not specifically examine the predictors of SCD separately in the first or after 30-days of myocardial infarction.[282] All these studies did not either find or examine whether individual medical conditions such as heart failure and diabetes were associated with the increased risk of SCD. Therefore, investigating predictors of SCD following myocardial infarction could contribute further to the evidence base.

### 6.1.2 Magnitude and predictors of sudden cardiac death after heart failure

Heart failure is associated with high cardiovascular mortality and has a six to nine-fold greater risk of SCD compared with the general population.[385] Sudden cardiac death is common among patients with mild to moderate heart failure (New York Heart Association class II) whereas death from pump failure increases as heart failure becomes more severe.[412] Age-adjusted cardiovascular mortality has decreased since 1980 but mortality specifically linked to SCD has risen in individuals with heart failure.[413] This may be due to the increasing prevalence of heart failure and shifts in the distribution of mortality as a result of increasing SCD and declining death from progressive and severe heart failure due to advances in medical and non-pharmacologic therapies.[414]

A few observational studies and some randomised controlled trials were available to quantify the magnitude of SCD in patients with heart failure. An observational study in the United States of 40,223 heart failure patients of all ages with left ventricular ejection fraction >50% reported the cumulative incidence of SCD was 1.0% at one year and 3.0% at five years.[415] Some randomised controlled trials are presented where the incidence rates of SCD were reported as a secondary analysis. Specifically, a multicentre randomised controlled trial of irbesartan recruited 4,128 heart failure patients who had a strict cohort recruitment criteria as follows: >60 years old, preserved ejection fraction ≥45%, New York Heart Association class II to IV, and at least one hospital presentation for heart failure in preceding six months.[416] This trial showed the cumulative incidence of SCD was
1.2% at one year and 6.0% at five years.[416] However, a small randomised controlled trial of atorvastatin in 110 heart failure patients with left ventricular ejection fraction <30% showed the cumulative incidence of SCD was 6.0% and 22.5% in patients with and without atorvastatin therapy respectively at one year ($P=0.012$).[417]

A randomised controlled trial of metoprolol controlled release/extended release in 3,991 heart failure patients aged 40-80 years with ejection fraction $\leq 40\%$ reported the cumulative incidence of SCD was 4.1% and 6.0% in patients with and without metoprolol controlled release/extended release respectively at one year ($P=0.0002$).[418] A randomised controlled trial of losartan compared with captopril in 3,152 heart failure patients aged 60 years with ejection fraction $\leq 40\%$ reported the cumulative incidence of SCD was 8.0% and 5.0% in patients with losartan and captopril respectively at one year ($P=0.08$).[419] The randomised controlled trial of eplerenone in 6,632 patients demonstrated the cumulative incidence of SCD was 4.3% and 5.2% in the patients with and without eplerenone therapy respectively at one year ($P=0.03$).[420]

There is a high prevalence of chronic conditions such as diabetes and hypertension among heart failure patients who tend to be older than other cardiac populations.[421] These chronic conditions greatly increase the mortality risk and the challenges in SCD prevention. Some chronic conditions have been reported to elevate the risk of all-cause mortality in heart failure patients who had different degrees of severity.[422-425] However, less is known about whether these chronic conditions are predictors of SCD in patients with heart failure.

Two studies have tried to identify the predictors of SCD presented as follows.[415, 416] One study in the United States used the Duke databank to compile data from all in-hospital patients who have undergone a cardiac catheterisation from 1995 to 2004. The patients included in this study had left ventricular ejection fraction $>50\%$.[415] It was found that diabetes, myocardial infarction up to three days prior to the date of first cardiac catheterisation, the presence of mild mitral regurgitation, and the
severity of heart failure and coronary artery disease were found to be associated with an increase in the risk of SCD during a median follow-up of 4 years.[415]

The multicentre randomised controlled trial of irbesartan in heart failure patients as mentioned previously reported diabetes, myocardial infarction, left bundle branch block on the electrocardiogram, N-terminal prohormone of brain natriuretic peptide, age, and male gender were independently correlated to the increased risk of SCD after a mean follow-up of 4 years.[416] These may form another group of predictors of SCD following heart failure. Identifying predictors of SCD following heart failure becomes a critical first step for health care planning and future improvement of SCD.

6.1.3 Magnitude and predictors of sudden cardiac death after atrial fibrillation

Atrial fibrillation is the most common chronic cardiac rhythm disorder worldwide and associated with increased mortality compared to individuals without this disorder.[426-429] Emerging evidence indicates SCD is an important mode of death associated with atrial fibrillation.[204, 430] However, SCD was seldom specifically investigated in population-based studies. Only a few randomised controlled trials have reported the magnitude of SCD following atrial fibrillation.[166, 167] Two multination randomised controlled trials reported similar cumulative rates of SCD around 3.8% at 3 years.[166, 167] Specifically, the randomised controlled trial of dabigatran or warfarin recruited 18,113 atrial fibrillation patients who had at least one additional risk factor for stroke including left ventricular ejection fraction <40%, New York Heart Association class II, ≥75 years old or 65 to 74 years old plus diabetes, hypertension, or coronary artery disease.[166] The other randomised controlled trial of edoxaban recruited 21,105 atrial fibrillation patients aged ≥21 years with electrocardiographic evidence of atrial fibrillation within 12 months prior to randomisation, a CHADS2 score ≥2, and planned anticoagulation.[167] The annual incidence of SCD was 1.4% in patients treated with warfarin which was not significant lower than those treated with edoxaban (1.3%, \( P<0.05 \)). [167]
Few data are available to investigate the predictors of SCD in patients with atrial fibrillation although three studies have been identified.[166, 167, 431] The randomised controlled trial of dabigatran or warfarin in 18,113 atrial fibrillation patients presented previously reported heart failure, prior myocardial infarction, diabetes, hypertension, left ventricular ejection fraction <40%, intraventricular conduction delay, no statin use at baseline, no prior oral anticoagulant agent, and male gender were associated with an increased risk of SCD during a median follow-up of 2 years.[166]

Another randomised controlled trial examined the effect of antiarrhythmic drugs digitalis, a beta blocker, and a non-dihydropyridine calcium channel blocker, alone or in combination or electrical cardioversion without previous treatment with antiarrhythmic drugs in 522 patients with recurrent persistent atrial fibrillation.[431] This study reported prior myocardial infarction and presence of diabetes at inclusion were associated with an increased risk of SCD and the use of beta blockers during follow-up was a protective factor.[431] A concern of this study is that only patients with persistent atrial fibrillation were included, which was defined as non-self-terminating arrhythmia thereby requiring electrical cardioversion to restore normal sinus rhythm.

Recently, the randomised controlled trial of Xa inhibitor edoxaban with warfarin in 21,105 atrial fibrillation patients presented previously showed prior myocardial infarction, peripheral artery disease, New York Heart Association class I to II, non-use of beta blockers, digitals use, creatinine (per 10μmol/L increase), heart rate at baseline ≥80 bpm, weight (per 5 kg decrease), age≥75 years, and male gender were associated with the increased risk of SCD during a median follow-up of 2.8 years.[167] The results need to be applied with caution as SCD was predefined and adjudicated by a clinical end points committee where autopsies and specific details were not always available for each case, as acknowledged by the authors.[167] It is imperative to identify predictors of SCD following atrial fibrillation to facilitate the development of effective targeted interventions.
6.1.4 Magnitude and predictors of sudden cardiac death after stroke

The magnitude of SCD following acute stroke are often under-recognised although there were high proportions of cardiac arrhythmias and abnormal electrocardiogram occurring in 50% to 70% of acute stroke patients.[269, 270] Underlying cardiac problems or comorbidities may explain the high prevalence of cardiac arrhythmias following acute stroke.[263]

As few studies were available for the magnitude of SCD following stroke, fatal cardiac risk was reviewed as follows.[432-437] Epidemiological studies and randomised controlled trials showed 2% to 19% of stroke survivors died from fatal cardiac-related events in the short term (<3 months).[432-437] Studies of long-term cardiac risk (>30 days to 15 years) showed 3% to 41% of stroke patients had fatal events of myocardial infarction and ischaemic heart disease (IHD) or sudden death during the long term follow-up.[438-443] The common risk factors and pathological mechanisms between IHD and stroke, interaction between neurological and cardiovascular system, and central autonomic control disorders may contribute to cardiac arrhythmias in post-stroke patients and increase susceptibility to SCD.[444, 445]

Little is known about the predictors of SCD following acute stroke. Two studies have assessed the broader outcome of acute cardiovascular mortality but did not assess SCD specifically. The international stroke trials archive comprising multiple clinical trials (21 as of July 2006) in an academic database included patients of ischaemic stroke, stroke severity of <70 at baseline (range 0 to 100, the lower the score, the worse the neurologic deficit), and commencement of drug/placebo within 8 hours of stroke onset.[446] This study showed prior history of heart failure, diabetes, hypertension, baseline creatinine>115μmol/L, and a long QTc or ventricular extrasystoles on electrocardiography were associated with early cardiovascular mortality (<3 months) after stroke.[446] The Norwegian linkage data of National Population Register of Statistics and National Register of Cause of Death showed the predictors of long-term cardiovascular mortality (12 years or until death) to be stroke severity, haemorrhagic stroke, diabetes, IHD, right hemispheric stroke, age, and male gender.[447] It
is important to identify the predictors of SCD following stroke for planning potential prevention strategies of SCD.

6.1.5 Summary

Currently, there are a limited number of studies linking the incidence rates of SCD in individuals with incident CVD events of myocardial infarction, heart failure, atrial fibrillation, and stroke. Additionally, there are few population-based data on the predictors of SCD following the key CVD events. From a public health perspective, there is a need to examine the magnitude and predictors of SCD. Research on these likely reflects the magnitude of risk and the potential for prevention in high-risk individuals after myocardial infarction, heart failure, atrial fibrillation, and stroke. The focus of this chapter is to estimate the incidence rate of SCD following these four incident key CVD events. Subsequently, major medical conditions as candidate predictors were examined to predict SCD in a longer time after the incident event.

6.2 Study objectives

1. To estimate each the incidence rate of SCD following the incident CVD events of myocardial infarction, heart failure, atrial fibrillation, and stroke, in people aged 35 to 84 years in WA between 2000 and 2009.
2. To identify independent predictors of SCD separately in these four incident CVD events.

6.3 Methods

6.3.1 Dataset and study population

A linked individual-based mortality and morbidity data was used to identify the four incident CVD events from 2000 to 2009. Details of the dataset were shown in Chapter 3. The ICD-9 from 1979,
ICD-9-CM from 1988, and ICD-10-AM from July 1, 1999 were used to identify the four study subcohorts, potential predictors, and the outcome of SCD.

A low rate of SCD occurs in individuals aged <35 years (<3 in100,000 persons) and the predominant underlying pathology for SCD tends to be different in <35 and ≥35 year olds. [26, 39] At the other end of the age spectrum there is declining sensitivity for some medical conditions recorded as discharge diagnoses, such as myocardial infarction in individuals aged over 84 years old. [322] For these reasons, individuals aged <35 or >84 years were excluded in this study.

6.3.2 Identification of four incident subcohorts of myocardial infarction, heart failure, atrial fibrillation, and stroke

Incident myocardial infarction subcohort were identified from the linked dataset if myocardial infarction was recorded in the principal discharge diagnosis field and there was no hospitalisation history of myocardial infarction recorded in any discharge diagnosis fields in the preceding 15 years. Following the same practice, incident subcohorts of heart failure, atrial fibrillation, and stroke were identified separately. The coding for myocardial infarction, heart failure, atrial fibrillation, and stroke in the WA linked administrative health data was detailed in Chapter 3.

All incident cases of myocardial infarction, heart failure, atrial fibrillation, and stroke aged between 35-84 years were included in this study. There were a total of 54,871 incident CVD events of myocardial infarction, heart failure, atrial fibrillation, and stroke. This represented 51,373 individuals, with 6.5% of individuals appearing in more than one incident subcohort. As SCD incidence rate and clinical predictors were identified separately for the four subcohorts, the small number of individuals occurred in more than one subcohorts were retained in respective subcohorts.

Inter-hospital transfers of patients particularly with myocardial infarction are common for the purpose of diagnostic or therapeutic intervention, and thus were considered as part of the incident admission.
Therefore, inter-hospital transfers were identified when one day or less between hospitalisations was observed, and regarded as part of the incident episode of care.

For describing the comorbidities burden of the four subcohorts, a Charlson Comorbidity Index score was calculated for each individual. Of the 17 diagnostic categories in Charlson’s list of comorbidities (Supplementary Table S6.5), myocardial infarction was excluded for the incident myocardial infarction subcohort, as it was the primary focus of this chapter. Similarly, heart failure and cerebrovascular disease were excluded for the subcohorts of heart failure and stroke respectively. The presence of a Charlson comorbid condition was identified from any discharge diagnosis fields in a fixed 15-year lookback period prior to the incident admission or on the secondary diagnosis field at the incident admission.

### 6.3.3 Identification of predictors of sudden cardiac death

Candidate medical conditions as potential predictors of SCD refer to concurrent conditions at the incident admission or prior medical history of each condition in the fixed 15-year lookback preceding the incident event. Concurrent conditions were identified from the secondary discharge diagnosis fields at the incident admission whereas prior hospitalisation history of each condition was identified from any discharge diagnosis fields using a fixed 15-year lookback period prior to the incident admission. The exact same practice was used to identify candidate medical conditions including myocardial infarction, heart failure, atrial fibrillation, arrhythmia (including ventricular tachycardia, ventricular fibrillation, and cardiac arrest), diabetes, chronic kidney disease, hypertension, peripheral artery disease, chronic obstructive pulmonary disease, and stroke (including subarachnoid haemorrhage, intracerebral haemorrhage, occlusion and stenosis of precerebral arteries with cerebral infarction, and occlusion of cerebral arteries with cerebral infarction).

If a medical condition was used for identification of the study subcohort, the condition was not considered as a potential predictor for the subcohort. For example, in the subcohort of incident heart
failure, heart failure was not examined as a potential predictor in this subcohort. Myocardial infarction was considered by itself as a potential predictor in the subcohorts of incident heart failure, atrial fibrillation, and stroke. In the subcohort of incident myocardial infarction, prior IHD (including stable and unstable angina pectoris and chronic IHD) as the potential predictor were considered and identified from the prior hospitalisation history only.

Procedures including coronary revascularisation (percutaneous coronary intervention and coronary artery bypass grafting surgery) and implantable cardioverter-defibrillator were identified within 28 days of the incident admission. Given that coronary revascularisation procedures are most commonly used in patients with IHD, analysis of these procedures was only undertaken in the myocardial infarction and heart failure subcohorts. Preliminary analyses showed in the subcohort of myocardial infarction who had coronary revascularisation, 67% and 43% of patients underwent percutaneous coronary intervention and coronary artery bypass grafting respectively at the incident admission for myocardial infarction and/or within 28 days of the admission. Therefore, procedures occurring at the incident admission or within 28 days of the admission were included in the model. For the subcohort of heart failure who had coronary revascularisation, preliminary analyses showed 63% and 71% of patients underwent percutaneous coronary intervention and coronary artery bypass grafting respectively before the incident admission of heart failure. Less than 0.001% of patients had coronary revascularisation at the incident admission. Therefore, procedure identified from the 15-year look-back period prior to the incident admission was fitted to the models.

Demographic factors were adjusted in all the multivariable models in this chapter including age, sex, and Indigenous status. Age and sex status were taken from the incident admission. As under-reporting of Indigenous status is recognised in administrative health data collections, assessing more than one hospitalisation record assists the identification of Indigenous status. [449] If more than 25% of the number of hospitalisation records indicated Indigenous status out of the total number of hospitalisation records, an individual to be Indigenous was considered.
6.3.4 Follow-up

The primary endpoint was SCD, which was identified from the linked dataset by four established criteria and has been published elsewhere and detailed in Chapter 4 Section 4.3.3.[341] Follow-up was censored at the date of death for non-SCD cause(s) or at 30 June 2011, whichever came first. Six patients in the incident myocardial infarction subcohort, seven patients in the incident heart failure subcohort, two patients in the incident atrial fibrillation subcohort, and seven patients in the incident stroke subcohort who were recorded as dying during the follow-up period had a missing cause of death and were excluded from all analyses in this chapter. Specifically, two patients with the missing cause of death overlapped between two incident subcohorts of myocardial infarction and heart failure.

6.3.5 Statistical analysis

Baseline cohort characteristics are presented as mean and standard deviation for continuous variables and as percentages for categorical variables. A Charlson comorbidity index score was calculated for each case.

The overall incidence rates of SCD in four respective subcohorts were calculated using the total number of SCD cases that occurred in each subcohort during the follow-up as the numerator and the total number of each corresponding subcohort as the denominator. Considering each individual’s follow-up time, the incidence rates of SCD in each subcohort were calculated using SCD cases that occurred in each subcohort during the follow-up as the numerator and the total follow-up time for each individual in the corresponding subcohort as the denominator. Comparison of the incidence rates of SCD among each of the four subcohorts was made by dividing the incidence rate of SCD from each subcohort by the incidence rate of SCD from the general WA population. The incidence rate of SCD in the general WA population (from January 1, 2000 to June 30, 2011) was calculated using SCD cases as the numerator and the total follow-up time for the WA population for the period as the denominator.[327] Two-tailed values of $P<0.05$ were considered statistically significant.
Kaplan-Meier survival curves were used to estimate unadjusted cumulative incidence function of SCD where the LIFETEST Procedure in SAS version 9.4 was conducted for the Kaplan-Meier estimates. Log-rank $P$ values are presented for the comparison of unadjusted SCD rates between the four subcohorts.

Multivariable Cox regression models were used to determine the association between potential predictors and the hazard of SCD separately for the subcohorts of myocardial infarction, heart failure, atrial fibrillation, and stroke. Variables included in the models were candidate medical conditions (null value for each medical condition as the reference group), age (continuous), sex (female as the reference group), and Indigenous status (non-Indigenous as the reference group). For example, individuals without the medical condition of myocardial infarction were the reference group for those with myocardial infarction. The association coronary procedures and SCD in the subcohorts of myocardial infarction and heart failure was also fitted in the multivariable. Results are presented as hazard ratio (HR) with 95% confidence interval (CI). The proportional hazards assumption was tested with an interaction term for each variable and time. Violation of the assumption was found for most variables in the subcohort of myocardial infarction. No evidence of violation of the assumption was found in the subcohorts of heart failure, atrial fibrillation, and stroke. No evidence of poor model fit of all the Cox regression models was found.

To investigate whether common non-linear functions (inverse relation, quadratic, and exponential functions) exists between age and SCD, the variables of inverse of age, square of age, or exponential of age were separately added to the age-adjusted model. Statistically significant difference ($P<0.001$) was observed when separately adding the inverse of age, square of age, or exponential age into the models suggesting the presence of non-linear functions between age and SCD. R-square statistics for the age-adjusted models were calculated, for the inverse of age, square of age, and exponential age (17.6%, 17.7%, and 17.3% respectively). Therefore, square of age was selected and included in all multivariable adjustment models.
Secondary analysis

In the subcohort of myocardial infarction, some of the SCD cases occurred during the 28 days of incident myocardial infarction. These cases may be overestimated by relating to one of criteria for SCD identification developed in Chapter 4, despite multiple criteria for case identification may have improved this situation. To observe whether there was a possible overestimate, secondary analyses were conducted in 28-days survivors of myocardial infarction to estimate the cumulative incidence of SCD. The predictors of SCD in 28-days survivors of myocardial infarction were also analysed to observe whether the predictors changed after excluding death occurring during the first 28 days.

To observe whether the cumulative incidence of SCD in the other three subcohorts of heart failure, atrial fibrillation, or stroke was impacted by the risk of SCD occurring within the first 28 days of the incident event, the cumulative mortality of SCD was also estimated in 28-days survivors. The predictors of SCD in the 28-days survivors of incident heart failure, incident atrial fibrillation, or incident stroke were also analysed to observe whether the predictors changed after excluding death during the first 28 days. Patients surviving >28 days following the date of each incident key CVD event and aged between 35-84 years were included in the secondary analyses.

6.4 Results

A total of 20,356, 8,294, 12,015, and 14,160 individuals were identified with incident hospitalised myocardial infarction, heart failure, atrial fibrillation, and stroke respectively. When the cohorts were restricted to include only 28-day survivors of incident events, the cohorts comprised 19,145 people with myocardial infarction, 7,775 with heart failure, 11,910 with atrial fibrillation, and 12,184 with stroke.
6.4.1 Description of characteristics of the four subcohorts

Individuals with incident hospitalised heart failure had the highest mean age of all four subcohorts, followed by stroke, atrial fibrillation, and myocardial infarction. One in four incident myocardial infarction individuals was in the younger age group (35 to 54 years) while a third were in the older age group (70 to 84 years). One in ten individuals with incident heart failure were aged 35 to 54 years old whereas two thirds of individuals with incident heart failure were aged 70 to 84 years old. Just over half of individuals with atrial fibrillation or stroke were in the 70-84-year age group. Over two-thirds of incident myocardial infarction individuals were men whereas just over half of the other three respective subcohorts were men.

Individuals with incident atrial fibrillation had the lowest prevalence of all medical conditions examined compared to the other three subcohorts (Table 6.1). Hypertension was the most common medical condition recorded but with a high variation in the proportion across the four subcohorts, ranging from 37.4% in atrial fibrillation subcohort to 66.0% in stroke subcohort. Diabetes was the second most common medical condition recorded in the subcohorts of myocardial infarction, atrial fibrillation, and stroke whereas atrial fibrillation was the second most common in heart failure subcohort. Approximately half of individuals with incident myocardial infarction or incident atrial fibrillation had Charlson comorbidity index score at least one. Half of individuals with incident heart failure had Charlson comorbidity score at least three. Half of individuals with incident stroke had Charlson comorbidity score at least four. Approximately half of incident myocardial infarction individuals underwent percutaneous coronary intervention therapy within 28 days of incident admission, 33 times higher than individuals with incident heart failure. The subcohort of myocardial infarction also had higher proportion of coronary artery bypass grafting therapy than the subcohort of heart failure.
Table 6.1. Characteristics of cases with incident hospitalisation for myocardial infarction, heart failure, atrial fibrillation, and stroke, aged 35-84 years in Western Australia

<table>
<thead>
<tr>
<th></th>
<th>Myocardial infarction (n=20,356)</th>
<th>Heart failure (n=8,294)</th>
<th>Atrial fibrillation (n=12,015)</th>
<th>Stroke (n=14,160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, years (SD)</td>
<td>64.9 (12.3)</td>
<td>71.7 (10.9)</td>
<td>66.5 (11.8)</td>
<td>69.2 (12.0)</td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-54 years</td>
<td>24.1</td>
<td>9.7</td>
<td>17.9</td>
<td>15.1</td>
</tr>
<tr>
<td>55-69 years</td>
<td>36.6</td>
<td>25.8</td>
<td>37.7</td>
<td>28.8</td>
</tr>
<tr>
<td>70-84 years</td>
<td>39.3</td>
<td>64.5</td>
<td>44.4</td>
<td>56.1</td>
</tr>
<tr>
<td>Male</td>
<td>70.1</td>
<td>57.4</td>
<td>59.1</td>
<td>55.6</td>
</tr>
<tr>
<td>Indigenous status</td>
<td>4.6</td>
<td>5.7</td>
<td>1.7</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Medical conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>NI</td>
<td>17.9</td>
<td>6.2</td>
<td>9.0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>18.6</td>
<td>NI</td>
<td>13.1</td>
<td>11.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.1</td>
<td>34.6</td>
<td>13.5</td>
<td>25.8</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>14.0</td>
<td>25.2</td>
<td>7.5</td>
<td>12.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>55.7</td>
<td>62.8</td>
<td>37.4</td>
<td>66.0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>15.6</td>
<td>38.1</td>
<td>NI</td>
<td>22.7</td>
</tr>
<tr>
<td><em>Arrhythmias</em></td>
<td>7.2</td>
<td>4.7</td>
<td>2.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.7</td>
<td>7.6</td>
<td>2.4</td>
<td>NI</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>9.6</td>
<td>15.1</td>
<td>5.1</td>
<td>10.5</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>11.5</td>
<td>24.8</td>
<td>9.8</td>
<td>13.2</td>
</tr>
<tr>
<td>Prior ischaemic heart disease</td>
<td>22.3</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>46.2</td>
<td>21.0</td>
<td>53.1</td>
<td>1.5</td>
</tr>
<tr>
<td>1</td>
<td>17.1</td>
<td>19.8</td>
<td>18.7</td>
<td>22.0</td>
</tr>
<tr>
<td>2</td>
<td>11.7</td>
<td>14.5</td>
<td>11.8</td>
<td>10.0</td>
</tr>
<tr>
<td>3</td>
<td>8.3</td>
<td>12.5</td>
<td>6.3</td>
<td>24.2</td>
</tr>
<tr>
<td>4</td>
<td>5.1</td>
<td>9.7</td>
<td>3.6</td>
<td>13.4</td>
</tr>
<tr>
<td>5</td>
<td>3.6</td>
<td>7.3</td>
<td>1.8</td>
<td>9.4</td>
</tr>
<tr>
<td>≥6</td>
<td>8.0</td>
<td>15.3</td>
<td>4.7</td>
<td>19.6</td>
</tr>
<tr>
<td><strong>Prior procedures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>4.3</td>
<td>7.5</td>
<td>4.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>2.2</td>
<td>6.8</td>
<td>2.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>0.1</td>
<td>0.8</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Procedures at incident admission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>15.8</td>
<td>0.1</td>
<td>0.02</td>
<td>0</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>&lt;0.001</td>
<td>1.0</td>
<td>0.06</td>
<td>0</td>
</tr>
<tr>
<td><strong>Prior procedures and/or procedures at incident admission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>19.4</td>
<td>7.5</td>
<td>4.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>2.4</td>
<td>6.8</td>
<td>2.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>0.1</td>
<td>1.7</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Procedures within 28 days of incident admission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>43.5</td>
<td>1.3</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>6.3</td>
<td>0.8</td>
<td>0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>0.4</td>
<td>1.5</td>
<td>0.2</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data are percentage (%) unless otherwise indicated.
*includes concurrent conditions at incident admission and prior medical history unless otherwise indicated; cases could have multiple medical conditions.
*includes ventricular tachycardia, ventricular fibrillation, and cardiac arrest.
*includes subarachnoid haemorrhage, intracerebral haemorrhage, occlusion and stenosis of precerebral arteries with cerebral infarction, and occlusion of cerebral arteries with cerebral infarction.
*includes stable and unstable angina pectoris and chronic ischaemic heart disease, identified from the prior medical history only.
*identified within 28 days of the incident admission (inclusive).
SD, standard deviation; NI, not included.
6.4.2 Incidence rates of sudden cardiac death in the four subcohorts

Over a maximum follow-up of 11.5 years, the overall incidence rate of SCD was 6.5%, 4.2%, 1.5%, 1.4% in the subcohorts of myocardial infarction, heart failure, atrial fibrillation, and stroke respectively. Taking into account how many years each case contributed to the study, the incidence rate of SCD was higher in the subcohort of myocardial infarction, followed by heart failure, and then stroke and atrial fibrillation (Table 6.2). The incidence rates of SCD were 26.0 times, 21.8 times, 6.8 times, and 5.6 times higher in the subcohorts of myocardial infarction, heart failure, stroke, and atrial fibrillation respectively than the general WA population (0.5 per 1,000 person-years for the general WA population aged 35-84 years old). The range of median follow-up time was 3.2 to 5.0 years.

Table 6.2. Incidence rates of sudden cardiac death following incident hospitalised myocardial infarction, heart failure, atrial fibrillation, and stroke, in individuals aged 35-84 years in Western Australia

<table>
<thead>
<tr>
<th>Study subcohorts</th>
<th>Number of sudden cardiac death</th>
<th>Person-years</th>
<th>Incidence rate (per 1,000 person-years)</th>
<th>Median follow-up time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1,318</td>
<td>101,070</td>
<td>13.0</td>
<td>4.6</td>
</tr>
<tr>
<td>Heart failure</td>
<td>350</td>
<td>32,134</td>
<td>10.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>183</td>
<td>64,479</td>
<td>2.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>202</td>
<td>59,381</td>
<td>3.4</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Figure 6.1 shows the cumulative incidence of SCD in four subcohorts. Significant difference was found in the cumulative SCD incidence rates among the four subcohorts (Log-Rank 739.9, \( P<0.0001 \)). At the 29th days following the incident event, the cumulative incidence of SCD was high in the subcohort of myocardial infarction (4.3%, 95% CI 4.0% to 4.6%), but did not appreciably increase out to one year. At one year, the cumulative incidence of SCD remained highest in the subcohort of myocardial infarction (5.0%, 95% CI 4.7% to 5.3%), followed by the subcohort of heart failure (1.6%, 95% CI 1.3% to 1.9%). At five years, the subcohort of myocardial infarction still had the highest cumulative incidence of SCD (6.4%, 95% CI 6.0% to 6.4%), followed by the subcohort of heart failure (5.0%, 95% CI 4.4% to 5.6%). From eight years onwards, the cumulative incidence of SCD became higher in the subcohort of heart failure (8.1%, 95% CI 7.1% to 9.1%), followed by the subcohort of myocardial infarction (7.4%, 95% CI 7.0% to 7.8%).
The cumulative incidence of SCD was equivalent in subcohorts of atrial fibrillation and stroke at one year (0.4%, 95% CI 0.3% to 0.5%). The cumulative incidence at five years were similar in the subcohorts of atrial fibrillation and stroke (1.4%, 95% CI 1.2% to 1.6% for atrial fibrillation; 1.7%, 95% CI 1.4% to 2.0% for stroke).

Figure 6.1. Kaplan-Meier cumulative mortality curves for sudden cardiac death (SCD) following incident hospitalised myocardial infarction (MI), heart failure (HF), atrial fibrillation (AF), and stroke (Str) in individuals aged 35-84 years in Western Australia (Log-Rank 739.9, P<0.001)

When the subcohorts were analysed including only those who survived the first 28 days, the incidence rate of SCD was higher in the incident heart failure rather than incident myocardial infarction subcohort (Supplementary Table S6.2). The cumulative incidence of SCD at five years was highest in 28 days survivors of incident heart failure, followed by incident myocardial infarction (4.4%, 95% CI 3.8% to 5.0% versus 2.1%, 95% CI 1.9% to 2.3% ) (Supplementary Figure S6.1). The incidence rates
of SCD in 28 days survivors of incident atrial fibrillation and incident stroke were similar to the results observed in the overall subcohorts.

### 6.4.3 Predictors of sudden cardiac death in the four subcohorts

Table 6.3 presents multivariable-adjusted hazard ratios for the association of various medical conditions with the hazard of SCD for the four subcohorts after adjustment for age, sex, Indigenous status, and all candidate predictors. Arrhythmias and chronic obstructive pulmonary disease were associated with a 5.2-times and 1.2-times respectively greater hazard of SCD following incident myocardial infarction. Individuals in the subcohort of myocardial infarction had 83% and 64% higher hazard of SCD if they had stroke or chronic kidney disease. Atrial fibrillation had borderline association with SCD. Hypertension and atrial fibrillation were associated with a lower hazard of SCD (HR 0.81, 95% CI 0.72, 0.92; HR 0.86, 95% CI 0.76, 0.98 respectively).

When coronary procedures were added to the model for the incident myocardial infarction subcohort, the hazard of SCD was 62%, 61%, and 94% lower for individuals who underwent the percutaneous coronary intervention therapy (HR 0.38, 95% CI 0.33 to 0.44), coronary artery bypass grafting therapy (HR 0.39, 95% CI 0.29 to 0.52), or implantable cardioverter-defibrillator therapy (HR 0.06, 95% CI 0.01 to 0.42) respectively. However there was limited change in the multivariable-adjusted hazard for all medical conditions after adjustment for procedures undergone within 28 days of the incident admission.
Table 6.3. Multivariable-adjusted hazard ratios and 95% confidence intervals of sudden cardiac death following incident hospitalised myocardial infarction, heart failure, atrial fibrillation, and stroke in individuals aged 35-84 years in Western Australia

<table>
<thead>
<tr>
<th>Medical conditions</th>
<th>Myocardial infarction (n=20,356)</th>
<th>Heart failure (n=8,294)</th>
<th>Atrial fibrillation (n=12,015)</th>
<th>Stroke (n=14,160)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age£</td>
<td>1.05 (1.04, 1.06)</td>
<td>1.02 (1.01, 1.04)</td>
<td>1.06 (1.04, 1.07)</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>0.87 (0.77, 0.98)</td>
<td>1.22 (0.98, 1.52)</td>
<td>1.04 (0.77, 1.40)</td>
</tr>
<tr>
<td></td>
<td>Medical conditions§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td>NI</td>
<td>1.82 (1.43, 2.32)</td>
<td>1.94 (1.29, 2.92)</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td>2.16 (1.90, 2.44)</td>
<td>NI</td>
<td>2.59 (1.86, 3.59)</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>1.00 (0.87, 1.13)</td>
<td>1.01 (0.79, 1.28)</td>
<td>1.47 (1.02, 2.12)</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease</td>
<td>1.64 (1.44, 1.87)</td>
<td>1.23 (0.96, 1.59)</td>
<td>1.37 (0.89, 2.11)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>0.81 (0.72, 0.92)</td>
<td>0.87 (0.69, 1.10)</td>
<td>1.09 (0.79, 1.51)</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
<td>0.86 (0.76, 0.98)</td>
<td>0.91 (0.73, 1.14)</td>
<td>NI</td>
</tr>
<tr>
<td></td>
<td>Arrhythmias*</td>
<td>5.15 (4.54, 5.83)</td>
<td>2.78 (1.96, 3.92)</td>
<td>2.19 (1.17, 4.12)</td>
</tr>
<tr>
<td></td>
<td>Stroke‡</td>
<td>1.83 (1.54, 2.17)</td>
<td>0.90 (0.58, 1.40)</td>
<td>0.99 (0.46, 2.13)</td>
</tr>
<tr>
<td></td>
<td>Peripheral artery disease</td>
<td>1.14 (0.98, 1.33)</td>
<td>1.30 (0.98, 1.72)</td>
<td>1.44 (0.90, 2.29)</td>
</tr>
<tr>
<td></td>
<td>Chronic obstructive pulmonary disease</td>
<td>1.20 (1.05, 1.39)</td>
<td>1.25 (0.99, 1.59)</td>
<td>1.27 (0.85, 1.88)</td>
</tr>
<tr>
<td></td>
<td>Prior ischaemic heart disease†</td>
<td>1.08 (0.96, 1.23)</td>
<td>NI</td>
<td>NI</td>
</tr>
</tbody>
</table>

£hazard ratios at mean age.
§includes concurrent conditions at incident admission and prior medical history unless otherwise indicated.
*includes ventricular tachycardia, ventricular fibrillation, and cardiac arrest.
‡includes subarachnoid haemorrhage, intracerebral haemorrhage, occlusion and stenosis of precerebral arteries with cerebral infarction, and occlusion of cerebral arteries with cerebral infarction.
†includes stable and unstable angina pectoris and chronic ischaemic heart disease, identified from the prior medical history only.
NI, not included.
In contrast, a few medical conditions had significant associations with the hazard of SCD after adjusting for age, sex, Indigenous status, and all medical conditions stated in the table in the subcohort of heart failure (Table 6.3). Individuals in the subcohort of heart failure had 82% and 178% higher hazard of SCD if they had myocardial infarction and arrhythmias respectively. Slight changes of the hazard ratios were observed when adjusting for procedures within 28 days of incident admission. Percutaneous coronary intervention undergone before the incident admission was associated with a lower hazard of SCD (HR 0.56, 95% CI 0.36, 0.86). No prior coronary artery bypass grafting or implantable cardioverter-defibrillator therapy was found to be significantly associated with the hazard of SCD (HR 0.79, 95% CI 0.53 to 1.20; HR 1.26, 95% CI 0.50 to 3.16).

Independent predictors of SCD observed in the subcohort of atrial fibrillation were slightly different to the former two subcohorts. Diabetes was the independent predictors of SCD in this subcohort while it was not in the former two subcohorts. Heart failure and arrhythmias had 2.6-fold and 2.2-fold respectively increased hazard of SCD following incident atrial fibrillation after adjusting for age, sex, Indigenous status, and all medical conditions stated in the table. Individuals in this subcohort had 94% and 47% greater hazard of SCD if they had myocardial infarction and diabetes respectively (Table 6.3).

Independent predictors of SCD were also observed differently in the subcohort of stroke compared to the other three subcohorts (Table 6.3). Myocardial infarction, chronic kidney disease, and peripheral artery disease were associated with 86%, 100%, and 105% respectively higher hazard of SCD following incident stroke after multivariable adjustment. Individuals in this subcohort had borderline association with the increased hazard of SCD if they had atrial fibrillation.

The secondary analyses showed some predictors of SCD changed in 28 days survivors of incident myocardial infarction. Diabetes, prior IHD, and peripheral artery disease became predictors of SCD whereas arrhythmia no longer predicted SCD in 28 days survivors of myocardial infarction. Predictors of SCD slightly changed in 28 days survivors of incident heart failure and stroke.
Arrhythmia was not predictive of SCD while peripheral artery disease became the predictor in 28 days survivors of incident heart failure. Chronic obstructive pulmonary disease was found to have borderline association with the increased hazard of SCD in 28 days survivors of incident stroke. Predictors of SCD did not change in the secondary subcohort of atrial fibrillation (Supplementary Table S6.3).

6.5 Discussion

This chapter observed that the magnitude of SCD was high following incident hospitalisation for key CVD events compared to the general WA population. Specifically, the incidence rate of SCD was highest in the subcohort of myocardial infarction, followed by heart failure, stroke and then atrial fibrillation during an approximately median follow-up of 4.1 years.

The predictors of SCD observed in the four subcohorts were distinct from each other although some common predictors were recognised. Arrhythmia and myocardial infarction were the most common predictors of SCD mostly across the subcohorts. Arrhythmia and heart failure had the highest hazard of SCD among all the medical conditions in the subcohorts of myocardial infarction, heart failure, and atrial fibrillation. Both percutaneous coronary intervention and coronary artery bypass grafting were strong protective factors of SCD in the subcohort of myocardial infarction. The novelty of this study is that it extends the findings of the predictors of SCD following the four major CVD events to the Australian population.

6.5.1 Various incidence of sudden cardiac death

6.5.1.1 Comparison of incidence of sudden cardiac death following myocardial infarction

The cumulative incidence function of SCD in the subcohort of myocardial infarction was different from that observed in literature.[171, 281-283] This WA study reported 3.6 times and 1.7 times
higher cumulative incidence of SCD at the 29th days and at one year respectively than those observed in the community study in Olmsted County (1.2% at 30 days and 3.0% at one year).[282] However, the gap in cumulative rates in both studies closed somewhat at five years (6.4% from the WA study versus 6.9% from the Olmsted County study).[282]

The secondary analysis in this WA study demonstrated lower cumulative incidence of SCD in 28-days survivors of myocardial infarction compared to the defibrillator implantation trial and the observational study in the FuWai Hospital.[171, 283] The randomised controlled trial of use of defibrillator showed 2.5% in individuals undergoing implantable cardioverter-defibrillator therapy at one year and 5.0% at four years in the myocardial infarction survivors at 6 to 40 days over a maximum follow-up of four years.[171] The observational study in the FuWai Hospital showed the cumulative incidence of SCD was 2.5% in individuals undergoing revascularisation at one year and 3.2% at five years in 40-days survivors of myocardial infarction during a median follow-up of 2.5 years.[283] This WA study of the low cumulative incidence of SCD in 28 days survivors is similar to the FINland-GERmany study showing that 1.0% and 2.5% of post-myocardial infarction patients undergoing revascularisation had an SCD at one year and at four years respectively during a mean follow-up of 2.9 years.[281]

Comparison of the magnitude of SCD among various study populations with different enrolment criteria, different duration of follow-up time, and different medication and procedures treatment is problematic. The differences in cumulative incidence of SCD may be attributed to several factors. First, the incidence rates of SCD after myocardial infarction in observational studies could be higher than that reported in randomised controlled trials, reflecting potential limits of external validity from the strict selection process for the internal validity of treatment trials.[453]

Second, a conservative definition of incident myocardial infarction was applied in the WA study. First-ever myocardial infarction was identified from the principal hospital discharge diagnosis. A fixed 15-year lookback period was applied to clear out any prior hospitalisation history of myocardial
infarction. However, the incident myocardial infarction status was ascertained by reviewing the medical records available for the abstractors in the community study in Olmsted County.[282] A long look-back period used in this thesis to exclude any prevalent events facilitates the identification of a “clean” incident cohort for myocardial infarction, thus more accurately identifying first-ever events.

Third, the difference seen in these studies may also relate to the study populations who may have a different genetic background.[454] A higher admission-based age-standardised case fatality after acute myocardial infarction observed in Australia than Denmark, New Zealand, and United States appear to support the higher cumulative incidence of SCD in Australia.[455]

Fourth, different gender distribution may have impacted the cumulative incidence of SCD. The incidence rates of SCD could increase by theory if men comprise a high proportion of the cohort as men have a much higher incidence rate of SCD than women before 75 years of age.[4, 341] This is supported by men constituting more than two thirds of the subcohort of myocardial infarction in the WA study compared to the study in Olmsted County (59% of the cohort).[282]

Fifth, aggressive evidence-based treatment including antiplatelets, thrombolysis, beta blockers, and coronary artery revascularisation therapy for myocardial infarction in hospital and on discharge in Australia has contributed to the decline in IHD mortality.[456] The improvement in medical treatment of myocardial infarction may have had an important impact on the observed low incidence rate of SCD the 28 days survivors of myocardial infarction in WA.

Considerably elevated risk of SCD observed in the first 28 days after myocardial infarction was replicated in many studies,[282, 353, 457] which is related to electrical instability of the myocardium.[458] After the first 28 days, the risk of myocardial infarction stably increased which is explained by the myocardial remodelling resulting in re-entrant fatal arrhythmia.[458] The risk of SCD in 28 days survivors of myocardial infarction decreased gradually with time, consistent with the literature.[282, 353, 457] These findings suggest the first 28 days may be the critical time for early
intervention and a potential role for SCD prevention. This is supported by the finding in this WA study that half of the individuals underwent coronary revascularisation therapy within 28 days. The SCD benefit of coronary revascularisation is suggested by ongoing evidence.[459, 460]

Implantable cardioverter-defibrillator therapy implanted within 28 days of the incident myocardial infarction being the strong predictive factor against SCD observed in this WA study also appears to support the timing despite a very small number (0.4%) of the subcohort of myocardial infarction had this therapy. The small number might be due to the short 28 days observed time as the clinical guidelines recommend the implantable cardioverter-defibrillator is implanted more than one month after the most recent myocardial infarction.[461] Even though the observed time was extended to the whole follow-up in this WA study, the number of individuals with implantable cardioverter-defibrillator remained small (1.9% of the total, data not shown).

6.5.1.2 Comparison of incidence of sudden cardiac death following heart failure

The cumulative incidence of SCD in the subcohort of heart failure was comparable to the studies, which recruited the heart failure patients with left ventricular ejection fraction \( \geq 45\% \).[415, 416] Specifically, the randomised controlled trial of irbesartan showed the cumulative incidence of SCD was 1.2% at one year and 6.0% at five years while another observational study using the Duke Databank for CVD reported the cumulative incidence of 1.0% and 3.0% at one year and five years respectively.[415, 416] However, the randomised controlled trial of atorvastatin reported on a worsening magnitude of SCD in heart failure patients with left ventricular ejection fraction <30% over one-year follow-up.[417] The cumulative incidence of SCD was 6.0% in patients received statin therapy and 23.0% in those received non-statin therapy.[417] Different left ventricular ejection fraction cut-offs for recruitment may explain the differential magnitude of SCD because there is an inverse association between the mortality and left ventricular ejection fraction which may have contributed to the increase in the cumulative incidence of SCD.[4, 356] Ejection fraction was not accessible in the administrative dataset.
6.5.1.3 Comparison of incidence of sudden cardiac death following atrial fibrillation

The incidence rate of SCD in the subcohort of atrial fibrillation was found to be lower than that observed in two clinical trials.[166, 167] Both the randomised controlled trials showed the cumulative incidence of SCD was approximately 1.2% at one year and 3.8% at three years in patients with atrial fibrillation during a median follow-up of around 2.5 years.[166, 167] The higher cumulative incidence of SCD observed in the clinical trials may in part be due to different eligibility criteria for recruitment. Patients recruited in the clinical trials had at least one additional cardiac risk factor or CHADS2 score ≥2 whereas those in the WA study was incident cases who had no prior hospitalisations for atrial fibrillation in the fixed 15 years lookback period.[166, 167] Half of the subcohort of atrial fibrillation in WA had a Charlson index score of zero. Atrial fibrillation patients in the WA study were six years younger than those in the clinical trials.[166, 167] All these may lend indirect support that incident atrial fibrillation patients in WA had a lower incidence rate of SCD.

6.5.1.4 Comparison of incidence of sudden cardiac death following stroke

Very little is known about the incidence rate of SCD after stroke. This study in WA reports the overall incidence rate of SCD following incident stroke was 1.4% during a median follow-up of 3.7 years, which was low in comparison to the clinical trials and epidemiological studies with a broader outcome such as cardiovascular death.[432-443] High variations in the overall incidence rate of fatal cardiac event (2% to 41%) in the reported studies irrespective of short-term (<3 months) and long-term (>30 days to 15 year) may in part be due to their composite outcome of fatal myocardial infarction, sudden death, and other cardiovascular death.[432-443] The low incidence rate of SCD observed in the WA study is similar to a registry-based study using the Ontario Stroke Registry showing that 2.5% of patients after ischaemic stroke had a cardiac arrest.[462]
6.5.2 Predictors of sudden cardiac death

6.5.2.1 Comparison with other studies

The WA study’s population-level data on the predictors of SCD following myocardial infarction add to the literature by showing heart failure, chronic kidney disease, arrhythmias, stroke, and chronic obstructive pulmonary disease were independent predictors of SCD. These observed predictors either were not examined in other multivariable analyses or did not reach statistical significance in other studies.[281, 282] Coronary revascularisation therapy was found to be a protective factor of SCD which is in accord with the published data.[281-283] This is in spite of differences in SCD identification, difference in follow-up duration, and single-centre versus population-based studies.[281-283] The results in the WA study confirm and emphasise the importance of coronary revascularisation therapy, possibly by providing important antiarrhythmic benefits thereby preventing SCD in the post-myocardial infarction population. Other mechanisms of coronary revascularisation therapy against SCD include revascularisation of jeopardised myocardium, improvement in pump function indicated by left ventricular ejection fraction, and promoting reverse remodelling.[280]

Only myocardial infarction and arrhythmias were observed to be predictors of SCD in the subcohort of heart failure. It is not readily apparent why other cardiovascular risk factors such as diabetes had no significant associations with the increased hazard of SCD which was discordant with the published findings.[415, 416, 463] Different findings across studies likely reflect multiple factors including different selection criteria for the study cohorts, different absolute risk of SCD across the study cohorts, different variables available for adjustment. This WA study included post incident hospitalised heart failure patients aged 35-84 years old and adjusted for the major chronic conditions. The overall incidence rate was 4.2% during a median follow-up time of 3.2 years. A chronic heart failure registry study recruited two thirds of patients with prior heart failure, and all patients with reduced ejection fraction (<50%).[463] The overall incidence rate of SCD was 3.5% during a mean follow-up of 26 months.[463] The other study using the Duke databank for Cardiovascular Disease comprising first-ever heart failure patients or patients with prior heart failure and with normal left
ventricular ejection fraction (>50%).[415] The overall incidence rate of SCD was 2.1% during a mean follow-up of 3.9 years.[415] A randomised controlled trial of irbesartan recruited heart failure patients with ejection fraction ≥45% and excluded patients with moderate or severe kidney disease.[416] The overall incidence rate of SCD was 5.6% during a mean follow-up of 4.1 years.[416] Some other risk factors were additionally reported in these studies which might lead to different results. These risk factors were left bundle branch block on electrocardiography, LnNT-proBNP, ejection fraction <30%, non-sustained ventricular tachycardia, left ventricular diastolic diameter ≥55mm, and brain natriuretic peptide.[415, 416, 463]

Myocardial infarction, heart failure, diabetes, and arrhythmias were found to be predictors of SCD in post-atrial fibrillation individuals, in agreement with the literature.[166, 167, 431] However, peripheral artery disease was not found to be associated with the increased hazard of SCD in this WA study but was reported as a predictor in the randomised controlled trial of edoxaban.[167] The different findings might be attributed to the higher risk population included in the randomised controlled trial (overall incidence rate of SCD 3.5% versus 1.5% in this WA study), which may have been related to the extent of the underlying atherosclerotic disease.

The finding of the independent predictors of SCD following stroke suggests some cardiac diseases recognised in the incident stroke event can predict the hazard of later fatal cardiac events, suggesting potential preventive interventions. Typically myocardial infarction and atrial fibrillation were reported to be predictors of cardiac mortality and/or cardiac arrest after stroke in the literature.[447, 462] The WA study also found peripheral artery disease and chronic kidney disease were predictors of SCD. Some studies have shown peripheral artery disease worsens the prognosis of cardiac events and predicted cardiovascular mortality.[464-466] Cumulating evidence supports chronic kidney disease as an independent marker for long-term cardiac mortality.[227, 467, 468]

Another main finding of this WA study is that arrhythmia (ventricular fibrillation, ventricular tachycardia, or cardiac arrest) was a strong predictor of SCD independent of other concomitant
cardiac conditions such as myocardial infarction in most subcohorts. A hazard ratio of more than 2 conferred by the presence of arrhythmia was observed in the subcohorts of myocardial infarction, heart failure, and atrial fibrillation. This is indirectly supported by the secondary analysis of this WA study which showed arrhythmia was no longer found to be a predictor of SCD in 28 days survivors of incident myocardial infarction or incident heart failure. This finding is not surprising because acute myocardial ischemia is regarded as the most common trigger of fatal arrhythmia.[469] However, arrhythmia was still predictive of SCD in the survivors of atrial fibrillation. Some evidence showed atrial fibrillation was found to facilitate provocation of lethal arrhythmias although the pathophysiologic substrates were unclear among atrial fibrillation, fatal arrhythmias, and SCD.[194, 470] Atrial fibrillation may result in high ventricular rates and later asystole.[4]

Hypertension was found to have borderline association with a reduced hazard of SCD in the subcohort of myocardial infarction, which was discordant with the published findings of a non-significant association between hypertension and SCD.[282, 283] The finding in WA seems to be contradictory to the fact that hypertension plays an important role in initiation and progression of atherosclerosis.[471, 472] However, the documentation of hypertension in the hospital morbidity data may be a proxy for hypertension treatment being given.[473] This is supported by this study that a considerably high proportion of hypertension was observed in the incident hospitalisation for the four key CVD events, although it is unclear why a similar reduced hazard was not seen for heart failure, atrial fibrillation, and stroke subcohorts. Mortality benefit of secondary prevention medications of beta blockers, angiotensin converting enzyme inhibitors, or angiotensin II-receptor blockers observed in patients with incident hospitalised myocardial infarction in WA also lends indirect support of current observation.[384]

6.5.2.2 Mechanisms relevant to predictors of sudden cardiac death

The occurrence of SCD is related to atherosclerosis progression.[474] Atherosclerosis can damage any artery in the body including arteries in the heart, brain, kidneys, and arms. As a consequence,
peripheral artery disease, chronic kidney disease, myocardial infarction, and stroke may develop, based on the arteries of which are affected. Peripheral artery disease doubled the hazard of SCD in the subcohort of stroke, appearing to support the presence of peripheral artery disease is a powerful hazard marker of cardiac and cerebral events.[243, 244] Chronic kidney disease was observed to be the independent predictor of SCD only in the subcohorts of myocardial infarction and stroke. The complete mechanism of chronic kidney disease with a worsening kidney function increasing the hazard of SCD are under investigation although there is emerging evidence that chronic kidney disease is a marker for cardiovascular risk.[475-477] In addition, diabetes is well established to involve the initiation and development of atherosclerosis.[478, 479]

The mechanism attributable to the relationship among chronic obstructive pulmonary disease and SCD remain largely unknown. Chronic airflow obstruction has been reported to be a better marker of cardiac-specific death than other well-known predictors such as serum cholesterol.[480-482] There is ongoing evidence that chronic obstructive pulmonary disease increase the risk of SCD in a community-based or population-based setting.[207, 483, 484] This WA study adds to the literature by demonstrating the association between chronic obstructive pulmonary disease and SCD in a subcohort of myocardial infarction. All these suggest the interplay among chronic obstructive pulmonary disease and SCD following myocardial infarction is of considerable interest since chronic obstructive pulmonary disease is often encountered as a comorbidity. Smoking may be a trigger or an important mediator as most individuals with chronic obstructive pulmonary disease are current or ex-smokers. Future studies may consider smoking as a covariate in the multivariable model.

6.5.3 Study strengths and limitations

The main strengths of this study was its state-wide approach and high quality individual-based linkage dataset by which all hospitalised cases were identified in the designated study period.[313, 329] The study design of using first-ever cases of key CVD events indicated the natural history of SCD and excluded the potential over-representation derived from prevalent patients with a long course of
disease. Use of a fixed 15-year lookback period enabled determination of prior hospitalisations of myocardial infarction, heart failure, atrial fibrillation, and stroke, maximising our ability to identify the incident subcohorts. A fixed 15-year lookback period for prior medical conditions of hospitalisation also minimises the under-ascertainment of the status of the medical conditions as candidate predictors reported in this study.

This observational study has several limitations. As common cardiovascular risk factors such as smoking, alcohol use, and body mass index are either not well recorded or available in the administrative health data, whether these factors confound the observed association remain unknown. The results may not be generalisable to a younger or older or community population as cases included in this study were incident hospitalised key CVD events aged 35-84 years old. The incidence rates of SCD in the subcohort of myocardial infarction might be overestimated as the outcome of SCD was identified partly related to a hospitalisation for myocardial infarction defined from the principal diagnosis within last 28 days. However, identification of SCD which was informed by four criteria developed based on the published evidence (discussed in Chapter 4) attenuated the possible misclassification. The quality of the variable of “mode of separation” is unclear. Therefore this variable was not used to identify inter-hospital transfers. Information about clinical details and medication history was not available for this work.

6.5.4 Conclusions

This population-based study examined the magnitude of SCD and predictors in individuals with incident hospitalisation for key CVD events. The incidence rates of SCD in these populations were appreciable compared to the general population, calling for prevention efforts. Major cardiovascular conditions such as myocardial infarction, heart failure, and arrhythmias were predictors of SCD. The findings provide important information for clinical practice on the secondary prevention of SCD by informing patients who had first hospitalisation of the key CVD events about their risk profiles of
SCD, thereby requiring aggressive treatment on concurrent vascular conditions. Future research on other predictors may lead to a better understanding of SCD and its prevention.
6.6 Supporting Information

Supplementary Table S6.1. Incidence rates of sudden cardiac death in 28-days survivors of incident hospitalisation for myocardial infarction, heart failure, atrial fibrillation, and stroke aged 35-84 years in Western Australia

<table>
<thead>
<tr>
<th>Study subcohorts</th>
<th>Number of sudden cardiac death</th>
<th>Person-years</th>
<th>Incidence rate (per 1,000 person-years)</th>
<th>Median follow-up time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>439</td>
<td>101,051</td>
<td>4.3</td>
<td>4.9</td>
</tr>
<tr>
<td>Heart failure</td>
<td>304</td>
<td>32,121</td>
<td>9.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>175</td>
<td>64,475</td>
<td>2.7</td>
<td>5.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>193</td>
<td>59,347</td>
<td>3.3</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Supplementary Figure S6.1. Kaplan-Meier cumulative mortality curves for sudden cardiac death in 28-days survivors of incident hospitalisation for myocardial infarction, heart failure, atrial fibrillation, and stroke aged 35-84 years in Western Australia
Supplementary Table S6.2. Multivariable-adjusted hazard ratios and 95% confidence intervals of sudden cardiac death in post 28-days survivors of incident hospitalisation for myocardial infarction, heart failure, atrial fibrillation, and stroke aged 35-84 years in Western Australia

<table>
<thead>
<tr>
<th>Medical conditions§</th>
<th>Myocardial infarction (n=19,145)</th>
<th>Heart failure (n=7,775)</th>
<th>Atrial fibrillation (n=11,910)</th>
<th>Stroke (n=12,184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>NI</td>
<td>1.79 (1.38, 2.32)</td>
<td>1.82 (1.19, 2.78)</td>
<td>1.85 (1.26, 2.73)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.23 (1.79, 2.78)</td>
<td>NI</td>
<td>2.59 (1.85, 3.62)</td>
<td>1.24 (0.82, 1.89)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.42 (1.15, 1.75)</td>
<td>0.91 (0.70, 1.17)</td>
<td>1.55 (1.07, 2.25)</td>
<td>1.03 (0.75, 1.42)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.68 (1.34, 2.12)</td>
<td>1.24 (0.95, 1.64)</td>
<td>1.46 (0.95, 2.26)</td>
<td>1.91 (1.33, 2.74)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.26 (1.00, 1.58)</td>
<td>0.99 (0.77, 1.28)</td>
<td>1.13 (0.81, 1.57)</td>
<td>1.42 (0.99, 2.02)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.14 (0.91, 1.44)</td>
<td>0.94 (0.74, 1.20)</td>
<td>NI</td>
<td>1.40 (1.02, 1.93)</td>
</tr>
<tr>
<td>Arrhythmias*</td>
<td>0.97 (0.74, 1.28)</td>
<td>1.41 (0.87, 2.27)</td>
<td>2.17 (1.12, 4.19)</td>
<td>0.92 (0.40, 2.14)</td>
</tr>
<tr>
<td>Stroke†</td>
<td>1.49 (1.08, 2.05)</td>
<td>0.86 (0.53, 1.39)</td>
<td>1.05 (0.49, 2.26)</td>
<td>NI</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1.41 (1.09, 1.81)</td>
<td>1.45 (1.07, 1.95)</td>
<td>1.44 (0.89, 2.33)</td>
<td>2.07 (1.45, 2.95)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1.14 (0.89, 1.47)</td>
<td>1.30 (0.98, 1.67)</td>
<td>1.23 (0.82, 1.85)</td>
<td>1.47 (1.02, 2.12)</td>
</tr>
<tr>
<td>Prior ischaemic heart disease †</td>
<td>1.46 (1.18, 1.80)</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
</tbody>
</table>

§adjusted for age, age², sex, Indigenous status, and all medical conditions stated in this table.

†includes concurrent conditions at incident admission and prior medical history unless otherwise indicated.

*includes ventricular tachycardia, ventricular fibrillation, and cardiac arrest.

‡includes subarachnoid haemorrhage, intracerebral haemorrhage, occlusion and stenosis of precerebral arteries with cerebral infarction, and occlusion of cerebral arteries with cerebral infarction.

†includes stable and unstable angina pectoris and chronic ischaemic heart disease, identified from the prior medical history only.

NI, not included.
### Supplementary Table S6.3. List of International classification of disease codes for potential predictors

<table>
<thead>
<tr>
<th>Category</th>
<th>ICD-9/ICD-9-CM codes</th>
<th>ICD-10-AM codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease *</td>
<td>410-414</td>
<td>120-125</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>410</td>
<td>121,122</td>
</tr>
<tr>
<td>Hypertension</td>
<td>401-405</td>
<td>110-115</td>
</tr>
<tr>
<td>Heart failure</td>
<td>428</td>
<td>150</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>427.3</td>
<td>148</td>
</tr>
<tr>
<td>Arrhythmias †</td>
<td>427.1, 427.4, 427.5</td>
<td>146, 147.2, 149.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>250</td>
<td>E10-E14</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>AIHW definition [377]</td>
<td>AIHW definition [377]</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>440-444, 447, 448</td>
<td>170-179</td>
</tr>
<tr>
<td>Stroke</td>
<td>430, 431, 436, 433, 434,(433.x1,434.x1)</td>
<td>I60, I61, I63, I64</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>490-496</td>
<td>J40-J47</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>390-398,421,424</td>
<td>I00-I09,I33-I39,T82.0,T82.6-T82.9,Z95.2-Z95.4</td>
</tr>
<tr>
<td>Coronary revascularisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous transluminal coronary angiooplasty (balloon angioplasty only)</td>
<td>36.01, 36.02, 36.05, 5-363</td>
<td>35304-00, 35305-00, 38303-00, 38300-00</td>
</tr>
<tr>
<td>Percutaneous transluminal coronary angiooplasty with stents</td>
<td>36.06, 36.07</td>
<td>35338-00, 35338-01, 35344-00, 35344-01, 38312-00, 38312-01, 38318-00, 38318-01, 35310-00, 35310-01, 35310-02, 38306-00, 38306-01, 38306-02</td>
</tr>
<tr>
<td>Percutaneous transluminal coronary rotational atherectomy</td>
<td>-</td>
<td>38309-00, 38315-00</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>36.1, 5-361</td>
<td>38497-00, 38497-01, 38497-02, 38497-03, 38497-04, 38497-05, 38497-06, 38497-07, 38500-00, 38500-01, 38500-02, 38500-03, 38500-04, 38500-05, 38503-00, 38503-01, 38503-02, 38503-03, 38503-04, 38503-05, 90201-00, 90201-01, 90201-02, 90201-03, 38524-00, 38393-00, 38524-03, 90203-10, 38456-29, 38390-03, 38368-03, 38350-03, 38393-01, 38521-04, 38524-02, 90203-06</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>37.94, 37.96, 37.98</td>
<td></td>
</tr>
</tbody>
</table>

* includes myocardial infarction, stable and unstable angina pectoris and chronic ischaemic heart disease.
† includes ventricular tachycardia, ventricular fibrillation, and cardiac arrest.
§ The fifth digit extension of codes 433 (conditions due to disease of precerebral arteries) and 434 (conditions due to disease of the cerebral arteries) were available after 1 July 1994, thereby being used after this date in the candidate predictor identification.

## Supplementary Table S6.4. List of Charlson comorbidities

<table>
<thead>
<tr>
<th>Comorbid conditions</th>
<th>ICD-9/ICD-9-CM</th>
<th>ICD-10-AM</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>410.x, 412.x</td>
<td>I21.x, I22.x, I25.2</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x</td>
<td>I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>093.0, 437.3, 440.x, 441.x, 443.1–443.9, 47.1, 557.1, 557.9, V43.4</td>
<td>I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.5, K55.9, Z95.8, Z95.9</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>362.34, 430.x–438.x</td>
<td>G45.x, G46.x, H34.0, I60.x–I69.x</td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td>290.x, 294.1, 331.2</td>
<td>F00.x–F03.x, F05.1, G30.x, G31.1</td>
<td>1</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8</td>
<td>I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3</td>
<td>1</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>446.5, 710.0–710.4, 714.0–714.2, 714.8, 725.x</td>
<td>M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0</td>
<td>1</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>531.x–534.x</td>
<td>K25.x–K28.x</td>
<td>1</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.1, 573.3, 573.4, 573.8, 573.9, V43.4</td>
<td>B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes without chronic complication</td>
<td>250.0–250.3, 250.8, 250.9</td>
<td>E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9</td>
<td>1</td>
</tr>
<tr>
<td>Hemiplegia or paraplegia</td>
<td>334.1, 342.x, 343.x, 344.0–344.6, 344.9</td>
<td>G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9</td>
<td>2</td>
</tr>
<tr>
<td>Renal disease</td>
<td>403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0–583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x</td>
<td>I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2</td>
<td>2</td>
</tr>
<tr>
<td>Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin</td>
<td>140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6</td>
<td>C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x</td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>456.0–456.2, 572.2–572.8</td>
<td>I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7</td>
<td>3</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>196.x–199.x</td>
<td>C77.x–C80.x</td>
<td>6</td>
</tr>
<tr>
<td>AIDS/HIV</td>
<td>042.x–044.x</td>
<td>B20.x–B22.x, B24.x</td>
<td>6</td>
</tr>
</tbody>
</table>

ICD, International Classification of Disease; CM, Clinical Modification; AM, Australian Modification; AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.
CHAPTER 7. GENERAL DISCUSSION AND CONCLUSION

This chapter provides a summary of the major findings and wider implications of the studies presented in Chapter 4 to 6. The general discussion is divided into: sudden cardiac death (SCD) ascertainment using administrative health data, changing incidence rates of SCD, and exploration of clinical predictors of SCD. The broad strengths and limitations of the thesis and directions for future research following this PhD project are outlined.

7.1 Summary of key findings

This thesis has developed a method of identifying SCD using person-linked administrative mortality and morbidity data to investigate population-based epidemiology of SCD. The work supports and adds to the limited published evidence worldwide regarding the incidence rates of SCD in Western Australia (WA). The results in Chapter 4 indicate that the incidence rates of SCD were higher in men than in women. Ischaemic heart disease (IHD) was the most recorded underlying cause of death not only in middle-aged and older adults but also in individuals aged <35 years old (including children, adolescents, and young adults). Notably, the risk of SCD was substantially higher in middle-aged and older individuals with prior cardiovascular disease (CVD) hospitalisation than in those without.

Overall declining trends in SCD in men and women are demonstrated in Chapter 5 although limited improvement was observed in 35-to-54-year-olds in a whole-population setting. The declining trends were evident in SCD cases with and without prior CVD hospitalisation history. Those with prior CVD hospitalisation history had a three times higher incidence rates of SCD than those without.

The magnitude of SCD was investigated in potentially high-risk groups of individuals with four selected key CVD events in Chapter 6. The incidence rates of SCD were 26-fold, 22-fold, 7-fold, and
6-fold higher respectively in patients after incident hospitalised myocardial infarction, followed by heart failure, stroke, and atrial fibrillation compared to the general WA population.

The analysis in Chapter 6 of clinical predictors of SCD following key CVD events has extended the understanding of SCD and suggests potential pathways for prevention. Clinical predictors of SCD observed in patients with incident hospitalisation for myocardial infarction, heart failure, atrial fibrillation, and stroke were not identical, with myocardial infarction, arrhythmias, heart failure, and chronic kidney disease being commonly recognised. Early and late cardiac procedures (within 28 days of incident admission) including percutaneous coronary intervention, coronary artery bypass grafting, implantable cardioverter-defibrillator were strong protective factors for SCD following first myocardial infarction. The recognised clinical predictors of SCD did not change after further adjusting for the cardiac procedures after their first hospitalised myocardial infarction or heart failure.

7.2 Implications of the main results

7.2.1 Sudden cardiac death ascertainment using administrative health data

A method with four criteria for SCD ascertainment was devised based on published evidence using high-quality linked administrative health data in Chapter 4. This multiple source methodology was designed to capture all SCD cases and potentially reduce the issues with the single source methodologies (such as the death-certificate based method).[17] This developed method with four criteria highlights the importance of the underlying cause of death derived from the death certificate and involved essential components for each criterion. In addition to the underlying cause of death, each criterion is integrated with one or two other components including place, time, hospital discharge diagnosis, associated cause(s) of death, and/or indication of a post-mortem. Specifically, associated causes of death were an important supplement source for the circumstances of death has seldom been applied in SCD identification. Other components such as hospital discharge diagnosis or post-mortem have been applied as one of the multiple sources in SCD identification.[17, 65, 485] It is unknown
which of these components contributed mostly to the reliability of this method, warranting further research.

The validity of this developed method is highly dependent on the quality of the data. Limited available validation data demonstrates the underlying cause of death in the mortality data was reasonably accurate.[321] Available validation studies on the hospital morbidity data used reported moderate to high levels of accuracy of the hospital discharge diagnosis.[322-324, 326, 486] This developed method as a whole has not been validated for SCD, and in this study validation was not possible under the study approvals.

Using multiple sources for case identification has been proposed as a strong approach to capture SCD compared to a single source method.[343] Ischaemic heart disease recorded as the main underlying cause of SCD found in WA using this method accords with the finding using another multiple source method.[17, 65] There were also differences noted when compared in a standardised manner against other studies such as standardisation of rates using the approaches comparable to the literature.[13, 16, 79, 344] This could be because different actual incidence rates and various risk profiles exist among different study populations.

This comprehensive method developed in this thesis did not rely on any one source alone such as the autopsy data although the post-mortem examination can be an important source of assisting in adjudicating a death as sudden especially for the unwitnessed death. Nevertheless, autopsy data alone have seldom been used to identify SCD and studies using the autopsy data as the main data source appeared to report a lower incidence rate of SCD.[12, 19] Overall hospital autopsy rates have declined since 2000.[66, 67, 69] In Australia, following a worldwide decline in autopsy rates, however, the proportion of coronial cases (most of which require post-mortem examination) as a percentage of total WA deaths between 2000 and 2009 were stable at approximately 13%. The requirement for coronial investigation under the Coroners Act 1996 (WA) has not changed.[301] Natural disasters may impact on resource availability and affect the number of post-mortem being
conducted and the reason should be investigated carefully before a statistical solution. The multiple
data source method developed in this thesis supports the statistical solution of manipulation of the
cases in the affected years through cases identified from the unaffected years and other three criteria.

This newly developed method provides the opportunity to extend the knowledge of SCD by
addressing some of the current challenges of SCD case identification.[10] Improvements in routine
health data collection and more validation studies of cause of death and diagnosis coding will enable
greater utility and applicability of this method. The generalisation of this method to other populations
appears to be feasible as many countries also have administrative health data collections.[13, 79]

7.2.2 Changing incidence rates of sudden cardiac death

Magnitude of SCD at a population level

There are few population-based studies using a multiple source method for case identification
although there are a number of community-based studies reporting the incidence rate of SCD, ranging
from 40 per 100,000 persons-year to 100 per 100,000 persons-year.[13, 344] The SCD incidence rate
in the general population of Australia was low compared to a population-based study in the United
States,[79] a community-based study in China,[13] a community study in United States,[17] and a
community study in Northern Ireland,[344] all of which used multiple sources for case ascertainment.
Although when the well-accepted definition and multiple sources of ascertainment were applied to the
community studies,[17, 344] differences in quality of data sources and differing risk profiles in the
study populations may explain the variation in absolute risk of SCD observed in these studies.[26]

Epidemiology of SCD is closely linked with IHD. First, prevalence of cardiac ischaemia differs by
age. The study in Chapter 4 showed that IHD was the most frequent cause of SCD, accounting for
80%, corresponding to the finding in the United States and Greece where all age groups and 1-80
years of age respectively were included.[17, 19] However, other studies reported IHD was the cause
of 13% to 50% of the SCD cases aged ≤50 years old.[42, 44, 62, 346, 347] Differing age group
categories applied among studies appeared to be responsible for the apparent difference observed in the proportion of IHD being the underlying culprit. Second, higher incidence rates of SCD were in men than in women similar to the differences of IHD incidence rates by gender. The findings in Chapter 4 were consistent with the literature with more men dying from SCD than women.\cite{16, 18, 19}

All these data highlight that measurement of SCD incidence rates may be optimal if stratified by different levels such as disease categories, sex, and age groups.

**Implication of trends in sudden cardiac death incidence**

The SCD incidence rates may have changed with time reflecting the potential for SCD prevention. Declining trends in incidence rates of SCD have been reported using either population-based or community-based data in the United States, Europe, and Asia since the 1990s.\cite{13, 17, 65, 79, 344} In Australia, there have been no contemporary trend studies of SCD and thus the study in Chapter 5 fills this gap in the national context. Marked declines occurred in the incidence rates of SCD both in men and women and in those with and without CVD hospitalisation history. It is likely that the findings of the WA population can be generalised to most other Australian jurisdictions due to the similar socio-demographic and health economic indicators.\cite{329}

The importance of a continued clinical and public health focus on primary and secondary prevention of the underlying cause of SCD was suggested by the observed SCD trends in WA. The falling incidence rates of SCD in people with prior CVD hospitalisation are consistent with widespread advancements in the secondary prevention of CVD. As individuals with heart failure or myocardial infarction had substantially elevated risk of SCD as shown in Chapter 6, effective evidence-based treatment of acute coronary syndrome and heart failure\cite{129, 296, 372-376} could have contributed to the declining risk of SCD. Although medication data were not available for this study, a combination of beta blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins has improved survival in patients after first hospitalised myocardial infarction at a WA population level.\cite{384} In addition, the mortality benefit of coronary revascularisation therapy in patients with
myocardial infarction has been widely reported.[281-283] The findings in Chapter 6 showed half of incident hospitalised myocardial infarction patients received coronary revascularisation therapy within 28 days of the incident event, primarily with percutaneous coronary intervention therapy. Continuing to target improved utilisation of cardiovascular medications and coronary revascularisation therapies could help to reduce the risk of SCD in people with known heart disease.

Whilst improvements in secondary prevention of CVD have likely contributed to the observed decrease in incidence rates of SCD, half of all SCD cases do not have any warning signs and so are less likely to benefit from secondary prevention programs.[330] These cases, therefore, may rely on the primary prevention programs targeted at the general or a low-risk population. Indeed, declines in incidence rates of SCD in people without prior hospitalisation of CVD in WA suggest that primary prevention of CVD particularly in management of risk factors has been effective. The targets for lifestyle and risk factor management in Australia are in agreement with the global recommendations,[487-490] which includes tobacco smoking control, promoting regular physical activity, healthy eating, and encouraging healthy weight.[491, 492] Effective primary prevention may have contributed to the decline in SCD incidence rates but how much reduction was attributable to management of these risk factors was unknown. A recent Australian report on monitoring CVD has shown tobacco smoking rates in adults has declined steadily since the 1970s and the proportion of Australians exercising insufficiently has improved slightly.[32] However, a high proportion of Australians still have unhealthy dietary behaviours and overweight and obesity are increasing at alarming rates.[32] These changes in risk factors could change the epidemiology of SCD in the future, suggesting long-term surveillance of SCD is imperative. An initiative for improved management of risk factors may maintain encouraging trends in SCD.

In addition to the promising effects of primary and secondary prevention of the underlying cause of SCD, implantable cardioverter-defibrillator therapy is an effective treatment modality targeting SCD itself. This is particularly investigated in selected patients with incident myocardial infarction.[271] As shown in Chapter 6, the implantable cardioverter-defibrillator therapy was observed to reduce the
hazard of SCD by 94%, although there were only a very small proportion of patients following incident myocardial infarction who received implantable cardioverter-defibrillator therapy within 28 days of the incident event. There is an indirect support for the beneficial effect of an implantable cardioverter-defibrillator therapy that <1% of SCD cases received the implantable cardioverter-defibrillator therapy in the preceding 10 years (shown in Chapter 5). This coincided with the observation of increasing implanting rates of implantable cardioverter-defibrillators in the WA population from 0.8 in 100,000 in 1995 to 14.9 in 100,000 in 2009.[378] As an increasing population receives the implantable cardioverter-defibrillator therapy for primary prevention of SCD, further outcome studies particularly for SCD are warranted.

7.2.3 Exploration of clinical predictors of sudden cardiac death

From a prevention perspective, exploration of clinical predictors of SCD after key CVD events provides risk profiles for medical practitioners to consider pre-existing and/or concurrent medical conditions which elevate the risk of SCD. The findings of Chapter 6 demonstrate different clinical predictors of SCD following the key CVD events although some common medical conditions such as myocardial infarction, heart failure, chronic kidney disease, diabetes, and stroke were recognised. This underscores two challenges of offering optimal care for patients. First, the various clinical predictors of SCD suggest that current management model for disease-oriented care may not effectively address the health care needs for the four CVD events of myocardial infarction, heart failure, atrial fibrillation, and stroke. Clinical guidelines for the four CVD events mainly focus on treatment for the four CVD events themselves.[493-496] Understanding of multiple clinical predictors of SCD facilitates optimisation of treatment directed at the key CVD events while simultaneously providing treatment for these comorbid conditions, and ultimately reduces the incidence rates of SCD.

Second, the clinical predictors of SCD involved in more than one body system increase the challenge of successful treatment as this adds to the overall complexity of care. For example, in patients with
first-ever myocardial infarction, the urinary system, respiratory system, and cardiovascular system were involved through chronic kidney disease, chronic obstructive pulmonary disease, and stroke which were observed to be independent clinical predictors of SCD (see Chapter 6). Although not every patient had the clinical predictors of SCD across the body systems, it is still a potential concern. For example, half of patients with first-ever stroke were found to have Charlson comorbidity index scores ≥ 3 and half of patients with first-ever heart failure had Charlson comorbidity index scores ≥ 2 (see Chapter 6). The presence of comorbid conditions if involved in more than one body system may add the complexity of managing the key CVD events which may affect the prognosis.[497, 498] A coordinated comprehensive system of care delivery may be required to address the potentially multiple comorbid conditions for a patient.

7.3 Study strengths

This thesis has developed a multiple source method to identify SCD at a population level. Using this developed methodology, the thesis provides estimates of the magnitude of SCD and important insights into further prevention initiatives to improve SCD. This thesis also adds to the literature by the investigation of incidence rates and clinical predictors of SCD in four selected high-risk populations (patients with the key CVD events) in Australia.

The utilisation of the high-quality administrative health data collections in this thesis has considerable advantages. First, the data was collected by specific systems such as hospital morbidity data collection. Second, hospital morbidity data are coded by clinical coders in hospital systems and cause of death coding is undertaken through an automated coding process by the Australian Bureau of Statistics. Validation studies on the coding of common medical conditions suggest moderate to high validity such as myocardial infarction and heart failure thus ensuring the robust results.[313, 321-326] Third, both the hospital morbidity and mortality data were linked at a person level by the Western Australian Data Linkage System (WADLS). Fourth, the use of complete collections allows the study to represent the whole WA population as the morbidity data cover all inpatient data from acute public,
private, and non-affiliated day hospitals which are required by the WA Department of Health. The mortality data include all deaths occurred in WA including out-of-hospital deaths. Lastly, the use of longitudinal person-linked data enabled long lookback periods for prior hospitalisations, comorbidities, and incident events to be identified.

7.4 Study limitations

A number of limitations of the studies in the thesis need to be noted. Lack of data on emergency medical services (including paramedics and resuscitation records) is one of the limitations of this work. These extra data might capture onset of symptoms and abnormal heart rhythms thereby improving the understanding of the cause and circumstances of death where the emergency medical service was called. These data could be contained in the wider WADLS in the future and potentially linked. Adjudicating a death as SCD according to the well-accepted definition relies primarily on the circumstances of the death such as place, time, cause of death, and conditions prior to death. Therefore, it is favourable to have more information on the fatal event.

The ability to use post-mortem data to identify SCD during the period 2002-2006 was limited in this work due to two regional disasters which occurred in 2002 and 2004 resulting in under-resourcing and affecting the post-mortem practice during this period in WA. The incidence rates of SCD reported in Chapter 4 may under-estimate the actual incidence rates because the reduction in autopsies was not adjusted for between 2002 and 2006. The multiple data source method developed in this thesis could potentially attenuate the impact and a statistical solution could help.

Behavioural and biomedical factors (such as tobacco smoking, dietary behaviour, physical activity, high blood cholesterol, body mass index) were not available in the existing linked data for this work. These data would potentially lead to a better understanding of the impact of these factors on SCD. Medication use data was not available either. Medication treatment during the hospital admission for the key CVD events as well as persistence and adherence in patients discharge with the key CVD
events treated with the dispensed drugs could improve the prognosis of the incident key CVD events thus impacting the clinical predictors of SCD observed currently.

7.5 Future research

There is a need for further research to replicate the study using the multiple source method developed by the administrative health data for SCD identification. The quality of the administrative health data used in the method is imperative to ensure the validity of the developed method for case ascertainment. Regular validation studies on these data sources could improve the quality of data. Establishing a national registry of SCD could greatly benefit the long-term SCD surveillance, further the understanding of the underlying cause, and substantially reduce the number of SCD fatalities occurring.

Future research could consider the possibility of linking potential national risk factor surveys and community-based studies of cardiovascular risk factor such as tobacco smoking and body mass index to the routinely collected administrative health data currently used. This would be particularly helpful in drawing a conclusion on whether the encouraging trends in incidence rates of SCD will continue. These data may also improve the identification of current predictors for SCD. In addition, the linkage of the hospital pharmacy data and pharmaceutical benefits scheme data to the administrative health data could potentially help to assess whether medication use could alter the clinical predictors of SCD observed currently.

This research has investigated the clinical predictors of SCD for those with first-ever key CVD events. Future studies may also examine the clinical predictors of SCD for those with recurrent CVD events and observe whether there is any difference in the clinical predictors of SCD between the first-ever event and the recurrent event. Furthermore, there may be another focus on determining the predictors of SCD in those without any medical history or first clinical presentation of CVD as the underlying
cause of SCD. The magnitude of SCD in this low-risk subgroup was relatively small as demonstrated in Chapter 5 as the denominators in this subgroup were much larger than in high-risk subgroups.

7.6 Final conclusions

This thesis reports the magnitude of SCD in a population setting using a multiple source method of ascertaining SCD where the findings generated are mostly in line with the literature. The data extend contemporary knowledge of the epidemiology of SCD by estimating population-based trends in SCD incidence rates. The favourable trends were evident and independent of sex and prior CVD hospitalisations although limited improvements were observed in young adults. The thesis also estimates and compares the magnitude of SCD with the higher incidence rate of SCD in individuals hospitalised for incident myocardial infarction, followed by incident heart failure, incident stroke, and incident atrial fibrillation, highlighting the potential for SCD prevention in these four selected high-risk groups. Clinical predictors of SCD following four key CVD events are identified, providing clinicians with a valuable picture of risk profiles for treatment consideration. The work in this thesis highlights the importance of providing optimal treatment directed at the key CVD events as well as pre-existing and/or concurrent medical conditions as suggested by the clinical predictors to improve SCD prevention.
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## APPENDICES

### Appendix A

Variables within the extracted dataset for this study

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Variable Code</th>
<th>Variable Description</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission Age</td>
<td>age</td>
<td>Age in years on admission</td>
<td>Numeric</td>
</tr>
<tr>
<td>Date of Birth</td>
<td>dob</td>
<td>Date of birth of patient</td>
<td>MMYY</td>
</tr>
</tbody>
</table>
| Gender            | sex           | Sex of patient                            | 1=Male  
2=Female  
3=Indeterminate  
4=Other (transsexual) |
| Indigenous Status | aborig        | Indigenous status of patient on admission | 1=Aboriginal not Torres Strait Islander (TSI) origin  
2=TSI not Aboriginal  
3=Both Aboriginal and TSI origin  
4=Not stated Aboriginal nor TSI origin |
| Admission Date    | adm_date      | Date patients was admitted                | DDMMYYYY                                                               |
| Separation Date   | sep_date      | Date patient was discharged               | DDMMYYYY                                                               |
| Principal diagnosis | diag1     | Principal diagnosis of episode of care    | ICD-8 to ICD 10 diagnosis codes                                        |
| Additional diagnoses | diag2-diag21 | Additional diagnoses of episode of care   | ICD-8 to ICD 10 diagnosis codes                                        |
| Procedure date    | proc_date1-proc_date11 | Date procedure was undertaken  | DDMMYYYY                                                               |
| Principal procedure | proc1     | Principal procedure of episode of care    | ICD-8 to ICD 10 procedure codes                                        |
| Additional procedures | proc2-proc11 | Additional procedures of episode of care  | ICD-8 to ICD 10 procedure codes                                        |
| Post mortem       | POSTMORT      | Determines whether a post-mortem was, was not or is to be carried out | C=Carried out  
T=To be carried out  
N=Not carried out  
NS=Not stated  
W=Will be Carried out (1969-1990) |
| Date of death     | DOD           | Date of death                             | DDMMYYYY                                                               |
| Cause of death code (ABS) | CODCODE   | Underlying cause of death                 | ICD codes                                                               |
| Entity Axis data  | ENTITY_AXIS_DATA | Multiple ICD coding from death certificate | Concatenation of index and ICD code- 
a list of 48 fields which represent the 6 lines of the death certificate with 8 causes per line allowed |
| Record Axis data  | RECORD_AXIS_DATA | Multiple ICD coding from death certificate | ICD codes                                                               |
Appendix B

Government of Western Australia
Department of Health

HUMAN RESEARCH ETHICS COMMITTEE AHREC EC00442

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DHFWA HREC
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EAST PERTH WA 6004

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Prof Matthew Knuijman
Winthrop Professor
The University of Western Australia
School of Population Health
M431, 35 Stirling Highway
CRAWLEY WA 6009

Dear Prof Knuijman

Project 2014/55 - The real and changing atherothrombotic disease burden and secondary prevention

Date of commencement: 01/01/2009
Date of next annual progress report: 08/10/2015
Research team: Matthew Knuijman, Tom Briffa, Frank Sanfilippo, Elizabeth Geelhocht, Joe Hung, Paul Norman, Graeme Hanley, Anna Poeters, Danja Sarink, Lee Nedkoff, Emily Atkins and Jia-Li Feng

DOH data required: Yes
Data linkage required: Yes
Datasets to be accessed: Emergency Department Data System, Electoral Roll, Hospital Morbidity Data System and Mortality Register

Date of ethical review: 08/10/2014
Ethics approval validity: 08/10/2017

I am pleased to advise that the Department of Health WA Human Research Ethics Committee (DOH HREC) has granted ethical approval for this project.

The Committee considered your application under the National Statement on Ethical Conduct in Human Research 2.3.10 and was satisfied that it met the criteria to grant a waiver of consent.

This letter constitutes ethics approval only. You will not receive the data requested for your project until the release of the data has also been approved by the data steward.

As Principal Investigator you are responsible for the ethical conduct of the project and the security of the personal health information.

This approval is subject to your continued compliance with your obligations under the Practice Code for the Use of Personal Health Information including the following conditions. You are required to:

1. Report to the DOH HREC anything which might warrant review of ethical approval of the project including:
   - any breaches or complaints and any adverse events affecting the security and confidentiality of the data; and

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1. Unforeseen events that might affect the continued ethical acceptability of the project.
2. Notify the DOH HREC if the project is discontinued or withdrawn before the expected date of completion and to give reasons for this action.
3. Provide an annual progress report to the DOH HREC and a final report at the completion of the project.
4. Obtain approval from the DOH HREC for:
   - any changes or amendments to the research protocol, including methodology, data required, duration of the project and any changes to the approved data storage arrangements;
   - any changes of personnel in the research team, and provide a DOH Confidentiality Agreement/Confidentiality Acknowledgement form for any addition to the research team.

We wish you well with your project.

Yours sincerely

[Signature]

A/Professor Judy Allen
Chair
Department of Health WA Human Research Ethics Committee

9 October 2014
Appendix C

Number of the incident myocardial infarction patients stratified by the calendar year of incident admission

<table>
<thead>
<tr>
<th>Year of incident admission</th>
<th>Incident myocardial infarction patients identified between 2000 and 2009</th>
<th>Outcome of sudden cardiac death occurred during the follow-up until 30 June 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28 days survivors</td>
<td>Died within 28 days</td>
</tr>
<tr>
<td>2000</td>
<td>1,610</td>
<td>139</td>
</tr>
<tr>
<td>2001</td>
<td>1,627</td>
<td>160</td>
</tr>
<tr>
<td>2002</td>
<td>1,801</td>
<td>128</td>
</tr>
<tr>
<td>2003</td>
<td>1,777</td>
<td>119</td>
</tr>
<tr>
<td>2004</td>
<td>1,839</td>
<td>130</td>
</tr>
<tr>
<td>2005</td>
<td>1,847</td>
<td>126</td>
</tr>
<tr>
<td>2006</td>
<td>2,014</td>
<td>113</td>
</tr>
<tr>
<td>2007</td>
<td>2,171</td>
<td>114</td>
</tr>
<tr>
<td>2008</td>
<td>2,183</td>
<td>87</td>
</tr>
<tr>
<td>2009</td>
<td>2,276</td>
<td>95</td>
</tr>
<tr>
<td>Total</td>
<td>19,145</td>
<td>1,211</td>
</tr>
</tbody>
</table>

8 incident myocardial infarction patients died between 1 January 2000 and 30 June 2011 with a missing cause of death and therefore excluded from this analysis. (6 died after 28 days of incident admission, 2 died within 28 days of incident admission)

Follow-up of the incident myocardial infarction patients identified between 2000 and 2009

<table>
<thead>
<tr>
<th></th>
<th>Incident myocardial infarction patients</th>
<th>Counts</th>
<th>minimum</th>
<th>maximum</th>
<th>median</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days survivors</td>
<td></td>
<td>19,145</td>
<td>29 days</td>
<td>11.5 years</td>
<td>4.9 years</td>
</tr>
<tr>
<td>Died within 28 days</td>
<td></td>
<td>1,211</td>
<td>0 day</td>
<td>28 days</td>
<td>3 days</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>20,356</td>
<td>0 day</td>
<td>11.5 years</td>
<td>4.6 years</td>
</tr>
</tbody>
</table>
### Number of the incident heart failure patients stratified by the calendar year of incident admission

<table>
<thead>
<tr>
<th>Year of incident admission</th>
<th>Incident heart failure patients identified between 2000 and 2009</th>
<th>Outcome of sudden cardiac death occurred during the follow-up until 30 June 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28 days survivors Died within 28 days</td>
<td>Sudden cardiac death occurred after 28 days of incident admission</td>
</tr>
<tr>
<td>2000</td>
<td>723 58</td>
<td>38</td>
</tr>
<tr>
<td>2001</td>
<td>776 45</td>
<td>44</td>
</tr>
<tr>
<td>2002</td>
<td>781 54</td>
<td>33</td>
</tr>
<tr>
<td>2003</td>
<td>719 53</td>
<td>36</td>
</tr>
<tr>
<td>2004</td>
<td>803 53</td>
<td>44</td>
</tr>
<tr>
<td>2005</td>
<td>772 51</td>
<td>28</td>
</tr>
<tr>
<td>2006</td>
<td>759 60</td>
<td>26</td>
</tr>
<tr>
<td>2007</td>
<td>826 48</td>
<td>23</td>
</tr>
<tr>
<td>2008</td>
<td>788 47</td>
<td>18</td>
</tr>
<tr>
<td>2009</td>
<td>828 50</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>7,775 519</td>
<td>304</td>
</tr>
</tbody>
</table>

*8 incident heart failure patients died between 1 January 2000 and 30 June 2011 with a missing cause of death and therefore excluded from this analysis. (7 died after 28 days of incident admission, 1 died within 28 days of incident admission)*

### Follow-up of the incident heart failure patients identified between 2000 and 2009

<table>
<thead>
<tr>
<th>Incident heart failure patients</th>
<th>Follow-up</th>
<th>Counts</th>
<th>minimum</th>
<th>maximum</th>
<th>median</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days survivors</td>
<td></td>
<td>7,775</td>
<td>29 days</td>
<td>11.5 years</td>
<td>3.5 years</td>
</tr>
<tr>
<td>Died within 28 days</td>
<td></td>
<td>519</td>
<td>0 day</td>
<td>28 days</td>
<td>7 days</td>
</tr>
<tr>
<td>Total of incident heart failure patients</td>
<td></td>
<td>8,294</td>
<td>0 day</td>
<td>11.5 years</td>
<td>3.2 years</td>
</tr>
</tbody>
</table>
Number of the incident atrial fibrillation patients stratified by the calendar year of incident admission

<table>
<thead>
<tr>
<th>Year of incident admission</th>
<th>Incident atrial fibrillation patients identified between 2000 and 2009</th>
<th>Outcome of sudden cardiac death occurred during the follow-up until 30 June 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28 days survivors</td>
<td>Died within 28 days</td>
</tr>
<tr>
<td>2000</td>
<td>1,097</td>
<td>9</td>
</tr>
<tr>
<td>2001</td>
<td>1,048</td>
<td>9</td>
</tr>
<tr>
<td>2002</td>
<td>1,125</td>
<td>9</td>
</tr>
<tr>
<td>2003</td>
<td>1,045</td>
<td>9</td>
</tr>
<tr>
<td>2004</td>
<td>1,091</td>
<td>15</td>
</tr>
<tr>
<td>2005</td>
<td>1,157</td>
<td>8</td>
</tr>
<tr>
<td>2006</td>
<td>1,234</td>
<td>11</td>
</tr>
<tr>
<td>2007</td>
<td>1,314</td>
<td>11</td>
</tr>
<tr>
<td>2008</td>
<td>1,305</td>
<td>10</td>
</tr>
<tr>
<td>2009</td>
<td>1,494</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>11,910</td>
<td>105</td>
</tr>
</tbody>
</table>

*2 incident atrial fibrillation patients died after 28 days of incident admission between 1 January 2000 and 30 June 2011 with a missing cause of death and therefore excluded from this analysis.

Follow-up of the incident atrial fibrillation patients identified between 2000 and 2009

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Incident atrial fibrillation patients</th>
<th>Counts</th>
<th>minimum</th>
<th>maximum</th>
<th>median</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days survivors</td>
<td>11,910</td>
<td>29 days</td>
<td>11.5 years</td>
<td>5.0 years</td>
<td></td>
</tr>
<tr>
<td>Died within 28 days</td>
<td>105</td>
<td>0 day</td>
<td>28 days</td>
<td>9 days</td>
<td></td>
</tr>
<tr>
<td>Total of incident atrial fibrillation patients</td>
<td>12,015</td>
<td>0 day</td>
<td>11.5 years</td>
<td>5.0 years</td>
<td></td>
</tr>
</tbody>
</table>
Number of the incident stroke patients stratified by the calendar year of incident admission

<table>
<thead>
<tr>
<th>Year of incident admission</th>
<th>Incident stroke patients identified between 2000 and 2009</th>
<th>Outcome of sudden cardiac death occurred during the follow-up until 30 June 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28 days survivors Died within 28 days</td>
<td>Sudden cardiac death occurred after 28 days of incident admission</td>
</tr>
<tr>
<td>2000</td>
<td>1,246 Died within 28 days</td>
<td>32</td>
</tr>
<tr>
<td>2001</td>
<td>1,174 Died within 28 days</td>
<td>25</td>
</tr>
<tr>
<td>2002</td>
<td>1,131 Died within 28 days</td>
<td>21</td>
</tr>
<tr>
<td>2003</td>
<td>1,138 Died within 28 days</td>
<td>25</td>
</tr>
<tr>
<td>2004</td>
<td>1,242 Died within 28 days</td>
<td>17</td>
</tr>
<tr>
<td>2005</td>
<td>1,265 Died within 28 days</td>
<td>32</td>
</tr>
<tr>
<td>2006</td>
<td>1,253 Died within 28 days</td>
<td>12</td>
</tr>
<tr>
<td>2007</td>
<td>1,237 Died within 28 days</td>
<td>13</td>
</tr>
<tr>
<td>2008</td>
<td>1,262 Died within 28 days</td>
<td>10</td>
</tr>
<tr>
<td>2009</td>
<td>1,236 Died within 28 days</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>12,184 Died within 28 days</td>
<td>193</td>
</tr>
</tbody>
</table>

*9 incident acute stroke patients died between 1 January 2000 and 30 June 2011 with a missing cause of death and therefore excluded from this analysis. (7 died after 28 days of incident admission, 2 died within 28 days of incident admission)*

Follow-up of the incident stroke patients identified between 2000 and 2009

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Incident acute stroke patients</th>
<th>Counts</th>
<th>minimum</th>
<th>maximum</th>
<th>median</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days survivors</td>
<td>12,184 Died within 28 days</td>
<td>29 days</td>
<td>11.5 years</td>
<td>4.5 years</td>
<td></td>
</tr>
<tr>
<td>Died within 28 days</td>
<td>2,022 Died within 28 days</td>
<td>0 day</td>
<td>28 days</td>
<td>4 days</td>
<td></td>
</tr>
<tr>
<td>Total of incident acute stroke patients</td>
<td>14,206 Died within 28 days</td>
<td>0 day</td>
<td>11.5 years</td>
<td>3.7 years</td>
<td></td>
</tr>
</tbody>
</table>