THE CHANGING EPIDEMIOLOGY OF CORONARY HEART DISEASE IN PEOPLE WITH DIABETES IN WESTERN AUSTRALIA

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School of Population Health

Faculty of Medicine, Dentistry and Health Sciences

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STATEMENT OF ORIGINAL CONTRIBUTION

I declare that the work contained within this thesis is my own, except where referenced or acknowledged otherwise. This thesis has not been previously submitted for a degree at this or any other university.

This thesis originated from a larger project funded by the National Health and Medical Research Council — The Atherothrombotic Disease Project (grant number 572558). One of the aims of this project was to investigate the impact of comorbidities in atherothrombotic disease. I therefore developed the specific focus of this thesis as a component of this study, in consultation with my doctoral supervisors, Research Associate Professor Tom Briffa, Professor Matthew Knuiman and Professor Joe Hung.

The main linked dataset used in this study was provided by the Data Linkage Branch (Department of Health, Western Australia), and was imported and formatted for our research group by Mr Steve Ridout. I carried out all data analyses for all studies within the thesis, except for Table 8.2, which was created by Emily Atkins. I undertook the planning, analysis and writing of all manuscripts and am the primary author on each of the papers, and my contribution to each of these studies is greater than 80%.

This thesis is presented as a series of papers and therefore contains published work and work submitted for publication, all of which has been co-authored. The bibliographical details of the work and where each one appears in the thesis are outlined below.


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

Lee Nedkoff      Professor Matthew Knuiman
PhD Candidate     Coordinating Supervisor
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<tr>
<td>ACCORD</td>
<td>Action to Control Cardiovascular Risk in Diabetes</td>
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<tr>
<td>ACEi</td>
<td>Angiotensin-converting enzyme inhibitors</td>
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<td>ACS</td>
<td>Acute coronary syndrome</td>
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<td>ADVANCE</td>
<td>Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation</td>
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<td>AM</td>
<td>Australian modification</td>
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<td>ARB</td>
<td>Angiotension receptor blocker</td>
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<td>ARIC</td>
<td>Atherosclerosis Risk in Communities</td>
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<td>AusDiab</td>
<td>Australian Diabetes, Obesity, and Lifestyle Study</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>CABG</td>
<td>Coronary artery bypass grafting</td>
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<td>CeVD</td>
<td>Cerebrovascular disease</td>
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<td>CHD</td>
<td>Coronary heart disease</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>CM</td>
<td>Clinical modification</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>DCCT</td>
<td>Diabetes Control and Complications Trial</td>
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<td>DM</td>
<td>Diabetes mellitus</td>
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<td>EDIC</td>
<td>Epidemiology of Diabetes Interventions and Complications</td>
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<td>FIELD</td>
<td>Fenofibrate Intervention and Event Lowering Diabetes</td>
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<tr>
<td>FPG</td>
<td>Fasting plasma glucose</td>
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<td>HbA1c</td>
<td>Glycated haemoglobin</td>
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<td>HDL-C</td>
<td>High-density lipoprotein cholesterol</td>
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<td>HMDC</td>
<td>Hospital Morbidity Data Collection</td>
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<td>HMDS</td>
<td>Hospital Morbidity Data System</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<td>HWSS</td>
<td>Health and Wellbeing Surveillance System</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>ICPM</td>
<td>International Classification of Procedures in Medicine</td>
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<td>IRR</td>
<td>Incidence rate ratios</td>
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<td>LDL-C</td>
<td>Low-density lipoprotein cholesterol</td>
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<td>MI</td>
<td>Myocardial infarction</td>
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<td>MONICA</td>
<td>Monitoring of trends and determinants in cardiovascular disease</td>
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<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<td>NPV</td>
<td>Negative predictive value</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<td>NSTEMI</td>
<td>Non-ST-segment elevation MI</td>
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<td>NSW</td>
<td>New South Wales</td>
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<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<td>PAD</td>
<td>Peripheral Arterial Disease</td>
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<td>PCI</td>
<td>Percutaneous coronary intervention</td>
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<td>PPV</td>
<td>Positive predictive value</td>
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<tr>
<td>REACH</td>
<td>REDuction of Atherothrombosis for Continued Health</td>
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<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>STEMI</td>
<td>ST-segment elevation MI</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
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<td>VADT</td>
<td>Veteran Affairs Diabetes Trial</td>
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<td>US</td>
<td>United States</td>
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<td>WA</td>
<td>Western Australia</td>
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<td>WADLS</td>
<td>Western Australian Data Linkage System</td>
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<td>WHO</td>
<td>World Health Organization</td>
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ABSTRACT

INTRODUCTION

Diabetes and coronary heart disease (CHD) are two common chronic conditions with contrasting epidemiological trends. CHD incidence and mortality rates have been declining for some decades but the prevalence of diabetes has been increasing. The association between CHD and diabetes is complex and multifactorial. The pathological processes which underlie CHD are exacerbated by the presence of diabetes. Historical data show that once CHD is manifest, people with diabetes have worse short-term outcomes, receive less evidence-based treatment, and have poorer long-term outcomes compared with their non-diabetic counterparts. The ability to determine whether changing approaches to acute CHD treatment and management, and primary and secondary prevention are having a positive impact requires long-term population level data. However, there are limited international and no Australian population level data detailing trends in the incidence of CHD in people with diabetes. There are also few settings where the full spectrum of incidence, short-term case fatality and longer-term outcomes following CHD have been measured in the same population, both overall and specifically for people with diabetes.

The primary aim of this thesis was to investigate the changing epidemiology of CHD in people with diabetes in the context of the changing epidemiology of CHD and cardiovascular disease more broadly in the population of Western Australia. The specific objectives were:

1. To establish the reliability of the coding of diabetes in WA hospital morbidity data for CHD patients
2. To estimate the impact of the increasing prevalence of diabetes on the population-level incidence of CHD; and
3. To measure the risk of short and long-term outcomes following myocardial infarction (MI) in diabetic people.

METHODS

The study objectives were investigated using high-quality linked health data extracted from the Western Australian Data Linkage System for the period 1985 to 2011. The main study dataset contained linked hospitalisation and mortality data for the period
1985 to 2011 enabling a variety of analyses of trends in incidence, recurrence and outcomes to be conducted using logistic, Poisson and Cox regression modelling.

RESULTS

This thesis is presented as a series of papers. Chapters 4–9 contain the six papers undertaken for the thesis. Chapters 4–8 are final manuscript versions of papers that have already been published and Chapter 9 is the version of the manuscript that has been submitted to a peer-reviewed journal for publication.

Chapter 4 describes a study undertaken to determine the accuracy of the recording of diabetes status in hospitalisation data for CHD patients. Comparing the recording of diabetes in hospital data and data collected from hospital records, concordance was high with the use of an extended lookback period (sensitivity >90%, positive predictive value 92%).

Chapter 5 analyses demonstrate that the incidence and recurrence of hospitalised CHD declined between 2000 and 2007. This was supported by reductions in CHD mortality rates over the same period, and concurrent falls in cerebrovascular disease (CeVD) and peripheral arterial disease (PAD) incidence and recurrence rates. Rates of polyvascular disease declined more rapidly than single territory disease. Age-standardised prevalence of diabetes in incident cases increased from 21.5% to 26.0% in men and from 26.3% to 29.0% in women over the same period.

Chapter 6 analyses with stratification of MI cases by diabetes status showed that MI incidence rates in people with diabetes fell substantially between 1998 and 2010 whereas concurrent reductions in rates in non-diabetic patients were marginal. The trends in diabetic people occurred despite increasing levels of chronic kidney disease, hypertension and prior CHD hospitalisations in these patients.

Chapter 7 focuses on short-term outcomes following incident MI in people with and without diabetes. The results show that age- and sex-adjusted 30-day case fatality declined by 10.6%/year in people with diabetes and 6.9%/year in people without diabetes. The trends meant that by the end of the study period there was no longer any difference in the adjusted risk of 30-day death following incident MI according to diabetes status.

Chapter 8 shows that long-term MI recurrence and mortality remain high following incident MI in the WA population, particularly in 70–84-year-olds. Men and women
aged 35–54 years and 55–69 years have similar event probability through eight years of follow-up. When trends in mortality outcomes were analysed by diabetes status (Chapter 9), unadjusted 5-year all-cause mortality following incident MI was about two-fold higher in people with diabetes and there was no significant change in the multivariable-adjusted hazard ratio comparing people with diabetes to those without from 1998 to 2009.

**CONCLUSION**

In conclusion, trends in a whole-population setting show that there is decreasing incidence, recurrence and mortality rates of CHD and vascular disease more broadly, with concurrent increasing diabetes prevalence. In this context, there are mixed results for CHD outcomes in people with diabetes. Trends in incidence rates of MI have fallen substantially in people with diabetes, as have short-term deaths following incident MI over an extended contemporary period. In contrast, longer-term all-cause mortality has not improved in diabetic people. These data are extremely important for the implications of the likely effect of changing primary prevention approaches and acute care following MI for people with diabetes, whereas secondary prevention, particularly in people with diabetes, appears to have had little impact on the survival differential by diabetes status.
PUBLICATIONS ARISING FROM THIS THESIS


**Nedkoff L**, Knuiman M, Hung J, Briffa T. Trends in long-term all-cause and cardiovascular mortality following incident myocardial infarction in people with and without diabetes (*submitted for publication*).

CONFERENCE PRESENTATIONS ARISING FROM THESIS


**OTHER PUBLICATIONS RELEVANT TO THIS THESIS**


Briffa TG, **Nedkoff LJ**, Knuiman MW, Hankey GJ, Norman PE, Hung J, Thompson PL, Hickling S, Bremner A, Sanfilippo FM. Cross vascular risk for first and recurrent

AWARDS RELATED TO THIS THESIS


The Cardiac Society of Australia and New Zealand Travelling Fellowship – European Society of Cardiology Congress 2014.


Affiliate Travel Scholarship, The Cardiac Society of Australia and New Zealand, Annual Scientific Meeting, Brisbane Australia, August 2012.


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CHAPTER 1. GENERAL INTRODUCTION

1.1 BACKGROUND

Diabetes mellitus (‘diabetes’) and coronary heart disease (CHD) are two common chronic conditions which impose a high morbidity and mortality burden. Diabetes is a major risk factor for developing CHD, and has been labelled a CHD-risk equivalent from an outcomes perspective [1]. At a population level, there are contrasting changes in the epidemiology of the two conditions, with declining CHD incidence and improved survival, yet rapidly increasing prevalence of diabetes. The impact of these diverging trends is not fully understood, particularly in Australia.

CHD is the most common form of cardiovascular disease (CVD) and the leading cause of death in Australia [2]. Globally, it is the leading cause of years of life lost [3]. However, CHD mortality rates in Australia and other Western countries have fallen consistently since the late 1960s [4–9], with these trends also beginning in some Eastern European countries in the late 1990s [10]. The reductions in CHD mortality have been attributed to cardiovascular risk factor prevention and management, and improvements in medical diagnosis, management and treatment [9].

In contrast, diabetes is a condition increasing in its impact on the community. Globally, its prevalence has increased from 4% in 1995 [11] to current estimates of 8.3% [12], a trend seen across a diverse range of countries and societies. In Australia, similar upward trends in prevalence are noted, with estimated increases from around 650,000 Australians in 1995 (3.5% of the population) [13] to the most recent International Diabetes Federation estimates of 9.9% [12]. The increasing impact of this condition was demonstrated by its inclusion as a National Health Priority Area by the Australian government in 1997. There are predictions that up to 2 million adults in Australia will have diabetes by 2025, but greater increases are suspected if current trends in obesity (upward) and mortality (decreasing) continue [14].

The association between CHD and diabetes is complex and multifactorial. The pathological processes which underlie coronary artery disease are exacerbated by the presence of diabetes, meaning that the morbidity and mortality risk is elevated when both conditions are present [15]. Historically it has been stated that people with diabetes
have a two- to four-fold greater risk of developing CHD [1, 16]. However, improved management of cardiovascular risk factors in diabetic patients, including hypertension and dyslipidaemia, has increasingly occurred since the late 1990s, and this translation of clinical trial findings into clinical guidelines has the potential to influence the population burden of CHD in diabetic people.

The changing epidemiology of diabetes has raised concerns about the possibility of a reversal of the positive trends in CHD mortality at a population level. Modelling studies have shown that increasing population prevalence of diabetes has contributed to a 10% increase in CHD mortality rates [9], although currently the positive effects of improvements in smoking, cholesterol and blood pressure, and acute and secondary treatments outweigh this adverse effect of diabetes [8, 9, 17, 18]. Careful evaluation of the impact of increasing diabetes prevalence is therefore required to determine its impact on the CHD burden.

1.2 STUDY RATIONALE

The series of papers presented in this thesis were conceptualised to address the limited availability of trend data addressing the epidemiology of CHD in the context of diabetes, and to add to existing data internationally. Because CHD trends in people with diabetes should be interpreted in the context of broader CHD and CVD epidemiology, this thesis also includes papers on trends in incidence, recurrence and outcomes of CVD (including CHD and myocardial infarction (MI)). The findings of the CVD trend studies informed development of the studies specifically addressing the impact of diabetes on CHD incidence and outcomes, and provide context for interpreting the results of the diabetes analyses. A whole-population approach has been taken throughout the thesis, namely for the state of Western Australia (WA), as this uniquely demonstrates the impacts of treatment and prevention efforts at this population level, and supplements known clinical trial, registry and cohort study data.

Despite the high risk of developing CHD in people with diabetes, there is limited international and no Australian population level data detailing trends in the incidence of CHD in people with diabetes. In Australia, there is a dearth of temporal trend data measuring CHD outcomes in people with diabetes. There are also few settings where the spectrum of incidence, short-term case fatality and longer-term outcomes following MI have been measured in the same population, both overall and specifically for people with diabetes.
The ability to estimate CHD incidence in the diabetic population is an important epidemiological measure as it can indicate the population level impacts of the recent changes in the management of people with diabetes. However, population-level analyses require knowledge of changing diabetes prevalence in the population under investigation, including age and sex distribution. While prospective cohort studies have the capacity to capture these data because the required information (diabetes and prior MI status) are known for the whole cohort, results may be less generalisable to the whole population.

Data linkage infrastructure is not yet uniformly available nationally and is in varying stages of implementation in other Australian states. The long-standing WA Data Linkage System (WADLS) therefore provides a unique opportunity for investigating the full spectrum of CHD and CVD epidemiology in the whole WA population and in those with diabetes. Firstly, it allows a whole-population cohort of hospitalised CHD patients to be defined, as there are statutory requirements for reporting from all hospitals (public and private) in WA. Secondly, the capture of all hospitalisations for diabetes or diabetes-related conditions is possible. While hospital data cannot identify all prevalent diabetes cases in any population [19], it can be used to determine the diabetes status in all hospitalised CHD patients. However, its reliability in this setting needs to be evaluated because changes to coding standards for diabetes in Australia have occurred which may result in artefactual trends in diabetes hospitalisations. Thirdly, while not containing clinical data, the linked administrative data provide the ability to measure a number of variables important for such epidemiological studies including CHD history for delineating incident or recurrent status; long lookback periods for identifying comorbidities; and full mortality data for outcome studies.

1.3 ORGANISATION OF THESIS

The primary aim of this study was to use the WA linked health data to investigate the changing epidemiology of CHD in people with diabetes in the context of the changing epidemiology of CHD and CVD more broadly in the WA population. The specific objectives are delineated at the end of Chapter 2.

This thesis is presented as a series of papers. Chapter 2 provides a background of the literature pertinent to the studies undertaken within the thesis. Chapter 3 provides a brief overview of the data sources used in the studies, focusing on issues which influenced methodology decisions; and also provides data from preliminary analyses relevant to
these decisions. Chapters 4–9 are the Results chapters for the thesis and include abstract, introduction, methods, results and discussion for each separate study. Chapters 4–8 are published papers which are presented as published in their respective journals, with formatting in these papers retained as per the published version. Chapter 9 is presented as a manuscript which has been submitted to a peer-reviewed journal. Chapter 10 provides a summary of the main findings of the studies, integrating these data and detailing the implications of the results, study limitations and unanswered questions raised by these studies.

1.4 REFERENCES


Diabetes is a multifaceted metabolic condition which is heterogeneous in nature and characterised by the presence of hyperglycaemia [1, 2]. The primary pathogenic processes which cause diabetes are cellular-mediated autoimmune destruction of the beta-cells in the pancreas which result in insulin deficiency (type 1) or processes which lead to resistance to insulin action (‘insulin resistance’), relative insulin deficiency and an insulin secretory defect (type 2) [2]. The majority of cases of diabetes are classified as type 2 (~90% of cases). A small proportion of cases result from other pathologies including endocrinopathies, genetic defects, drug and chemical induced, and gestational effects [2].

The testing and diagnostic threshold for establishing a clinical diagnosis of diabetes has been modified over the past four decades (Table 2.1), in line with an increasing knowledge of risk thresholds relating to glycaemic levels. The 1997 American Diabetes Association guidelines recommended use of casual blood glucose (plus symptoms of diabetes), fasting plasma glucose (FPG) or an oral glucose tolerance test (OGTT) to diagnose diabetes, with confirmation of diagnosis via any of these tests on a subsequent day [3]. This was a shift from previous guidelines where OGTT was only recommended if blood glucose levels were within an ‘uncertain’ range [4, 5]. Importantly, a downward shift in the diagnostic threshold for FPG levels was also implemented in the 1997 guidelines (7.8 mmol/L to 7.0 mmol/L) and subsequently adopted by the World Health Organization (WHO) in 1999 [6]. In Australia, the recommended guidelines for diagnosing diabetes have been based on the WHO guidelines since 1999 [6, 7].

The lowering of the FPG threshold to diagnose diabetes was implemented to reflect the risk of development of retinopathy associated with these glycaemic thresholds [3]. The previous lack of diagnostic equivalence between the OGTT and FPG levels also meant that the prevalence of detected diabetes was likely to be lower where only FPG tests were used for diagnosis. Until recently, the measurement of glycated haemoglobin (HbA$_{1c}$) has been primarily used in monitoring diabetes control and treatment, but was
added as one of the criteria for diagnosing diabetes by the American Diabetes Association in 2010 [2] and by the WHO in 2011 [8].

The presence of diabetes is variably identified in epidemiological studies, usually dependent on the available data source and extending beyond the clinical classification algorithm. Studies investigating cardiovascular incidence and outcomes commonly use an algorithm of combinations of medical history, self-report, blood glucose levels and drug treatment [9–12]. The prospective Framingham Heart Study identifies diabetes in the presence of fasting blood glucose of $>7.0$ mmol/L, or use of insulin or oral hypoglycaemic drugs, with sensitivity analyses used to determine the effect of changes in diagnostic thresholds [13]. Administrative data has also been used to identify diabetes status for epidemiological studies and details relevant to this thesis are outlined in Section 3.3.


Table 2.1. Summary of the major changes in the glycaemic thresholds for diagnosing diabetes.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Casual or random blood glucose (mmol/L)†</th>
<th>Fasting plasma glucose (mmol/L)</th>
<th>2-hour post glucose load (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance, 1979 [5]</td>
<td>≥11.1</td>
<td>≥8.0</td>
<td>+/– ≥11.0</td>
</tr>
<tr>
<td>World Health Organization: Expert Committee on Diabetes Mellitus, 1980 [14]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Diabetes Association: Diagnosis and Classification of Diabetes Mellitus, 2010** [2]</td>
<td>≥11.1</td>
<td>≥7.0</td>
<td>≥11.1</td>
</tr>
</tbody>
</table>

† Based on measurement of venous plasma glucose concentration and where accompanied by symptoms of diabetes

*Diagnosis of diabetes requires one of these three criteria to be confirmed on a subsequent day

**HbA1c ≥6.5% also introduced as one of the diagnostic criteria

2.2 Incidence and Prevalence of Diabetes

There is strong evidence that the burden of diabetes has risen markedly in developed countries [15, 16]. Rising prevalence of diabetes is underpinned by an increase in the incidence of diabetes [17, 18], accompanied in recent years by declining diabetes-related mortality [19]. Increasing incidence of type 2 diabetes has been reported from the United Kingdom (UK), based on national primary care data [20]. An important finding of this study was an apparent downward shift in the age at diagnosis of diabetes.
A population-level study in Ontario, Canada, demonstrated an increase of 31% in diabetes incidence between 1998 and 2005 [21]. The Framingham Heart Study reported that diabetes incidence increased significantly since the 1970s, although with plateauing of these trends in the recent decade [22].

Concurrent with these trends is an increase in the global prevalence of diabetes. Prevalence estimates from 2000 onwards range from 4.2% in Denmark [19], 5.8% in the National Health and Nutrition Examination Survey (NHANES) cohort in the United States (US) [23] and 8.8% in Ontario, Canada [21]. The latter study noted that the rate of increase in diabetes prevalence in their population exceeded the projections for prevalence estimated for global and Canadian increases [24]. The most recent estimate of the global prevalence of diabetes from the International Diabetes Federation is 8.3% (Figure 2.1) [15]. Although the lowering of the diagnostic threshold for diabetes and increased screening and awareness may have contributed to the greater detection of diabetes, the ageing of the population and increasing levels of obesity are posited as major contributors to these upward trends in prevalence [21, 25].

In Australia, there is no single source for estimating diabetes prevalence, although indications are that trends in diabetes prevalence are consistent with those seen elsewhere. National Health Survey data, based on self-report of diabetes status, indicate that diabetes prevalence has increased in Australia from around 2% in 1989–1990 [26] to 4.2% in 2011–2012 [27]. However, estimates of diabetes prevalence are higher from other data sources, including comparable state-based self-report survey data (4.7% in 2002, 6% in 2011) [28] and the cross-sectional Australian Diabetes, Obesity and Lifestyle (AusDiab) study (7.4% in 2000), which included diagnosed and undiagnosed cases of diabetes [29]. Projections to the year 2030 indicate that the prevalence of diabetes in Australia will be 9.0% in adults aged >20 years [24].
CHAPTER 2. CHANGING EPIDEMIOLOGY OF DIABETES AND CORONARY HEART DISEASE

Figure 2.1. Global comparative prevalence of diabetes in adults aged 20–79 years in 2013. Estimates are shown as percentages [15].

2.3 PATHOPHYSIOLOGY OF ATEROTHROMBOTIC VASCULAR DISEASE IN DIABETES

Inflammatory processes which affect the arterial endothelium are a major driver of atherogenesis in coronary artery disease [30]. This process is mediated by a complex interaction of risk factors including dyslipidaemia, vasoconstrictor hormones associated with hypertension, cytokines released from adipose tissue and hyperglycaemia, which lead to a proinflammatory and prothrombotic state and the development of plaque lesions [30]. The development of atheromatous plaques is promoted by the entry and accumulation of low-density lipoprotein-cholesterol (LDL-C) particles into the tunica intima of the arterial wall, as well as the migration of smooth muscle cells which can contribute to the formation of a fibrous cap on the plaque [31]. Symptomatic clinical presentation most commonly results from stenotic plaques which limit blood flow, or thrombus formation which commonly arise after fracture of the fibrous cap of the plaque [31].

Diabetes has a marked atherogenic impact on the macrovasculature and is characterised by the acceleration of these atherothrombotic processes [32]. Endothelial function is disrupted to a greater extent because the processes which lead to vascular inflammation are heightened by the presence of hyperglycaemia [1]. The imbalance between nitric
oxide availability, accumulation of reactive oxygen species (caused by oxidative stress) and the increased synthesis of vasoconstrictors and prostanoids promotes endothelial dysfunction and is a prime pathway through which hyperglycaemia acts to mediate the onset of diabetic vascular disease [33]. Additional to the direct effects of insulin resistance and hyperglycaemia are the effects of increased lipid storage and changes in the lipid profile leading to high triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), small dense LDL-C particles and elevated apolipoprotein B [33].

The triggering of proinflammatory pathways in diabetes is mediated by the presence of obesity, particularly central adiposity [34]. Increased adiposity is associated with higher levels of circulating inflammatory markers [35]. The prothrombotic state in diabetes results from the impacts of insulin resistance and hyperglycaemia on coagulation and platelet activity. These processes result in platelet hyperreactivity and hypercoagulability, and impaired fibrinolysis which contribute to thrombus formation [36]. An emerging concept is that of ‘hyperglycaemic memory,’ where the effect of transient or early hyperglycaemic stress continues to impact on the vasculature, despite normalisation of glycaemic levels [33]. The presence of reactive oxygen species and epigenetic factors may be involved in this process [37].

The effects of insulin resistance and impaired glucose tolerance occur for many years prior to diagnosis of diabetes, particularly in type 2 diabetes [38]. Imaging studies have shown that people with diabetes and coronary artery disease have more severe and diffuse atherosclerotic changes in their coronary arteries and higher levels of multivessel disease [39]. In people with diabetes without a history of coronary artery disease, high levels of subclinical atherosclerosis are noted [1] and a higher incidence of subclinical myocardial damage in the presence of diabetes or pre-diabetes is associated with higher rates of heart failure and mortality [40]. Additionally, there are more intracoronary thrombi formations, greater lipid cores in plaques and a greater tendency for acute disruption of plaques in diabetic patients [1].

### 2.4 Diabetes and Coronary Heart Disease Risk

Diabetes is an independent risk factor for the development of CHD [41], imposing a two to four times greater risk of CHD incidence or cardiovascular mortality than in the non-diabetic population [10, 42]. This elevated cardiovascular risk may be present up to 15 years prior to diagnosis of diabetes [43]. Diabetes has been called a ‘CHD risk-equivalent,’ a concept underpinned by the findings of a seminal observational study by
Haffner et al. [44]. This study reported that diabetic patients with no previous MI have an adjusted CHD mortality risk equivalent to that of non-diabetic patients with a prior MI, findings which were supported by subsequent studies [45, 46]. However, the results of later studies were less consistent [47]; the impact of diabetes relative to a prior history of MI was shown to be age and sex dependent [48] and related to longer duration of diabetes [49, 50].

Given the high levels of cardiovascular risk associated with diabetes, Section 2.4 outlines the major cardiovascular risk factors associated with the development of CHD in people with diabetes, with a focus on modifiable risk factors and their trends. There is also a brief overview of the association of chronic kidney disease (CKD) and heart failure with diabetes and CHD because of their relevance to the data in this thesis.

2.4.1 HYPERGLYCAEMIA

The presence of hyperglycaemia is independently associated with the development of CHD [42] and this risk is present even where blood glucose levels are below the diagnostic threshold for diabetes (Figure 2.2) [51, 52]. The presence of impaired fasting glucose (FPG 5.6 mmol/L to 6.9 mmol/L) or impaired glucose tolerance (OGTT 7.8 mmol/L to 11.0 mmol/L) are considered risk factors for the future development of diabetes [2] and CVD [52]. In Australia, the definition of this pre-diabetic state is based on the WHO guidelines, where the lower glucose threshold for defining impaired fasting glucose is 6.1 mmol/L [53].

A positive association between cardiovascular risk and varying measures of blood glucose including HbA1c, FPG and post-load glucose measures has been reported. The association between FPG and cardiovascular risk has been shown to be log-linear [54], however, a J-shaped relationship has also been reported, with FPG levels <5.1 mmol/L [52] and <4.0 mmol/L [55] associated with increased all-cause mortality. Post-load glucose measures have generally shown a linear association with CVD, even after accounting for cardiovascular risk factors including hypertension, smoking, dyslipidaemia and history of prior CVD events [52, 56]. In CVD-free non-diabetic participants in the Atherosclerosis Risk in Communities (ARIC) study, HbA1c was predictive of CHD risk at levels even below those advocated in guidelines (<6.5%) [57].
There is strong evidence that tighter control of hyperglycaemia in type 1 and type 2 diabetes lowers the risk of microvascular events [58, 59, 60] yet results have been less consistent for the effect on macrovascular risk. Individual trials, including the United Kingdom Prospective Diabetes Study (UKPDS) [59], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial [61] and the Veterans Affairs Diabetes Trial (VADT) [62] generally demonstrated non-significant reductions in the risk of major cardiovascular end-points with intensive glycaemic control, while the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was ceased early because of higher mortality rates in the intensive control group [63]. A meta-analysis of these four trials, including 27,049 patients with type 2 diabetes, demonstrated significant risk reductions of 9% and 15% for a composite cardiovascular endpoint and MI (fatal or nonfatal) respectively, with an average length of follow-up of 4.4 years [64]. However, no significant improvement was seen in all-cause or CVD mortality with intensive glycaemic control. The results of a further meta-analysis supported these findings [65] while a meta-analysis which included 13 randomised controlled trials found no reduction in CVD mortality with intensive glycaemic control [60].

Longer-term follow-up (10 years’ post-trial) in the UKPDS demonstrated significant risk reductions of 15% for MI and 13% for all-cause mortality in those patients using sulfonylurea/insulin, a finding also seen in the overweight patients taking metformin.
In the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study with 17 years of follow-up, intensive treatment of glycaemic levels in people with type 1 diabetes was associated with a 42% reduction in any cardiovascular event [67]. However, the ADVANCE and ACCORD trials both demonstrated no change in cardiovascular outcomes with intensive glucose lowering therapy over 5.4 years and 3.5 years respectively [68, 69], and longer-term follow-up in the VADT showed no improvement in either cardiovascular or all-cause mortality [70]. Thus, the longer term effect of tighter glycaemic control on cardiovascular risk is currently uncertain.

### 2.4.2 AGGREGATION OF CARDIOVASCULAR RISK FACTORS AND DIABETES

Major modifiable cardiovascular risk factors including hypertension, smoking, dyslipidaemia, diabetes and obesity, along with psychosocial factors, low fruit and vegetable consumption, alcohol consumption and physical inactivity, account for 90% of the population-attributable risk for MI [71]. Diabetes is itself associated with an aggregation of these cardiovascular risk factors, including higher levels of dyslipidaemia, obesity and hypertension [72, 73]. The clustering of increased blood pressure, glucose intolerance, central obesity and abnormal lipid levels in an individual is termed the metabolic syndrome [35] and is common in people with diabetes. The prevalence of the metabolic syndrome ranges from ~9% in cohorts free of CVD and diabetes at baseline [74], to over 80% in patients with diagnosed diabetes [75]. The effect of these risk factors in the presence of diabetes may be additive, particularly in those CVD-free at baseline [75].

The dyslipidaemic profile associated with diabetes differs from that of non-diabetic people. Atherogenic dyslipidaemia, comprising increased triglyceride levels, low levels of HDL-C and small dense LDL-C particles, is typically found in people with diabetes, often in the presence of normal LDL-C levels [76, 77]. Elevated triglyceride and low HDL-C levels are both reported as independent predictors of cardiovascular risk in diabetic people [77]; however, the association of triglycerides may be mediated through the effect of non-HDL-C [78]. Increased total cholesterol, non-HDL-C and LDL-C levels are also associated with the incidence of CHD [78–80]. The Asia Pacific Cohort Studies Collaboration reported a similar strength of association between total cholesterol and the risk of CHD in this large cohort, indicating that the impact of dyslipidaemia on CHD risk may be similar in diabetic and non-diabetic people [80].
Hypertension is also highly prevalent in people with diabetes. Its strong association with the risk of cardiovascular events results from its effect on endothelial dysfunction, subsequent vascular inflammation and increased activity of the renin-aldosterone-angiotensin system [81]. Up to two-thirds of people with diabetes have hypertension compared with 20–30% of people without diabetes [44, 72, 82]. An 18% increase in the risk of major cardiovascular events has been reported for every 10 mm Hg increase in systolic blood pressure (SBP) [83]. As with the effects of dyslipidaemia, observational data suggest that the effect of elevated SBP on cardiovascular risk is similar irrespective of diabetes status [83].

The association between hypertension, dyslipidaemia and diabetes is underpinned by evidence supporting the efficacy of treatment of these risk factors. The efficacy of cholesterol-lowering drugs in CHD prevention and treatment has been well documented [84–86]. In people with diabetes, despite the characteristic lipid profile, the effects of treatment occur predominantly through reduction of LDL-C levels [87]. The Heart Protection Study [88] and Collaborative Atorvastatin Diabetes Study [89] demonstrated a 25% and 37% risk reduction respectively in major vascular event rates with the use of statins in diabetic populations without established CHD. These effects were seen in older patients, people with different durations of diabetes, presence of hypertension, and type 1 and type 2 diabetes [89].

Similarly, there is strong evidence of the effect of blood pressure lowering in CVD prevention [90], with these effects also seen in diabetic patients. The post-trial follow-up of the ADVANCE trial demonstrated a continuous reduction in the risk of mortality with blood pressure lowering versus placebo out to six years, although no significant difference was seen for nonfatal CHD events [68]. A meta-analysis confirmed that lowering of blood pressure in type 2 diabetes patients with SBP≥140 mm Hg at baseline was significantly associated with a reduction in the risk of CHD events, as well as reduced risk of all-cause mortality, major CVD events and stroke [91]. Tighter blood pressure control (<150/85 mm Hg) compared with less tight control (<180/105 mm Hg) in people with diabetes resulted in a significant 37% reduction in a composite macrovascular end-point over 8.4 years in the UKPDS trial, however the 21% reduction in MI events was not significant [92]. Results from the ACCORD trial contrasted somewhat with these results, with intensive control of blood pressure not superior to
standard therapy [93]. These differences are postulated to have arisen because of higher baseline SBP in the UKPDS trial.

A significant proportion of people with diabetes are overweight or obese [94]. This association is highlighted by the increased risk of developing diabetes in those with higher body mass index (BMI), particularly at younger ages [95]. Increasing BMI is associated with the incidence of CHD and CVD, and all-cause mortality [96, 97] and this relationship is also seen with other measures of adiposity, including waist-to-hip ratio and waist circumference [98]. The presence of obesity imparts a doubling of risk for MI in diabetic people compared with around 1.5 times greater risk in people with diabetes of normal weight [99]. Although it is independently associated with the development of CHD, the risk associated with BMI above the normal range in diabetes is also mediated by the effects of an abnormal lipid profile and blood pressure, more so in people in the overweight than obese range [97].

Other modifiable risk factors are also associated with increased cardiovascular risk in diabetic patients. Some are independent predictors of cardiovascular events and mortality, including smoking [12], low cardiorespiratory fitness [100] and physical inactivity [99]. Smoking prevalence is often similar in diabetic and non-diabetic groups in cohort studies [12, 82] compared with the clustering of other risk factors in diabetic people. Smoking cessation reduces the risk of CVD; however, the potential weight gain often seen following cessation may confound this relationship in diabetic people [101]. Although there is limited evidence of an association between lifestyle modification alone (weight loss and physical activity) and reduction of cardiovascular events, the effect of lifestyle modification (diet, exercise and smoking cessation interventions) in conjunction with intensive glycaemic, blood pressure and lipid control significantly reduces the risk of major cardiovascular events [102].

Age and gender also play a significant role in the onset of CHD in people with diabetes [103]. Because CHD incidence in the general population is strongly age-dependent, this may partly explain the strong association between increasing age and the risk of developing macrovascular complications in people with diabetes, independent of the effect of diabetes duration [104]. This contrasts with the lack of independent association between increasing age and the risk of microvascular disease, a relationship strongly mediated by the duration of diabetes [104]. There are also noted gender differences, with the relative risk of CHD events and mortality in diabetic versus non-diabetic
women being greater than the same comparison in men [9, 12, 105]. A meta-analysis demonstrated that the excess risk in diabetic women was largely accounted for by the presence of comorbidities and traditional cardiovascular risk factors [106], although the residual risk may persist even after adjustment [105].

2.4.3 TRENDS IN RISK FACTORS AND MANAGEMENT IN PEOPLE WITH DIABETES

There are differing trends in the population-level prevalence of some major cardiovascular risk factors. Large international health surveys have reported moderate declines in SBP globally over the past three decades [107], with relatively unchanged levels of total cholesterol [108], and increasing prevalence of diabetes and body mass index [109, 110]. Australasian data in these studies shows stronger downward trends in hypertension and cholesterol levels than in many other high-income countries. Risk factor survey data for 1980 to 1999 for Perth, WA, is consistent with these findings, with concurrent falling cholesterol levels and increasing BMI [111]. Smoking prevalence nationally has halved, from 26% in the early 1990s to current levels of 12.8% [94], underpinned by falling rates of daily smokers in people aged <49 years in the most recent decade. Reductions in hypertension, dyslipidaemia and smoking prevalence are estimated to account for 73% of the decline in CHD mortality in men and 81% in women in Australia [112].

There are indications that these risk factor trends are also occurring in people with diabetes. Reductions in the proportion of diabetic people in the NHANES cohorts have been reported for high cholesterol (72% to 55%), high blood pressure (64% to 37%) and smoking prevalence (32% to 17%) between 1971 and 2000 [113], although with limited improvement in hypertension in the subsequent decade [114]. Improvements in risk factor prevalence in people with diabetes are also reported from the Framingham Heart Study [115]. In contrast, the Tromsø Study in Norway reported adverse trends in HDL-C and triglycerides in people with diabetes between 1994 and 2008, although total cholesterol and mean blood pressure levels decreased significantly [116]. Data regarding BMI appears consistent across studies, with upward trends noted in people with diabetes [115–117].

There are indications in Australia that risk factor management in people with diabetes is increasing, in line with upward trends for treatment of dyslipidaemia and blood pressure in European and US cohorts of diabetic people [115, 116]. Data from an audit of specialist diabetes centres in Australia reports increasing treatment of hypertension and
dyslipidaemia in diabetic patients to 2011 [118]. The AusDiab study showed that diabetes was associated with a greater likelihood of hypertension being treated [119]. National survey data from Australia also suggests that the prevalence of overweight and obesity remains markedly higher in people with diabetes — 88% in diabetic people compared with 63% in the general population [94].

2.4.4 IMPACT OF CHRONIC KIDNEY DISEASE AND HEART FAILURE

CKD is a common comorbid condition in people with diabetes. A survey of general practitioners in Australia reported that half of the patients with type 2 diabetes had concurrent CKD [120]. It is an independent predictor of cardiovascular mortality [121], even in diabetic patients in the earlier stages (stages 1–3) of the disease [122]. While the risk of developing CKD in people with diabetes is present with albuminuria levels still within the normal range, there is evidence that treatment of blood pressure at this stage can prevent progression to overt proteinuria [123]. A common cause of CKD is diabetic nephropathy, which is itself a microvascular complication of diabetes [123]. The prevalence of diabetes-related CKD in Australia has increased, with the proportion of cases of treated end-stage CKD rising from 13% in 1991 to 33% in 2010 [124]. This pattern has also been reported in the US, although a plateauing in upward trends has been observed since the mid-2000s [125].

Heart failure is also a frequent comorbid condition in people with diabetes and is associated with high levels of multi-morbidity [126]. Insulin resistance is independently associated with the development of heart failure [127], and people with diabetes are 2.5 times more likely to develop heart failure than those without diabetes [128]. The risk factors common in people with diabetes are also associated with the development of heart failure, including hypertension, CHD, elevated HbA1c, and overweight and obesity. Mortality rates are high in patients with heart failure, with nearly half of heart failure patients dying within five years of onset [129] and, with concomitant diabetes, this risk is even higher [130, 131].

The burden of heart failure is reported to have increased underpinned by high levels of rehospitalisation and increased survival [132]. In WA, the incidence of heart failure hospitalisations declined between 1990 and 2005, accompanied by improving short-term survival [133]. The proportion of the incident heart failure patients with concomitant diabetes increased from 18.5% to 26.9% during this period, while a declining proportion presented with a history of prior MI.
2.5 IMPACT OF DIABETES ON TRENDS IN CORONARY HEART DISEASE INCIDENCE

2.5.1 BACKGROUND POPULATION TRENDS IN CORONARY HEART DISEASE INCIDENCE

Declining incidence of CHD has been reported in many populations over the past four decades [134, 135], mirrored by declines in other manifestations of CVD including cerebrovascular disease (CeVD) [136–138] and peripheral arterial disease (PAD) [139]. The downward trends in CHD incidence have been reported from community and primary-care based studies [140, 141] and from studies using hospitalisation data to identify CHD incidence [142, 143]. These trends represent a broad spectrum of CHD across community- and hospital-level presentations within populations, suggesting a real decline in this disease. Population-level data which we have previously published in WA shows that the prevalence of hospitalised CHD has decreased marginally in the recent decade [144] which, if downward trends in CHD mortality continue [145], suggests that CHD incidence may also be declining in our population.

The contribution of trends in MI incidence to declining CHD incidence and mortality were not consistent internationally during the 1980s and 1990s. The major community-based and surveillance projects in the US reported small (~1%/year) non-significant declines or no change in incident MI in their populations [134, 146–148] and the Olmsted County study reported an increase in MI incidence in women of 2.2%/year, underpinned by increasing rates in the older age group [146]. In contrast, studies conducted during the same time period in European populations demonstrated declines in the incidence of MI of between 2% and 5% per year [149–153]. Similar declines in MI incidence were reported in Australia during the same period, based on registry and Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) data from the Perth (WA) and Newcastle (New South Wales) centres [154, 155]. Rates of decline in Perth were less than estimated from the Newcastle population.

Understanding trends in MI incidence has been complicated by the addition of troponin testing to the diagnostic criteria for MI since the late 1990s [156–158]. The change in the definition of MI has been linked to the attenuation of MI hospitalisation trends both in WA [159] and elsewhere [160–162]. I have reported in a previously published study that incidence rates of hospitalised acute coronary syndrome (ACS) declined in WA between 1996 and 2007. This trend was underpinned by limited reductions in MI and greater reductions in unstable angina incidence [163]. Against the overall trend, ACS incidence increased in 35–54-year-old women over the same period. A number of
studies have shown continuing overall declining hospitalisation or incidence rates of MI during this period [164], including national data from England [165], Ireland [166] and Denmark [167], although with some attenuation of trends in the early 2000s in the latter study possibly due to the impact of increasing non-ST-segment elevation MI (NSTEMI) cases. Recent data from Norway [168] and the US [169] demonstrate that declines in MI incidence are underpinned by greater reductions in rates of out-of-hospital deaths. Collectively these latter findings may indicate a shift in the burden of MI from pre-hospital deaths to hospitalised cases.

2.5.2 TEMPORAL TRENDS IN CHD AND MI INCIDENCE IN PEOPLE WITH DIABETES

There have been limited data specifically investigating temporal trends in CHD and MI incidence in people with diabetes but emerging evidence suggests that CHD incidence may have declined in diabetic people. The Framingham Heart Study reported a nearly 50% reduction in the incidence of a broader CVD endpoint, including MI, stroke and CHD death, over an extended period (1950–1966 to 1977–1995) [13]. Results from the ARIC study in a more recent time period (1987–1996 to 2003–2009) are consistent with these findings [170]. Improved control of LDL-C and increased use of lipid-lowering medications were associated with the reductions in CHD incidence. Data from the NHANES cohort estimated that the 10-year risk of CHD incidence in people with diabetes fell from 21.1% in 1999–2000 to 16.4% in 2007–2008, concurrent with reductions in SBP, total cholesterol, total cholesterol/HDL-C ratio and mean HbA1c in this cohort [171].

Contrasting trends are reported from two European studies, both using data derived from their respective MONICA MI registries. In the northern Sweden MONICA cohort, MI incidence was unchanged in people with diabetes from 1989 to 2000. Concurrent trends in people without diabetes were stable in women and decreased by 3% per year in men [172]. Disparate trends between men and women with diabetes were reported from the southern German MONICA registry from 1985 to 2006, with MI incidence declining annually by 2% in women, but with an average annual increase of 1% in men (although of marginal statistical significance) [173]. These trends were concurrent with a significant decline in MI incidence in people without diabetes (1.5%–2% annual reductions).

In both MONICA studies, no detectable trend in diabetes prevalence was noted in four population risk factor surveys carried out during the study periods. This is despite an
increase in the use of glucose-lowering drugs in men and women, and an increase in diabetes prevalence from 3.7% to 4.6% in men in the German study [173]. This contrasts with the Framingham study which, although conducted over a much longer time period, demonstrated an increasing diabetes prevalence of 2.7% to 7.8% between the early and later cohorts [13]. Underestimation of an increase in diabetes prevalence (and thus no increase in the at-risk diabetic population) could attenuate any real reduction in risk in people with diabetes.

Concurrent with declining incidence rates are reductions in event rates (rather than first-ever events) in diabetic people. In a large US study using a number of national probability survey databases, a decline of 67.8% in rates of hospitalisation for MI among people with diabetes was reported from 1990 to 2010, greater than declines in the non-diabetic population [174]. These declines were also greater than declines seen for other major complications of diabetes, including stroke, end-stage renal disease and amputations. These results are consistent with falling hospitalisation rates of MI in people with diabetes in a whole-population setting in Ontario [175] and with trends using national data for England, although the rate of decline was similar in non-diabetics [176]. Rates of other cardiac and cardiovascular manifestations also declined, including stroke [175] and angina [176].

2.6 DIABETES AND OUTCOMES IN PEOPLE WITH CORONARY HEART DISEASE

2.6.1 FACTORS IMPACTING OUTCOMES FOLLOWING MYOCARDIAL INFARCTION

Following MI, there is an increased risk of recurrence and mortality [177–179]. This is particularly evident in the acute phase immediately after an MI and is related to the systemic inflammatory reaction and exacerbation of plaque inflammation and thrombosis induced by the infarction process [180]. Observational studies have shown that this elevated risk persists well beyond the acute post-MI phase [181–183]. Around half of CHD hospitalisations will occur in those with a prior history of CHD [184], consistent with the strong association between the presence of established vascular disease and poor outcomes following an incident event [185].

Temporal improvements have consistently been reported in short-term case fatality following MI over the past three decades. These trends have been evident for in-hospital deaths and also for mortality within one month of MI [167, 186–188]. In the MONICA study, the hospital component of overall case fatality declined more than pre-hospital
death rates, including in the Australasian centres [155]. These trends have continued in WA, with 28-day case-fatality following MI hospitalisation declining from 13.5% to 4.7% in men and from 18.1% to 7.1% in women between 1980 and 2004 (Figure 2.3) [159]. Notably, the rate of decline was greatest during the latter part of the study period (1998–2004). Mortality rates at one to two years post-MI of up to 30% are reported from studies conducted in the 1980s and 1990s [189, 190] while contemporary data suggests lower rates [191].

Figure 2.3. Age-standardised case fatality following myocardial infarction in the population of the Perth Statistical Division (Western Australia). OR(slope) represents the odds ratio for the change in case fatality per year from age-adjusted logistic regression models [159].

The mortality risk with longer-term follow-up is high, with an English national linked data study reporting that the risk of all-cause mortality at seven years in 30-day survivors of MI was twice that of the general population [192]. Temporal trend data suggest that this elevated longer-term mortality, as well as recurrence rates of MI, have declined [193–195]. The Olmsted County study demonstrated that the risk of a recurrent ischaemic event or sudden cardiac death within three years following MI fell by 24% from 1979–1985 to 1993–1998 [177]. Trends in this study were seen across all age, sex
and comorbidity groupings. Bata et al. reported improved survival at five years in patients who had an MI in 1989–1993 versus in 1984–1988 [196]. A study of the MONICA cohort in WA also showed improvements in mortality after MI, with a 28% relative risk reduction out to 12 years post-MI [197].

The association between guideline-advocated acute coronary care and survival following MI is well established [198–200]. Increasing use of these recommended therapies, including reperfusion therapy, evidence-based medicines (antiplatelet therapies, beta blockers, statins and angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs)) and coronary revascularisation have been significantly associated with the downward trends in early deaths following MI [182, 201, 202]. A recent comparative analysis of 30-day case fatality after MI in the UK and Sweden [203] showed that the reduction in excess case fatality in the UK was consistent with increasing use of primary percutaneous coronary intervention (PCI), as well as overall increases in evidence-based medication use.

Increasing use of evidence-based medical therapies has been reported from Perth since the 1980s. Data from the MONICA project at that time reported significant increases in the use of beta blockers, and antiplatelet and thrombolytic therapy, trends which predated some clinical trial evidence [204]. These trends have continued in the more recent era, with contemporary registry data from Australia and New Zealand consistent with this pattern [205]. Between 2000 and 2007, increasing rates of PCI, including emergency revascularisation in ST-segment elevation MI (STEMI) patients (from 11% to 27%) and increasing use of evidence-based drugs, particularly statins and antiplatelet therapy, was evident. These findings were concurrent with falling rates of in-hospital mortality in both STEMI and NSTEMI patients from 2002 to 2007. Improvements in longer-term outcomes have also been associated with these changes in medical management, including in-hospital treatment [197], as well as guideline-advocated combination drug therapy at hospital discharge [206].

2.6.2 FACTORS AFFECTING OUTCOMES FOLLOWING MYOCARDIAL INFARCTION IN PATIENTS WITH DIABETES

The presence of diabetes imposes a significantly-elevated risk of adverse short- and long-term outcomes [10, 12]. Diabetic patients have more extensive coronary disease burden at MI presentation, a greater risk of complications such as acute heart failure and, historically, around double the risk of an early death after MI [207, 208]. With
longer-term follow-up, the difference in mortality rates by diabetes status appears to widen, with the multivariable-adjusted risk of mortality associated with diabetes being up to four times greater than in non-diabetic patients [209]. The impact of prior vascular disease is high, with diabetic patients with established vascular disease having higher cardiovascular event rates, particularly non-fatal events, than diabetic patients with cardiovascular risk factors but no prior vascular disease [210].

The disparity in mortality rates post-MI for diabetic patients has been associated with an evidence-treatment gap, particularly in the context of acute treatment. This is despite the association of guideline-advocated therapies with reduced early mortality, even in high-risk patients [211] including in those with diabetes [212]. Gaps in inpatient use of therapies and utilisation at discharge exist [207, 209]. Australian registry data from the mid-2000s demonstrated that patients with diabetes received ~5% lower levels of aspirin, beta blockers and statins, and 7% lower levels of clopidogrel and ACEi/ARBs at discharge following MI. They were also less likely to have undergone a PCI (35.5% versus 53.8%) although coronary artery bypass grafting (CABG) was more frequent [213]. There is evidence from Swedish and US studies that the gap in the application of these therapies between diabetic and non-diabetic patients has reduced more recently, concurrent with improvements in case fatality in diabetic patients [209, 214].

Historical data showing an evidence-treatment gap for longer-term secondary prevention in diabetic patients is less consistent. The REduction of Atherothrombosis for Continued Health (REACH) study of stable outpatients with either established atherothrombotic disease or three or more risk factors showed that diabetic patients received higher levels of some therapies (lipid lowering drugs, ACEi/ARBs, calcium channel blockers) but not others (beta blockers, antiplatelet therapy) [210]. Some studies have shown that diabetic patients have similar levels of persistence with cardiovascular medications as non-diabetic patients following MI [215]. However, there is also evidence of a disparity in the use of longer-term secondary prevention measures. Data from the EUROASPIRE III survey showed that although there were similar levels of prescribing of individual drug classes to diabetic and non-diabetic patients, only 50% of patients with prevalent diabetes were taking a combination of four evidence-based medications [216]. Although this was higher than seen in a previous survey, treatment targets were less frequently achieved in diabetic patients.


2.6.3 TRENDS IN SHORT-TERM CASE FATALITY AFTER MYOCARDIAL INFARCTION IN PATIENTS WITH DIABETES

There is increasing evidence that the trend towards declining levels of early case fatality following MI has extended to people with diabetes [217]. A single-centre study from the Netherlands covering an extended period (1985–2008) reported a 77% reduction in 30-day case fatality after MI in diabetic patients — the concurrent reduction in non-diabetic MI patients was 63% [218]. The trend persisted in both groups of patients after adjustment for age, sex, risk factors and MI type. Although this was a single-centre study with only moderate disparities by diabetes status in medical treatment and coronary revascularisation even in the earliest period, similar trends have been noted more recently in registry- and population-based studies [209, 214, 219]. In some studies, the relative difference between diabetic and non-diabetic patients has reduced to the point where there is little difference in in-hospital or 30-day mortality rates between the patient groups [214, 219].

The introduction of troponin assays did not initially impact trends in short-term case fatality [159, 160, 162]. Increasingly sensitive assays have been implemented since these early data. The subsequent increasing proportion of MI cases classified as NSTEMI could be more prevalent in diabetic patients because low levels of circulating troponin are commonly detected in diabetic patients [220]. Consequently, relatively greater reductions in case fatality in diabetic patients could ensue because of an increasing proportion of lower severity MIs in the diabetic group. However, in a study where in-hospital mortality declined more in diabetic than non-diabetic patients, Gore et al. demonstrated a similar decrease in the proportion of MIs recorded as STEMI in diabetic and non-diabetic MI patients, and in the relative mortality risk associated with diabetes for both MI types [214]. In-hospital mortality in patients with diabetes has fallen in studies confined to hospitalised STEMI patients [221] and NSTEMI patients [222], indicating that these trends have been seen across the spectrum of MI presentation.

There are limited Australian data in this context. Data from the Australian MONICA centre in Newcastle (NSW) showed no reduction in 28-day deaths after first MI in people with diabetes despite significant reductions in non-diabetic patients [223]. The study period (1985–1994) predates the contemporary management approach and was also restricted to 30–69-year-olds, which reduces its generalisability to the current
population. Pre-hospital deaths were also included, which importantly captured the broader spectrum of early deaths associated with MI. However, the more recent shift from pre-hospital to hospitalised presentations, as discussed earlier [167–169], demonstrates the importance of investigating hospitalised MI separately. Between-country comparisons highlight that 30-day case fatality may not improve at the same rate in all populations [203]. Given the disparity in therapies and management between diabetic and non-diabetic patients which was still apparent in Australian registry data in the mid-2000s, understanding early post-MI mortality rates in the diabetic population across this period will help to determine whether case fatality trends seen elsewhere extend to diabetic patients in an Australian setting.

2.6.4 TRENDS IN LONG-TERM OUTCOMES AFTER MYOCARDIAL INFARCTION IN PATIENTS WITH DIABETES

When examining long-term mortality following MI in people with diabetes, it is useful to understand the background trends in mortality rates in the overall diabetic population. Much epidemiological research has centred on whether excess mortality has improved over time in the broader diabetic population. Studies reporting data from the 1970s to 1990s mostly indicate that despite decreasing all-cause mortality rates in people with diabetes, the difference in mortality between people with and without diabetes did not reduce [224–227]. However, evidence is emerging from more contemporary studies that the mortality gap may be lessening as standardised mortality ratios for diabetes have declined in Denmark [19] and Australia [228] since the late 1990s.

The lack of reduction in excess mortality for diabetic patients has also been described for post-MI patients [219]. Data from the ACS Israeli Survey, a national population survey of hospitalised ACS patients, indicated that the adjusted risk of 1-year mortality in diabetic ACS patients persisted across study periods (2000–2005 to 2006–2010) [229]. Similar findings are reported from the UK, which showed that despite a reduction in the excess mortality of 30-day deaths in diabetic ACS patients, the mortality difference at 18 months persisted [217].

There is also limited evidence that the gap in longer-term mortality rates between diabetic and non-diabetic patients has closed following an MI. Substantial reductions in mortality rates in people with diabetes are reported from some studies, for example, absolute reductions in 5-year mortality of 24% in men and 29% in women between 1985–1989 and 2000–2004 in a single-centre study in the Netherlands [218]; falls of
27% in 5-year mortality in people with diabetes in the southern German MONICA registry [230]; and absolute reductions of 14% in men and 21% in women with diabetes in the Northern Sweden MONICA registry [231]. Despite these downward trends, the gap in mortality by diabetes status did not close in each of these studies. This pattern of temporal declines in long-term mortality rates but no reduction in excess mortality in diabetic patients following MI has also been described in a number of sub-groups, including for NSTEMI and STEMI in diabetic patients [209] and across all age and sex strata [219].

In contrast, a significant reduction in the relative risk of mortality in post-MI diabetic patients was reported from a population-level study from Sweden [209]. The risk ratio in this study decreased from 1.44 in 1995–1998 to 1.31 in 1999–2002. These data differ from the trends seen in most other studies, including the Northern Sweden MONICA registry [231]. The findings were attributed to improvements in evidence-based treatment for diabetic patients and occurred despite findings that excess mortality in women aged <65 years did not improve [232]. The large sample size (n=70,822) of the former study may have increased the ability to detect differences in trends with their whole-population approach.

Although the risk of CVD events is high in people with diabetes, up to 50% of deaths are attributed to non-vascular causes, particularly cancer [233]. In Australia, the proportion of non-vascular deaths is higher than this and has increased since 1997 [228]. Commonly, all-cause mortality remains the endpoint of interest in studies investigating excess mortality in people with diabetes following MI, and there is limited cause-specific mortality trend data following MI in this patient population. This is despite the fact that the proportion of deaths attributable to CVD may be higher in people with manifest CHD. A study using whole-population data from Finland measured CVD mortality at 1-year following ACS presentation and also showed similar downward trends in 1-year CVD mortality in diabetic and non-diabetic patients [219]. The authors reported a marked unadjusted excess in CVD mortality rates in diabetic patients at 1-year (187% in men and 484% in women) although all-cause mortality rates were not presented for comparison. The difference was more marked in younger men and women (adjusted hazard ratios 2.87 and 5.84 respectively).

Thus, the literature on medium and long-term mortality following MI suggests an ongoing excess mortality in people with diabetes. This is despite declines in mortality...
rates in this patient population. The falling mortality rates in the broader diabetic population in Australia [228] suggest that mortality for diabetic patients with CHD could also have improved. This is particularly pertinent given the apparent falling CVD mortality rates in diabetic people shown in that study. Although data from WA show a marked decrease in the relative risk of long-term mortality following MI during the 1980s and 1990s [197], there is no contemporary data in this regard, particularly in the context of the diabetic population.

2.7 AIMS AND OBJECTIVES OF THE STUDY

The primary aim of this study was to investigate the epidemiology of CHD in people with diabetes, in the context of the changing epidemiology of CHD and CVD more broadly in the population of WA. The specific objectives to meet this aim were:

Objective 1: To establish the reliability of the coding of diabetes in WA hospital morbidity data for CHD patients (Chapter 4).

Objective 2: To estimate the impact of the increasing prevalence of diabetes on the population-level incidence of CHD:

i) To measure trends in the incidence, recurrence and mortality of atherothrombotic vascular disease in WA from 2000 to 2007, in association with trends in risk factors including diabetes in hospitalised atherothrombotic disease patients (Chapter 5).

ii) To describe trends in the incidence of MI and CHD in people with diabetes compared to people without diabetes from 1998 to 2010 in WA (Chapter 6).

Objective 3: To measure the risk of mortality following MI in diabetic people:

i) To examine trends in short-term mortality following incident MI in people with diabetes compared to people without diabetes from 1998 to 2010 (Chapter 7).

ii) To examine the overall and age-specific gender differences in long-term MI recurrence and cardiovascular and all-cause mortality following incident MI in WA (Chapter 8).

iii) To measure trends in long-term all-cause and cardiovascular mortality in people with diabetes versus people without diabetes following incident myocardial infarction including gender-specific trends (Chapter 9).
2.8 REFERENCES


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CHAPTER 2. CHANGING EPIDEMIOLOGY OF DIABETES AND CORONARY HEART DISEASE


CHAPTER 2. CHANGING EPIDEMIOLOGY OF DIABETES AND CORONARY HEART DISEASE


232. Norhammar A, Stenestrud U, Lindbäck J, Wallentin L, on behalf of the Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA). Women younger than 65 years with diabetes mellitus are a high-risk group after

CHAPTER 3. DATA SOURCES AND METHODOLOGY

The availability of a high quality administrative-linked data system in WA provides a unique ability to undertake epidemiological analyses of CHD and diabetes in a whole-population setting. The ability to maximise data accuracy and the subsequent interpretation of results requires an informed understanding of the data sources and knowledge of the limitations of the data.

This chapter, therefore, provides an overview of the data sources used in the studies in the thesis and the general methods applied. The specific details of the methods used in each sub-study are provided separately in the published and submitted paper chapters (Chapters 4 to 9) and are not described in detail in this chapter. However, details of preliminary analyses which informed the methodology are outlined, particularly where these data are not included in the relevant published papers. The primary areas covered in this chapter are an outline of the linked data system in WA and the dataset parameters for the thesis studies; issues impacting the identification of MI and CHD cohorts, baseline history data and outcome variables; and the use of administrative data to identify people with diabetes in the context of CHD epidemiology and known changes in diabetes recording in hospital data.

3.1 OVERVIEW OF DATA SOURCES

3.1.1 WESTERN AUSTRALIAN DATA LINKAGE SYSTEM

WADLS is a comprehensive population-level data system which has been used extensively for health and epidemiological research [1]. It is unique in the Australian context and is one of few systems internationally comprised of multi-dataset systematic infrastructure enabling whole-population health research covering an extended period of time. Systems are now being implemented in other states and territories within Australia under a structured national approach, with the Centre for Health Record Linkage in NSW, established in 2006, being the most advanced [2].

WADLS currently comprises eight core health administrative data collections which capture all relevant records for these datasets for the population of WA (Figure 3.1) [3]. The core datasets are linked by the Data Linkage Branch, which operates within the WA Department of Health. Linkages between these core datasets are maintained with regular
updates. Linkages to other health and related datasets occur on an *ad hoc* basis or as requested for specific research projects.

**Figure 3.1. Core datasets of the Western Australian Data Linkage System and additional data sources available for linkage [4].**

Linkage of the datasets by WADLS occurs via an electronic probabilistic matching process. This has been shown in an earlier audit to provide high accuracy for correct linking of records [5]. Because there is no unique personal identifier in Australia, a number of demographic and identifying variables are used in the linkage process, including name, date of birth, address, sex and date of record. There are also other identifiers available on some of the datasets, for example, in the hospital morbidity dataset, there is a unique hospital number (unit medical record number) which is assigned for all hospital admissions for a person within a specific hospital [6]. Manual checking of uncertain links occurs in a small proportion of cases where certainty of correct record linkage cannot be established [3].
3.1.2 STUDY DATASET AND PARAMETERS

The linked dataset that was available for the studies within this thesis was part of a larger project (“The real and changing atherothrombotic disease burden and secondary prevention”) which investigated trends and outcomes of atherothrombotic disease in coronary, cerebral and peripheral arterial territories, and the impact of comorbidities on these measures. A copy of the Human Research Ethics Committee approval for this project is shown in Appendix A. The dataset comprised linked data from three core datasets of the WADLS — the Hospital Morbidity Data System (HMDS; or Hospital Morbidity Data Collection), Death Registrations and the WA Electoral Roll. The de-identified linked dataset was extracted by the Data Linkage Branch.

Extraction of the study dataset was based on the recording of hospital and mortality data using the relevant International Classification of Diseases (ICD) revision. The dataset includes records for all people hospitalised for or dying from CVD in WA (ICD-9/ICD-9-Clinical modification (CM) 390-459; ICD-10-Australian modification (AM) I00–I99) or diabetes (ICD-9/ICD-9-CM 250; ICD-10-AM E10–E14). These codes were identified if recorded in any discharge diagnosis field in the HMDS, and for death records, where recorded in the underlying cause of death field. Hospitalisations or deaths occurring outside of WA are not captured by the WADLS. Rates of migration out of WA were consistently low throughout the study period (~2.6%/year) [7] and are therefore unlikely to affect identification of incident status of CHD events.

The initial study dataset provided by the Data Linkage Branch covered 1985 to 2007; a subsequent update of the dataset covered the extended period 1985 to 2010; and a further update of cause of death data allowed full follow-up of cause-specific mortality to 30 June 2011. The extracted file included all hospitalisation records for the period covered by the dataset (including non-CVD and non-diabetes records) and any mortality record for each person in the dataset. The dataset available at the time of each sub-study within the thesis influenced decisions on study periods, lookback periods for assessment of morbidity history and the follow-up period for outcomes.

A separate preliminary dataset (“Linked Vascular File”) was available prior to the study datasets becoming available. This preliminary dataset contained data from 1980 to 2008 and was provided to conduct preliminary analyses to assess the feasibility of projects and to develop extraction instructions for the main study datasets. A copy of the Human
Research Ethics Committee approval for this dataset is shown in Appendix A. This dataset had the same ICD code and selection parameters as the main study dataset.

Additional clinical data for subsets of the people in the study dataset were derived from two other major projects — “Monitoring acute coronary heart disease in the modern era” and “More informed action to improve Aboriginal heart health in WA” (see Appendix A for the Human Research Ethics Committee approvals) [8]. Clinical data derived from these two studies were used to estimate the reliability of the recording of diabetes in administrative data for CHD patients (Chapter 4) and the details of these additional data and how they were used are described in that chapter. The age range of patients included for the study in Chapter 4 (35–79 years for non-Indigenous patients and 25–79 years for Indigenous patients) was used because of the parameters of the existing study. Data describing dispensing of inpatient and discharge drugs for hospitalised MI patients in 1998 and 2003 were also obtained from these study datasets. Similar drug data were available for 2008 from the discharge pharmacy dispensing systems of the three major teaching hospitals in Perth. These combined drug data are described and analysed in Chapter 7.

3.1.3 USE OF INTERNATIONAL CLASSIFICATION OF DISEASES CODING IN ADMINISTRATIVE DATA IN WA

The ICD versions in use in Australia during the period covered by the preliminary analysis dataset and the main study dataset are described in Table 3.1. A separate coding system was used for recording procedures during the ICD-9 era (International Classification of Procedures in Medicine (ICPM)), whereas coding of procedures since that time is incorporated into the relevant ICD revisions.

ICD-10 was introduced in Australia as a modified form of the WHO ICD-10 [9] in July 1998 (termed ICD-10-AM) but was first implemented in WA in July 1999. Updated editions of ICD-10-AM have been published in Australia every two to three years since its inception, with the most recent edition relevant to the data in this thesis being the 7th edition in 2010 [10]. ICD-10-AM contains some codes which are unique to the Australian revision, including some diabetes complications codes, but these are all included in the usual diabetes rubric (described in Section 3.3.1). Any changes in ICD codes which occurred between editions, particularly coronary revascularisation procedure codes (some new codes were included and some codes rescinded) have all been accounted for in analyses.
## TABLE 3.1. INTERNATIONAL CLASSIFICATION OF DISEASES REVISIONS AND VERSIONS USED IN WESTERN AUSTRALIA DURING THE PERIOD COVERED BY THE THESIS STUDIES.

<table>
<thead>
<tr>
<th>Period</th>
<th>International Classification of Diseases Revision/ Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 1979 – December 1987</td>
<td>ICD-9 / ICPM</td>
</tr>
<tr>
<td>July 1999 – June 2013*</td>
<td>ICD-10-Australian Modification (1st to 7th editions)</td>
</tr>
</tbody>
</table>

*ICD-10-AM was implemented in all other Australian states in July 1998.


Australian coding standards for ICD-9-CM and ICD-10-AM indicate that the principal diagnosis is defined as the condition which is established to be primarily responsible for causing the patient's episode of care in hospital [11, 12]. Additional diagnoses (commonly referred to as secondary diagnoses) are comorbidities or complications that affect patient care while in hospital because they require clinical evaluation, therapeutic treatment, diagnostic procedures, extended length of hospital stay or increased nursing care and/or monitoring [11, 12]. The datasets used in the thesis included 20 additional diagnosis fields. A variable indicating whether an additional diagnosis is an acute or chronic condition has only been recorded in hospital data in Australia since 2008 and was not available in the datasets provided for this project.

### 3.2 USE OF ADMINISTRATIVE DATA TO IDENTIFY STUDY POPULATION COHORTS, COMORBIDITIES AND OUTCOMES

#### 3.2.1 IDENTIFICATION OF STUDY POPULATION COHORTS

This section outlines preliminary analyses undertaken to assist with identifying the study population cohorts and provides details of the study cohorts. The study described in Chapter 5 investigated trends in the broader grouping of hospitalised atherothrombotic disease, comprising CHD, CeVD and PAD. All patients hospitalised with these conditions between 2000 and 2007 were included and stratified according to the incident or recurrent status using their prior hospitalisation history. While
hospitalisation data will underestimate true population rates and prevalence of CHD, CeVD and PAD, the focus of this study was that of hospitalised cases. Recognised cases of MI are likely to be almost fully captured by hospitalisation data [13], although undiagnosed or silent cases of MI will not be identified with this data source. For the studies described in Chapters 6 to 9, the focus was on incident MI, thus the study population cohort consisted of people hospitalised for a first MI.

The ICD codes used to identify the study population cohorts are provided in Appendix B. The major focus of this thesis, CHD, is commonly identified by ICD-9-CM 410–414 and ICD-10-AM I20–I25 codes. However, it is noted that the mapping of CHD codes from ICD-9 to ICD-10 is not fully congruent. Mapping tables indicate that the ICD-10 code I23 (certain current complications following acute MI) maps directly to codes outside the CHD rubric (ICD-9-CM 423.0, 429.5–429.7x) [14]. The number of hospitalisations attributed to this code in the ICD-10 era in our dataset was n≤5 per year. Given this, and the widely published use of ICD-10 I20–I25 and ICD-9-CM 410–414 codes as equivalent groupings, this code was retained for defining CHD.

The use of I22 for identifying incident MI cases was also reviewed. This code represents an MI occurring within 28 days of an acute MI (I21) [10]. When incident events in the ICD-10 era were identified using I21 or I22, there were 44 incident MI cases identified based on I22 coded in the principal diagnosis field. Eleven of these cases had an I21 code in either a secondary diagnosis field or on the record immediately following the index admission (usually following a transfer). Of those events with no I21 code, the use of the lookback period ensured that there were no prior admissions for MI (either 410, I21 or I22), coded in any diagnosis field. Therefore, ICD-10-AM I22 was retained for the purpose of defining incident MI cases.

Identification of incident events – length of lookback period

Identification of incident or ‘first-ever’ events from linked administrative health data relies on using a lookback period to determine the prior history of disease. Prevalent cases (those with prior hospitalisations for the condition under investigation and still alive and living in WA) can be identified from hospitalisation and linked death records, and, therefore, can be separated from incident cases. Optimal lengths of lookback period for MI have been described in previous studies. Osler et al. reported that 90% of recurrent MI events occurred within 5 years of an index event, implying that a lookback period of 5 years will exclude 90% of prevalent MI cases [15]. However, these data are
predicated on baseline MI cases from 1980 and included nonfatal and fatal cases as recurrent events. In a Norwegian trends analysis, analysing a more recent baseline MI cohort (2004 to 2009), lookback periods of 3 and 5 years overestimated incident event numbers by 11.8% in men and 10.1% in women, and 7.2% in men and 5.7% in women respectively, compared with a lookback period of 10 years [16]. The level of absolute overestimation was greater in older than younger people. Notably, the shorter lookback periods impacted trends in women, resulting in smaller average annual reductions in MI incidence compared with a 10-year lookback period.

As the risk of recurrence of MI has fallen [17], it is conceivable that a longer length of lookback period may be required to exclude prevalent cases, as demonstrated by the difference between the studies described above [15, 16]. The availability of datasets covering an extended time period, as was available for this thesis, necessitates balancing the lookback period and study period. Therefore the preliminary analyses focused on two situations:

A) The problem of individuals being identified as having two ‘incident’ events when the study period is longer than the lookback period.

B) The optimal length of lookback period for excluding prevalent cases.

For the purposes of this preliminary analysis, cases of MI were identified from the principal diagnosis field and the study period was defined as 1996 to 2010, a contemporary period covering changes in treatment and management of CHD and diabetes, and commencing at the beginning of the use of troponin assays for the diagnosis of MI in WA.

A. Longer study period than lookback period:

When the lookback period is shorter than the length of the study period, there is the potential for identification of an individual with more than one ‘incident’ event. This will occur in calendar years in the latter part of the study period. For this analysis, a 10-year lookback period was used to exclude prior events. Hence the lookback period was shorter than the 15-year study period (1996 to 2010). The results of the analysis are shown in Figure 3.2. There are a small number of patients (n=157) who had two ‘incident’ events identified during this study period. The ‘second incident event’ for each of these patients occurred from 2006 onwards, with an increasing number identified, ranging from 11 in 2006 to 55 in 2010. These cases are a small proportion of
the total number of incident MI cases in each calendar year (0.5% in 2006, 1.90% in 2010) and are therefore unlikely to appreciably alter trends. However they are problematic for studies analysing outcomes following incident MI and would need to be excluded from the baseline cohort.

The use of a 3-year and 5-year lookback period was also tested. These resulted in a marked increase in the number of people flagged as having more than one incident MI event during the study period. There were 1673 people identified more than once using a 3-year lookback and 949 using a 5-year lookback. This demonstrates that the use of increasingly short lookback periods is likely to be problematic when analysing longer study periods such as are available in the main study dataset.

**Figure 3.2.** Number of incident myocardial infarction cases identified each year from 1996 to 2010, using a 10-year lookback period. Cases identified as a second ‘incident’ event are shown in red.

**B. Differing lengths of lookback period**

Figure 3.3 shows the number of incident MI cases identified using lookback periods ranging from 3 to 15 years for the period 1996 to 2010. A lookback period of 20 years was also applied for MI cases hospitalised during 2000 to 2010. When compared with a lookback period of 15 years, the largest overestimation of incident MI cases was seen...
with the 3- and 5-year lookback periods (average annual overestimation 10.09% and 7.38% respectively (Appendix C)). There was a marginal difference in the use of a 13-year versus 15-year lookback period (0.89% average annual difference). There was little additional reduction in overestimation of incident cases using a 20-year lookback period. The events in the latter part of the study period which are ‘second’ incident events (relevant for the 3-, 5- and 10-year lookback periods, because the lookback period is shorter than the study period) have been retained in the data shown in Figure 3.3. This demonstrates the need to consider both issues when determining lookback and study period lengths.

**Summary:**

The following methods for the identification of incident cases were therefore adopted for the studies in this thesis, in relation to these data:

1. The study described in Chapter 5 had available the original dataset covering 1985 to 2007. A study period of 2000 to 2007 was defined, with a 15-year lookback period to identify incident CHD, CeVD and PAD cases.
2. As a new extended dataset became available for the remaining studies, a compromise between a longer study period and a shorter lookback period than used in Chapter 5 was decided on to identify incident MI and CHD cases (Chapters 6, 7 and 9). These studies used a 13-year study period (1998 to 2010), with a 13-year lookback period. For the outcomes study in Chapter 8, which investigated outcomes in an incident MI cohort in a contemporary period only (no trend data), a shorter study period (2003–2009) and longer lookback period (16 years) was used. These choices minimised the inclusion of prevalent cases and ensured that only one event was identified for any individual within the study period and, in the latter study, allowed for adequate follow-up.

3.2.2 BASELINE COMORBIDITY DATA

Baseline comorbidity variables for individuals in the study cohort were defined using their hospitalisation history from the main study dataset. Two main elements which influence the accuracy of the HMDS for defining baseline variables, particularly comorbidities are: i) correct documentation of conditions in medical notes and discharge summaries and correct transfer of this information to administrative data by coders, and ii) the definition of additional diagnoses (Section 3.1.3). This definition implies that the presence of a condition or disease does not mean that it will be recorded at every hospital admission for an individual patient.

There are some validation data demonstrating moderate to high levels of accuracy in the WA HMDS for comorbidities of interest such as heart failure (positive predictive value (PPV) >92% compared with hospital records or Boston Diagnostic criteria) [18]. The length of hospitalisation history available in the main study dataset enabled a lookback period equivalent to that used for identifying the incident cohort to identify comorbidities. Conditions recorded on the incident admission only were also classed as comorbidities in the baseline data. The exception was a history of prior CHD hospitalisations, where the incident MI admission was not included. This was because the ICD-10-AM code for chronic ischaemic heart disease (I25) is frequently coded as an additional diagnosis concurrent with MI. This practice is used to indicate underlying disease aetiology. Identification of this code on the incident MI admission would, therefore, result in overestimation of prior CHD hospitalisations.
A number of important cardiovascular risk factors are coded in HMDS but were not used in the studies in this thesis because of concerns regarding the accuracy and temporal consistency of hospital data to capture these conditions. These include obesity (ICD-9-CM 278.0, 278.1; ICD-10-AM E66), dyslipidaemia (272; E78) and smoking (305.1; Z72.0). Recording of obesity in hospital data has been shown to have poor agreement with BMI derived from self-report surveys in NSW linked data (kappa=12.8 using lookback admissions) [19]. The sensitivity for ever smoking and dyslipidaemia was reported as <0.30 in a population-based cohort of men in WA with the use of linked hospitalisation history of nearly 20 years [20]. Therefore, it was felt that these variables would not be sufficiently accurate to include in the analyses. Variables indicating socioeconomic status are also available in the linked dataset. These measures of socioeconomic advantage and disadvantage (Socio-Economic Indexes for Area) are indices based on income, education, unemployment and motor vehicle ownership data from the national census. However, changes to the classification of these indices during the period of the present studies [21] mean that it is difficult to achieve temporal consistency for these variables, therefore these were not used in the analyses in this thesis.

3.2.3 OUTCOME DATA

Outcome data (nonfatal and fatal events) were identified from the HMDS and mortality data within the main study dataset. The specific methods used for identifying recurrent events and death outcomes are described in detail in each of the relevant chapters, however, a brief outline of pertinent methodological issues is outlined in this section.

Outcomes of interest identified in each of the sub-studies were:

- Recurrent atherothrombotic events (CHD, CeVD and PAD) (Chapter 5)
- Recurrent MI (Chapter 8)
- CVD death (Chapters 8 and 9)
- All-cause mortality (Chapters 7, 8 and 9).

For the identification of recurrent CHD events in Chapter 5, a 28-day episode of care definition was applied to all CHD events. This method has been commonly used in analyses of WA hospital morbidity data for CHD to reduce the impact of elective readmissions for coronary procedures and subsequent overcounting of events [22].
The mortality outcomes of interest in the follow-up studies were cardiovascular and all-cause mortality. In Chapters 8 and 9, where the focus is on longer-term outcomes, people dying within 30 days of an incident MI were excluded from the analyses. The initial main dataset only included underlying cause of death. This was therefore used for the mortality rate analyses in Chapters 5 and 8. The most recent iteration of the main study dataset included multiple cause of death fields which were used in a more detailed analysis of CVD mortality in people with diabetes in the last study (Chapter 9).

### 3.3 IDENTIFICATION OF DIABETES STATUS FROM HOSPITAL DATA

#### 3.3.1 INTERNATIONAL CLASSIFICATION OF DISEASES CODES FOR DIABETES

The standard ICD codes used for identifying diabetes in administrative data are shown in Table 3.2. Diabetes is most frequently coded in a secondary diagnosis field [23] because it often does not meet the criteria for a principal diagnosis. The ICD-10-AM code E12 was introduced in Australia in the first edition of ICD-10-AM but was rescinded in the second edition (July 2000). However, it was retained in the definition of diabetes used in this thesis to capture the small number of cases (n<5) coded with this condition and for consistency with international definitions (the WHO version of ICD-10 has retained the E12 code). A preliminary analysis of all people hospitalised with any recording of diabetes from the preliminary dataset showed that ~89% of patients were classified as type 2 diabetes, based on the ICD codes (Table 3.2). There was some misclassification of diabetes type noted in the administrative data, with 10% of patients with multiple admissions with diabetes recorded having more than one diabetes type coded throughout their hospitalisation history. The analyses in this thesis were therefore not stratified by diabetes type.
### Table 3.2. International Classification of Diseases Codes Used to Identify Diabetes.

<table>
<thead>
<tr>
<th>Diabetes type</th>
<th>ICD-9/ICD-9-CM</th>
<th>ICD-10-AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-dependent/type 1</td>
<td>250.x1, 250.x3</td>
<td>E10</td>
</tr>
<tr>
<td>Non-insulin dependent/type 2</td>
<td>250.x0, 250.x2</td>
<td>E11</td>
</tr>
<tr>
<td>Malnutrition-related</td>
<td>–</td>
<td>E12</td>
</tr>
<tr>
<td>Other specified</td>
<td>–</td>
<td>E13</td>
</tr>
<tr>
<td>Unspecified</td>
<td>250.x0, 250.x2</td>
<td>E14</td>
</tr>
</tbody>
</table>

ICD, International Classification of Diseases; CM, Clinical Modification; AM, Australian Modification.

### 3.3.2 Changes to Australian Coding Standards

A number of changes in coding standards for diabetes have occurred at a national level and within WA since the 1990s. Because of their potential influence on the identification of diabetes status for epidemiological studies, the impact of these standards was investigated prior to the main analyses for the thesis being undertaken (Table 3.3). The implementation of the Australian version of ICD-9-CM in 1995 introduced a coding standard for diabetes as an additional diagnosis which differed from most other conditions. This standard meant that diabetes should be coded whenever present, irrespective of treatment received in hospital [11]. This standard was revised with the introduction of ICD-10-AM, with diabetes again being coded as per the directives for all other additional diagnoses (outlined in Section 3.2.1) [23]. Further changes to coding standards were applied within WA and nationally between 1999 and 2007 [12, 24].
## Table 3.3. Timeline of changes in Australian Coding Standards pertaining to the recording of diabetes in hospitalisation data in Western Australia.

<table>
<thead>
<tr>
<th>Australian Coding Standard</th>
<th>Date implemented</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD-9-CM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0002 [11]</td>
<td>July 1995</td>
<td>“Certain conditions such as ...diabetes...are examples of systemic diseases that ordinarily should be coded even in the absence of documented active intervention” (p5)</td>
</tr>
<tr>
<td>ICD-10-AM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0002 (modified) [12]</td>
<td>July 1999</td>
<td>Modified so that the usual rules for coding of additional diagnoses are also applied to diabetes (“...should be interpreted as conditions that affect patient management in terms of requiring any of the following: therapeutic treatment, diagnostic procedures, increased nursing care and/or monitoring” (p13))</td>
</tr>
<tr>
<td>0401 [23]</td>
<td>July 2000</td>
<td>Diabetes coded as a diabetes complication code even if causality between diabetes and the complication is not established or stated</td>
</tr>
<tr>
<td>0401 (modified) [25]</td>
<td>July 2002–July 2008</td>
<td>‘One BSL rule’ introduced – recording of even one blood sugar test is interpreted as monitoring, meeting the criteria for ACS 0002, and therefore diabetes recorded even with minimal monitoring or intervention</td>
</tr>
<tr>
<td>DOH directive* [24]</td>
<td>July 2003–July 2008</td>
<td>For all renal dialysis admissions (single day admissions), aetiology of renal disease should also be coded (frequently diabetes)</td>
</tr>
<tr>
<td>0401 (modified) [24]</td>
<td>July 2008</td>
<td>Rescinding of the ‘One BSL rule’ and the requirement for all renal dialysis admissions to be co-coded with diabetes</td>
</tr>
<tr>
<td>0401 (modified) [12]</td>
<td>July 2010</td>
<td>Causality of diabetes and any recorded complications had to be established by coders before diabetes could be coded (rescinding prior directions in ACS 0401)</td>
</tr>
</tbody>
</table>

*This coding standard was implemented in WA only.

CM, clinical modification; AM, Australian modification; BSL, blood sugar level; ACS, Australian Coding Standard; WA, Western Australia; DOH, Department of Health.
Preliminary analysis of unlinked diabetes-related hospitalisations was undertaken to determine the impact of the changes shown in Table 3.3. Firstly, all diabetes-related hospital admissions with diabetes coded (including single day admissions and transfers) were identified. Secondly, all admissions determined to be “regular/uncomplicated” renal dialysis admissions (Appendix E) with diabetes coded in a secondary field were excluded.

Figure 3.4 shows the results of this analysis. There was a consistent increase in the number of hospitalisations related to diabetes from 1980 to 1992, with a discernible increase in the rate of change during the remainder of the decade. A marked increase in the latter years of the period (124% increase from 2003 to 2007) was apparent. When renal dialysis admissions were excluded, the increase in admission numbers from 2003 to 2007 was only 44%. This resulted in a more linear increase from the late 1990s. The downturn in 2008 (when the “one BSL” rule was also rescinded) indicates that this standard may also have impacted on the rapid increase in diabetes admission numbers.

**Figure 3.4. Diabetes-related hospitalisations in Western Australia from 1980 to 2008.**

3.3.3 PREVALENCE OF DIABETES FROM ADMINISTRATIVE DATA

None of the studies in this thesis rely on the HMDS to accurately measure diabetes prevalence. However, the findings in Chapter 6 are interpreted in the context of the age-and sex-specific trends in the prevalence of diabetes in WA during the period of the study. The aim of the study undertaken in Chapter 6 was to measure incidence rates of MI in people with diabetes. To calculate the at-risk population for the rates denominators, the prevalence of diabetes in the population under investigation, including the age/sex distribution, is required. The main study dataset included all diabetes and diabetes-related hospitalisations in WA for 1985 to 2010. Use of hospitalisation data alone has been shown to underestimate population-level diabetes prevalence when compared with the use of outpatient or multiple administrative data sources [26], therefore we investigated the accuracy of the data source in relation to trends. All people in WA with any hospitalisation/s for diabetes, coded in any diagnosis field, were identified. Prevalent cases were defined as those with any hospitalisation/s for diabetes in the 13 years prior to 30 June in each calendar year, and who were alive at that date. Prevalence was then calculated using the age, sex and year specific population size for WA.

For comparison, we also obtained diabetes prevalence data from the WA Health and Wellbeing Surveillance System (HWSS) [27]. The HWSS is a self-report survey conducted by the WA Department of Health which commenced in 2002 and is designed to collect data on the health and wellbeing of Western Australians. Sampling is conducted monthly across the whole state, with 2010 data showing that ~55,000 adults had been surveyed to that date, with a crude response rate of 74.9% in 2010 [28]. The annual age-standardised diabetes prevalence estimates from HWSS are published and publicly available. To enable comparison of prevalence estimates between the HMDS and the survey data, diabetes prevalence based on the linked data was age-standardised by 10-year age groups, which is the method used by the HWSS (personal communication S. Joyce, Epidemiology Branch, Department of Health, WA) with the 2006 WA population used as the standard.

Figure 3.5 shows that the HMDS underestimates diabetes prevalence by an average of ~2%/year but that this pattern is consistent over time in men and women. To further check whether both data sources yield similar trend estimates, age-adjusted (by 10-year age groups) trends were estimated from logistic regression models for both the HMDS
and HWSS-defined diabetes prevalence. For 2003–2010, the prevalence odds ratio representing change per year for men was 1.023 (95% CI (CI) 1.021, 1.024) and for women, 1.016 (95% CI 1.014, 1.018) from HWSS. For the equivalent HMDS data, the odds ratio for men was 1.028 (95% CI 1.026, 1.03) and for women, 1.025 (95% CI 1.023, 1.027).

![Figure 3.5](image)

**Figure 3.5. Age-standardised prevalence of diabetes in Western Australia from the linked hospital morbidity data system (HMDS) and self-report data from the Western Australian Health and Wellbeing Surveillance System (HWSS).**

### 3.3.4 Identification of Diabetes Status for Hospitalised CHD Cases

Diabetes status was identified in this thesis primarily in the context of stratification of CHD, and specifically MI, patients according to their diabetes status (Chapters 6, 8 and 9). There has been no previous investigation regarding the validity of using WA HMDS data to identify diabetes status in hospitalised cardiac patients. A NSW study found that in 1765 patients admitted to hospital for ischaemic heart disease or heart failure, the false negative rate for the recording of diabetes was lower than for other conditions (11%), with a false-positive rate of less than 1% when compared against hospital records [29]. A Canadian study of 817 patients admitted for PCI found that agreement between the recording of comorbidities, including diabetes, in administrative data and
hospital charts was good to very good according to the kappa value [30]. The sensitivity for diabetes recording was 78% and specificity 98% in this study.

There is evidence from a study of administrative data in WA that the validity of recording of diabetes in HMDS across a broad range of medical and surgical conditions is reasonable, although the study period only covered the use of ICD-9-CM (1991 to 1996) [31]. A low false negative (12%) and low false positive (<1%) rate for diabetes without complications were reported compared with review of hospital charts (considered the ‘gold standard’). Diabetes ‘with end organ damage’ (analogous to ‘diabetes with complications’ in ICD codes) was poorly coded in this study, albeit with a small sample size (n=15). A more recent Australian study compared self-report of chronic conditions from the 45 and Up cohort study in NSW with recording of conditions in the NSW linked data system [19]. Diabetes was recorded more accurately than other chronic morbidities (kappa = 0.79), a measure which improved to 0.83 with the use of lookback admissions. Positive predictors of diabetes being recorded in the administrative data were male sex and emergency admission. Of note was the finding of between-hospital variance for the recording of morbidities, although variance was lower for diabetes than other conditions such as hypertension.

Due to the lack of existing validation data for identification of diabetes status in CHD and MI patients extending into the ICD-10-AM period, this thesis included a specific study of this issue using additional clinical validation data for 1998 and 2002–2004 (Chapter 4).
3.4 REFERENCES


CHAPTER 4. ACCURACY OF ADMINISTRATIVE DATA FOR IDENTIFYING DIABETES STATUS

PUBLISHED PAPER

This chapter is the published version of the following paper:

Concordance between administrative health data and medical records for diabetes status in coronary heart disease patients: a retrospective linked data study


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Keywords: Coronary heart disease, Diabetes, Administrative data, Hospital morbidity data, Concordance, Comorbidity
PREAMBLE

Preliminary analyses and investigation of coding standards relating to the recording of diabetes in hospitalisation data are outlined in Chapter 3.3. These analyses identified issues which could impact the consistency of the recording of diabetes in hospitalisation data over time. Some of these inconsistencies are relevant to Australian and international administrative data, and some relate specifically to WA data. The ability to accurately identify diabetes status in CHD patients is important for the main diabetes-focused analyses in this thesis (Chapters 6, 7 and 9). Interpretation of the results of these studies is predicated on understanding the reliability of the HMDS for identifying diabetes status. It was therefore recognised that there was a need to investigate the accuracy of the WA HMDS for identifying diabetes status specifically in the cohort of CHD patients.

The availability of relevant data within the dataset used for the study in this chapter meant that it was possible to specifically examine the recording of diabetes for Indigenous people hospitalised with CHD. However, the conditions of ethics granted for the work in the remainder of the studies within the thesis (Chapters 5 to 9) did not allow for specific analysis by Indigenous status, and thus further detailed analyses were not undertaken.
4.1 ABSTRACT

Background: Administrative data are a valuable source of estimates of diabetes prevalence for groups such as coronary heart disease (CHD) patients. The primary aim of this study was to measure concordance between medical records and linked administrative health data for recording diabetes in CHD patients, and to assess temporal differences in concordance. Secondary aims were to determine the optimal lookback period for identifying diabetes in this patient group, whether concordance differed for Indigenous people, and to identify predictors of false positives and negatives in administrative data.

Methods: A population representative sample of 3943 CHD patients hospitalized in Western Australia in 1998 and 2002–04 were selected, and designated according to the International Classification of Diseases (ICD) version in use at the time (ICD-9 and ICD-10 respectively). Crude prevalence and concordance were compared for the two samples. Concordance measures were estimated from administrative data comparing diabetes status recorded on the selected CHD admission (‘index admission’) and on any hospitalization in the previous 1, 2, 5, 10 or 15 years, against hospital medical records. Potential modifiers of agreement were determined using chi-square tests and multivariable logistic regression models.

Results: Identification of diabetes on the index CHD admission was underestimated more in the ICD-10 than ICD-9 sample (sensitivity 81.5% versus 91.1%, underestimation 15.1% versus 4.4% respectively). Sensitivity increased to 89.6% in the ICD-10 period using at least 10 years of hospitalization history. Sensitivity was higher and specificity lower in Indigenous patients, and followed a similar pattern of improving concordance with increasing lookback period. Characteristics associated with false negatives for diabetes on the index CHD hospital admission were elective admission, in-hospital death, principal diagnosis, and in the ICD-10 period only, fewer recorded comorbidities.

Conclusions: The accuracy of identifying diabetes status in CHD patients is improved in linked administrative health data by using at least 10 years of hospitalization history. Use of this method would reduce bias when measuring temporal trends in diabetes prevalence in this patient group. Concordance measures are as reliable in Indigenous as non-Indigenous patients.
4.2 BACKGROUND

Linked administrative health data provide a unique resource for investigating whole-population diabetes mellitus (‘diabetes’) prevalence in different patient groups. Administrative data systems are commonly designed to collect resource utilisation data rather than as repositories for research purposes, with recording of comorbid conditions often not required at every hospital admission [1]. An understanding of the reliability of hospital data can assist in accurately estimating the impact of diabetes in the high-risk coronary heart disease (CHD) patient population [2, 3]. In unlinked administrative databases where comorbidity information is obtained from a single admission, it is important to understand the reliability of coding and which patient groups may be underestimated or overestimated from this data source. Use of information from a single admission only could underestimate diabetes prevalence and inaccurately identify diabetic patients. Applying a lookback period to identify prior admissions in which diabetes was recorded can increase detection of diabetes status in linked datasets [4]. Many studies identify diabetes using a lookback of less than two years [5, 6] but information is limited on the optimal length of hospitalization history required and whether this method is consistent over time.

Changes in International Classification of Disease (ICD) versions could potentially impact the recording of conditions such as diabetes. Significant changes in coding directives for diabetes were introduced in Australia in 2000 [7], with a subsequent 20% increase in the number of diabetes-related admissions to 2003–04 [8]. Accordingly, the national health statistics body in Australia does not measure trends spanning the ICD-9 and ICD-10 periods for overall diabetes-related hospitalizations [8]. Whether these coding changes have impacted in the same manner on CHD hospitalizations is unknown.

There is limited available data on the accuracy of recording of diabetes in population sub-groups, including in Indigenous Australians. The risk of diabetes in Indigenous people is known to be many times higher than in the general population [9], and because a high proportion of Indigenous people reside in rural and remote areas, they are more likely to be admitted to a non-metropolitan hospital. These factors could impact on identification of diabetes from administrative data for these patients. With high and increasing incidence of diabetes in this group [9, 10] it is imperative that the utility of administrative data for identifying diabetes status is investigated.
The primary aim of this study was to measure the concordance of administrative data and medical records for the recording of diabetes in a sample of CHD patients, and determine whether this has changed over time. Secondary aims were to determine the optimal lookback period for identifying diabetes in this patient group, whether concordance differed for Indigenous people with CHD, and to identify predictors of false negatives and false positives in administrative data.

4.3 METHODS

4.3.1 STUDY SETTING

The current study was performed in the state of Western Australia (WA) which is representative of the major sociodemographic and health economic indicators for Australia [11]. The population of WA in 2004, the latter period of the study, was 1.99 million, with 75% residing in the capital city, Perth [12]. Indigenous people comprise 3.5% of the WA population [13], with around 65% living in regional, rural or remote areas [14]. Data was sourced from the population-based electronic linked health database (WA Data Linkage System) which is managed by the Department of Health WA and has been used extensively for health-related research [15]. The current study used two of the system’s core databases - the Hospital Morbidity Data Collection (HMDC) and the Mortality register. Statutory requirements mean that all hospitalizations and deaths in WA are recorded within these collections. The datasets are linked by probabilistic matching based on name, date of birth, gender and address, with manual clerical checking of uncertain links, and are regularly audited for quality [16]. Hospital discharge diagnoses are coded in the HMDC by trained coders using the prevailing ICD version and relevant modifications (ICD-9 from 1978, and ICD-10 from July 1, 1999).

4.3.2 STUDY SAMPLE

The study sample was selected from two existing projects: Monitoring CHD in the Modern Era (Study 1), and More Informed Action to Improve Aboriginal Heart Health in WA (Study 2). The sampling frames for these studies have been described elsewhere [17]. A stratified sample of patients aged 35–79 years with a hospital discharge diagnosis of any cardiac condition or chest pain in 1998 or 2003, admitted to a major public or private metropolitan hospital, was identified from a linked dataset containing all cardiovascular (CVD) morbidity and mortality records. The second study similarly
identified all Indigenous patients and a sample of non-Indigenous patients, aged 25–79 years, admitted to any metropolitan or rural hospitals in 2002–04. Hospital record review for these samples was undertaken and information collected and stored in a medical records database. Because of the overlap in time period between the 2003 sample in Study 1 and the Study 2 sample (2002–04), 134 patients appeared in both sampling frames. These were included only once in the medical records database.

Patients in the medical records database were included in the current study if they had a principal discharge diagnosis of CHD recorded in the HMDC (ICD-9-CM 410–414, ICD-10-AM I20–I25), because of the high recording accuracy of CHD in the principal compared with secondary diagnosis fields [18] The first CHD admission for each patient in each time period was defined as the ‘index admission’ and selected for inclusion in the study. The administrative data for the CHD patients were linked to the medical records database via a unique identification number assigned to every hospital admission in WA. Because of known underestimation of identification of Indigenous status in hospital discharge data [19], a patient was included as Indigenous if 25% or more of all of their HMDC records since 1980 were recorded as Indigenous.

**4.3.3 MEDICAL RECORD REVIEW**

Trained research assistants collected data from medical records. Thirty-nine admissions could not be reviewed due to missing medical notes. Data were obtained from admission notes from the emergency department and inpatient medical records, and each comorbidity documented as present, absent, or not recorded. Treatment of diabetes with insulin or oral hypoglycaemic drugs was identified from inpatient and discharge drug records for the admission under investigation. Patients were classified as having diabetes if it was documented as ‘present’ in the medical notes or if drug treatment for diabetes was identified. Patients with ‘not recorded’ as their diabetes status and no diabetic drugs recorded (n = 66) were classified in the no diabetes group, and a sensitivity analysis with these patients removed showed minimal difference in all concordance measures across the two samples.

Data quality was initially assessed by review of three medical records by all research assistants within two weeks of commencing data collection. Medical records of a total of 11 patients were subsequently assessed by all data collectors in each study. The observed agreement between data collectors in Study 1 was high for selected medical history (92%) and drugs (100%) and similarly for Study 2 (93% and 87% respectively).
4.3.4 IDENTIFICATION OF DIABETES STATUS FROM HOSPITAL DISCHARGE DATA

ICD-9-CM was in use in WA at the time of the 1998 admissions, and ICD-10-AM at the time of the 2002–04 sample. Diabetes (Type 1, Type 2, other specified or unspecified diabetes mellitus) was identified in hospital discharge data for the CHD sample if coded in any of 21 diagnosis fields (ICD-9/ICD-9-CM 250, ICD-10-AM E10-E14), using a range of lookback periods for each individual patient – index CHD admission only, and 1, 2, 5, 10 and 15 years prior to the CHD admission.

Approval for this study was obtained from the Ethics Committees of The University of Western Australia and the Department of Health WA, and from the Western Australian Aboriginal Health Ethics Committee.

4.3.5 STATISTICAL ANALYSIS

The crude prevalence of diabetes in the CHD patient sample was calculated for the index admission and each lookback period using the administrative data, and from the medical records database. Observed agreement, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Kappa were used as measures of concordance between administrative and medical records data, with the latter designated the reference standard. Concordance measures were calculated for each lookback period and also for sub-group and supplementary analyses. The percentage of under or overestimation of diabetes recording in hospital discharge data was calculated by \((\text{Sensitivity}/\text{PPV} – 1) \times 100\) [17]. All analyses were stratified by period, with the 1998 sample corresponding to ICD-9, and the 2002–04 sample to ICD-10. Differences in prevalence between medical records and administrative data were tested using McNemar’s test, and concordance measures between the two ICD samples were tested using a Pearson chi-square or z-test (for under/overestimation).

Because of the possible impact of sociodemographic and clinical factors on concordance, and the potential for changing criteria for admission to hospital for CHD, variables derived from the administrative data on the index CHD admission were examined for their association with false positives and false negatives, separately for the ICD-9 and ICD-10 samples. Univariable associations were analysed using the Pearson chi-square test (or Fisher’s exact test where cell counts were small). The variables tested were length of stay (1–2, 3–5, ≥6 days), age group (25–50, 51–65, 66–79 years), gender, admission type (elective versus emergency), Indigenous status, Charlson Comorbidity Index (excluding diabetes; 0, 1–4, ≥5), number of comorbidities on the index admission.
(excluding diabetes; 0–3, 4–7, ≥8), hospitalization in the previous 90 days, hospital location (metropolitan versus rural), hospital type (public versus private), transfer in or out on index CHD admission, in-hospital death, principal diagnosis (myocardial infarction, unstable angina, other CHD), and first-ever versus recurrent CHD admission. First-ever CHD admission was identified where there was no CHD admission in the previous 15 years. Variables were tested using binary values unless otherwise indicated and all analyses undertaken separately for each ICD period. Significant univariable variables in each period were entered into a multivariable logistic regression model and odds ratios with 95% confidence intervals (CI) were calculated. All data analyses were undertaken using SAS (version 9.3, Cary, NC, USA) and statistical significance for all analyses was set at p < 0.05.

4.4 RESULTS

The final study sample comprised 3943 index CHD admissions, with 24 patients having an admission in both periods. Table 4.1 shows the clinical and demographic characteristics of the sample. There were 1685 patients in the ICD-9 sample, and 2258 in the ICD-10 sample, with Indigenous patients comprising 23.2% of the latter sample. The majority of cases (94.1%) were admitted for acute coronary syndromes (myocardial infarction or unstable angina).
### Table 4.1. Characteristics of the study sample.

<table>
<thead>
<tr>
<th></th>
<th>ICD-9 (n = 1685)</th>
<th>ICD-10 (n = 2258)</th>
<th>Whole sample (n = 3943)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>64.1 (10.8)</td>
<td>61.1 (12.3)</td>
<td>62.4 (11.8)</td>
</tr>
<tr>
<td>Males</td>
<td>1154 (68.5)</td>
<td>1530 (67.8)</td>
<td>2684 (68.1)</td>
</tr>
<tr>
<td>Indigenous people</td>
<td>25 (1.5)</td>
<td>525 (23.2)</td>
<td>550 (13.9)</td>
</tr>
<tr>
<td>Principal diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>860 (51.0)</td>
<td>1061 (47.0)</td>
<td>1921 (48.7)</td>
</tr>
<tr>
<td>UA</td>
<td>737 (43.7)</td>
<td>1052 (46.6)</td>
<td>1789 (45.4)</td>
</tr>
<tr>
<td>Other CHD</td>
<td>88 (5.2)</td>
<td>145 (6.4)</td>
<td>233 (5.9)</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>284 (16.8)</td>
<td>635 (28.1)</td>
<td>919 (23.3)</td>
</tr>
<tr>
<td>3–5</td>
<td>714 (42.4)</td>
<td>1011 (44.8)</td>
<td>1725 (43.8)</td>
</tr>
<tr>
<td>≥6</td>
<td>687 (40.8)</td>
<td>612 (27.1)</td>
<td>1299 (32.9)</td>
</tr>
<tr>
<td>Charlson index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>777 (46.1)</td>
<td>1163 (51.5)</td>
<td>1940 (49.2)</td>
</tr>
<tr>
<td>1–4</td>
<td>807 (47.9)</td>
<td>963 (42.6)</td>
<td>1770 (44.9)</td>
</tr>
<tr>
<td>≥5</td>
<td>101 (6.0)</td>
<td>132 (5.8)</td>
<td>233 (5.9)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>507 (30.1)</td>
<td>1155 (51.1)</td>
<td>1662 (42.1)</td>
</tr>
<tr>
<td>4–7</td>
<td>868 (51.5)</td>
<td>862 (38.2)</td>
<td>1730 (43.9)</td>
</tr>
<tr>
<td>≥8</td>
<td>310 (18.4)</td>
<td>241 (10.7)</td>
<td>551 (14.0)</td>
</tr>
<tr>
<td>Hospital location, rural</td>
<td>22 (1.3)</td>
<td>741 (32.8)</td>
<td>763 (19.3)</td>
</tr>
<tr>
<td>Hospital type, private</td>
<td>434 (25.8)</td>
<td>386 (17.1)</td>
<td>820 (20.8)</td>
</tr>
<tr>
<td>Booked admission</td>
<td>224 (13.3)</td>
<td>198 (8.8)</td>
<td>422 (10.7)</td>
</tr>
</tbody>
</table>

All figures shown as numbers (percentages) except where indicated. ICD, International Classification of Diseases; MI, myocardial infarction; UA, unstable angina; CHD, coronary heart disease.
4.4.1 PREVALENCE OF DIABETES IN CHD PATIENTS

In the ICD-9 sample, there was a small but significant difference between diabetes prevalence from medical records (22.5%) and index administrative data (21.5%, p < 0.0001) (Table 4.2). The difference was also significant (p < 0.0001) in the ICD-10 sample (34.9% from medical records compared with 29.7% from the administrative data), but prevalence increased to 34.2% using all previous hospital admissions to 15 years. There was a similar pattern in the Indigenous sample, although absolute prevalence levels were higher in this patient group.

<table>
<thead>
<tr>
<th>Lookback period</th>
<th>Medical records (n)</th>
<th>Hospital discharge data (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole sample</td>
<td>ICD-9, n (%)</td>
<td>ICD-10, n (%)</td>
</tr>
<tr>
<td>(n = 1685)</td>
<td>380 (22.5)</td>
<td>789 (34.9)</td>
</tr>
<tr>
<td>Indigenous people*</td>
<td>ICD-10, n (%)</td>
<td>ICD-10, n (%)</td>
</tr>
<tr>
<td>(n = 2258)</td>
<td>670 (29.7)‡</td>
<td>295 (56.2)‡</td>
</tr>
<tr>
<td>(n = 525)</td>
<td></td>
<td>256 (48.8)‡</td>
</tr>
</tbody>
</table>

*Indigenous patient sample from the ICD-10 sample only.

P-values are comparing prevalence from medical records with hospital discharge data, separately for ICD-9, ICD-10, and Indigenous sample. †p < 0.05; ‡p < 0.0001.

4.4.2 CONCORDANCE MEASURES

Observed agreement was high and Kappa very good in both samples and across all lookback periods for the recording of diabetes in the two data sources (Table 4.3). Sensitivity was significantly lower in the ICD-10 compared with ICD-9 sample from the index admission (81.5% versus 91.1%, p < 0.0001), but improved to 89.6% using to
10 years of hospitalization history. NPV was significantly higher in the ICD-9 than ICD-10 sample (p < 0.0001 for all lookback periods), although the difference diminished with increasing lookback. Specificity was high in both samples, with a small decrease as lookback period increased. PPV declined with use of an increased lookback period, but there was no statistical difference between the two time periods. Diabetes status was underestimated by 15% from the hospital discharge index admission in the ICD-10 sample, which reduced to 2.2% using a 10-year lookback period (Table 4.3).

Because of the oversampling of Indigenous patients in Study 2, the ICD-10 sample was stratified to compare concordance for the ICD-10 patients from Study 1 only with the total ICD-10 sample (Study 1 plus Study 2) (see Additional file S4.1). There was little difference between the restricted and full sample for all concordance measures, with a similar pattern of increasing sensitivity and a small drop in PPV with increasing lookback period.

### 4.4.3 CONCORDANCE MEASURES IN INDIGENOUS PATIENTS

Sensitivity was higher in Indigenous compared with non-Indigenous people for every lookback period, although the difference was only significant for lookback periods of two years or more (Table 4.4). Maximal sensitivity was achieved with 10 years lookback in Indigenous patients (93.6%). Specificity was lower in Indigenous than non-Indigenous patients, with an increasing differential with increasing lookback period (p < 0.05). Diabetes status was underestimated from the hospital discharge index admission in Indigenous people by 13.3% reducing to 0.3% using a 10-year lookback period.

### 4.4.4 FALSE NEGATIVES AND FALSE POSITIVES

Significant univariable predictors in both periods for false negatives were elective admission, in-hospital death, and non-acute CHD principal diagnosis (Table 4.5). These remained significant after multivariable adjustment in both periods. A lower number of comorbidites (0–3) were associated with higher odds of a false negative in the ICD-10 but not the ICD-9 period. The level of false positives was low in both the ICD-9 (n = 22, 1.3%) and ICD-10 (n = 40, 1.8%) samples, with no significant univariable association with any of the variables tested, and therefore no multivariable analyses were undertaken.
### Table 4.3. Concordance measures for the recording of diabetes in hospital discharge data compared with medical records, in the sample of coronary heart disease patients.

<table>
<thead>
<tr>
<th>Lookback period</th>
<th>Observed agreement, %</th>
<th>Kappa, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive predictive value, %</th>
<th>Negative predictive value, %</th>
<th>Underestimation (–) / overestimation (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICD-9</td>
<td>ICD-10</td>
<td>ICD-9</td>
<td>ICD-10</td>
<td>ICD-9</td>
<td>ICD-10</td>
<td>ICD-9</td>
</tr>
<tr>
<td>Index admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>96.6</td>
<td>93.4</td>
<td>90.2</td>
<td>85.3</td>
<td>91.6</td>
<td>86.3†</td>
<td>98.1</td>
</tr>
<tr>
<td>2 years</td>
<td>96.6</td>
<td>93.4</td>
<td>90.3</td>
<td>85.4</td>
<td>92.1</td>
<td>87.3†</td>
<td>97.9</td>
</tr>
<tr>
<td>5 years</td>
<td>96.5</td>
<td>93.6</td>
<td>90.0</td>
<td>85.9</td>
<td>92.4</td>
<td>89.3</td>
<td>97.7</td>
</tr>
<tr>
<td>10 years</td>
<td>96.5</td>
<td>93.5</td>
<td>90.0</td>
<td>85.6</td>
<td>92.6</td>
<td>89.6</td>
<td>97.6</td>
</tr>
<tr>
<td>15 years</td>
<td>96.4</td>
<td>93.4</td>
<td>89.7</td>
<td>85.5</td>
<td>92.6</td>
<td>89.6</td>
<td>97.5</td>
</tr>
</tbody>
</table>

* Calculated from (Sensitivity/PPV – 1) × 100. Negative values represent the percentage underestimation and positive values the percentage overestimation of diabetes recording in hospital discharge data compared with medical records.

P-values are from comparison of ICD-9 and ICD-10 for each lookback period. †p < 0.05. ‡p < 0.0001.

ICD, International Classification of Diseases.
## Table 4.4. Concordance Measures for the Recording of Diabetes in Hospital Discharge Data Compared with Medical Records in Indigenous (n = 525) and Non-Indigenous (n = 1733) Coronary Heart Disease Patients.

<table>
<thead>
<tr>
<th>Lookback period</th>
<th>Observed agreement, %</th>
<th>Kappa, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive predictive value, %</th>
<th>Negative predictive value, %</th>
<th>Underestimation (−) / overestimation (+), (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index admission</td>
<td>Indigenous</td>
<td>90.3</td>
<td>80.6</td>
<td>84.7</td>
<td>97.4</td>
<td>97.7</td>
<td>83.3†</td>
</tr>
<tr>
<td></td>
<td>Non-Indigenous</td>
<td>93.0</td>
<td>81.4</td>
<td>79.6</td>
<td>98.3</td>
<td>94.9</td>
<td>92.3</td>
</tr>
<tr>
<td>1 year</td>
<td>Indigenous</td>
<td>91.4</td>
<td>82.8</td>
<td>88.8</td>
<td>94.8†</td>
<td>95.6</td>
<td>86.8†</td>
</tr>
<tr>
<td></td>
<td>Non-Indigenous</td>
<td>94.1</td>
<td>85.0</td>
<td>84.8</td>
<td>97.8</td>
<td>93.7</td>
<td>94.2</td>
</tr>
<tr>
<td>2 years</td>
<td>Indigenous</td>
<td>92.2</td>
<td>84.2</td>
<td>90.5†</td>
<td>94.3†</td>
<td>95.4</td>
<td>88.6†</td>
</tr>
<tr>
<td></td>
<td>Non-Indigenous</td>
<td>93.8</td>
<td>84.5</td>
<td>85.4</td>
<td>97.2</td>
<td>92.3</td>
<td>94.4</td>
</tr>
<tr>
<td>5 years</td>
<td>Indigenous</td>
<td>92.9</td>
<td>85.7</td>
<td>92.9†</td>
<td>93.0†</td>
<td>94.5</td>
<td>91.1†</td>
</tr>
<tr>
<td></td>
<td>Non-Indigenous</td>
<td>93.8</td>
<td>84.7</td>
<td>87.2</td>
<td>96.4</td>
<td>90.7</td>
<td>95.0</td>
</tr>
<tr>
<td>10 years</td>
<td>Indigenous</td>
<td>92.9</td>
<td>85.7</td>
<td>93.6†</td>
<td>92.2†</td>
<td>93.9</td>
<td>91.8</td>
</tr>
<tr>
<td></td>
<td>Non-Indigenous</td>
<td>93.6</td>
<td>84.3</td>
<td>87.2</td>
<td>96.2</td>
<td>90.2</td>
<td>95.0</td>
</tr>
<tr>
<td>15 years</td>
<td>Indigenous</td>
<td>92.9</td>
<td>85.7</td>
<td>93.6†</td>
<td>92.2†</td>
<td>93.9</td>
<td>91.8</td>
</tr>
<tr>
<td></td>
<td>Non-Indigenous</td>
<td>93.6</td>
<td>84.1</td>
<td>87.2</td>
<td>96.1</td>
<td>90.0</td>
<td>95.0</td>
</tr>
</tbody>
</table>

Concordance measures calculated using the ICD-10 sample only.

*Calculated from (Sensitivity/PPV − 1) × 100. Negative values represent the percentage underestimation and positive values the percentage overestimation of diabetes recording in hospital discharge data compared with medical records.

P-values are from comparisons between Indigenous and non-Indigenous patients for each lookback period. †p < 0.05, ‡p < 0.0001.
### Table 4.5. Characteristics Associated with False Negatives in Administrative Data on Index Admission.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ICD-9</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>False negatives, n (%)*</td>
<td>Multivariable model, odds ratio</td>
</tr>
<tr>
<td></td>
<td>(n = 34)</td>
<td>(95% CI)*</td>
</tr>
<tr>
<td>Admission Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Booked</td>
<td>12 (25.5)†</td>
<td>3.35 (1.36, 8.28)</td>
</tr>
<tr>
<td>Emergency</td>
<td>22 (6.6)</td>
<td>—</td>
</tr>
<tr>
<td>In-hospital death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (19.5)‡</td>
<td>2.61 (0.97, 7.02)</td>
</tr>
<tr>
<td>No</td>
<td>26 (7.7)</td>
<td>—</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>4 (7.3)†</td>
<td>0.47 (0.14, 1.56)</td>
</tr>
<tr>
<td>3–5</td>
<td>11 (5.3)</td>
<td>0.50 (0.21, 1.19)</td>
</tr>
<tr>
<td>≥6</td>
<td>19 (16.4)</td>
<td>—</td>
</tr>
<tr>
<td>Principal diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>16 (8.3)‡</td>
<td>0.29 (0.09, 0.86)</td>
</tr>
<tr>
<td>UA</td>
<td>9 (5.6)</td>
<td>0.24 (0.07, 0.76)</td>
</tr>
<tr>
<td>Other CHD</td>
<td>9 (33.3)</td>
<td>—</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>4 (5.3)</td>
<td>—</td>
</tr>
<tr>
<td>4–7</td>
<td>15 (7.5)</td>
<td>58 (16.5)</td>
</tr>
<tr>
<td>≥8</td>
<td>15 (14.3)</td>
<td>17 (12.7)</td>
</tr>
</tbody>
</table>

*Percentage is the proportion of false negatives within each category for each variable (FN / FN + TP in each category). Multivariable models are adjusted for all variables which are significant univariable predictors of false negatives in each period, and all are included in the models as categorical variables. Comorbidities was not included in the multivariable model for the ICD-9 sample. †p < 0.05, ‡p < 0.0001.

ICD, International Classification of Diseases; CI, confidence interval; MI, myocardial infarction; UA, unstable angina; CHD, coronary heart disease; FN, false negative; TP, true positive.
4.5 DISCUSSION

This study found that identification of diabetes status from linked administrative health data using the index CHD admission underestimated the prevalence of diabetes in CHD patients to a greater degree in the ICD-10 period, with a correspondingly lower sensitivity and NPV. Sensitivity improved from 81.5% to 89.6% using a 10 year lookback in the ICD-10 period, with marginal improvement in any measures with a longer lookback period out to 15 years. Sensitivity was higher and specificity lower for Indigenous compared with non-Indigenous CHD patients at the index admission and with an increasing lookback period. In-hospital death, elective admission type, and a non-acute CHD principal diagnosis were significantly associated with false negatives on the index CHD admission in both periods. The level of false positives was low in both periods.

Our results highlight the potential for changes in the accuracy of administrative data over time. Although specificity was high in both periods, sensitivity was significantly lower in the ICD-10 period. A study of myocardial infarction patients also found that following the change from ICD-9 to ICD-10, sensitivity reduced from 80% to 66% for diabetes with complications using hospitalization data [20]. In contrast, Chen et al. [21] found no impact of this change on the validity of diabetes and other comorbidities, possibly because of the use of multiple data sources (hospitalization and physician claims data). Our results suggest that although diabetes is reasonably accurately recorded in administrative data compared with other comorbidities [6, 22–24], use of data from the index admission only would attenuate likely upwards trends in diabetes prevalence in this population of CHD patients because of the lower sensitivity and NPV in the more recent ICD-10 period. Use of prior hospitalization history would reduce this difference. For example, a 10 year lookback period would increase sensitivity from 81.5% to 89.6% and NPV from 90.8% to 94.5%, with little loss of specificity and still maintaining a high PPV (91.9%) in the ICD-10 sample, and provide similar levels of concordance to that of the ICD-9 sample.

Published comparisons for the accuracy of recording of diabetes in administrative data for Indigenous people are limited. A Canadian study found that sensitivity was higher (91.1% versus 86%) and specificity lower (92.8% versus 97%) for identifying prevalent diabetes cases in the Aboriginal compared with non-Aboriginal population [25]. Our results are consistent with this pattern. The likelihood of diabetes being recorded at
index admission may be higher in Indigenous patients because diabetes is more actively diagnosed and treated during hospitalization due to the known high burden in this population. The significantly lower NPV in Indigenous people at index admission may result from the higher prevalence of diabetes in this group. However, despite an increased risk of CHD recurrence in Indigenous people [26], similar length of lookback periods (five to 10 years) optimized concordance measures between Indigenous and non-Indigenous people. Because the use of hospitalization history draws on all hospital admissions, not just those for CHD, this potentially reflects the higher hospitalization rates in all diabetics compared with the general population [27].

Whilst hospital morbidity data may underestimate population-level diabetes prevalence [28, 29], our results demonstrate that use of a lookback period can provide an accurate measure of diabetes prevalence in a defined population such as hospitalized CHD patients. Comorbidities used in the Charlson Comorbidity Index identified from the index hospitalization are underestimated by 46% during the ICD-9 period [22], although there is some evidence that the use of the index admission only provides optimal model discrimination in mortality outcome studies [24, 30]. Use of additional data sources such as claims data, where available, to identify diabetic status in this sample of patients may reduce the need for longer lookback periods. However, our results suggest that ICD-9 administrative data are reasonably accurate for identifying diabetic and non-diabetic cases but that the index admission alone may not correctly identify prevalent diabetic patients in the ICD-10 era, which is important information for jurisdictions where multiple data sources are not available.

The period differences shown in this study may relate to changes in coding practices. In many administrative health databases, conditions secondary to the principal reasons for admission to hospital are only coded if actively treated or investigated during the hospital stay [1]. However, during the 1990s in Australia, diabetes was required to be coded irrespective of documented intervention [1] which would contribute to the high levels of concordance between the two data sources in the ICD-9 period. Coding standards implemented with the introduction of ICD-10 reversed this requirement [7]. Further directives regarding coding of diabetic complications have apparently led to a marked increase in hospitalizations for complications of diabetes. This highlights the need to understand local coding directives and changes to standards which are relevant to the condition being investigated. Our results show that despite the incongruent effect
of these coding changes, the use of specified lookback periods would allow for continuity in trends of diabetes prevalence in CHD patients.

In contrast to other studies, we found no significant association of increasing age or recent hospitalization with false negatives, and also no association of sex [31, 32]. Differing and potentially changing impacts of age and sex mean that they are important variables for stratification in epidemiological studies of CHD trends [33] and our results show that such studies would not be biased across age and sex groupings. The only difference ascertained between time periods was an association of fewer comorbidities being recorded in the ICD-10 sample. This has important implications, as diabetes is more likely to be coded as a secondary than primary diagnosis [7]. It is unlikely that this finding is due to the number of available coding fields [21], as up to 21 diagnosis fields are available to researchers. Additional analysis of all CHD and CVD admissions in WA showed a small significant decrease in the number of comorbidities coded on admissions during the period of this study (data not shown), indicating a trend towards recording lower numbers of comorbidities during the more recent time period. A sensitivity analysis was undertaken where variables reaching significance at the p < 0.1 level in univariable analyses were included in the multivariable models. There were no differences in the significance levels of the existing variables in the models, which confirmed their significant association with false negatives as shown in the main analysis.

4.5.1 LIMITATIONS

The generalizability of our results to other hospitalized conditions, particularly non-cardiac conditions, is uncertain because concordance has been specifically measured in a sample of CHD patients. However, within a restricted population hospitalized with CHD, administrative data appear to reliably detect diabetes status. Although we have used recording of diabetes status in the medical records as a reference standard, there are potential limitations in this data source. Patients with less severe diabetes who are treated with diet alone may be less likely to be recorded in medical records as diabetic. There is also the possibility of inaccurate transfer of comorbid conditions to the discharge summary, but review of the whole medical record including drug charts limits the impact of this on identifying diabetic patients. Our results may not be generalizable to patients aged over 80 years due to the age range selected in our sample. However, the lack of significant association between increasing age and under-recording of diabetes
suggests that any difference in concordance measures in the very elderly may be small. The differences between the study samples could conceivably contribute to the differences in concordance measures demonstrated in our results, however, stratification by Indigenous status and by study source clearly demonstrate a similar pattern as seen in the main results. We were unable to demonstrate whether concordance measures have remained consistent since the latter period of our study.

4.6 CONCLUSION

This study has identified a temporal difference in concordance between medical records and administrative health data for the identification of diabetes in CHD patients. In linked administrative data, using up to ten years of hospitalization history to identify diabetes status reduces the temporal difference, improving concordance levels in the later ICD-10 period to those of the ICD-9 period. The use of unlinked administrative data to identify diabetes status would still provide reasonably high levels of accuracy however trends over time would be biased and prevalence of diabetes underestimated in the later period. Importantly, the level of concordance was as high in Indigenous as non-Indigenous patients in this setting, supporting the use of administrative data to identify diabetic status in this population group where diabetes and CHD impose a significant burden.

4.7 ACKNOWLEDGEMENTS

The authors wish to thank the staff at the Western Australian Data Linkage Branch, and the Department of Health Inpatient Data Collections and Registrar General, for the provision of data. This work was supported by project grants from the National Health and Medical Research Council of Australia (NHMRC) (#353671 and 479222). LN is supported by funding from the NHMRC and National Heart Foundation of Australia.
4.8 REFERENCES


**4.9 SUPPORTING INFORMATION**

Additional File S4.1. Concordance measures for the recording of diabetes in hospital discharge data with medical records, comparing a restricted ICD-10 sample (Study 1 only, n=1099) and the whole ICD-10 sample (Study 1 plus 2, n=2258), stratified by lookback period.

<table>
<thead>
<tr>
<th>Lookback period</th>
<th>Observed agreement %</th>
<th>Kappa</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Positive Predictive Value, %</th>
<th>Negative Predictive Value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Restricted sample</td>
<td>Full sample</td>
<td>Restricted sample</td>
<td>Full sample</td>
<td>Restricted sample</td>
<td>Full sample</td>
</tr>
<tr>
<td>Index admission</td>
<td>93.3</td>
<td>92.3</td>
<td>83.2</td>
<td>82.5</td>
<td>82.0</td>
<td>81.5</td>
</tr>
<tr>
<td>1 year</td>
<td>94.4</td>
<td>93.4</td>
<td>86.4</td>
<td>85.3</td>
<td>87.2</td>
<td>86.3</td>
</tr>
<tr>
<td>2 years</td>
<td>94.3</td>
<td>93.4</td>
<td>86.0</td>
<td>85.4</td>
<td>87.5</td>
<td>87.3</td>
</tr>
<tr>
<td>5 years</td>
<td>94.4</td>
<td>93.6</td>
<td>86.4</td>
<td>85.9</td>
<td>89.6</td>
<td>89.3</td>
</tr>
<tr>
<td>10 years</td>
<td>94.2</td>
<td>93.5</td>
<td>86.0</td>
<td>85.6</td>
<td>89.6</td>
<td>89.6</td>
</tr>
<tr>
<td>15 years</td>
<td>94.1</td>
<td>93.4</td>
<td>85.8</td>
<td>85.5</td>
<td>89.6</td>
<td>89.6</td>
</tr>
</tbody>
</table>

ICD, International Classification of Diseases
CHAPTER 5. POPULATION-LEVEL TRENDS IN ATHEROTHROMBOTIC DISEASE

PUBLISHED PAPER

This chapter is the published version of the following paper:

Temporal trends in the incidence and recurrence of hospitalised atherothrombotic disease in an Australian population, 2000–07: data linkage study


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Keywords: Epidemiology; Coronary heart disease; Cerebrovascular disorders; Peripheral arterial disease
PREAMBLE

The aim of this chapter was to provide a broad analysis of population-level temporal trends in atherothrombotic disease in WA. The availability of data covering this spectrum of disease made it possible to investigate this aim across CHD, CeVD and PAD in a whole-population setting. The long hospitalisation history available in the dataset allowed differentiation between incident and recurrent events and calculation of trends in both these indicators. Trends in mortality rates over the same period were also measured, as a means of confirming (or otherwise) whether there had been a shift from hospitalised incidence and recurrence to fatal cases.

The focus of this study was on CVD of atherothrombotic aetiology, therefore ICD codes were specifically selected for this purpose, rather than measuring the broader CVD rubric available in ICD coding. Because the findings of this study were also to be used to provide context to the specific diabetes analyses in this thesis, analyses were undertaken to determine the prevalence of diabetes in the broader atherothrombotic patient population in WA, and to determine whether this prevalence was changing during the study period.
5.1 ABSTRACT

Objectives: To examine temporal trends in the incidence and recurrence of hospitalised coronary heart disease (CHD), cerebrovascular disease (CeVD) and peripheral arterial disease (PAD) separately and combined, and by history of all forms of atherothrombotic disease.

Design: Population-based longitudinal data linkage study.

Setting: Western Australia.

Participants: All patients aged 35–84 years hospitalised in Western Australia for CHD, CeVD or PAD from 2000 to 2007.

Main outcome measures: Age-standardised incidence and recurrence rates of CHD, CeVD and PAD stratified by atherothrombotic disease history, sex and age.

Results: 107,576 events (65.9% men) were identified; 70% of all admissions were for CHD. In patients without a history of any ATD, incidence rates declined significantly in all groups, although the reduction in incident CHD in women was marginal (−0.7%/year, 95% CI −1.5 to +0.1%). The largest annual reductions in incidence rates were for PAD (men, −6.4%/year, 95% CI −7.7 to −5.0%; women, −5.4%/year, 95% CI −7.2 to −3.6%) and CeVD in women (−4.0%/year, 95% CI −5.0 to −3.0%). Falls in overall recurrence rates were greatest for CeVD (men, −3.2%/year, 95% CI −4.7 to −1.6%; women −4.6%/year, 95% CI −6.4 to −2.7%). Trends across all categories of polyvascular ATD were generally downward, although not all changes were statistically significant.

Conclusion: The incidence and recurrence rates of hospitalised ATD have decreased over time, including in patients with disease involving multiple vascular territories. This implies that primary and secondary prevention strategies have been broadly effective. However, high absolute rates of recurrence and limited reduction in 35–54-year-old individuals highlight patient groups to target to reduce further the burden of ATD.

5.2 INTRODUCTION

Coronary, cerebral and peripheral atherothrombotic disease (ATD) combined dominate morbidity and mortality worldwide [1]. In middle and high income countries including Australia, this is exemplified by ATD leading hospitalisation statistics [2]. There is a shared atherosclerotic pathology and heightened risk of atherothrombotic events across
the vascular territories. Examining trends in the incidence and recurrence of all hospitalised ATD is therefore important for determining the overall burden of ATD, for public health planning, and for assessing the effectiveness of shared cardiovascular disease treatment and risk factor interventions across the vascular territories.

Contemporary studies have selectively investigated event rates and outcomes across vascular territories [3, 4] yet a paucity of data exists for temporal trends across the continuum of ATD measured concomitantly in the same population. Community and population-based studies demonstrate declining incidence of coronary heart disease (CHD) [5, 6], cerebrovascular disease (CeVD) [7, 8] and peripheral arterial disease (PAD) separately [9, 10]. However, the risk of a new event in patients with established ATD remains high, particularly in those with polyvascular disease [11, 12]. Common risk factors and prevention approaches mean that our understanding of the effectiveness of both primary and secondary prevention is improved by describing trends across the whole spectrum of ATD. In addition, this would confirm whether any improvements extend to the highest-risk group of patients with polyvascular disease. Reporting trends in the incidence and recurrence of ATD by previous history will therefore benchmark the collective effectiveness of preventive strategies. The population-based data linkage system in Western Australia (WA) provides a unique opportunity for undertaking this study.

The aims of this study were to describe trends in incidence and recurrence rates of hospitalised CHD, CeVD and PAD in WA from 2000 to 2007, and to determine whether trends differed according to the history of ATD in other vascular territories.

5.3 METHODS

5.3.1 SETTING AND DATA SOURCE

The population of WA in 2010 was 2.3 million, with 75% residing in the capital city, Perth [13]. WA is representative of the Australian population in major sociodemographic and health economic indicators [14]. Data for all hospitalisations and deaths in WA are contained in the Hospital Morbidity Data Collection (HMDC) and Mortality Register, respectively, both of which are regularly audited [15]. All hospitalisations and death records for an individual are linked within the WA Data Linkage System (WADLS) by probabilistic matching which has >99% accuracy [15]. The dataset for this study contained all admissions and/or deaths for cardiovascular
disease in patients aged 35–84 years from 1985 to 2007. The upper age limit was imposed due to lack of validation of ATD in the very elderly. Events were identified using the prevailing International Classification of Diseases (ICD) version and relevant modifications (ICD-9 from 1979, and ICD-10 from 1 July 1999). Approval for this study was obtained from the Ethics Committees of The University of Western Australia and the WA Department of Health.

5.3.2 DEFINITION OF ATHEROTHROMBOTIC EVENTS

We identified hospital admissions with a principal diagnosis of CHD, CeVD or PAD, with ICD codes selected to ascertain events of atherothrombotic origin. CHD was defined as myocardial infarction (MI), unstable angina, stable angina or other ischaemic heart disease (ICD-9 410–414; ICD-10 I20–I25); CeVD as cerebral infarction, transient ischaemic attack, precerebral or cerebral artery disease without infarction, unspecified stroke or intracerebral haemorrhage (431, 433–436, 438; I61, I63, I64, I66, I69, G45); and PAD as atherosclerosis of the aorta, renal arteries or arteries of the extremities, unspecified peripheral vascular disease, Buerger's disease or stricture of arteries (440, 443.1, 443.9, 447.1; I70, I73.1, I73.9, I77.1). Previous validation of HMDC coding showed a positive predictive value for MI [16] and coronary death [17] of 83% and over 90%, respectively, and positive predictive value for stroke and other CeVD of 85% and 69%, respectively [17]. Review of coding of PAD in surgical admissions showed a tendency towards overestimation, which was insufficient to influence PAD trends [10]. Inter-hospital transfers were identified where there was 1 day or less between hospitalisations and counted as part of the same admission. A readmission for CHD within 28 days of an index CHD admission was considered part of the same event to reduce overcounting of recurrent events due to readmissions for revascularisation and diagnostic procedures [17]; for CeVD and PAD, readmissions within 1 day of an index hospitalisation were deemed part of the same event.

CHD, CeVD and PAD events with an admission date between 1 January 2000 and 31 December 2007 were included in the study, and each was classified as incident or recurrent using a 15-year lookback period, shown to differentiate first-time events [18]. An event was deemed incident if there was no hospitalisation for the same type of event during the lookback period, and otherwise was considered recurrent. A 15-year lookback period was also used to identify history of CHD, CeVD or PAD for each
incident and recurrent event, and events were categorised into four groups according to the number and type of other vascular territories involved (see Tables 2 and 3).

ATD-related deaths were classified using the ICD codes described above for incident and recurrent events. A sensitivity analysis was undertaken to analyse use of codes not included in our ATD definitions. For CHD, deaths coded to cardiac arrest, respiratory arrest or unspecified cardiovascular disease were also incorporated in the analyses (CHD + I46, R09.2, I51.6); and the broader coding groups for all CeVD (I60–I69, G45) and peripheral vascular disease (I70–I79) were also analysed.

The following comorbidities were identified from any diagnosis field of the HMDC using a 15-year hospitalisation history for each event: diabetes (250, E10–E14); hypertension (401–405; I10–I15); chronic kidney disease (based on the Australian Institute of Health and Welfare definition) [2]; atrial fibrillation (427.3; I48); heart failure (428; I50); chronic obstructive pulmonary disease (490–496; J40–J47); and cancer (140–239; C00–D48). Codes are consistent with those used in CHD patients in an Australian study, in which agreement between administrative data and medical records was greater than 88% for these comorbidities [19]. Invasive diagnostic and interventional procedures were identified from any procedure field, and included coronary angiography, percutaneous coronary intervention, or coronary artery bypass surgery for CHD; cerebral angiography, embolectomy, thrombectomy or endarterectomy of the carotid or intracranial arteries for CeVD; and peripheral angiography, revascularisation or repair of peripheral or abdominal arteries, and lower limb amputation or revision procedure for PAD. An acute event was an emergency hospitalisation for acute coronary syndrome (for CHD), cerebral infarction or transient ischaemic attack (for CeVD), and atherosclerosis of the lower extremities (for PAD). There were fewer than 0.001% missing values for any of the variables used in this study.

5.3.3 STATISTICAL ANALYSIS

Men and women were analysed separately. Characteristics of the study population are presented as mean (SD) for continuous variables and frequencies (%) for categorical variables, and are calculated separately for incident and recurrent events. Incidence and recurrence rates by calendar year were calculated for each ATD type overall and by ATD history group. Counts of incident or recurrent events in each group were the numerator, while the denominator was the population at risk for each type of event in
each study year, including by ATD history. The denominator for incidence rates was calculated using the whole WA population [20] minus the prevalent population for each ATD type and history group. The method for identifying the prevalent ATD population has been described previously [21]. The denominator for recurrence rates was the prevalent population in WA for each ATD type and history group [21]. Mortality rate numerators were the counts of deaths for each ATD type separately, and the denominators were the WA population in each calendar year [20]. Annual age-standardised and age-specific rates were calculated by the direct method using 5-year age groups, with the WA population in 2007 as the standard population for incidence and ATD mortality rates [20], and the prevalent ATD population in WA in 2007 as the standard population for recurrence rates [21]. Age-standardised comorbidity prevalence was calculated for each calendar year for all incident ATD with no ATD history, and for all ATD cases combined, using the age distribution of all ATD cases in 2007 as the standard population.

Trends in age-adjusted rates by calendar year were estimated using Poisson log-linear regression models that included 5-year age group and calendar year (continuous). Model fit was tested and no overdispersion was found. Annual changes in rates were calculated using the exponential of the beta-coefficient for calendar year, and are presented as estimated annual percentage changes. Interactions for ATD type and calendar year were tested to determine homogeneity of trends across ATD history groups. Age-adjusted trends in the prevalence of selected comorbidities were estimated using logistic regression models that included 5-year age group and calendar year. Statistical significance was set at p<0.05 for all analyses, which were undertaken using SAS statistical software (SAS Institute Inc, version 9.2).

5.4 RESULTS

There was a total of 70,844 atherothrombotic events in men and 36,732 in women aged 35–84 years between 2000 and 2007 (Table 5.1). Approximately half of these events were classified as incident for CHD and PAD, whereas 75% of CeVD cases were incident. The mean age of patients hospitalised with incident CHD was 62.2 and 66.5 years in men and women, respectively; this was younger than for CeVD (68.5 and 70.9 years, respectively) and PAD (69.0 and 71.5 years, respectively). A similar pattern was seen for recurrent cases (Table 5.1). The percentage of cases occurring among the oldest age group (70–84 years) varied from 30% for incident CHD in men, to 73% for
recurrent CeVD and PAD in women. The most common recorded comorbidity was hypertension. Diabetes, chronic kidney disease and atrial fibrillation were also prevalent in incident and recurrent cases (Table 5.1). PAD patients were less likely to be admitted acutely and more likely to undergo angiography and/or invasive intervention than CHD or CeVD patients (Table 5.1).

CHD dominated incident (66.3% in men, 59.3% in women) and recurrent hospitalisations (79.4% in men, 75.0% in women) (Tables 5.2 and 5.3). Only 7% of incident CHD events had previous ATD recorded, compared with incident CeVD (26% men, 18% women) and incident PAD (39% men, 29% women). Recurrent cases were more likely than incident cases to have a history of ATD in other vascular territories (Table 5.3).

5.4.1 TRENDS IN ATD INCIDENCE RATES

Figure 5.1 shows the trends in overall age-standardised ATD incidence rates and Table 5.2 the estimated annual change in age-adjusted incidence rates overall and by ATD history. Statistically significant declining overall trends in CHD, CeVD and PAD incidence were observed in men and women, with annual rates of decline greatest for PAD in men (−6.4%/year, 95% CI −7.7 to −5.0%) and women (−5.4%/year, 95% CI −7.2 to −3.6%). A marked annual decline of 4.0%/year (95% CI −5.0 to −3.0) was also seen in women with CeVD. There were reductions in age-standardised incidence rates in all groups with no history of any ATD, although the trend was not significant in women with incident CHD (−0.7%/year, 95% CI −1.5 to +0.1%) (Table 5.2). The rates of decline in incidence were generally greater in those groups with a history of other ATD but not all were statistically significant. There was increasing incidence in women aged 35–54 years in each of the vascular territories, and for men in this age group with CeVD, although trends were only significant in women with CHD (Table 5.4).
**CHAPTER 5. POPULATION-LEVEL TRENDS IN ATHEROTROMBOTIC DISEASE**

**TABLE 5.1. CHARACTERISTICS OF THE STUDY POPULATION.**

<table>
<thead>
<tr>
<th></th>
<th>CHD</th>
<th>CeVD</th>
<th>PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Incident cases, n</td>
<td>24,668</td>
<td>12,732</td>
<td>8894</td>
</tr>
<tr>
<td>Mean age, years (±SD)</td>
<td>62.2 (11.5)</td>
<td>66.5 (11.6)</td>
<td>68.5 (10.9)</td>
</tr>
<tr>
<td>Patients aged 70–84 y, %</td>
<td>29.8</td>
<td>46.1</td>
<td>53.8</td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>19.4</td>
<td>23.2</td>
<td>25.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44.1</td>
<td>55.3</td>
<td>60.5</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>7.9</td>
<td>9.3</td>
<td>11.7</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11.0</td>
<td>12.8</td>
<td>20.1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9.4</td>
<td>13.8</td>
<td>10.2</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>6.1</td>
<td>9.8</td>
<td>10.2</td>
</tr>
<tr>
<td>Cancer</td>
<td>8.0</td>
<td>9.7</td>
<td>14.3</td>
</tr>
<tr>
<td>Non-fatal event, %*</td>
<td>97.6</td>
<td>96.6</td>
<td>91.5</td>
</tr>
<tr>
<td>Acute admission, %†</td>
<td>50.5</td>
<td>52.5</td>
<td>72.7</td>
</tr>
<tr>
<td>Procedure, %</td>
<td>74.5</td>
<td>61.5</td>
<td>27.0</td>
</tr>
<tr>
<td>Recurrent cases, n</td>
<td>26,757</td>
<td>11,461</td>
<td>3033</td>
</tr>
<tr>
<td>Mean age, years (±SD)</td>
<td>66.0 (10.7)</td>
<td>69.7 (10.7)</td>
<td>71.6 (9.5)</td>
</tr>
<tr>
<td>Patients aged 70–84 y, %</td>
<td>42.0</td>
<td>58.2</td>
<td>66.0</td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>30.8</td>
<td>37.8</td>
<td>32.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>72.1</td>
<td>81.5</td>
<td>78.3</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>17.6</td>
<td>20.1</td>
<td>17.1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>21.0</td>
<td>21.6</td>
<td>26.6</td>
</tr>
<tr>
<td>Heart failure</td>
<td>21.5</td>
<td>29.5</td>
<td>16.2</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>15.1</td>
<td>21.6</td>
<td>18.3</td>
</tr>
<tr>
<td>Cancer</td>
<td>13.7</td>
<td>9.5</td>
<td>18.9</td>
</tr>
<tr>
<td>Nonfatal event, %*</td>
<td>97.2</td>
<td>97.5</td>
<td>91.1</td>
</tr>
<tr>
<td>Acute admission, %†</td>
<td>37.3</td>
<td>43.9</td>
<td>61.9</td>
</tr>
<tr>
<td>Procedure, %</td>
<td>71.2</td>
<td>55.8</td>
<td>28.5</td>
</tr>
</tbody>
</table>

* Survival more than 28 days following date of atherothrombotic disease event.
† Emergency admission for acute coronary syndrome, cerebral infarction or transient ischaemic attack, or atherosclerosis of the lower extremities.

CeVD, cerebrovascular disease; CHD, coronary heart disease; PAD, peripheral arterial disease.
### Table 5.2. Trends in age-adjusted incidence rates of hospitalised CHD, CeVD and PAD in 35–84-year-old individuals, 2000–07.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) Person-years Annual % change (95% CI)</td>
<td>n (%) Person-years Annual % change (95% CI)</td>
</tr>
<tr>
<td>Incident CHD</td>
<td>24 668 3 636 430 −1.7 (−2.2 to −1.1)</td>
<td>12 732 3 820 658 −1.0 (−1.8 to −0.3)</td>
</tr>
<tr>
<td>No previous ATD</td>
<td>23 107 (94) 3 573 441 −1.5 (−2.1 to −1.0)</td>
<td>11 863 (93) 3 774 354 −0.7 (−1.5 to +0.1)</td>
</tr>
<tr>
<td>Previous CeVD only</td>
<td>931 (4) 45 414 −2.7 (−5.4 to 0)</td>
<td>545 (4) 35 313 −3.2 (−6.7 to +0.5)</td>
</tr>
<tr>
<td>Previous PAD only</td>
<td>518 (2) 15 070 −1.2 (−4.9 to +2.5)</td>
<td>266 (2) 9742 −6.9 (−11.8 to −1.9)*</td>
</tr>
<tr>
<td>Previous CeVD and PAD</td>
<td>112 (0.5) 2505 −7.2 (−14.5 to +0.8)</td>
<td>58 (0.5) 1249 −3.2 (−13.7 to +8.6)</td>
</tr>
<tr>
<td>Incident CeVD</td>
<td>8894 3 845 493 −1.9 (−2.8 to −1.0)</td>
<td>6778 3 901 989 −4.0 (−5.0 to −3.0)</td>
</tr>
<tr>
<td>No previous ATD</td>
<td>6579 (74) 3 573 441 −1.2 (−2.3 to −0.2)</td>
<td>5533 (82) 3 774 354 −3.7 (−4.8 to −2.6)</td>
</tr>
<tr>
<td>Previous CHD only</td>
<td>1907 (21) 248 304 −3.2 (−5.1 to −1.3)*</td>
<td>1031 (15) 114 256 −5.0 (−7.5 to −2.4)</td>
</tr>
<tr>
<td>Previous PAD only</td>
<td>233 (3) 15 070 −2.6 (−7.9 to +3.0)</td>
<td>149 (2) 9742 −4.5 (−11.0 to +2.6)</td>
</tr>
<tr>
<td>Previous CHD and PAD</td>
<td>175 (2) 8678 −3.9 (−10.1 to +2.6)</td>
<td>65 (1) 3637 −6.7 (−16.2 to +3.9)</td>
</tr>
<tr>
<td>Incident PAD</td>
<td>3617 3 883 134 −6.4 (−7.7 to −5.0)</td>
<td>1967 3 931 723 −5.4 (−7.2 to −3.6)</td>
</tr>
<tr>
<td>No previous ATD</td>
<td>2196 (61) 3 573 441 −5.7 (−7.4 to −4.0)</td>
<td>1392 (71) 3 774 354 −4.6 (−6.7 to −2.4)</td>
</tr>
<tr>
<td>Previous CHD only</td>
<td>961 (26) 24 8304 −5.7 (−8.3 to −3.0)</td>
<td>356 (18) 114 256 −6.6 (−10.7 to −2.2)</td>
</tr>
<tr>
<td>Previous CeVD only</td>
<td>246 (7) 49 630 −7.6 (−12.6 to −2.4)</td>
<td>144 (7) 31 097 −8.0 (−14.4 to −1.1)</td>
</tr>
<tr>
<td>Previous CHD and CeVD</td>
<td>214 (6) 15 975 −10.7 (−15.9 to −5.2)*</td>
<td>75 (4) 7800 −5.3 (−14.4 to +4.7)</td>
</tr>
</tbody>
</table>

*Comparison using no previous ATD group as reference in each category, p-value<0.05.

ATD, atherothrombotic disease; CeVD, cerebrovascular disease; CHD, coronary heart disease; PAD, peripheral arterial disease.
### Table 5.3. Trends in age-adjusted recurrence rates of hospitalised CHD, CeVD and PAD in 35–84-year-old individuals, 2000–07.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) Person-years Annual % change (95% CI)</td>
<td>n (%) Person-years Annual % change (95% CI)</td>
</tr>
<tr>
<td>Recurrent CHD</td>
<td>26 757 275 231 –2.4 (–2.9 to –1.9)</td>
<td>11461 126 489 –2.3 (–3.1 to –1.5)</td>
</tr>
<tr>
<td>No previous other ATD</td>
<td>23 027 (86) 248 304 –2.4 (–3.0 to –1.9)</td>
<td>9813 (86) 114 256 –2.2 (–3.1 to –1.4)</td>
</tr>
<tr>
<td>Previous CeVD only</td>
<td>2009 (8) 15 975 –0.2 (–2.1 to +1.8)*</td>
<td>971 (8) 7800 –0.2 (–3.0 to +2.6)†</td>
</tr>
<tr>
<td>Previous PAD only</td>
<td>1343 (5) 8678 –2.3 (–4.5 to +0.1)</td>
<td>520 (5) 3637 –3.1 (–6.7 to +0.7)</td>
</tr>
<tr>
<td>Previous CeVD and PAD</td>
<td>378 (1) 2274 –3.7 (–7.9 to +0.8)</td>
<td>157 (1) 796 –7.7 (–14.0 to –1.0)†</td>
</tr>
<tr>
<td>Recurrent CeVD</td>
<td>3033 66 168 –3.2 (–4.7 to –1.6)</td>
<td>2018 45 158 –4.6 (–6.4 to –2.7)</td>
</tr>
<tr>
<td>No previous other ATD</td>
<td>1851 (61) 45 414 –1.1 (–3.1 to +0.9)</td>
<td>1438 (71) 35 313 –3.9 (–6.0 to –1.6)</td>
</tr>
<tr>
<td>Previous CHD only</td>
<td>876 (29) 15 975 –6.2 (–8.9 to –3.4)*</td>
<td>452 (22) 7800 –5.0 (–8.8 to –1.0)</td>
</tr>
<tr>
<td>Previous PAD only</td>
<td>164 (5) 2505 –4.5 (–10.7 to +2.2)</td>
<td>71 (4) 1249 –11.7 (–20.6 to –1.7)</td>
</tr>
<tr>
<td>Previous CHD and PAD</td>
<td>142 (5) 2274 –9.4 (–15.9 to –2.4)*</td>
<td>57 (3) 796 –10.1 (–20.0 to +1.1)</td>
</tr>
<tr>
<td>Recurrent PAD</td>
<td>3875 28 527 –2.0 (–3.3 to –0.6)</td>
<td>1776 15 424 –1.6 (–3.6 to +0.05)</td>
</tr>
<tr>
<td>No previous other ATD</td>
<td>2087 (54) 15 070 –0.1 (–1.8 to +2.0)</td>
<td>1113 (63) 9742 +0.4 (–2.1 to +3.0)</td>
</tr>
<tr>
<td>Previous CHD only</td>
<td>1191 (31) 8678 –4.2 (–6.6 to –1.7)</td>
<td>436 (25) 3637 –2.8 (–6.8 to +1.3)</td>
</tr>
<tr>
<td>Previous CeVD only</td>
<td>324 (8) 2505 –1.9 (–6.5 to +2.9)†</td>
<td>148 (8) 1249 –6.0 (–12.6 to +1.1)</td>
</tr>
<tr>
<td>Previous CHD and CeVD</td>
<td>273 (7) 2274 –9.5 (–14.2 to –4.5)**†</td>
<td>79 (4) 796 –12.0 (–20.4 to –2.8)*</td>
</tr>
</tbody>
</table>

* Comparison using no previous other ATD group as reference for each category, p-value < 0.05.
† Pairwise comparison between groups with previous ATD history, p-value < 0.05.

ATD, atherothrombotic disease; CeVD, cerebrovascular disease; CHD, coronary heart disease; PAD, peripheral arterial disease.
### Table 5.4. Trends in age-specific incidence and recurrence rates by gender and age group

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gender</th>
<th>Age Group</th>
<th>Incidence</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Annual % change (95% CI)</td>
<td>Annual % change (95% CI)</td>
</tr>
<tr>
<td>CHD</td>
<td>Men</td>
<td>35–54 yrs</td>
<td>6654</td>
<td>-1.3 (-2.3 to -0.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55–69 yrs</td>
<td>10664</td>
<td>-1.4 (-2.2 to -0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70–84 yrs</td>
<td>7348</td>
<td>-2.4 (-3.4 to -1.4)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>35–54 yrs</td>
<td>2304</td>
<td>+2.0 (+0.2 to +3.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55–69 yrs</td>
<td>4560</td>
<td>-1.0 (-2.3 to +0.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70–84 yrs</td>
<td>5868</td>
<td>-2.2 (-3.3 to -1.1)</td>
</tr>
<tr>
<td>CeVD</td>
<td>Men</td>
<td>35–54 yrs</td>
<td>1114</td>
<td>+1.9 (-0.7 to +4.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55–69 yrs</td>
<td>2995</td>
<td>-0.7 (-2.3 to +0.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70–84 yrs</td>
<td>4785</td>
<td>-2.9 (-4.1 to -1.7)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>35–54 yrs</td>
<td>753</td>
<td>+1.3 (-1.8 to +4.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55–69 yrs</td>
<td>1631</td>
<td>-5.0 (-7.0 to -3.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70–84 yrs</td>
<td>4394</td>
<td>-4.5 (-5.7 to -3.3)</td>
</tr>
<tr>
<td>PAD</td>
<td>Men</td>
<td>35–54 yrs</td>
<td>361</td>
<td>-4.5 (-8.7 to -0.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55–69 yrs</td>
<td>1302</td>
<td>-5.7 (-7.9 to -3.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70–84 yrs</td>
<td>1954</td>
<td>-6.8 (-8.6 to -4.9)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>35–54 yrs</td>
<td>160</td>
<td>+4.8 (-2.0 to +12.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55–69 yrs</td>
<td>477</td>
<td>-7.7 (-11.3 to -4.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70–84 yrs</td>
<td>1330</td>
<td>-5.6 (-7.8 to -3.3)</td>
</tr>
</tbody>
</table>

*Age-specific trends for each sex-age group are adjusted by five year age groups in Poisson regression models.

CeVD, cerebrovascular disease; CHD, coronary heart disease; PAD, peripheral arterial disease.
CHAPTER 5. POPULATION-LEVEL TRENDS IN ATHEROTHROMBOTIC DISEASE

Figure 5.1. Age-standardised incidence rates of hospitalised coronary heart disease (CHD), cerebrovascular disease (CeVD) and peripheral arterial disease (PAD) for men and women aged 35–84 years, 2000–07.
5.4.2 TRENDS IN ATD RECURRENCE RATES

Figure 5.2 shows the trends in overall age-standardised ATD recurrence rates and Table 5.3 the estimated annual decline in age-adjusted recurrence rates overall and by ATD history. The annual rates of decline ranged from 1.6%/year (95% CI –3.6 to +0.05%) in women with recurrent PAD, to 4.6%/year (95% CI –6.4 to –2.7%) in women with recurrent CeVD. For recurrent PAD, the rate of decline was significantly greater in those with a history of CHD and CeVD compared with those without other ATD. Greater declines were also seen in men with recurrent CeVD with CHD and PAD history, and with previous CHD only, compared with no other ATD history. Trends were generally downward across all age groups, with the exception being men with CeVD and women with PAD in the 35–54 year old age group, although these upward trends were not statistically significant (Table 5.4).

5.4.3 TRENDS IN ATD MORTALITY RATES

There were significant declines in age-standardised mortality rates for CHD and CeVD (Figure 5.3). Age-standardised mortality rates for PAD were low, and there was no significant change in rates (men –2.1%/year, 95% CI –8.6 to +4.8%; women –4.3%/year, 95% CI –11.8 to +3.8%). Using a broader definition of CHD and CeVD deaths produced no significant effect on trends in CHD and CeVD mortality (data not shown). The broader definition for PAD deaths showed that mortality rates remained low in this group, ranging from 21.7/100 000 to 14.5/100 000 person-years in men, and 13.3/100 000 to 7.0/100 000 person-years in women. Trends persisted downwards in men and women, although became significant in men (–4.5%/year, 95% CI –7.8 to –1.2%) while the trend in women remained non-significant.

5.4.4 TRENDS IN COMORBIDITY PREVALENCE

Trends and estimated annual percentage changes in age-standardised prevalence of hypertension, diabetes, atrial fibrillation and chronic kidney disease in incident ATD without ATD history, and in all ATD, are shown in Figure 5.4. There were significant increases in the age-adjusted prevalence of hypertension in incident and in all ATD cases, and also significant increases in diabetes prevalence in incident and all ATD cases in men and all ATD cases in women.
Figure 5.2. Age-standardised recurrence rates for hospitalised coronary heart disease (CHD), cerebrovascular disease (CeVD) and peripheral arterial disease (PAD) for men and women aged 35–84 years, 2000–07.
**Figure 5.3.** *Age-standardised mortality rates for coronary heart disease (CHD), cerebrovascular disease (CeVD) and peripheral arterial disease (PAD) for men and women aged 35–84 years, 2000–07.*
FIGURE 5.4. AGE-STANDARDISED PREVALENCE OF HYPERTENSION, DIABETES, ATRIAL FIBRILLATION (AF) AND CHRONIC KIDNEY DISEASE (CKD) IN (A) FIRST EVER INCIDENT ATHEROTHROMBOTIC DISEASE AND (B) ALL ATHEROTHROMBOTIC DISEASE EVENTS. PERCENTAGE CHANGES INDICATE AVERAGE ANNUAL CHANGE. *P-VALUE<0.0001; †P-VALUE <0.05.
5.5 DISCUSSION

This state-wide Australian study of 107,576 atherothrombotic events is the first to report on temporal trends in incidence and recurrence concurrently across vascular territories and according to ATD history. Overall incidence and recurrence rates for hospitalised ATD declined between 2000 and 2007 in a whole population setting. Importantly, stratifying trends by ATD history showed that incidence rates also declined in those with no previous ATD of any type, although the reduction in women with incident CHD was limited. There was also limited reduction in incidence rates in the younger age group across all vascular territories, particularly in women. Our results also demonstrate that incidence and recurrence rates have generally fallen to a greater extent in those with polyvascular disease, suggesting the benefit of shared prevention treatments across multiple vascular territories. Although declining, recurrence rates for hospitalised ATD in our population remained many times higher than comparable incidence rates. This study also demonstrates that CHD is the major burden of hospitalised ATD (70% of cases).

5.5.1 STRENGTHS AND LIMITATIONS

The use of high-quality linked administrative data with an extensive lookback period allowed analysis of rates by vascular territory and atherothrombotic history, and differentiation between first and recurrent events. We were also able to calculate events based on episodes of care for an individual due to person-based linkage of records in WA [15]. Although there is the potential for exclusion of true recurrent CHD events when imposing 28-day episodes, a sensitivity analysis showed that CHD patients were twice as likely to be readmitted within 28 days of an index admission as patients with CeVD or PAD, highlighting that admission practices are likely to drive this difference. Although out-of-hospital deaths are not included in our definition of incident and recurrent events, declines in these rates are unlikely to be due to a shift from non-fatal to fatal cases. This is because fatal incident CHD rates, including out-of-hospital deaths, have fallen in WA [22] and the current study shows declining ATD mortality rates. This is consistent with concurrent falls in event rates and mortality rates for MI and stroke elsewhere [23–25]. Changing thresholds for diagnostic tests and hospital admissions over time could impact on trends. Troponin testing has attenuated downward trends in MI incidence [26]; however, the inclusion of all CHD hospitalisations means that any apparent increase in MI counts is likely to be offset by a shift in diagnosis from other
variants of CHD. There may be a greater propensity to treat less severe PAD in community or outpatient setting relative to comparable CHD or CeVD cases, which could underestimate the total relative burden of PAD. The decline in PAD rates is unlikely to be due to a shift of diagnostic testing to the outpatient setting, as preliminary analysis showed that there was limited change in the proportion of PAD patients undergoing peripheral angiography as inpatients. Identification of events was based on clinical advice and previous validation studies locally [10, 16, 17]. A limitation is the potential misclassification of diagnostic coding which could contribute to over or underestimation of absolute event numbers, but is unlikely to have varied during the study period and consequently would be unlikely to bias trend estimates. Events were identified only from the principal diagnosis field as validity of coding is higher than for secondary diagnoses [17].

5.5.2 COMPARISONS WITH OTHER STUDIES

The declines in overall incidence in our study are consistent with historical trends in WA for coronary events [27], stroke [28] and PAD-related admissions [10], and with reductions seen elsewhere in community and hospital settings [7, 25, 29, 30], including reductions in first-time hospitalisations for acute MI in Denmark [23]. Temporal trend data on recurrence rates are limited, but recurrence rates have fallen concurrently with declines in MI incidence in Finland and Sweden [6, 31] and stroke incidence in Scotland [7, 32]. There are limited data on recurrence rates for hospitalised PAD, and on incidence and recurrence according to atherothrombotic history across vascular territories. The age-standardised trends in our study mask possible attenuation of declines in rates in 35–54-year-old individuals. Other population-based studies have reported limited reductions in MI and stroke rates in this age group [7, 24]; however of note in our study was the significant increase in CHD incidence in younger women, a trend also seen in this group for acute coronary syndromes in WA [33]. Notably, CHD dominated incident and recurrent events in our population. This was similar to the REACH study [4], which investigated stable outpatients, but in contrast to the findings of the Oxford Vascular Study [3], in which stroke dominated and which included acute hospitalised and non-hospitalised cases with no upper age limit. The ratio of acute incident cerebrovascular to coronary events in Oxfordshire was higher than in our study population (1.19 vs 0.6). This difference was primarily driven by a higher ratio in women in the former study, and also associated with a higher mean age. Although our
upper age limit of 84 years to improve case validity would have contributed to this
difference, there is also the possibility of differing population demographics and
hospital admission thresholds, particularly in women. Despite these apparent variances,
downward trends in incident stroke have also been reported in Oxfordshire [25].

5.5.3 IMPLICATIONS OF RESULTS

Trends in incidence when there is no history of any ATD are an important indicator of
the effectiveness of primary prevention in the community. Hence declines in incidence
that occurred in men and women without previous ATD implied positive effects of
primary prevention in the WA population. Also, the rates of decline in incidence were
observed to be generally greater in groups with a history of other ATD (Table 5.2),
although in PAD, incidence declined markedly irrespective of other atherothrombotic
history, suggesting a shared benefit of cardiovascular treatments and prevention
measures across vascular territories and possibly a greater impact of primary prevention
in this group compared with CHD or CeVD. In Australia, rapid uptake of
antihypertensive and cholesterol-lowering medication and long-term anti-smoking
campaigns are likely contributors to these declines [34]. A greater uptake of
hypertension treatment in women compared with men has been shown in the UK [35], a
pattern which if duplicated in WA could account for the greater falls in CeVD incidence
seen in women in our study. Although hypertension prevalence increased in incident
ATD cases in our study, this may represent improved targeting and admission practices
for high-risk ATD patients.

The flat or increasing trends in incidence in 35–54-year-old individuals in our study,
particularly in women, may indicate the effect of adverse risk factor trends. National
data show that men and women aged 30–34 years in 1980 gained on average 8 kg and
12 kg, respectively, over the subsequent 20-year period [34]. The prevalence of diabetes
in Australia has increased during the same period and is higher than in many other
developed countries [36]. The concurrent attenuation of downward trends in CHD
mortality in younger people [22, 37–39] further supports the impact of unfavourable
trends in these risk factors.

Declining recurrence rates for CHD, CeVD and PAD reflect the effectiveness of well-
established secondary prevention. In particular, reductions in incidence and recurrence
rates in those with polyvascular disease may indicate that evidence-based cardiovascular
treatments and prevention measures aimed at secondary prevention in one vascular
trend territory (predominantly CHD) may have reduced the progression of atherothrombosis to other vascular territories. This is supported by large falls in recurrence rates in the highest risk groups, particularly recurrent PAD with concomitant CHD and CeVD in men (−9.5%/year) and women (−12.0%/year).

Importantly, this study identifies targets for further reduction of the ATD burden. The proportion of incident admissions with no previous ATD history is high (86%). Many asymptomatic persons at high cardiovascular risk are not targeted for prevention nor have their risk factors optimally controlled [40], therefore targeting of this group in the primary care setting would decrease the atherothrombotic burden. Despite falling recurrence rates, the current study highlights that absolute rates of recurrence are 15–20 times higher for CHD and CeVD and over 100 times higher for PAD than equivalent incidence rates. This supports evidence that the risk of recurrence and rehospitalisation for cardiovascular events remains high [4], and reinforces the need for optimising application of evidence-based treatments in patients with established disease.

5.6 CONCLUSIONS

This study has shown that incidence and recurrence rates of hospitalised atherothrombotic CHD, CeVD and PAD declined between 2000 and 2007 in a state-wide Australian setting. Reductions were generally greater in those with polyvascular disease for both incident and recurrent cases, implying that primary and secondary prevention strategies have been broadly effective in our state. However, there was evidence of attenuation of downward trends in 35–54-year-old individuals, particularly in women, and increasing prevalence of hypertension and diabetes in hospitalised ATD patients. Population-based monitoring is therefore an essential means of identifying target groups such as these to reduce further the burden of ATD.
WHAT IS ALREADY KNOWN ON THE SUBJECT

- Incidence rates of CHD, CeVD and PAD have declined in developed nations over four decades.
- There is limited evidence for temporal trends on polyvascular or ATD recurrence.

WHAT THIS STUDY ADDS

- Age-standardised incidence and recurrence rates of hospitalised CHD, CeVD and PAD declined between 2000 and 2007 in 35–84-year-olds in WA.
- Age-standardised incidence rates for CHD, CeVD and PAD declined in those without previous ATD, but marginally so in women with CHD, and declines were limited in those aged 35–54 years.
- Rates of decline were generally greater in those with polyvascular disease, particularly for recurrent cases, suggesting positive effects of secondary prevention.

5.7 ACKNOWLEDGEMENTS

The authors acknowledge the Data Linkage Branch (WA Department of Health) for extraction and provision of the data used in this study.
CHAPTER 5. POPULATION-LEVEL TRENDS IN ATEROTRHMOTIC DISEASE

5.8 REFERENCES


CHAPTER 6. TRENDS IN THE INCIDENCE OF MYOCARDIAL INFARCTION AND CORONARY HEART DISEASE IN PEOPLE WITH AND WITHOUT DIABETES

PUBLISHED PAPER

This chapter is the published version of the following paper:

Comparative trends in the incidence of hospitalized myocardial infarction and coronary heart disease in adults with and without diabetes mellitus in Western Australia from 1998 to 2010

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Keywords: Coronary disease; Diabetes mellitus; Incidence; Myocardial infarction; Trends
CHAPTER 6. DIABETES AND MYOCARDIAL INFARCTION INCIDENCE

PREAMBLE

The main focus of Chapter 5 was to measure temporal trends in incidence and recurrence rates of CHD and atherothrombotic vascular disease more broadly in a whole-population setting. The results demonstrated that CHD has generally decreased at a population level in WA. However, concurrent with these trends was an increase in the age-standardised prevalence of diabetes in incident cases.

Therefore given the trends in diabetes prevalence and that CHD comprises the majority (~two-thirds) of incident atherothrombotic disease cases, this chapter specifically focused on the incidence of CHD in the diabetic population. The incidence of MI was the primary event of interest in this study, with hospitalised CHD included as a secondary analysis. This was included to provide a broader understanding of trends in this population, and because the use of troponin testing during the study period may have influenced trends in MI. Analysis of hospitalised CHD reduces the impact of the changing diagnostic criteria for MI and helps to inform interpretation of the results.
6.1 ABSTRACT

Background: The risk of myocardial infarction (MI) is elevated in people with diabetes mellitus (DM) compared to non-DM counterparts. The aim of this study was to compare population trends in the incidence of hospitalized MI and coronary heart disease (CHD) in adults with and without DM.

Methods and results: All incident hospitalized MI and CHD events were identified from whole-population hospital data in Western Australia for 1998–2010. Annual age-standardized MI and CHD incidence rates were calculated for people with and without DM aged 35 to 84 years, and age-adjusted trends estimated from Poisson regression. There were 26 610 incident MI and 56 142 incident CHD cases during the study period. MI incidence rates fell in men (–2.9%/y, 95% confidence interval [CI], −3.7 to −2.1) and women (−3.8%/y, 95% CI, −4.8 to −2.1) with DM, representing overall reductions of 35% and 43% respectively, with comparable reductions in incident CHD. Downward trends in MI incidence in those with DM were most apparent in 55- to 84-year olds. In adults without DM, there was no decline in MI incidence but a small significant decrease in incident CHD (men −1.5%/y, 95% CI −1.8 to −1.2; women −1.3%/y, 95% CI −1.8 to −0.9). Incidence rate ratios for MI in men with versus without DM declined from 4.5 (95% CI 4.2–4.8) to 3.1 (95% CI 2.9–3.3), and from 6.0 (95% CI 5.4–6.6) to 3.8 (95% CI 3.5–4.1) in women between 1998 and 2010.

Conclusions: There have been significant reductions in incidence rates of MI and CHD in adults with DM between 1998 and 2010; however, the excess risk of MI incidence remains 3 to 4× greater in people with DM.

6.2 INTRODUCTION

The risk of cardiovascular disease (CVD) in people with diabetes mellitus (DM) is 2 to 4× greater than in people without DM [1, 2]. Better treatment of DM and associated CVD risk factors may counter this elevated risk of macrovascular complications. Declining rates of first myocardial infarction (MI) and coronary heart disease (CHD) among people with DM are an indicator of improved treatment and primary prevention efforts, yet temporal trend data are scarce.

Major advances in medical therapies and cardiovascular prevention have contributed to long-term declines in CHD mortality and MI incidence; however, the downward trajectory of these trends may be impacted because of the increasing prevalence of DM
and obesity [3]. In Western Australia (WA), the impact of troponin testing on the
diagnosis of MI has led to an attenuation of declines in MI rates [4], although
hospitalized CHD incidence and recurrence rates have continued to fall [5]. These
differences highlight the necessity of understanding trends across both disease
groupings.

There is limited international and no Australian data showing long-term population
trends in MI and CHD incidence separately for patients with and without DM. Data
from European populations are equivocal as to whether MI incidence has declined in
people with DM [6, 7]. The Framingham Heart Study has shown a long-term reduction
in CVD incidence in people with DM [8], but an increasing population attributable risk
which indicates a growing impact of DM relative to other risk factors [9].

The prevalence of DM has increased in the past decade in WA to 6.5% [10], consistent
with global trends [11]. Clinical trial evidence supports a greater focus on
cardiocirculatory risk management for people with DM [12], in tandem with improving
glycemic control at an individual level [13]. Changing DM epidemiology including
decreasing age at diagnosis [14], longer duration, and improved survival for those with
DM [15] means that the impact of these factors on the onset of MI in people with DM is
poorly characterized. We therefore analyzed temporal trends in incidence rates of
hospitalized MI and CHD between 1998 and 2010 in adults with and without DM.
Second, we determined whether the risk of incident MI and CHD in people with versus
without DM changed during this period.

6.3 METHODS

6.3.1 DATA SOURCE

The population of WA was 2.3 million in 2010 [16], and is representative of the
Australian population in demographic and health economic indicators [17]. WA has a
mixed public and private health system. The major tertiary hospitals are situated in the
capital city, Perth, where the majority of acute coronary care and all invasive
revascularization services are provided. Data for this study were obtained from the
Hospital Morbidity Data System and Mortality Registrations, with links established
through the WA Data Linkage System. This system centrally links core health
administrative datasets by probabilistic matching on key variables (name, sex, date of
birth, and address) with manual checking of uncertain links, and >99% accuracy
reported for this process [18]. Data available included hospital inpatient information on patient demographics, principal diagnosis at discharge, secondary diagnoses, and inpatient procedures. The data set contained all CVD and diabetes morbidity and death records for patients aged 35 to 84 years from 1985 to 2010. Approval for this study was obtained from the ethics committees of The University of Western Australia and the WA Department of Health.

6.3.2 IDENTIFICATION OF INCIDENT MI AND CHD

All patients admitted to hospital in WA between 1998 and 2010 with a principal discharge diagnosis of MI (International Classification of Diseases-Ninth Revision [ICD-9]-Clinical Modification 410; ICD-10-Australian Modification I21, I22) were identified. Incident MI events were defined as those with no prior MI admissions recorded in the principal or 20 secondary diagnosis fields using a fixed 13-year clearance period from each MI admission, which would correctly identify the majority of prior MI events [19]. The validity for identifying MI in linked hospital data has been tested in WA by validating MI recorded in hospital morbidity data against an algorithm based on American Heart Association criteria for MI diagnosis, with clinical data derived from medical and pathology records [20]. Decreasing sensitivity in the older age group was the reason for exclusion of >85-year olds. Patients presenting with MI who died in the emergency department were not included in the study. Incident CHD events were similarly identified from the principal diagnosis field and included hospitalization for any of MI, unstable or stable angina, or other acute or chronic CHD (410–414, I20–I25), where there was no CHD admission coded in the previous 13 years.

6.3.3 IDENTIFICATION OF DM STATUS

DM was identified from any diagnosis field in the linked dataset (ICD-9-CM 250, ICD-10-AM E10–E14). Incident MI and CHD cases were classified as having DM where there was ≥1 hospital admission in the 13 years before, or in the 28-days after, the incident admission. This method of defining DM status was evaluated by comparing DM recorded in hospital morbidity data with DM identified from medical records for CHD patients in 1998 and 2002 to 2004. When DM status was identified from the index CHD admission only, sensitivity was significantly lower in the later period compared with 1998. Use of an extended lookback improved the accuracy of identifying DM
(sensitivity 93% and 90% in 1998 and 2002 to 2004, respectively; positive predictive value, 92% in both periods) [21].

6.3.4 PATIENT CHARACTERISTICS

Baseline characteristics and comorbidities for patients with incident MI and CHD were identified from the linked dataset using all diagnosis fields. A 13-year lookback period including each incident event was used to identify hypertension (ICD-10-AM I10–I15/ICD-9-CM equivalent), heart failure (I50), atrial fibrillation (I48), prior stroke (I60–I64), peripheral arterial disease (I70–I79), chronic kidney disease (Australian Institute of Health and Welfare definition) [22], chronic obstructive pulmonary disease (J40–J47), and cancer (C00–D48). Patients were identified as undergoing a revascularization procedure (percutaneous coronary intervention or coronary artery bypass grafting) where it was recorded on or within 30 days of the incident MI admission date in any of the 11 procedure fields.

Patients with incident MI with admissions for angina, or other acute or chronic ischemic heart disease (ICD-9 411–414, ICD-10-AM I20, I23–I25) in the 13 years before the incident MI were classified with prior CHD history. This excluded admissions in the 28 days immediately preceding the incident admission, as these were transfers or deemed to be related to the incident event. Patients with incident MI with prior percutaneous coronary intervention or coronary artery bypass grafting were similarly identified.

Patients were classified as having ST-segment elevation MI (STEMI) according to ICD-10-AM codes I21.0–I21.3.

6.3.5 STATISTICAL ANALYSIS

All analyses were conducted separately by sex. Trends in patient characteristics were assessed separately for patients with and without DM from unadjusted linear and logistic regression models for continuous and categorical variables, respectively, and similarly for differences in the overall prevalence of characteristics between patients with DM and without DM.

Annual incidence rates of MI were calculated using counts of incident MI in each group for each calendar year as the numerator, and the at-risk population in each year for the denominator. To estimate the at-risk population, annual counts of prevalent diabetic cases were calculated by identifying people with any hospital admission for DM using a 13-year lookback from 30th June in each study year, and who were alive at this date.
People with a prior history of MI were excluded from counts of annual DM prevalence. The annual counts of prevalent DM cases with no MI history were the denominator for MI incidence rates in people with DM. For rates in the non-DM population, the prevalent DM population was subtracted from the whole WA population in each study year [16]. The same method was used to determine the at-risk population for CHD incidence. Rates were standardized using the direct method by 5-year age group for overall and age-specific rates, with the population of WA in 2010 as the standard population. Annual percentage changes were estimated using Poisson regression, adjusting for 5-year age group, and calculated from the exponential of the β-coefficient for calendar year. Annual age-adjusted incidence rate ratios (IRR) in patients with versus without DM were calculated, and are presented for 1998 and 2010. The age-adjusted trend in IRRs was estimated for the whole study period, using a model which included 5-year age group, DM status, calendar year and an interaction term (DM status \( \times \) calendar year). Statistical significance levels were set at \( P < 0.05 \) and SAS v9.4 (Cary, NC) used for all statistical analyses.

6.4 RESULTS

6.4.1 PATIENT CHARACTERISTICS AND COMORBIDITIES

Tables 6.1 and 6.2 show the trends in patient characteristics and comorbidities separately for patients with and without DM at incident MI. There were 26,610 incident MI admissions in WA from 1998 to 2010, with DM cases comprising 22.8% in men and 29.6% in women. The mean age at first MI presentation was higher in men with DM but not in women relative to their non-DM counterparts. There was no significant fall in mean age during the study period in patients with DM, whereas it decreased in people without DM (men, \(-0.6\) years; \(P < 0.05\) and women, \(-2.2\) years; \(P < 0.0001\)). Indigenous Australians were significantly over-represented in men and women with versus without DM (\(P < 0.0001\)).

Comorbidity levels at incident MI were significantly higher in patients with DM (\(P < 0.05\) for all overall comparisons with non-DM patients, Tables 6.1 and 6.2). Hypertension increased in both groups (\(P < 0.0001\), and the proportion of patients with heart failure was 2- to 3-fold higher in those with DM compared with those without, although the prevalence fell in both. Trends in concomitant chronic kidney disease were contrasting, with significant increases in patients with DM (20.4%–26.2% in men and 22.0%–29.3% in women) whereas falling in patients with no DM (8.8%–5.6% in men).
and 9.2%–6.4% in women). Prior CHD history was increasingly more prevalent in patients with DM. The proportion of patients with incident MI undergoing percutaneous coronary intervention increased significantly, although levels at the end of the study remained higher in non-DM men (62.9% versus 46.2%) and women (42.9% versus 35.8%). There was a significant reduction in the recording of STEMI in men and women in both groups ($P<0.0001$ for all groups).

When incident hospitalized CHD was analyzed, 56,142 cases were identified. Compared with incident MI cases only, a lower proportion was classified with DM (18.0% in men and 21.7% in women; Supplementary Table S6.1). Mean age at incident CHD was on average 2 to 3 years younger than observed for incident MI. Trends in characteristics and comorbidities were generally similar to those seen for incident MI, except for a significantly decreasing proportion of patients with DM and without DM undergoing coronary artery bypass grafting at incident admission (Supplementary Table S6.1).

### 6.4.2 AGE-STANDARDIZED TRENDS

Age-standardized rates of incident MI declined significantly in patients with DM (Figure 6.1), representing an average age-adjusted annual decline of $-2.9\%$ (95% confidence interval [CI], $-3.7$ to $-2.1$) in men and $-3.8\%$ (95% CI, $-4.8$ to $-2.1$) in women (Table 6.3). Assuming a log-linear decline, the age-adjusted risk of an incident MI in patients with DM in 2010 compared with 1998 was 0.65 (95% CI, 0.55–0.76) in men and 0.57 (95% CI, 0.46–0.71) in women, representing overall falls of 35% and 43%, respectively. Incidence rates for MI in patients without DM were unchanged, and the equivalent age-adjusted risk for the study period in non-DM patients was 0.97 (95% CI, 0.89–1.05) and 0.95 (0.84–1.08) in men and women respectively.

Incidence rates of CHD fell significantly in patients with DM ($-3.8%/y$ in men and $-4.7%/y$ in women) and also declined significantly in the non-DM group, although to a lesser extent (Table 6.4; Figure 6.2).

Age-adjusted IRRs for MI in men with versus without DM fell from 4.5 (95% CI, 4.2–4.8) in 1998 to 3.1 (95% CI, 2.9–3.3; $P<0.0001$ for trend) by 2010. There was a similar reduction in IRR in women with DM (6.0; 95% CI, 5.4–6.6 in 1998 and 3.8; 95% CI, 3.5–4.1; $P<0.0001$) in 2010) (Table 6.3). There were similar reductions in the IRR for CHD in patients with versus without DM during the study (Table 6.4).
CHAPTER 6. DIABETES AND MYOCARDIAL INFARCTION INCIDENCE

**Figure 6.1.** Age-standardized myocardial infarction incidence rates in adults aged 35 to 84 years with and without diabetes mellitus (DM) in Western Australia, 1998 to 2010. Bars represent 95% confidence intervals.

**Figure 6.2.** Age-standardized coronary heart disease incidence rates in adults aged 35 to 84 years with and without diabetes mellitus (DM) in Western Australia, 1998 to 2010. Bars represent 95% confidence intervals.
6.4.3 AGE-SPECIFIC TRENDS

Incidence rates of MI fell significantly in patients with DM in 55- to 69- and 70- to 84-year olds, with average annual declines of 3% to 5% across each age and sex grouping (Table 6.3). For those without DM, significant reductions were only apparent in 70- to 84-year olds (men, –1.3%/y and women, –1.5%/y). Rates in the 35- to 54-year-old age group with DM were unchanged across the study period, and increased in the non-DM group by 1.1%/y (95% CI, +0.3 to +1.9) in men and 2.3%/y (95% CI, +0.5 to +4.2) in women (Table 6.3; Figure 6.3). Age-specific trends for CHD incidence were in contrast to the MI trends, with significant declines in all age groups except for 35- to 54-year-old women without DM (+1.1%/y; 95% CI, +0.1 to +2.1).

Incidence rates were high in 35- to 54-year olds with DM, with age-specific IRRs for MI and CHD in those with DM 2- to 3-fold higher in the 35- to 54-year age group relative to older age groups (Figure 6.3A and 6.3C). There was a reduction in IRRs between 1998 and 2010 in all age groups, although not significantly so for 35- to 54-year-old men ($P=0.23$ for incident MI and $P=0.42$ for incident CHD; Tables 6.3 and 6.4).
CHAPTER 6. DIABETES AND MYOCARDIAL INFARCTION INCIDENCE

Figure 6.3. Age-specific myocardial infarction incidence rates in men with diabetes mellitus (A), men with no diabetes mellitus (B), women with diabetes mellitus (C), and women without diabetes mellitus (D) in Western Australia, 1998 to 2010.
### Table 6.1. Characteristics of patients (men) with an incident myocardial infarction aged 35 to 84 years, stratified by diabetes mellitus status, in Western Australia, 1998 to 2010.

<table>
<thead>
<tr>
<th></th>
<th>Diabetes Mellitus</th>
<th>No Diabetes Mellitus</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>65.0 (11.2)</td>
<td>64.3 (11.5)</td>
<td>65.8 (11.9)</td>
</tr>
<tr>
<td>Indigenous</td>
<td>6.9 (2.6)</td>
<td>9.4 (2.2)</td>
<td>8.2 (2.7)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>21.5 (31.6)</td>
<td>38.4 (46.4)</td>
<td>40.8 (54.7)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>58.3 (38.1)</td>
<td>66.4 (38.4)</td>
<td>75.8 (46.7)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>30.1 (14.2)</td>
<td>37.7 (12.8)</td>
<td>35.9 (13.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16.1 (10.9)</td>
<td>18.1 (12.4)</td>
<td>19.4 (12.6)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>6.2 (3.1)</td>
<td>6.3 (2.6)</td>
<td>6.1 (2.0)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>18.1 (16.1)</td>
<td>15.7 (8.0)</td>
<td>15.2 (7.4)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>20.4 (8.8)</td>
<td>21.8 (6.6)</td>
<td>23.6 (6.8)</td>
</tr>
<tr>
<td>Cancer</td>
<td>19.2 (16.1)</td>
<td>22.6 (19.3)</td>
<td>26.5 (21.8)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>17.6 (9.5)</td>
<td>11.8 (8.5)</td>
<td>11.5 (6.3)</td>
</tr>
<tr>
<td>Prior coronary heart disease</td>
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<td>32.2 (17.9)</td>
<td>33.2 (19.8)</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>8.7 (5.8)</td>
<td>10.5 (5.9)</td>
<td>11.7 (6.7)</td>
</tr>
<tr>
<td>ST-segment elevation MI</td>
<td>61.9 (67.7)</td>
<td>43.7 (51.9)</td>
<td>32.4 (43.0)</td>
</tr>
</tbody>
</table>

Categorical variables are shown as percentage. MI indicates myocardial infarction.

* P value represents period trend in patient characteristics, from linear regression models for continuous variables, and logistic regression models for categorical variables, separately for patients with and without diabetes mellitus.
### Table 6.2. Characteristics of Patients (Women) with an Incident Myocardial Infarction Aged 35 to 84 Years, Stratified by Diabetes Mellitus Status, in Western Australia, 1998 to 2010.

<table>
<thead>
<tr>
<th></th>
<th>Diabetes Mellitus</th>
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<th>Trend P value*</th>
<th>Diabetes Mellitus</th>
<th>No Diabetes Mellitus</th>
<th>Trend P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>68.3 (11.3)</td>
<td>68.5 (11.8)</td>
<td>68.5 (12.0)</td>
<td>68.1 (11.7)</td>
<td>69.6 (11.5)</td>
<td>69.6 (11.6)</td>
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<tr>
<td>Indigenous</td>
<td>12.6</td>
<td>12.4</td>
<td>13.4</td>
<td>16.4</td>
<td>23.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Percutaneous coronary</td>
<td>15.9</td>
<td>26.6</td>
<td>37.3</td>
<td>35.8</td>
<td>&lt;0.0001</td>
<td>23.2</td>
</tr>
<tr>
<td>intervention</td>
<td>Coronary artery</td>
<td>5.3</td>
<td>5.7</td>
<td>5.9</td>
<td>7.5</td>
<td>0.14</td>
</tr>
<tr>
<td>bypass grafting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>69.8</td>
<td>80.2</td>
<td>84.7</td>
<td>88.3</td>
<td>&lt;0.0001</td>
<td>53.6</td>
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<td>Heart failure</td>
<td>42.6</td>
<td>40.7</td>
<td>36.5</td>
<td>33.2</td>
<td>&lt;0.05</td>
<td>23.1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16.7</td>
<td>22.3</td>
<td>21.8</td>
<td>17.6</td>
<td>0.61</td>
<td>16.2</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>7.6</td>
<td>8.4</td>
<td>7.7</td>
<td>6.8</td>
<td>0.54</td>
<td>4.5</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>15.6</td>
<td>14.8</td>
<td>15.5</td>
<td>13.4</td>
<td>0.37</td>
<td>9.7</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>22.0</td>
<td>22.6</td>
<td>29.1</td>
<td>29.3</td>
<td>&lt;0.05</td>
<td>9.2</td>
</tr>
<tr>
<td>Cancer</td>
<td>25.4</td>
<td>26.9</td>
<td>28.1</td>
<td>30.2</td>
<td>0.06</td>
<td>19.8</td>
</tr>
<tr>
<td>Chronic obstructive</td>
<td>19.8</td>
<td>19.6</td>
<td>16.0</td>
<td>18.6</td>
<td>0.32</td>
<td>17.8</td>
</tr>
<tr>
<td>pulmonary disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior coronary heart disease</td>
<td>31.4</td>
<td>35.3</td>
<td>35.8</td>
<td>35.1</td>
<td>0.17</td>
<td>20.9</td>
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<td>Prior revascularization</td>
<td>6.6</td>
<td>8.1</td>
<td>11.9</td>
<td>11.2</td>
<td>&lt;0.05</td>
<td>3.7</td>
</tr>
<tr>
<td>ST-segment elevation MI</td>
<td>56.2</td>
<td>36.3</td>
<td>30.6</td>
<td>22.7</td>
<td>&lt;0.0001</td>
<td>60.6</td>
</tr>
</tbody>
</table>

Categorical variables are shown as percentage. MI indicates myocardial infarction.

*P value represents period trend in patient characteristics, from linear regression models for continuous variables, and logistic regression models for categorical variables, separately for patients with and without diabetes mellitus.
### Table 6.3. Age-adjusted trends in myocardial infarction incidence rates in patients with and without diabetes mellitus, aged 35 to 84 years, 1998–2010.

| Age group, y | Diabetes Mellitus | | | No Diabetes Mellitus | | | | Incidence rate ratios | | | |
|-------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| | Incident cases, n | Person-years | Average annual ASR/100 000 | Annual % change (95% CI) | Incident cases, n | Person-years | Average annual ASR/100 000 | Annual % change (95% CI) | 1998 | 2010 | P value for IRR trend* |
| Men | | | | | | | | | | | |
| 35–84 y | 4254 | 279 944 | 1390.2 | −2.9% (−3.7, −2.1) | 14,416 | 6 008 302 | 270.1 | −0.1% (−0.6, +0.3) | 4.5 | 3.1 | <0.0001 |
| Age group, y | | | | | | | | | | | |
| 35–54 | 877 | 63 852 | 1222.9 | −0.3% (−2.1, +1.6) | 4273 | 3 766 009 | 115.0 | +1.1% (9.1, 12.3) | 10.6 | 9.2 | 0.23 |
| 55–69 | 1706 | 113 954 | 1578.2 | −4.4% (5.6, −3.2) | 5713 | 1 616 243 | 357.6 | −0.1% (4.9, 6.1) | 5.4 | 3.2 | <0.0001 |
| 70–84 | 1671 | 102 138 | 1681.7 | −2.8% (4.1, −1.5) | 4430 | 626 050 | 732.8 | −1.3% (2.3, 2.8) | 2.5 | 2.0 | 0.03 |
| Women | | | | | | | | | | | |
| 35–84 y | 2348 | 264 229 | 687.6 | −3.8% (4.8, −2.1) | 5592 | 6 194 029 | 94.7 | −0.2% (5.4, 6.6) | 6.0 | 3.8 | <0.0001 |
| Age group, y | | | | | | | | | | | |
| 35–54 | 349 | 63 988 | 516.7 | −0.4% (−3.3, +2.5) | 861 | 3 748 105 | 23.0 | +2.3% (19.0, 31.8) | 24.6 | 17.2 | 0.09 |
| 55–69 | 715 | 93 718 | 771.7 | −4.7% (−6.6, −2.8) | 1644 | 1 642 327 | 99.3 | +1.0% (8.6, 12.3) | 10.3 | 5.2 | <0.0001 |
| 70–84 | 1284 | 106 523 | 1224.3 | −4.1% (−5.5, −2.7) | 3153 | 803 597 | 388.6 | −1.5% (3.2, 4.1) | 3.6 | 2.6 | <0.01 |

ASR, age-standardized rate; CI, confidence interval; and IRR, incidence rate ratio.

*P value for the trend in annual age-adjusted incidence rate ratios for 1998 to 2010, estimated from Poisson regression models including 5-year age group, diabetes mellitus status, calendar year, and diabetes mellitus x calendar year.

<table>
<thead>
<tr>
<th>Age group, y</th>
<th>Incident cases, n</th>
<th>Person-years</th>
<th>Average annual ASR /100 000</th>
<th>Annual % change (95% CI)</th>
<th>Incident cases, n</th>
<th>Person-years</th>
<th>Average annual ASR /100 000</th>
<th>Annual % change (95% CI)</th>
<th>1998</th>
<th>2010</th>
<th>P value for IRR trend*</th>
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<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–84 y</td>
<td>6824</td>
<td>210 307</td>
<td>2965</td>
<td>−3.8</td>
<td>30 769</td>
<td>5 743 781</td>
<td>636</td>
<td>−1.5</td>
<td>4.2</td>
<td>3.0</td>
<td>&lt;0.0001</td>
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<td>3842</td>
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<td>920</td>
<td>5 101</td>
<td>−1.3</td>
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<td>2223</td>
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<td>6061</td>
<td>718 065</td>
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<td>3.0</td>
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</tr>
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<td>−4.7</td>
<td>14 519</td>
<td>6 042 684</td>
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<td>5.3</td>
<td>3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
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<td>1269</td>
<td>2940</td>
<td>−3.0</td>
<td>3 733 302</td>
<td>80</td>
<td>18 648</td>
<td>+1.1</td>
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</tr>
<tr>
<td>55–69</td>
<td>1528</td>
<td>78 991</td>
<td>1998</td>
<td>−5.8</td>
<td>1 591 317</td>
<td>354</td>
<td>6 867</td>
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<td>80 694</td>
<td>2223</td>
<td>−4.4</td>
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<td>&lt;0.01</td>
</tr>
</tbody>
</table>

ASR, age-standardized rate; CI, confidence interval; and IRR, incidence rate ratio.

*P value for the trend in annual age-adjusted incidence rate ratios for 1998 to 2010, estimated from Poisson regression models including 5-year age group, diabetes mellitus status, calendar year, and diabetes mellitus x calendar year.
6.5 DISCUSSION

We found a substantial reduction in MI incidence rates of 35% in men and 43% in women with DM over a 13-year period in a whole-population setting. This finding is supported by concordant falls in incident hospitalized CHD in people with DM. These trends occurred despite higher levels of comorbidity and some adverse risk factor trends in these patients. However in people without DM, incident MI rates were unchanged and CHD incidence reduced at a lesser rate than in patients with DM. The age-adjusted risk of an incident MI in adults with versus without DM fell by nearly half, although some of the improvement could be attributed to the limited decline in MI incidence rates in non-DM patients. Overall trends in patients with DM were driven by reductions in rates in 55- to 84-year olds, whereas only 70- to 84-year olds demonstrated declining rates in the non-DM group.

Uniquely, we have shown that population incidence rates of MI and CHD have fallen more quickly in adults with versus without DM. There is evidence that people with DM have experienced smaller or similar improvements in mortality [15, 23]; however data are limited for trends in nonfatal events. Our results are consistent with a declining 10-year risk for developing CHD in people with DM in the National Health and Nutrition Examination Study (NHANES) cohort [24], and the Framingham Heart Study has demonstrated comparable reductions in CVD incidence in people with and without DM over a 50-year period [8]. Contrasting trends are reported from European populations, with MI incidence unchanged in those with DM in a Swedish cohort [7] but increasing in men and decreasing in women with DM in a German setting [6]. Differing upper age ranges (64 and 74 years, respectively) may have contributed to these contrasting findings. Our study showed that MI incidence in people with DM has declined in WA, concurrent with an increasing population prevalence of DM. However, if the increase is mainly because of the inclusion of less severe and lower risk cases, this may explain some of the declining MI incidence in people with DM. Our analysis of CHD incidence, which provides a broader representation of disease incidence and prevention efforts, confirms a real downward trend in both men and women with DM.

Our findings occurred during a period of major change in the management of DM. Clinical trials have shown that intensive glycemic control results in significant reductions in microvascular outcomes [13]. Evidence is now emerging that this approach also reduces macrovascular outcomes [25], with patients with DM intensively
treated with sulfonylurea/insulin or metformin demonstrating a 15% and 33% reduction, respectively, in the 10-year risk of MI [26]. In Australia, increasing rates of oral hypoglycemic use, particularly metformin, are reported in national statistics [27]. Reductions in HbA1c in type 2 diabetics have been shown in the local Fremantle Diabetes Study [28], and during a 4-year period in the Fenofibrate Intervention and Event Lowering Diabetes (FIELD) study [29], but these changes were associated with intensification of glycemic therapy. This changing management approach is a potential contributor to the favorable trends seen in people with DM in our population.

Concomitantly there has been a shift toward more aggressive control of cardiovascular risk factors in patients with DM [12, 30]. In Australia, guidelines were modified in 2003 to recommend pharmacological treatment for patients with DM and no manifest CVD if blood pressure was >130/85 mmHg and total cholesterol >3.5 mmol/L [31]. National prescribing criteria were changed in 2006 to subsidize statins for all patients with DM aged ≥60 years irrespective of lipid levels and for lower risk patients with DM where total cholesterol was >5.5 mmol/L [32]. Modeling of these changes suggests that provision of statins to normolipidemic patients with DM would prevent >3200 major cardiovascular events during a 4-year period [33]. Improving cardiovascular risk management in patients with DM is suggested by a national audit of specialist DM centres between 1998/99 and 2011, which showed an increase in the use of antihypertensive (36%–57%) and lipid-lowering therapies (19%–60%) in people with DM [34], and an increasing proportion of patients with DM in primary care meeting blood pressure and lipid targets [35]. These data may provide indirect evidence of the effects of improving cardiovascular risk factor management in this patient group.

The difference between trends in MI and CHD incidence in non-DM patients may be related to changes in the diagnostic algorithm for MI. The introduction of troponin testing for MI diagnosis attenuated declines in MI incidence [36] and hospitalization rates [4] because of the increased number of non-STEMI cases diagnosed. Although the coding of MI type in administrative data has not been fully tested, we identified similar large declines in the proportion of MI recorded as STEMI in adults with and without DM. Paradoxically, additional non-STEMI cases detected by troponin testing are more often in people with DM [37], and people with DM in the general population are more likely to have elevated levels of troponin because of the presence of subclinical microvascular disease [38]. This suggests that the trends in patients with DM presented
in the current study may actually represent an attenuation of larger downward trends in MI incidence. The increasing detection of non-STEMI could also affect the identification of the at-risk populations, leading to a lower risk MI-free population in the later part of the study. This effect may be greater in the DM population; however, the trend in CHD incidence, where the impact of troponin is reduced, lends weight to a real decline in MI incidence in patients with DM.

The reduction in MI incidence in patients with DM occurred in the context of an increasing proportion with previously diagnosed CHD. Although this might reflect the greater likelihood of hospitalization in diabetics [39], it is more likely because of increased diagnosis and receipt of treatment for CHD in these patients. For example, the proportion of patients with DM undergoing revascularization before first MI was double that of non-DM patients. Disparity in the use of percutaneous coronary intervention after incident MI in DM versus non-DM patients remained apparent. This has been noted previously in registry data [40] and may persist because of the perceived higher risk profile of these patients, particularly for women. DM is also a major risk factor for heart failure in people with acute CHD [41] and was found to be twice as common in patients with DM and incident MI, but declined significantly during the period. In contrast, chronic kidney disease in patients with DM and first MI increased to ≈30% by the end of the period, 5× higher than in patients with MI without DM, highlighting targets for treatment and reducing risk in these patients. Lower levels of guideline-recommended pharmacological and invasive treatments continue to be reported for patients with DM even after manifest CVD [40, 42].

We have shown previously that incidence rates of MI have increased in women and remained unchanged in men aged 35 to 54 years [43], consistent with adverse trends in younger people elsewhere [44]. Although MI incidence rates were unchanged in 35- to 54-year olds with DM and increasing in those without DM, encouragingly, CHD incidence declined. The exception was in women without DM where rates increased. Notably there was a trend towards incident MI occurring at a younger age in this group. A possible explanation is that changes in prevalence of other risk factors such as smoking are associated with these trends; there may also be a higher proportion of undiagnosed diabetics because younger people have less contact with the health system [39], or a higher threshold before diagnosis of type 2 DM is made in this age group. Further exploration of the impact of cardiovascular risk factors, and the diagnosis and
management of DM in younger people is needed to help understand these apparent incongruous trends.

6.5.1 LIMITATIONS

We have not included out of hospital deaths attributed to MI or CHD, as we were unable to ascertain the DM status for deaths with no prior hospitalization history from our data set. We have shown that trends would not be affected by the small degree of misclassification of DM status because of the use of an extended lookback period to determine DM status [21]. However, there may still be a degree of undiagnosed diabetes even after presentation to hospital, because of reluctance by doctors to label a patient in the acute setting with DM. This inclusion of patients with MI and DM in the non-DM group may overestimate rates in people without DM, but would only affect trends if there were changes in this practice over time. Information on comorbidities was obtained from hospitalization data, and therefore some cardiovascular risk factor data were not available. Smoking and dyslipidaemia are poorly recorded in hospital morbidity data and were not included in our study. Changes in coding standards over time can also impact the accuracy of comorbidity recording, but this is reduced by the use of a lookback period to identify these conditions.

DM prevalence is underestimated from hospital data because ascertainment of the at-risk DM population relies on a person with DM being hospitalized during the 13-year lookback period. Less severe cases of DM treated in the community are more likely to be misclassified as non-diabetic using this method. Therefore the incidence rates calculated in this study may overestimate true rates in patients with DM because a smaller and higher risk population is used in the denominator. However, correct classification of the diabetic population is potentially greater than for other conditions because of the high hospitalization rates in these patients, for example, 80% of patients with DM identified from a local primary care DM register were admitted to hospital within 10 years of diagnosis [39]. If trends in hospital-identified DM prevalence are reflective of population-based DM trends, the use of this data source for calculating the at-risk population for incidence rates will provide reliable trend estimates. As a sensitivity analysis, we calculated age-adjusted trends for hospital-identified DM prevalence, and compared this with state-based self-reported survey data [10] for 35- to 84-year olds. This was undertaken for 2003 to 2010 because of the availability of the survey data for that period. Similar upward trends in DM prevalence were seen for both
data sources (average increase of 2%/y), showing that hospital morbidity data are a reasonable data source for obtaining denominators for population-based rates. However, comparison of these data sources for >85-year olds showed that this age group was over-represented in hospital relative to survey data, in contrary to the underestimation in other age groups, and confirmed the exclusion of this age group from our analysis.

6.6 CONCLUSION

This study has demonstrated substantial downward trends in incidence rates of hospitalized MI and CHD in adults with DM and a reduction in the excess risk associated with DM for these major cardiovascular events. These changes have occurred during a period of significant change in the treatment and CVD risk management for patients with DM, suggesting that such prevention approaches have translated positively from clinical trials and may be particularly effective in a whole-population setting. The attenuation of MI incidence rates in people without DM deserves further attention because of the sustained flattening of rates beyond the initial introduction of troponin assays. Importantly, we have shown that the limited improvements in MI incidence in young adults occur in people with and without DM, meaning that the impact of other clinical and risk factors needs to be considered to address these unfavorable trends.
WHAT IS KNOWN

- The risk of a myocardial infarction is 2-4 times greater in people with diabetes mellitus than in those without.
- Trends in the incidence of myocardial infarction and coronary heart disease are an indicator of the effect of prevention approaches, yet there are limited data detailing these trends in people with diabetes mellitus at a population level.

WHAT THIS ARTICLE ADDS

- There was a substantial reduction in incidence rates of hospitalized myocardial infarction and coronary heart disease in men and women with diabetes mellitus in a whole population setting over a 13-year period.
- In contrast, the decline in the incidence of myocardial infarction in people without diabetes mellitus was limited, however, incidence rates of hospitalized coronary heart disease fell during the same period.
- These results highlight the likely impacts of changes in the management of people with diabetes mellitus at a population level. Despite these trends, the risk of an incident myocardial infarction remained ~2 times higher in people with versus without diabetes mellitus at the end of the study period.

6.7 ACKNOWLEDGEMENTS

The authors wish to thank the staff at the Western Australian Data Linkage Branch, the Department of Health Inpatient Data Collections and Registrar General, and the Epidemiology Branch (WA Department of Health) for the provision of data.
6.8 REFERENCES


33. Page MM, Sanfilippo FM, Geelhoed EA, Briffa TG, Hobbs MST. Earlier translation of evidence into public subsidy may prevent morbidity and mortality: an example using


35. APPC. Australian Primary Care Collaboratives Program 2011. 
http://www.apcc.org.au/about_the_APCC/program_results/


### 6.9 SUPPORTING INFORMATION

**Supplementary Table 6.1. Characteristics of patients with incident coronary heart disease aged 35 to 84 years, stratified by diabetes mellitus status in Western Australia, 1998 to 2010.**

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## Chapter 6. Diabetes and Myocardial Infarction Incidence

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Categorical variables are shown as percentage.

*P value represents period trend in patient characteristics, from linear regression models for continuous variables, and logistic regression models for categorical variables, separately for patients with and without diabetes mellitus.

†Procedures occurring during admission or within 30 days of hospitalization for the incident myocardial infarction. SD, standard deviation.
CHAPTER 7. CHANGING 30-DAY CASE FATALITY FOLLOWING INCIDENT MYOCARDIAL INFARCTION IN PEOPLE WITH DIABETES

PUBLISHED PAPER

This chapter is the published version of the following paper:

Improving 30-day case fatality after incident myocardial infarction in people with diabetes between 1998 and 2010


Lee Nedkoff¹, Matthew Knuiman¹, Joseph Hung² and Tom G Briffa¹

¹ School of Population Health, The University of Western Australia

² School of Medicine and Pharmacology, Sir Charles Gairdner Hospital Unit, The University of Western Australia

Keywords: Diabetes; Acute myocardial infarction; Epidemiology; Case fatality; Trends
PREAMBLE

The previous study demonstrated that the incidence of hospitalised MI and CHD has declined significantly in the diabetic population in WA in a contemporary period. However it was noticeable that the proportion of incident cases with major comorbidities, and particularly prior CHD hospitalisations in MI patients, increased during the study period. Additionally, despite the increase in the proportion of diabetic patients undergoing coronary revascularisation, a differential in PCI rates still remained.

The study in this chapter therefore aimed to determine whether differences between diabetic and non-diabetic patients for early case fatality following MI persist, or whether trends in the Australian context are consistent with findings emerging from studies reported elsewhere. The findings of the previous chapter made this of particular interest because of the potential for the changing comorbidity levels to negatively impact case fatality in diabetic people.
7.1 ABSTRACT

Objective: To compare population-level trends in 30-day case fatality following incident myocardial infarction (MI) in people with diabetes and those without diabetes.

Methods: We identified all hospitalised incident MIs in 35–84 year olds from the Western Australian Data Linkage System for 1998–2010, stratified by diabetes status. Crude and age- and sex-standardised 30-day case fatality were estimated, and age- and sex-adjusted trends calculated from logistic regression. We calculated the trend in risk of 30-day death associated with diabetes from multivariable logistic regression, adjusting for demographics, comorbidities and MI type.

Results: 26,610 hospitalised incident MI cases were identified, 24.8% of whom had diabetes. The prevalence of heart failure fell in people with diabetes, concurrent with increasing chronic kidney disease and prior coronary heart disease, and increasing levels of evidence-based therapies. Case fatality in people with diabetes fell from 11.65% in 1998–2001, to 3.96% by 2008–2010. Age- and sex-standardised case fatality declined at a greater rate in those with diabetes (−10.6%/year, 95% CI −12.8% to −8.2%) compared to non-diabetics (−6.9%/year, 95% CI −8.3% to −5.3%; interaction p=0.005). The adjusted risk of 30-day death after incident MI was 1.23 times higher in diabetics than non-diabetics in 1998–2001 (95% CI 1.01 to 1.50), but was lower by 2008–2010 (OR 0.64, 95% CI 0.46 to 0.88).

Conclusions: Greater improvements in 30-day case fatality following incident MI in people with diabetes during the 13-year study period has led to diabetes no longer being an independent predictor of early death following incident MI by 2008–2010.

7.2 INTRODUCTION

There is an elevated risk of mortality following myocardial infarction (MI) in people with diabetes [1]. Poorer short-term outcomes are associated with disparities in the use of evidence-based therapies and more adverse clinical risk characteristics [2, 3]. While early case fatality has consistently declined in MI patients over the past two decades [4–6], there is emerging evidence that this trend may be similar in people with diabetes [7–10]. Population-level trends in post-MI case fatality indicate the impact of acute care and disease severity, yet there is limited population-level data for people with diabetes. The use of evidence-based medications and acute revascularisation procedures are endorsed by best practice guidelines [11], yet people with diabetes are less likely to
receive such therapies [2, 3]. Background trends in major cardiovascular risk factor prevalence may have a role in determining 30-day outcomes because of their potential impact on atherosclerotic disease severity, and hence, the extent of myocardial damage incurred. Additionally, the greater detection of non-ST elevation MI (NSTEMI) due to increasingly sensitive troponin assays, implying smaller infarcts, may also complicate this picture [5].

Previously, we found a greater decline in MI incidence rates in diabetics than non-diabetics at a population level between 1998 and 2010, concurrent with an increasing prevalence of diabetes in the Western Australian (WA) population [12]. These trends may be associated with substantially better preventive management for patients with diabetes during this contemporary period. Therefore, this study aimed to compare population trends in 30-day case fatality following incident MI in people with diabetes versus without diabetes between 1998 and 2010, and to determine whether the risk of 30-day death associated with diabetes following an incident MI has changed over time.

7.3 METHODS

7.3.1 STUDY SETTING

This study used state-based linked health data from the WA Data Linkage System (WADLS). WA is representative of national sociodemographic and health indicators [13], with a population of 2.3 million in 2010 [14]. The majority of acute coronary care and all invasive revascularisation procedures are undertaken in the tertiary hospitals (public and private) situated in the capital city, Perth. The data for this study were obtained from two core statutory datasets—the Hospital Morbidity Data Collection and Mortality Register, which are linked by the WADLS using probabilistic matching. The single person-based linked dataset used for this study contained all records for any patient hospitalised or who died from cardiovascular disease or diabetes in WA between 1998 and 2010. Variables available included demographic information, principal and 20 secondary diagnosis fields, inpatient procedures, date and cause of death and admitting hospital location (metropolitan/rural).

Approval for this study was obtained from the ethics committees of The University of Western Australia and WA Department of Health.
CHAPTER 7. DIABETES AND 30-DAY CASE FATALITY FOLLOWING MYOCARDIAL INFARCTION

7.3.2 IDENTIFICATION OF INCIDENT MI

MI patients were identified from the linked dataset if recorded in the principal diagnosis field (ICD-9 410/ICD-10-AM I21, I22), and considered incident if there was no history of hospitalisation for MI recorded in any diagnosis field in the previous 13 years. Any records deemed to be interhospital transfers were classified as part of the incident admission. This study included only incident MI patients admitted to hospital, and excluded those who died out of hospital or in the emergency department. Patients were included if aged 35–84 years, with the upper age limit imposed because of decreasing sensitivity for MI from hospital morbidity data in the very elderly [15]. Thirty-day deaths were identified from the linked dataset where the recorded date of death was within 30 days of the incident MI admission date.

7.3.3 DIABETES STATUS

Patients with incident MI were classified with diabetes if recorded in any diagnosis field in the 13 years prior to or during the incident MI admission (ICD-9 250/ICD-10-AM E10–E14). This method of defining diabetes status using WA hospital morbidity data is reliable for CHD patients (sensitivity 93% and 90% in 1998 and 2002–2004 respectively, positive predictive value 92% in both periods) [16].

7.3.4 COMORBIDITIES AND ACUTE PRESENTATION

Comorbidities were identified using a 13-year hospitalisation history prior to and including each incident MI admission, from any diagnosis field: hypertension (ICD-10-AM I10–I15), heart failure (I50), atrial fibrillation (I48), stroke (I60–I64), peripheral vascular disease (I70–I79) and chronic kidney disease (CKD [17]). Prior CHD (I20.0 unstable angina, I20.1–I20.9 stable angina, I23–I25 chronic CHD) and prior revascularisation were identified similarly, although not if coded solely on the incident MI admission. A variable was created to identify the location of the admitting hospital (metropolitan/rural) and whether the patient was subsequently transferred.

Acute presentation characteristics were identified from the incident MI admission. Secondary diagnosis fields were used to identify indicators of disease severity including shock (ICD-10-AM R57 and ICD-9 equivalent), cardiac arrest (I46) and heart failure (I50). MI type was classified as ST-segment elevation MI (STEMI, ICD-9 410.0–410.6, 410.8/ICD-10 I21.0–I21.3), NSTEMI (410.7/I21.4) or unspecified (410.9/I21.9). Prior to 2004, ICD coding designated MI type as transmural, subendocardial or unspecified,
respectively. Acute percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) were identified from any of the 11 procedure fields.

7.3.5 **MEDICATION DATA**

Inpatient and discharge drug data were available from an existing study for a representative sample of MI patients admitted to metropolitan hospitals in WA in 1998 and 2003 [15]. Discharge drug data was also available from hospital pharmacy dispensing databases for all tertiary-hospital admitted MI patients in 2008 and linked to the main dataset used in the current study.

7.3.6 **STATISTICAL ANALYSIS**

Baseline characteristics are presented for all incident MI cases stratified by diabetes status and by time periods. Trends in categorical and continuous variables were calculated from age- and sex-adjusted logistic and linear models, respectively. Nominal trend p values without adjustment for multiple testing are presented for the average annual change. Medication data are presented as proportions.

Annual crude 30-day case fatality was calculated separately by diabetes status using annual counts of 30-day deaths as the numerator, and the annual number of hospitalised incident MI cases as the denominator. Age- and sex-adjusted annual percentage changes in case fatality were estimated from logistic models which included 5-year age group and calendar year, and are calculated from the exponential of the β-coefficient for calendar year. We also calculated crude and age- and sex-standardised case fatality for four periods using the direct method by 5-year age group, with the age and sex distribution of all incident MI cases in 2010 as the standard population. Results for case fatality in men and women were combined for all analyses because age-adjusted trends were similar by sex for patients with diabetes and those without diabetes (sex×year interaction p>0.05 for both groups). Because of the greater likelihood of diagnostic misclassification of MI in patients dying within 1 day of admission [18] and the potential for this to differentially influence trends between patients with and without diabetes, we also estimated age- and sex-adjusted trends where patients who died within 1 day of admission were excluded.

Logistic regression was used to estimate the association of diabetes with 30-day deaths following incident MI after adjustment for 5-year age group, sex, comorbidities, Indigenous status and MI type (unspecified/STEMI/NSTEMI). We also tested the
impact of individual comorbidities by adding each separately into the model (results not shown). Because of the strong effect of CKD, we tested the model with patients with CKD excluded to determine whether there was a similar trend in ORs. To further determine the impact of changing MI type, models were run including STEMI/unspecified cases only. Unspecified MI was included because these patients were deemed to be high risk (of these cases, 44% and 40% with and without diabetes, respectively, died within 1 day of admission). SAS v9.4 (Cary, North Carolina, USA) was used for all statistical analyses.

7.4 RESULTS

There were 26,610 incident MI cases in WA between 1998 and 2010. Patients with diabetes comprised 24.8% of the cohort (22.8% men and 29.6% women). Table 7.1 shows the frequency and trends in comorbidities and acute presentation and treatment variables for all incident MI by diabetes status and time periods. The prevalence of CKD and prior CHD history increased in patients with diabetes but declined in patients without diabetes, while the prevalence of hypertension increased at a greater rate in the diabetes group.

Trends in acute presentation characteristics were similar for patients with and without diabetes (Table 7.1), although the prevalence of heart failure complicating the MI admission in patients with diabetes was double than those without diabetes by 2008–2010 (21.2% vs 9.1%, respectively). There was a similar and declining occurrence of shock and cardiac arrest in patients with and without diabetes. The recording of NSTEMI increased more in the diabetes group (68.3% vs 57.4% by 2008–2010). The increase in acute PCI was similar in both groups; however, use remained about 15% lower in the diabetes group throughout the study period. Prescription of evidence-based drugs for the samples of MI patients is shown in Supplementary Table S7.1. Patients with diabetes were less likely than non-diabetics to receive β blockers, lipid lowering and antiplatelet drugs in-hospital and at discharge in 1998, but use increased over the period. Prescription of lipid-lowering drugs remained lower in 2008 in diabetes patients.
### Table 7.1. Frequency of baseline characteristics of all incident myocardial infarction patients in Western Australia, aged 35–84 years, stratified by diabetes status and period.

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>No diabetes</th>
<th>Trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>66.2 (11.4)</td>
<td>65.9 (11.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2005–2007 (n=1686)</td>
<td>2008–2010 (n=1741)</td>
<td></td>
</tr>
<tr>
<td>Gender, male</td>
<td>63.1</td>
<td>63.6</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
<td></td>
</tr>
<tr>
<td>Indigenous</td>
<td>64.3 (12.5)</td>
<td>64.4 (12.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2008–2010 (n=5373)</td>
<td>2008–2010 (n=5373)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>62.5</td>
<td>71.4</td>
<td>0.00001</td>
</tr>
<tr>
<td></td>
<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>14.1</td>
<td>14.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
<td></td>
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<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
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<tr>
<td>Atrial fibrillation</td>
<td>16.3</td>
<td>19.6</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
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<tr>
<td></td>
<td>2008–2010 (n=5373)</td>
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<td>Prior stroke</td>
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<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>17.1</td>
<td>15.4</td>
<td>0.07</td>
</tr>
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<td></td>
<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
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<td></td>
<td>2008–2010 (n=5373)</td>
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<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>21.0</td>
<td>23.2</td>
<td>0.00001</td>
</tr>
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<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
<td></td>
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<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
<td></td>
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<tr>
<td>Prior coronary heart disease</td>
<td>30.7</td>
<td>33.4</td>
<td>0.0005</td>
</tr>
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<td>2005–2007 (n=4749)</td>
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<td></td>
<td>2008–2010 (n=5373)</td>
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<tr>
<td>Acute presentation</td>
<td></td>
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<td></td>
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<tr>
<td>STEMI</td>
<td>59.8</td>
<td>41.0</td>
<td>&lt;0.0001</td>
</tr>
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<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
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<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
<td></td>
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<tr>
<td>NSTEMI</td>
<td>21.5</td>
<td>39.4</td>
<td>&lt;0.0001</td>
</tr>
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<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
<td></td>
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<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure during admission</td>
<td>30.0</td>
<td>28.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>3.5</td>
<td>3.9</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
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</tr>
<tr>
<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>4.1</td>
<td>3.5</td>
<td>0.0007</td>
</tr>
<tr>
<td></td>
<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
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</tr>
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<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
<td></td>
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<tr>
<td>Treatment in hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>16.6</td>
<td>30.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>4.4</td>
<td>5.7</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay, days (IQR)</td>
<td>5 (3,8)</td>
<td>4 (3,7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural admission</td>
<td>19.7</td>
<td>24.7</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>2002–2004 (n=4345)</td>
<td>2005–2007 (n=4749)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2008–2010 (n=5373)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Categorical variables are shown as %. Continuous variables are shown as mean (age) or median (length of stay).

*Age- and sex-adjusted p values for binary characteristics from logistic regression models, and age- and sex-adjusted p values for continuous characteristics from linear regression models (sex-adjusted only for trend in mean age).

NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.
7.4.1 30-DAY CASE FATALITY

From 1998 to 2010, the annual number of incident MI admissions increased by 32.1% and 35.3% in diabetics and non-diabetics, respectively, although the upward trend was attenuated in diabetes patients in the latter study years (Figure 7.1A). In contrast to increasing hospitalisation numbers, crude 30-day MI case fatality declined in both groups over the study period (Figure 7.1B and Table 7.2). Case fatality in 1998–2001 was higher in patients with diabetes (11.65% vs 8.23%), but there was little difference between the groups by 2008–2010 (3.96% vs 4.02%) (Table 7.2). Age- and sex-standardised case fatality fell at a greater rate in patients with diabetes (10.6% vs 6.9% average annual reduction; diabetes status × year interaction p=0.005). In age-stratified analyses (see Supplementary Table S7.2), there was a greater reduction in case fatality in 35–64 year olds with diabetes than in those without (average annual reduction 13.6% vs 3.4%, interaction p=0.0016), while reductions were similar according to diabetes status for the older age group.

The proportion of incident MI patients who died within 1 day of admission decreased during the study period (diabetes 3.5%–1.5%; no diabetes 3.0%–1.4%). When these cases were excluded, the reduction in 30-day case fatality was similar to that of the whole cohort (diabetes –11.0%/year, 95% CI –13.3 to –7.9; no diabetes –6.3%/year, 95% CI –8.1 to –4.4).

In 1998–2001, there was a significantly higher odds of death within 30-days of an incident MI in diabetes patients in 1998–2001 compared to those without diabetes from unadjusted and adjusted models. This difference significantly decreased over the study period (diabetes × period interaction p=0.02) and by 2008–2010, the odds in patients with diabetes was lower than in non-diabetics after adjustment for demographics, comorbidities and MI type (Table 7.3). Adjustment for comorbidities substantially reduced the ORs comparing patients with and without diabetes in each time period. When patients with CKD were excluded from the analysis, there was a similar downward trend in ORs; however, there was no longer a significant difference between the patients groups by 2008–2010 (OR 0.71, 95% CI 0.47 to 1.06).
FIGURE 7.1. (A) Annual number of hospitalisations for incident myocardial infarction in patients with and without diabetes, and (B) annual crude 30-day case fatality following incident myocardial infarction in patients with and without diabetes.

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>No diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30-day deaths, n</td>
<td>Crude case fatality, %</td>
</tr>
<tr>
<td>2008–2010</td>
<td>69</td>
<td>3.96</td>
</tr>
</tbody>
</table>
### Table 7.3. ORs for 30-Day Mortality Risk Comparing Patients with Versus Without Diabetes Following Incident Myocardial Infarction, From Unadjusted and Adjusted Logistic Regression Models.

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.47 (1.23, 1.76)</td>
<td>1.22 (0.98, 1.53)</td>
<td>1.34 (1.07, 1.68)</td>
<td>0.98 (0.75, 1.30)</td>
</tr>
<tr>
<td>Adjusted for:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age/sex</td>
<td>1.36 (1.13, 1.63)</td>
<td>1.14 (0.90, 1.43)</td>
<td>1.23 (0.97, 1.55)</td>
<td>0.82 (0.62, 1.09)</td>
</tr>
<tr>
<td>Above plus comorbidities*</td>
<td>1.25 (1.03, 1.51)</td>
<td>1.00 (0.78, 1.28)</td>
<td>1.01 (0.78, 1.30)</td>
<td>0.63 (0.46, 0.86)</td>
</tr>
<tr>
<td>Above plus Indigenous status</td>
<td>1.21 (1.00, 1.47)</td>
<td>0.95 (0.74, 1.23)</td>
<td>1.04 (0.81, 1.35)</td>
<td>0.61 (0.45, 0.84)</td>
</tr>
<tr>
<td>Above plus MI type</td>
<td>1.23 (1.01, 1.50)</td>
<td>0.96 (0.75, 1.25)</td>
<td>1.02 (0.79, 1.33)</td>
<td>0.64 (0.46, 0.88)</td>
</tr>
<tr>
<td>CKD patients excluded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.41 (1.15, 1.73)</td>
<td>1.08 (0.82, 1.42)</td>
<td>1.14 (0.85, 1.53)</td>
<td>0.78 (0.54, 1.13)</td>
</tr>
<tr>
<td>Adjusted for:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age/sex</td>
<td>1.36 (1.13, 1.63)</td>
<td>1.14 (0.90, 1.43)</td>
<td>1.23 (0.97, 1.55)</td>
<td>0.82 (0.62, 1.09)</td>
</tr>
<tr>
<td>Above plus comorbidities*</td>
<td>1.29 (1.04, 1.61)</td>
<td>0.99 (0.74, 1.33)</td>
<td>1.08 (0.79, 1.47)</td>
<td>0.67 (0.45, 0.99)</td>
</tr>
<tr>
<td>Above plus Indigenous status</td>
<td>1.26 (1.01, 1.57)</td>
<td>0.96 (0.71, 1.29)</td>
<td>1.10 (0.80, 1.50)</td>
<td>0.67 (0.45, 1.00)</td>
</tr>
<tr>
<td>Above plus MI type</td>
<td>1.27 (1.01, 1.58)</td>
<td>0.97 (0.72, 1.31)</td>
<td>1.12 (0.81, 1.54)</td>
<td>0.71 (0.47, 1.06)</td>
</tr>
</tbody>
</table>

*Includes hypertension, heart failure, CKD (except in analysis where CKD patients were excluded), stroke, peripheral vascular disease, atrial fibrillation, prior CHD, chronic obstructive pulmonary disease.

CKD, chronic kidney disease; MI, myocardial infarction.
7.5 DISCUSSION

The major finding of this population-level study is a greater rate of improvement in 30-day case fatality following incident MI in people with versus without diabetes over a 13-year period. There was little difference in case fatality according to diabetes status by the end of the study period. The adjusted case fatality risk after MI was initially higher in patients with diabetes but there was a significant temporal reduction in relative risk over the study period. These trends are apparent despite persisting lower rates of acute revascularisation, higher levels of heart failure and CKD and a generally worse risk profile in the diabetes group, although use of evidence-based drugs improved. This suggests that the severity of MI and/or the extent of underlying coronary artery disease may be lessening at first MI presentation in people with diabetes.

7.5.1 TRENDS IN 30-DAY CASE FATALITY

Case fatality following MI has decreased in community- and population-based settings since late 1980s [4–6, 19], with indications that these downward trends are also apparent in patients with diabetes [7–9, 20]. In contrast, an earlier Australian study of a MONICA population found no reduction in 28-day case fatality after incident MI in patients with diabetes from 1985 to 1994 [21]. These differences may be due to the inclusion of out of hospital deaths or may reflect the earlier time period in comparison to most other studies. Several population studies have shown that temporal reductions in case fatality after MI were similar in patients with and without diabetes [10, 22, 23], although greater absolute and adjusted reductions in 30-day case fatality in diabetes patients are reported from Sweden [8].

7.5.2 CHANGING PROGNOSTIC IMPACT OF DIABETES

Our results suggest that the prognostic impact of diabetes on short-term mortality has declined over time. The downward trend in adjusted risk in our study is similar to a US national registry-based study, which showed that by 2006, diabetes was no longer independently associated with an increased risk of in-hospital mortality following MI [7]. A study of Canadian patients from 1999 to 2008 reported that diabetes was an independent predictor of in-hospital death following MI [24], but this study was not restricted to incident MI and was likely influenced by the high prevalence of prior MI. The diverging trends in the prevalence of CKD and other comorbidities between the two groups in our study could exaggerate the decline in the association of diabetes with
early death after incident MI. However, this trend was also apparent in age- and sex-adjusted models, suggesting a real decline in the effect of diabetes on 30-day case fatality.

7.5.3 IMPACT OF EVIDENCE-BASED THERAPIES

The reasons for underutilisation of evidence-based therapies in patients with diabetes are complex [2, 25] and associated with a higher comorbidity burden, more diffuse coronary disease and older age at presentation [2, 3]. However, there is evidence that the gap in the use of drugs following MI has narrowed over the past decade, with increasing use of β blockers, aspirin and reperfusion therapy in patients with diabetes [7, 8]. Our data are consistent with these findings, although there was no narrowing of the differential in early revascularisation. Delay to PCI is an independent predictor of 30-day mortality following MI [26], and clinical guidelines advocate an early invasive management strategy even for NSTEMI patients. Therefore, the higher baseline risk in the diabetes group could contribute to the greater absolute reductions in case fatality despite this continued treatment gap.

7.5.4 CHANGING PRESENTATION OF MI

Since the late 1990s, there has been a shift from the higher risk STEMI presentation to NSTEMI, associated with increasingly sensitive troponin assays for MI diagnosis [5] and a higher proportion of NSTEMI detected in patients with diabetes [27]. Because in-hospital mortality is lower following NSTEMI [28], the higher proportion of NSTEMI cases in the diabetes group by the end of our study period could exaggerate the reductions in case fatality. However, early mortality following NSTEMI is still worse in patients with diabetes, particularly if insulin-treated [3]; therefore, it is unlikely that this shift fully accounts for the greater reduction in case fatality in the diabetes group in this study. A declining incidence of heart failure and shock following admission is a further indication of changing MI severity, although these complications still occurred more frequently in the diabetes group over the study period.

7.5.5 COMORBIDITIES

Declining in-hospital mortality in patients with diabetes has been reported in the setting of an increasing comorbidity burden [7, 10]. This is consistent with increasing CKD, hypertension and prior CHD in diabetics in our study. In contrast, falling prevalence of heart failure was identified, consistent with its declining incidence in our population
Patients with pre-existing risk factors may have a greater propensity to receive targeted risk factor management, which could explain the improvements in case fatality despite increasing comorbidities. We have also reported that a prior CHD history is associated with a reduced risk of case fatality in patients with heart failure complicating incident MI, suggesting a protective effect of secondary preventive therapies [29]. Alternatively, increasing use of evidence-based acute management following MI may overcome the immediate impact of existing comorbidities, although this may not be evident for longer term outcomes in patients with diabetes.

7.5.6 LIMITATIONS

The diagnostic criteria for MI have changed during the period of this study leading to a pool of potentially milder cases of MI. Similarly, there may have been milder cases of diabetes identified throughout the study period, due to a lowering of the glycaemic threshold for diabetes diagnosis around mid-1997. This could manifest as greater reductions in case fatality because of a larger proportion of patients with lower severity diabetes. Our ability to make inferences about the changing use of medications is limited because we did not have drug data available for all incident MI patients over the whole study period. There are limited validation data on the recording of MI type in hospital morbidity data. Although our data are consistent with the changing proportion of STEMI and NSTEMI from validated studies [5, 7], our unpublished data indicates that the reduction in STEMI may be overestimated by hospital morbidity data alone. Whether this occurs differentially according to diabetes status is untested. Additionally, we did not include out of hospital MI deaths because diabetes status is likely underestimated from mortality data. Overall mortality rates in people with diabetes have fallen in Australia during the period of our study [30], so it is unlikely that a shift from hospitalised MI to out of hospital death has occurred.

7.6 CONCLUSION

This population-based study has demonstrated greater absolute and relative reductions in 30-day case fatality following incident MI in patients with diabetes compared to those without over a 13-year period. The case fatality associated with diabetes following incident MI has reduced to the point where, after accounting for baseline risk factors, diabetes is no longer an independent predictor of early death. These improvements are concurrent with improving rates of evidence-based therapies for patients with diabetes, although disparities are still apparent. Hence sustained efforts at reducing coronary risk
factors and continuing to improve the acute treatment of diabetics following MI may further improve cardiovascular outcomes in this patient group.

WHAT IS ALREADY KNOWN ON THIS SUBJECT?

- People with diabetes have poorer outcomes following myocardial infarction, and receive less evidence-based medication and treatment.

WHAT MIGHT THIS SUBJECT ADD?

- Between 1998 and 2010, there was an absolute decrease of nearly 8% in 30-day case fatality following incident myocardial infarction in people with diabetes, and the relative decrease during the period was greater than in non-diabetics.
- By the latter part of the study period, diabetes was no longer an independent predictor of 30-day case fatality.
- These trends are apparent despite the persisting lower rates of acute revascularisation in the diabetes group although use of evidence-based drugs improved.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE?

- These findings indicate that substantial improvements in early mortality in patients with diabetes following incident MI have occurred over a 13-year period.

7.7 ACKNOWLEDGEMENTS

The authors wish to thank the staff at the Western Australian Data Linkage Branch, the Department of Health Inpatient Data Collections and Registrar General.
7.8 REFERENCES


## 7.9 SUPPORTING INFORMATION

**Supplementary Table S7.1. Inpatient and discharge drugs (%) for a sample of myocardial infarction patients admitted to tertiary hospitals in Western Australia.**

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Inpatient drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1998*</td>
<td>2003*</td>
</tr>
<tr>
<td></td>
<td>(n=208)</td>
<td>(n=139)</td>
</tr>
<tr>
<td></td>
<td>1998*</td>
<td>2003*</td>
</tr>
<tr>
<td></td>
<td>(n=690)</td>
<td>(n=350)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>66.3</td>
<td>81.3</td>
</tr>
<tr>
<td>ACE/ARBs</td>
<td>71.1</td>
<td>81.3</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>53.8</td>
<td>78.4</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>88.0</td>
<td>84.9</td>
</tr>
<tr>
<td>CCB</td>
<td>24.0</td>
<td>20.9</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>91.8</td>
<td>95.7</td>
</tr>
<tr>
<td>Hypoglycaemics</td>
<td>71.1</td>
<td>71.9</td>
</tr>
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<td><strong>Discharge drugs</strong></td>
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<td></td>
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<td></td>
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<td>2003*</td>
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<td>(n=139)</td>
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<tr>
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<td>2008†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=293)</td>
<td>(n=690)</td>
</tr>
<tr>
<td></td>
<td>(n=350)</td>
<td>(n=1260)</td>
</tr>
<tr>
<td>Beta blockers</td>
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<td>70.5</td>
</tr>
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<td>ACE/ARBs</td>
<td>68.9</td>
<td>73.4</td>
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<td>Anticoagulants</td>
<td>15.9</td>
<td>9.3</td>
</tr>
<tr>
<td>CCB</td>
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<td>15.8</td>
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<tr>
<td>Antiplatelet drugs</td>
<td>76.4</td>
<td>79.1</td>
</tr>
<tr>
<td>Hypoglycaemics</td>
<td>53.8</td>
<td>56.8</td>
</tr>
</tbody>
</table>

* Inpatient and discharge drug data for 1998 and 2003 from hospital records for a representative sample of myocardial infarction patients admitted to metropolitan hospitals in Western Australia.

†Discharge drugs data for 2008 are from hospital discharge pharmacy records for myocardial infarction patients admitted to tertiary hospitals in Western Australia in 2008.

ACE/ARBs, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; CCB, calcium channel blockers.
## Supplemental Table S7.2: Age-specific 30-day case fatality following incident myocardial infarction, 1998 to 2010.

<table>
<thead>
<tr>
<th>Period</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30-day case fatality, %</td>
<td>30-day case fatality, %</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Crude</td>
</tr>
<tr>
<td>35–64 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002–2004</td>
<td>23</td>
<td>3.65</td>
</tr>
<tr>
<td>2005–2007</td>
<td>27</td>
<td>3.94</td>
</tr>
<tr>
<td>2008–2010</td>
<td>9</td>
<td>1.22</td>
</tr>
<tr>
<td>65–84 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002–2004</td>
<td>92</td>
<td>10.57</td>
</tr>
<tr>
<td>2005–2007</td>
<td>89</td>
<td>8.89</td>
</tr>
<tr>
<td>2008–2010</td>
<td>60</td>
<td>5.96</td>
</tr>
</tbody>
</table>
CHAPTER 8. LONG-TERM OUTCOMES FOLLOWING INCIDENT MYOCARDIAL INFARCTION: AGE AND GENDER PERSPECTIVE

PUBLISHED PAPER

This chapter is the final version of the following paper, which was published in the ‘Strengthening Cardiovascular Disease Prevention’ special issue of the journal:

Age-specific gender differences in long-term recurrence and mortality following incident myocardial infarction: a population-based study


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Keywords: Myocardial infarction; Gender; Age-specific; Recurrence; Mortality
PREAMBLE

Understanding the burden of long-term outcomes following MI has become increasingly important. The declining incidence rates of MI and CHD and falling case fatality rates after MI, likely leave an increased pool of survivors at risk of cardiovascular events. One of the major findings of the study in Chapter 5 was the high rate of hospitalisation for recurrent CHD. Given that previous WA data for long-term outcomes had only extended to cohorts of MI patients up to the 1990s, it was felt that a contemporary baseline risk needed to be established.

Therefore this chapter focuses on investigating long-term outcomes (out to eight years) in a contemporary population cohort of incident MI patients in WA. Specifically, gender differences from an age-specific perspective are explored.
8.1 ABSTRACT

Background: Higher mortality following myocardial infarction (MI) is reported in women compared with men with short-term follow-up. Our study aim was to compare long-term gender- and age-specific outcomes following incident MI.

Methods: 30-day survivors of incident MI from 2003–2009 were identified from linked administrative data in Western Australia. Outcomes identified were recurrent MI, and cardiovascular and all-cause mortality. Follow-up data was available until 30\textsuperscript{th} June 2011. Unadjusted risk out to eight-years was estimated from Kaplan-Meier survival curves, and multivariate Cox regression models were used to estimate relative risk in women compared with men by age group.

Results: There were 14,420 30-day survivors of incident MI from 2003–2009 (males 71.2\%). Women had higher levels of comorbidities across all age groups compared with men. Unadjusted event risks were higher in women than men overall, underpinned by higher risk of recurrent MI in 55–69-year-old women and of cardiovascular mortality across all age groups in women. Gender differences were generally attenuated after adjustment for demographic factors and comorbidities.

Conclusions: This study highlights the elevated risk of cardiovascular events in women compared with men with long-term follow-up, and demonstrates the need for improved long-term secondary prevention in this patient group.

8.2 INTRODUCTION

Coronary heart disease (CHD) contributes significantly to the burden of morbidity and mortality in the general population [1]. Despite improvements in short and long-term survival following a myocardial infarction (MI) over recent decades [2,3], the risk of a subsequent MI or death remains elevated [4]. There is evidence of gender differences in survival, with women reported to have higher short-term mortality rates [5], however there are less data available on gender differences in long-term outcomes. It has been suggested that age and a greater prevalence of comorbidities may be associated with this apparent difference [5,6]. More recent reports suggest that the burden of adverse outcomes is also evident in younger women who experience an MI [6,7]. Given reports of an increase in the incidence of MI in younger people [8], and specifically in younger women in WA [9], this question warrants investigation in an Australian context to determine whether age-specific gender disparities exist.
Significant gaps still remain in the delivery of guideline-recommended levels of secondary prevention measures post-MI [10], and age and gender are important variables in determining the risk of future cardiovascular events in CHD patients. It is therefore imperative that age-specific gender outcomes are described to ascertain particularly high-risk target groups for enhanced secondary prevention measures. Thus the study aim was to determine the age-specific impact of gender on long-term MI recurrence and mortality in 30-day survivors of incident MI in a population-based setting.

8.3 METHODS

8.3.1 DATA SOURCE

Data for this study were obtained from two of the core datasets of the WA Data Linkage System (WADLS) — the Hospital Morbidity Data Collection (HMDC) and Death Register. These data are linked centrally by the WADLS using probabilistic matching, with >99% accuracy for this process [11]. The majority of acute coronary care and all invasive revascularisation procedures are undertaken in the tertiary hospitals (public and private) situated in the capital city, Perth. The person-based linked dataset available for this study contained all records for any patient hospitalised with or dying from cardiovascular disease (CVD) in WA from 1985–2010. Variables available included demographic information, principal discharge diagnosis, 20 secondary discharge diagnosis fields, and inpatient procedures. Discharge pharmacy data was available for incident MI cases admitted to the three adult tertiary hospitals, and linked to the matching hospital admission by a unique admission identifier. The data used in this study are de-identified, and the study was granted a waiver of informed consent from each ethics committee. Approval for this study was obtained from the ethics committees of The University of Western Australia and the WA Department of Health.

8.3.2 INCIDENT MI COHORT

All MI cases hospitalised in WA from 2003 to 2009 were identified using the principal discharge diagnosis field (ICD-10-AM I21,I22). Cases were classified as incident if there were no hospitalisations for acute coronary syndromes in the 16 years prior to the MI admission [12]. Patients aged 35 to 84 years of age who survived greater than 30 days following the incident MI, were included in the cohort.
8.3.3 PATIENT CHARACTERISTICS

Comorbidities were identified from the linked dataset if recorded in the 16 years prior to or on the incident admission. These included: hypertension (ICD 10-AM I10–I15 and ICD-9-CM equivalent), diabetes (E10–E14), heart failure (I50), atrial fibrillation (I48), stroke (I60–I64), peripheral arterial disease (I70–I79), and chronic kidney disease (CKD)[13]. History of coronary heart disease (CHD) was identified where there was prior hospitalisation for stable angina or other CHD (I20.1–I20.9, I24–I25).

Revascularisation procedures (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)) occurring during the incident episode (including following transfer to a metropolitan hospital) were identified from any of the 11 procedure fields. Utilisation of evidence-based medications following MI was determined by identifying drugs dispensed at discharge for tertiary hospital patients with a length of stay greater than one day and at least one pharmacy record in the dataset. The analysis was restricted to this sample of patients because discharge pharmacotherapy data are only available for linkage for tertiary hospital patients. The drug groups analysed were antiplatelet therapy (eg, aspirin), angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), lipid-lowering drugs, beta blockers, and calcium channel blockers. Aspirin use in pain management was excluded by checking the directions on prescriptions for aspirin 300 mg. Drugs dispensed as part of a clinical trial were excluded.

8.3.4 OUTCOMES

The endpoints of recurrent MI, CVD mortality and all-cause mortality were identified. Recurrent MI was identified where recorded in the principal discharge diagnosis field >30 days following the incident hospitalisation. CVD deaths were identified where the underlying cause of death was coded as any cardiovascular-related cause (ICD-10-AM I00–I99). Follow-up data were available to 30th June 2011 for all patients, providing minimum and maximum follow-up periods of 18 months and 8.5 years respectively.

8.3.5 STATISTICAL ANALYSES

Patient characteristics and discharge pharmacotherapy are presented separately for men and women. Differences in the proportion of men and women dispensed drugs from each category were compared by chi-squared tests. Unadjusted risks were derived from Kaplan Meier survival curves. Time to event was calculated from the date of the incident MI hospitalisation to the date of the event (MI, CVD death and all-cause
death), or censored at the end of followup or at an intervening event (death for recurrent MI endpoint or non-CVD death for the CVD death endpoint), whichever came first. The log-rank p-value test was used to compare men and women within each age group.

Cox regression models were used to examine the effect of gender on the risk of recurrent MI or death, stratified by age group. The proportional hazards assumption was tested using an interaction term between sex and time. No consistent evidence of violation of this assumption was found. In addition to the primary analysis where the full follow-up available for each patient was used, a further analysis was carried out using a fixed follow-up of two years. Additionally, we performed landmark analyses at two and four years, where patients were only included if alive and event-free at these time points. Age-adjusted (continuous variable) and multivariate models were run for each of these analyses. Variables entered into the multivariate models included age (continuous and with its square where needed), Indigenous status, diabetes, CKD, hypertension, atrial fibrillation, stroke, peripheral arterial disease, CHD, MI type (ST-segment elevation MI (STEMI), non-ST segment elevation MI (NSTEMI) or unspecified type, as recorded in the linked dataset), and PCI or CABG during the incident episode. For the landmark analyses, binary variables indicating revascularisation during the follow-up period but before the landmark time point were also included. Results are reported as hazard ratios (HR, 95% confidence interval, CI). All analyses were carried out using SAS v9.4 (Carey, USA), and the statistical significance level set at p<0.05.

### 8.4 RESULTS

There were 12 420 30-day survivors of incident MI from 2003 to 2009. Mean follow-up time was 4.05 years (SD 2.2 years). Males comprised 71.2% of the study cohort (Table 8.1). 28.6% of men and 50.6% of women were in the 70–84 year age group. The mean age for men was 61.7 years (SD 11.9) and 67.4 years (SD 12.1) in women. There was a higher proportion of Indigenous patients in women, with the greatest disparity in the 35–54 year age group (19.8% in women versus 9.3% in men). There was a higher prevalence of diabetes, hypertension and heart failure recorded for women compared with men within the three age groups.
8.4.1 PHARMACOTHERAPY AT HOSPITAL DISCHARGE

Of the total cohort, 5763 (46.4%) patients were admitted to a tertiary hospital with a length of stay greater than one day and had a discharge pharmacy record, and were therefore included in the analysis. A greater proportion of older patients had no pharmacy record at discharge, particularly females. Coverage was greatest for lipid-lowering drugs in both men (87.7%) and women (77.9%), though in younger women coverage was greatest for low-dose aspirin (86.5%; Table 8.2). Chi-squared comparisons within each age group and overall revealed a statistically significant lower proportion of women than men receiving statins or other lipid-lowering drugs, aspirin, ACEI/ARB, and beta blockers.

8.4.2 LONG-TERM SURVIVAL

Unadjusted risk of recurrent MI and CVD mortality, stratified by age group, are presented in Figures 8.1 and 8.2 respectively. Table 8.3 shows risk estimates by gender and age group for each outcome. The eight-year risk of recurrent MI was higher in women (14.9% versus 11.6% in men, log-rank p=0.04), with no significant difference between men and women in any of the age groups, although rates were nearly 4% higher in women than men in the 55–69 year age group (Table 8.3). There was a larger disparity for cardiovascular death (women 17.6%, men 9.7%, log-rank p<0.0001), with a significantly higher unadjusted risk of cardiovascular mortality in women than men in the 35–54 year age group (log-rank p=0.003). This difference persisted in women in the older age groups, although the differences were smaller and not statistically significant. The proportion of all deaths attributed to cardiovascular causes was similar between men and women in each age group (35–54 years, 45.0% versus 44.7%; 55–69 years 36.8% versus 37.2%; 70–84 years 48.2% versus 46.0% respectively).

8.4.3 MULTIVARIATE ADJUSTMENT

After multivariate adjustment, the hazard ratio comparing women to men for recurrent MI was generally less than one, although only statistically significant in the 35–54 year age group (HR 0.66, 95% CI 0.47, 0.94). This difference was also apparent in the fixed two-year followup. There was generally little difference between men and women for CVD mortality in the fully adjusted model. However, there was a tendency towards increased rates in 35–54 year old women (age-adjusted HR 2.08, 95% CI 1.26, 3.42) which was diminished after adjustment for comorbidities and demographic factors (HR 1.28, 95% CI 0.77, 2.15). A similar pattern was seen in each of the age groups when all-
cause mortality was the endpoint. In 35–54 and 55–69 year olds, the variables mainly responsible for attenuating the rates between the age-adjusted and multivariate models were diabetes, heart failure, chronic kidney disease and Indigenous status. There was little attenuation between the age-adjusted and multivariate models for the 70–84 year age group.

The landmark analyses which included two- and four-year survivors respectively demonstrated similar hazard ratios for each of the endpoints as for the full cohort, although the reduced rate of recurrent MI in 35–54 year old women versus men was no longer statistically significant (data not shown).
### CHAPTER 8. AGE AND GENDER DIFFERENCES IN MYOCARDIAL INFARCTION OUTCOMES

#### Table 8.1. Patient characteristics stratified by gender and age group.

<table>
<thead>
<tr>
<th></th>
<th>35–54 years</th>
<th>55–69 years</th>
<th>70–84 years</th>
<th>Total (35–84 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=2639)</td>
<td>Women (n=627)</td>
<td>Men (n=3672)</td>
<td>Women (n=1141)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>47.5 (5.0)</td>
<td>47.4 (5.0)</td>
<td>61.7 (4.3)</td>
<td>62.5 (4.2)</td>
</tr>
<tr>
<td>Indigenous status</td>
<td>9.3</td>
<td>19.8</td>
<td>2.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Acute PCI</td>
<td>60.7</td>
<td>41.0</td>
<td>56.1</td>
<td>42.9</td>
</tr>
<tr>
<td>Acute CABG</td>
<td>3.3</td>
<td>2.4</td>
<td>5.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Comorbidities</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
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<td>8.0</td>
<td>9.8</td>
<td>9.4</td>
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<td>Diabetes</td>
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<td>27.3</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
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<td>10.7</td>
<td>6.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>47.9</td>
<td>59.1</td>
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<tr>
<td>Heart failure</td>
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<td>7.8</td>
<td>8.4</td>
<td>11.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.8</td>
<td>0.8</td>
<td>1.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.5</td>
<td>3.0</td>
<td>9.2</td>
<td>9.0</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>1.9</td>
<td>2.9</td>
<td>5.4</td>
<td>6.5</td>
</tr>
</tbody>
</table>

|                         | Men (n=8838) | Women (n=3582) |
| Mean age, years (SD)    | 61.7 (11.9)  | 67.4 (12.1)    |
| Indigenous status       | 4.1         | 6.0            |
| Acute PCI               | 52.1        | 36.5           |
| Acute CABG              | 5.2         | 3.1            |
| CHD                     | 11.8        | 13.8           |
| Diabetes                | 21.4        | 27.7           |
| Chronic kidney disease  | 8.3         | 12.4           |
| Hypertension            | 49.0        | 62.8           |
| Heart failure           | 11.7        | 19.3           |
| Stroke                  | 2.8         | 4.6            |
| Atrial fibrillation     | 12.0        | 16.3           |
| Peripheral arterial disease | 7.0     | 7.8            |
### Table 8.2. Proportion (%) of Patients Who Received Pharmacotherapy on Discharge from Hospital in a Subset of 30-Day Survivors of Incident Myocardial Infarction in Western Australia (Patients Admitted to a Tertiary Hospital and with a Length of Stay >1 Day), N=5763.

<table>
<thead>
<tr>
<th></th>
<th>35–54 years</th>
<th>55–69 years</th>
<th>70–84 years</th>
<th>35–84 years</th>
</tr>
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<td></td>
<td>Men (n=1247)</td>
<td>Women (n=259)</td>
<td>Men (n=1756)</td>
<td>Women (n=532)</td>
</tr>
<tr>
<td>Statin and other lipid-lowering drugs</td>
<td>92.5</td>
<td>85.7†</td>
<td>89.2</td>
<td>84.4†</td>
</tr>
<tr>
<td>Aspirin (low dose)</td>
<td>91.4</td>
<td>86.5†</td>
<td>87.7</td>
<td>82.3†</td>
</tr>
<tr>
<td>Other antiplatelet drugs</td>
<td>86.8</td>
<td>82.2</td>
<td>85.0</td>
<td>75.4*</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>89.0</td>
<td>79.2*</td>
<td>84.5</td>
<td>78.6†</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>88.8</td>
<td>80.3†</td>
<td>86.4</td>
<td>77.1*</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>4.2</td>
<td>5.0</td>
<td>5.4</td>
<td>11.1*</td>
</tr>
</tbody>
</table>

*p<0.0001, †p<0.05, from chi-squared test comparing men and women.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers.
TABLE 8.3. ESTIMATES FROM KAPLAN-MEIER CURVES FOR THE RISK OF RECURRENT MYOCARDIAL INFARCTION, CARDIOVASCULAR DISEASE MORTALITY AND ALL-CAUSE MORTALITY FOLLOWING INCIDENT MYOCARDIAL INFARCTION.

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Follow-up time, years</th>
<th>Event risks, % (95% CI)</th>
<th>Myocardial infarction</th>
<th>Cardiovascular disease mortality</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>35–54</td>
<td>2</td>
<td>4.5 (3.7, 5.3)</td>
<td>3.4 (2.0, 4.9)</td>
<td>1.0 (0.6, 1.3)</td>
<td>1.8 (0.8, 2.8)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6.9 (5.9, 8.0)</td>
<td>6.0 (4.1, 8.1)</td>
<td>1.5 (0.1, 2.0)</td>
<td>2.9 (1.5, 4.3)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>11.0 (9.3, 12.8)</td>
<td>11.2 (6.8, 15.5)</td>
<td>3.3 (2.0, 4.6)</td>
<td>8.3 (2.1, 14.5)*</td>
</tr>
<tr>
<td>55–69</td>
<td>2</td>
<td>3.8 (3.2, 4.4)</td>
<td>4.6 (3.4, 5.8)</td>
<td>1.7 (1.3, 2.2)</td>
<td>1.6 (0.8, 2.3)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5.8 (5.0, 6.6)</td>
<td>6.5 (5.0, 8.1)</td>
<td>2.4 (1.9, 3.0)</td>
<td>2.9 (1.8, 4.0)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>9.4 (7.9, 10.9)</td>
<td>13.2 (8.9, 17.6)</td>
<td>4.5 (3.5, 5.3)</td>
<td>6.9 (4.3, 9.6)</td>
</tr>
<tr>
<td>70–84</td>
<td>2</td>
<td>7.8 (6.7, 8.9)</td>
<td>7.2 (6.0, 8.5)</td>
<td>8.3 (7.2, 9.4)</td>
<td>8.7 (7.4, 10.1)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>11.1 (9.8, 12.5)</td>
<td>10.1 (8.6, 11.7)</td>
<td>14.6 (13.0, 16.1)</td>
<td>13.3 (11.6, 15.0)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>16.0 (13.5, 18.5)</td>
<td>17.4 (14.1, 20.7)</td>
<td>25.6 (22.8, 28.5)</td>
<td>28.0 (24.0, 32.2)</td>
</tr>
<tr>
<td>35–84</td>
<td>2</td>
<td>5.1 (4.6, 5.6)</td>
<td>5.7 (4.9, 6.5)</td>
<td>3.3 (2.9, 3.7)</td>
<td>5.1 (4.4, 5.8)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>7.6 (7.0, 8.2)</td>
<td>8.2 (7.2, 9.2)</td>
<td>5.5 (5.0, 6.0)</td>
<td>8.1 (7.1, 9.0)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>11.6 (10.6, 12.7)</td>
<td>14.9 (12.6, 17.2)*</td>
<td>9.7 (8.7, 10.6)</td>
<td>17.6 (15.1, 20.1)†</td>
</tr>
</tbody>
</table>

Log-rank p-value comparing men and women, *p<0.05, †p<0.0001.
### Table 8.4. Age and Multivariate-Adjusted Hazard Ratios (95% CI)* for the Rates of Recurrent Myocardial Infarction, Cardiovascular Disease Mortality and All-Cause Mortality in Women Compared with Men in 30-Day Survivors of Incident Myocardial Infarction.

| Follow-up | Age group, years | Myocardial infarction | | Cardiovascular disease mortality | | All-cause mortality | |
|-----------|------------------|-----------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|           |                  | Age adjusted          | Multivariate             | Age adjusted             | Multivariate             | Age adjusted             | Multivariate             |
| All†      | 35–54            | 0.90 (0.65, 1.26)     | 0.67 (0.48, 0.95)        | 2.10 (1.28, 3.46)        | 1.30 (0.77, 2.19)        | 2.13 (1.52, 2.98)        | 1.29 (0.91, 1.84)        |
|           | 55–69            | 1.20 (0.94, 1.54)     | 1.03 (0.79, 1.32)        | 1.19 (0.83, 1.70)        | 0.84 (0.58, 1.21)        | 1.17 (0.94, 1.45)        | 0.87 (0.70, 1.09)        |
|           | 70–84            | 0.90 (0.74, 1.08)     | 0.89 (0.74, 1.08)        | 0.86 (0.73, 1.00)        | 0.86 (0.74, 1.01)        | 0.92 (0.83, 1.02)        | 0.92 (0.82, 1.02)        |
| All (35–84) | 0.98 (0.85, 1.12) | 0.88 (0.77, 1.01)     | 0.95 (0.83, 1.09)        | 0.91 (0.79, 1.05)        | 1.02 (0.93, 1.12)        | 0.96 (0.87, 1.05)        |
| 2 years   | 35–54            | 0.75 (0.47, 1.19)     | 0.54 (0.34, 0.88)        | 1.95 (0.95, 3.98)        | 1.39 (0.66, 2.94)        | 2.04 (1.23, 3.39)        | 1.39 (0.81, 2.38)        |
|           | 55–69            | 1.19 (0.87, 1.65)     | 0.99 (0.71, 1.38)        | 0.86 (0.51, 1.47)        | 0.62 (0.36, 1.07)        | 1.06 (0.78, 1.44)        | 0.80 (0.59, 1.10)        |
|           | 70–84            | 0.87 (0.69, 1.09)     | 0.84 (0.67, 1.07)        | 0.92 (0.74, 1.14)        | 0.95 (0.77, 1.19)        | 0.89 (0.76, 1.04)        | 0.90 (0.77, 1.05)        |
| All (35–84) | 0.93 (0.78, 1.11) | 0.83 (0.69, 0.98)     | 0.96 (0.79, 1.16)        | 0.93 (0.77, 1.13)        | 0.96 (0.84, 1.10)        | 0.92 (0.80, 1.05)        |

*Adjusted for 5-year age group, Indigenous status, diabetes heart failure, hypertension, atrial fibrillation, stroke, peripheral arterial disease, chronic kidney disease, coronary heart disease, acute percutaneous coronary revascularisation, acute coronary artery bypass grafting and myocardial infarction type.

†Reference level for each age group comparison is male gender.

‡Maximum follow-up for the whole cohort 30 June 2011.
Figure 8.1. Kaplan Meier curves for recurrent myocardial infarction following an incident myocardial infarction in men (A) and women (B), stratified by age group.
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**Figure 8.2.** Kaplan Meier curves for cardiovascular disease mortality following an incident myocardial infarction in men (A) and women (B), stratified by age group.
Chapter 8. Age and Gender Differences in Myocardial Infarction Outcomes

8.5 Discussion

This study provides important data on gender differences in long-term recurrence and mortality following incident MI in an Australian population-based setting. It affords a unique perspective because there is limited data on long-term outcomes in this high-risk patient group nationally. Our study shows that in patients who survive the acute phase of a first-ever MI, women have a higher unadjusted risk of recurrent MI and cardiovascular mortality than men up to eight years following the incident event. The disparity between men and women for recurrent MI is underpinned by the higher risk in 55–69 year old women, whereas a higher risk of CVD death in women is evident across all age groups. These differences were generally attenuated after multivariate adjustment, with the adjusted rate for recurrent MI being lower although not significantly so in women versus men, indicating the impact of increased CVD risk factors and comorbidities in women on long-term outcomes.

8.5.1 Comparisons of Mortality Outcomes

Previous studies have shown worse outcomes in women than men following MI [5,14,15]. Higher all-cause mortality at one-year in women aged <50 years [6], and at two-years in women aged <60 years [7] has been demonstrated to persist even after adjustment for demographic characteristics, comorbidities and early treatment. However Griffiths et al in a single-centre study reported increased long-term mortality in women at seven years following MI which was accounted for by these factors [16]. A systematic review of 5–10 year mortality outcomes following MI concluded that differences in age, comorbidities and treatment are responsible for the higher mortality risk in women even with very long-term follow-up, although there was significant heterogeneity in the magnitude of risk [17]. Our results are consistent with these findings, although we were unable to fully adjust for inhospital drug treatment during MI admissions.

Apparent gender differences may also be related to differing MI severity within study populations. The cohort of women in some studies may represent a higher-risk female population [18] with higher rates of inhospital complications [17]. Higher case-fatality in women may reflect these factors [18,19], and therefore exclusion of early deaths from our study cohort would limit the impact of this factor. The similar findings of the landmark analyses in our study indicate that the impact of comorbidities and treatment
at baseline persist into the longer term, with limited impact of subsequent revascularisation on rates.

Higher unadjusted CVD mortality risk in women versus men persisted across age groups, with similar disparities for all-cause mortality. Although a lower risk of CVD death may be expected in younger women than men, we found that women in the 35–54 year age group had a 5% absolute higher risk of CVD death than the corresponding men, and a doubling of risk which remained elevated, although not significantly so, after multivariate adjustment. Our results are in concordance with those from a national inpatient registry in Sweden, with evidence of a higher risk of all-cause mortality at four years following MI in 25–54 year old women versus men [20]. However, men in this age group were more likely to have a CVD-related death than women (55.4% vs 34.1% respectively). This is in contrast to our study, where the proportion of CVD deaths was similar between men and women across all age groups. This implies that the mortality differences in our study are not driven by a greater proportion of non-CVD deaths in women relative to men, and highlights the importance of addressing vascular risk, even in younger women with CHD.

The multivariate analyses in our study show that the poorer long-term survival in women may be associated with the higher comorbidity burden relative to men. Indigenous status, diabetes, heart failure and chronic kidney disease appeared to explain much of the increased risk in women for recurrent MI and mortality in the 35–54 and 55–69 year age groups, although the impact of Indigenous status was greater in the younger age group. Although excluding Indigenous people from the analysis reduced the disparity in absolute risk to a greater degree in 35–54 versus 55–69 year olds, further analysis showed that diabetes attenuated adjusted rates in the youngest age group independent of Indigenous status. This is of importance, as over a quarter of women in the 35–54 year age group in our study had diabetes and an adverse risk factor profile in younger women with diabetes is associated with relatively higher levels of all-cause mortality [21].

The use of evidence-based medications, including beta-blockers, ACEI/ARBs, statins and antiplatelet drugs, is associated with improved survival in patients with CHD [22]. Although there were reasonably high levels of dispensing of evidence-based drugs at discharge in our study, men had higher levels of dispensing across all age groups compared with women. Evidence suggests that this disparity is one of the factors which
CHAPTER 8. AGE AND GENDER DIFFERENCES IN MYOCARDIAL INFARCTION OUTCOMES

contributes to increased long-term risk in women [14,22]. Hence, it is likely that this level of drug uptake is not maintained in the long-term. Use of evidence-based drugs is lower in community-based CHD patients compared with patients following an acute event [23]. Yusuf et al reported that women and younger people are less likely to take medication in a community setting, and that use of antiplatelet therapy, statins and ACEI/ARBs decreases significantly with increasing time after index event [24]. Women with CHD are less likely to be prescribed statins in the primary care setting, despite a higher prevalence of hyperlipidaemia [25]. It has also been reported that three-quarters of all acute coronary syndrome patients don’t receive optimal evidence-based secondary prevention, including referral to rehabilitation and lifestyle modification, by the time of hospital discharge [10]. These issues may all contribute to the gender differences reported. Whether these patterns are related to patient adherence or system-level issues such as formal pathways for medical follow-up and rehabilitation requires explanation. It is also possible that because increasing age is a known risk factor for cardiovascular events, less aggressive cardiovascular management is provided to younger women, even in the presence of existing CHD.

8.5.2 STRENGTHS AND LIMITATIONS

The strength of our study lies in the ability to capture all incident MIs occurring in a whole-population, and in the availability of complete long-term follow-up data for this cohort. Because of the person-based record linkage available in WA and long hospitalisation history available for this study, we were able to accurately identify first-ever MI cases and capture comorbidity history in this population. However, linked administrative data has inherent limitations which need to be considered. These include the accuracy of recording of MI in hospital morbidity data, which has been validated in our population (sensitivity 74%, positive predictive value 94% against American Heart Association epidemiological criteria) [26]. Additionally, data for baseline clinical indicators and in-hospital medications are not available in the administrative datasets. We also did not have data related to continued use of pharmacotherapy and other secondary prevention measures following hospital discharge in these patients. Nor was there any data on preadmission pharmacotherapy, so we did not have any information on drugs used prior to admissions. The use of increasingly sensitive troponin assays in MI diagnosis during the study period could lead to an increasing proportion of lower severity MI cases in our cohort, which is unlikely to lead to a higher risk of CVD.
mortality in women. Other potential confounders of age-specific gender disparities such as smoking, diet, psychosocial factors and socioeconomic status were not able to be accounted for in our analyses, and therefore residual confounding for the relationship of age and gender with outcomes may be present.

8.6 CONCLUSION

This study contributes to the limited data on gender differences in long-term outcomes following MI in an Australian setting. It highlights the elevated cardiovascular risk in women compared with men over the long-term, and that this difference is not limited to older women. These differences are apparent despite reasonable, although not optimal, levels of dispensing of evidence-based drugs at discharge from hospital. These data demonstrate that the need for ongoing secondary prevention is imperative, and that measures should not be restricted to the early period following an acute event. In particular, health professionals should be aware that women, even in the younger age group, have a high CVD risk factor and comorbidity burden and remain at high risk of adverse outcomes over an extended period of time.

8.7 ACKNOWLEDGEMENTS

This study is funded by a project grant from the National Health and Medical Research Council (#572558). LN is funded by a National Health and Medical Research Council / Heart Foundation Postgraduate Scholarship. EA is funded by an Australian Postgraduate Award and PhD Completion Scholarship.
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8.8 REFERENCES


CHAPTER 9. DIABETES AND TRENDS IN LONG-TERM MORTALITY FOLLOWING INCIDENT MYOCARDIAL INFARCTION

PAPER SUBMITTED FOR PUBLICATION

This chapter is based upon the final submitted version of the following manuscript:

Trends in long-term all-cause and cardiovascular mortality following incident myocardial infarction in people with and without diabetes

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Keywords: Diabetes; Myocardial infarction; Mortality; Trends
The previous chapter established the baseline risk for long-term recurrence and mortality outcomes following incident MI in the WA population. Because of the age/gender perspective of the analyses, the findings demonstrated that the elevated risk of cardiovascular outcomes was seen across all age groups in women relative to men, highlighting the importance of gender stratification.

Given that Chapters 6 and 7 demonstrated improving trends in MI and CHD incidence and 30-day case fatality in people with diabetes following incident MI, an understanding of whether these trends extended to longer term mortality following MI in people with diabetes was sought. This is of interest because of the implications for ongoing prevention and risk factor management in this patient group. Therefore the study in Chapter 9 was designed to examine whether there have been temporal improvements in long-term mortality after MI in the diabetic relative to non-diabetic population in WA. The stratification of all results by gender was incorporated into the study in view of the relative differences in outcomes between men and women reported in the study in Chapter 8.
CHAPTER 9. DIABETES AND TRENDS IN LONG-TERM MORTALITY FOLLOWING INCIDENT MYOCARDIAL INFARCTION

9.1 ABSTRACT

*Background:* Long-term mortality following myocardial infarction (MI) is higher in diabetic than non-diabetic individuals. Early case-fatality after MI has improved but it is unclear whether trends extend to long-term mortality. We aimed to determine whether the disparity in long-term all-cause and cardiovascular disease (CVD) mortality by diabetes status has decreased.


*Results:* There were 22,594 30-day survivors of incident MI. There was little change across the three periods in all-cause mortality in diabetic men (27.1%, 28.2%, 25.5%) and women (34.9%, 36.8%, 36.1%), but small declines from first to last periods in non-diabetic men (14.5% to 12.1%, \( p=0.03 \)) and women (21.0% to 19.4%, \( p=0.08 \)). There was no temporal change in the increased all-cause mortality HRs in diabetic versus non-diabetic men and women. Multivariable-adjusted risk for CVD mortality remained elevated in diabetic women (2006–2009 HR 1.73, 95% CI 1.29, 2.32) but not so in men (2006–2009 HR 1.08, 95% CI 0.85, 1.37).

*Conclusions:* The excess long-term mortality associated with diabetes and excess CVD mortality in diabetic women indicates a need for improved secondary prevention in diabetic patients, especially women.

9.2 INTRODUCTION

Myocardial infarction (MI) is a frequent and serious complication of diabetes. Individuals with diabetes who suffer an MI are at high risk of further vascular complications [1–3]. The elevated mortality associated with diabetes is predominantly cardiovascular-related, but up to 40% of the excess risk of death may relate to non-vascular causes [4]. Better secondary prevention and treatment of people with diabetes with manifest cardiovascular disease (CVD) has the potential to impact long-term outcomes in this group. Although long-term mortality following MI in people with
diabetes has improved in recent decades, there is limited evidence that the gap between people with diabetes and without diabetes has reduced [5–7], despite temporal improvements in mortality rates in the broader diabetic population [8, 9].

CVD mortality has also improved substantially in diabetes, however a lack of data exists on trends in CVD mortality after MI [10–13]. There is some evidence of improved CVD mortality in patients with diabetes within 1-year of a first acute coronary syndrome presentation [14], but limited data regarding CVD mortality with longer-term follow-up. Additionally, there is evidence that temporal changes in the proportion of misclassified CVD-related deaths in people with diabetes could overestimate downward trends in CVD mortality in this patient group [15].

Changing patterns of comorbidities, treatment and MI severity over time can all impact long-term mortality after MI. The combined impact of these factors at a population level is of particular interest in our population, due to falls in incidence rates of MI in people with diabetes since the late 1990s, with concurrent significant reductions in 30-day case fatality in MI patients with diabetes [16, 17]. These population-level trends likely indicate improved management of cardiovascular risk factors and acute care in people with diabetes, but whether these findings extend to improvements in longer-term outcomes is unknown. Therefore, the aim of this study was to estimate trends in long-term all-cause and CVD mortality following incident MI in people with diabetes and in those without diabetes and determine whether the excess mortality associated with diabetes has reduced over time.

9.3 METHODS

9.3.1 DATA SOURCE AND PARTICIPANTS

Data for this study were obtained from the WA Data Linkage System (WADLS) which systematically links population-based administrative health datasets using probabilistic matching [18]. The current study used a de-identified dataset containing linked records from two of the core WADLS sources, the Hospital Morbidity Data System and the Mortality Register. This linked dataset covered the period 01 January 1985 to 30 June 2011. The linked dataset contained records for all hospitalisations and deaths recorded as CVD or diabetes, and all hospital and death records within the period of coverage for each person in the dataset. The statutory nature of these data collections ensures capture of all hospitalisations (public and private) and deaths in WA. Variables contained within
the linked dataset included demographic data, principal discharge and 20 secondary discharge diagnosis fields, inpatient procedures, admission and discharge dates, date of death, and cause of death (underlying and associated). Approval to conduct this study was obtained from the Human Research Ethics Committees of The University of Western Australia and the WA Department of Health (#2009/18) under a waiver of consent.

The linked dataset was used to identify all patients aged 35 to 84 years hospitalised for MI in WA between 1998 and 2009. Incident cases of MI were identified from the principal discharge diagnosis field (ICD-9 410, ICD-10-AM I21, I22), where there was no hospitalisation for MI in the 13 years preceding the incident event. Prior hospitalisation was defined as any MI hospitalisation in a principal or secondary discharge diagnosis field during the lookback period. Patients were classified with diabetes if it was recorded on the incident MI episode of care or on any hospitalisation in the 13 years prior to the incident MI (ICD-9 250, ICD-10-AM E10–E14). Patients surviving >30 days following the date of incident MI were included in the cohort.

9.3.2 FOLLOW-UP

Outcomes of interest were long-term all-cause and CVD mortality. A standard definition of CVD was used for the primary analysis, where the underlying cause of death was coded as any CVD (ICD-9 390–459, ICD-10-AM I00–I99). Sensitivity analyses were conducted using a modified CVD mortality definition to account for the potentially increasing underestimation during the study period of deaths attributed to CVD in people with diabetes [15]. Therefore in patients with diabetes, we also identified CVD deaths where uncomplicated diabetes (E10.9, E11.9, E12.9, E13.9, E14.9) or diabetes with circulatory complications (E10.5, E11.5, E12.5, E13.5, E14.5) were coded as the underlying cause of death, with concurrent coding of a restricted range of CVD codes (I10–I25, I60–I69) in other cause of death fields.

The incident MI cases were analysed in three periods representing the year of occurrence of incident MI (1998–2001, 2002–2005, 2006–2009). Follow-up was censored at the date of death or at five years' post-incident MI admission date for the first two periods, and for the third period, at date of death, five years following incident MI, or at 30 June 2011 (maximum length of dataset), whichever came first. The third cohort of patients therefore had a median follow-up time of 3.16 years. Of the patients recorded as dying during the follow-up period, seven had a missing cause of death.
(three with diabetes and four without diabetes) and were excluded from all CVD mortality analyses.

9.3.3 COMORBIDITIES

Comorbidity variables were identified from the linked dataset. A fixed 13-year lookback period from and including the date of each incident MI was used, except for prior coronary heart disease (CHD) where recording of unstable angina or other CHD codes within the same episode of care were excluded. ICD codes used to identify the comorbidities of interest were hypertension (ICD-10-AM I10–I15 and ICD-9CM equivalent), heart failure (I50), stroke (I60–I64), chronic kidney disease (CKD, as per the Australian Institute of Health and Welfare definition) [19], and CHD (I20, I23–25).

9.3.4 STATISTICAL ANALYSES

All results are presented by period, gender and diabetes status. Baseline cohort characteristics are presented as mean (SD) for continuous variables, and as proportions for categorical variables. Trends in proportions were analysed using chi-squared tests. Unadjusted 5-year mortality was estimated from Kaplan Meier survival curves, and log-rank p-values are presented for comparisons in unadjusted mortality between periods for each gender and diabetes status grouping separately. Cox proportional hazards regression models were used to estimate the effect of diabetes on the risk of all-cause and CVD mortality. Stepwise addition of variables to the model was undertaken to determine the impact of each covariate on the estimated diabetic versus non-diabetic hazard ratios (HR). Covariates included in the models were age (continuous) and age², Indigenous status, CKD, hypertension, heart failure, stroke and prior CHD. Results are presented as HR with 95% CI. To test for a change in HRs over the study period, an interaction term (period × diabetes status) was added to the model. The proportional hazards assumption was tested with an interaction term for diabetes status and time, separately for each period and gender grouping. No evidence of violation of the assumption was found. Statistical significance levels are set at p<0.05. All statistical analyses were undertaking using SAS v9.4 (Cary, NC).

9.4 RESULTS

There were 24,186 incident MI cases identified between 1998 and 2009. Patients who died within 30 days of MI hospitalisation (n=1592) were excluded from the study, leaving 22,594 people in the study cohort. The proportion of MI cases with diabetes
increased from 20.4% to 24.1% in men, and from 27.7% to 31.8% in women over the study period (Table 9.1). Men with diabetes were on average 3 years older in each period than their non-diabetic counterparts (p<0.0001 in each period), while there was no significant difference in women by diabetes status. People with diabetes had higher levels of all comorbidities in each period (p<0.0001). There was a small increase over time in the proportion of diabetic people who were Indigenous, but no increase in non-diabetic MI cases. Similar trends in the proportion with heart failure (decreasing) and hypertension (increasing) were apparent in diabetic and non-diabetic patients. The proportion with CKD increased over time in diabetic men and women but remained unchanged in those without diabetes.

There were 3780 deaths, with 26.9% of people with diabetes and 13.4% of people without diabetes dying during the follow-up period out to five years. The proportion of deaths recorded as CVD was higher in non-diabetic men (50.2%) than men with diabetes (46.0%), but similar in diabetic and non-diabetic women (49.8% and 48.0% respectively). This level did not change for diabetic women (p=0.16), but decreased in non-diabetic men and women, and in men with diabetes (all p<0.01). When the modified definition of CVD death was applied, trends in the proportion of deaths attributed to CVD were similar to those for the standard definition across each gender/diabetes grouping.

9.4.1 **TRENDS IN ALL-CAUSE MORTALITY**

Figure 9.1 shows that the 5-year survival curves were consistently worse in men and women with diabetes, with no temporal improvement over consecutive periods. Unadjusted all-cause mortality remained stable over the study period for diabetic men (from 27.1% to 25.5%; p=0.30) and women (from 34.9% to 36.1%; p=0.59) (Table 9.2). There were small marginally significant decreases over time in unadjusted all-cause mortality in non-diabetic people (men, 14.5% to 12.1%, p=0.03; women 21.0% to 19.4%, p=0.08).

The estimated unadjusted and age-adjusted 5-year mortality was about two-fold higher in men and women with diabetes than those without diabetes (Table 9.3, Figure 9.2). There was no significant change in the unadjusted or multivariable-adjusted HRs throughout the study period in men or women (fully adjusted models p=0.99 and p=0.85 respectively) (Table 9.3, Figure 9.2). The adjusted hazard of all-cause mortality in men...
and women remained, respectively, 31% and 43% greater in those with diabetes versus without diabetes in the last calendar period.

9.4.2 TRENDS IN CVD MORTALITY

Unadjusted 5-year CVD mortality was nearly two-fold higher in men and women with diabetes than those without diabetes in the first calendar period (Table 9.2). For men and women without diabetes, and for men with diabetes, there was a significant decrease in unadjusted CVD mortality over time (non-diabetic men and women p<0.0001, men with diabetes p=0.006). However for women with diabetes, CVD mortality was unchanged across the three periods (20.4%, 19.2%, 20.6% respectively, p=0.79). Therefore, the absolute difference between women with and without diabetes increased from the first (−8.1%) to last calendar periods (−13.3%) (Table 9.2).

There was no significant change in the age-adjusted and fully adjusted risk of CVD mortality in diabetic versus non-diabetic men from the first to last periods (Table 9.3, Figure 9.2). The estimated multivariable-adjusted HR was 1.12 (95% CI 0.91, 1.38) in 1998–2001, 1.43 (1.18, 1.75) in 2002–2005 and decreased to become non-significant in 2006–2009 (HR 1.08, 95% CI 0.85, 1.37; p=0.89). In women, there was a consistent increase in relative risk throughout the study period (1.38 in 1998–2001; 1.73 in 2006–2009) although no significant trend was detected (p=0.22) (Figure 9.2).

When the modified definition of CVD mortality was used for people with diabetes, unadjusted rates were on average 1% higher than those estimated using the standard CVD mortality definition, and comparisons between periods remained significant in men (p=0.0013) but not so in women (p=0.75) (data not shown).

9.4.3 EFFECT OF COVARIATES

Adjusting for age had a large effect on the HRs, although in opposite directions for men (decreasing) and women (increasing) (Table 9.3). Adjustment for CKD and heart failure produced appreciable attenuation of the HRs but adjustment for Indigenous status, hypertension, stroke and prior CHD had little impact. The effect of adjustment for CKD was greater in each subsequent period, with attenuation of the HR from 1.94 to 1.58 in men, and from 2.03 to 1.71 in women by the last period.
### CHAPTER 9. DIABETES AND TRENDS IN LONG-TERM MORTALITY FOLLOWING INCIDENT MYOCARDIAL INFARCTION

**Table 9.1. Characteristics of men and women aged 35–84 years with an incident myocardial infarction, stratified by diabetes status.**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Diabetes</th>
<th>No diabetes</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=949; 20.4%)</td>
<td>(n=1186; 23.0%)</td>
<td>(n=1500; 24.1%)</td>
<td>(n=3699; 79.6%)</td>
<td>(n=3965; 77.0%)</td>
<td>(n=4714; 75.9%)</td>
<td></td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>64.38 (11.2)</td>
<td>64.06 (11.36)</td>
<td>64.75 (11.62)</td>
<td>61.45 (12.12)</td>
<td>61.79 (12.19)</td>
<td>61.36 (11.94)</td>
<td></td>
</tr>
<tr>
<td>Indigenous, %</td>
<td>6.7</td>
<td>9.6</td>
<td>8.9</td>
<td>2.7</td>
<td>2.6</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>58.4</td>
<td>67.5</td>
<td>79.7</td>
<td>37.6</td>
<td>39.3</td>
<td>47.6</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>19.6</td>
<td>21.2</td>
<td>23.4</td>
<td>8.0</td>
<td>6.1</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>27.0</td>
<td>25.4</td>
<td>22.6</td>
<td>12.3</td>
<td>11.2</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>6.7</td>
<td>6.7</td>
<td>5.4</td>
<td>3.2</td>
<td>2.5</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Prior coronary heart disease</td>
<td>28.3</td>
<td>28.0</td>
<td>32.0</td>
<td>15.4</td>
<td>14.6</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=530; 27.7%)</td>
<td>(n=646; 29.9%)</td>
<td>(n=796; 31.8%)</td>
<td>(n=1386; 72.3%)</td>
<td>(n=1513; 70.1%)</td>
<td>(n=1710; 68.2%)</td>
<td></td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>67.67 (11.42)</td>
<td>68.15 (11.87)</td>
<td>68.14 (11.67)</td>
<td>68.81 (11.65)</td>
<td>68.45 (11.82)</td>
<td>67.51 (12.12)</td>
<td></td>
</tr>
<tr>
<td>Indigenous, %</td>
<td>13.0</td>
<td>12.8</td>
<td>14.4</td>
<td>2.6</td>
<td>2.6</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>71.5</td>
<td>79.6</td>
<td>88.7</td>
<td>53.2</td>
<td>55.8</td>
<td>57.4</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>19.8</td>
<td>25.4</td>
<td>28.3</td>
<td>8.4</td>
<td>8.4</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>41.3</td>
<td>36.8</td>
<td>35.2</td>
<td>20.6</td>
<td>17.4</td>
<td>12.7</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>7.9</td>
<td>8.4</td>
<td>7.7</td>
<td>4.2</td>
<td>4.2</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Prior coronary heart disease</td>
<td>30.0</td>
<td>31.4</td>
<td>33.2</td>
<td>19.0</td>
<td>17.2</td>
<td>17.1</td>
<td></td>
</tr>
</tbody>
</table>
# Chapter 9. Diabetes and Trends in Long-term Mortality Following Incident Myocardial Infarction

## Table 9.2. Trends in 5-Year Mortality Following Incident Myocardial Infarction in Men and Women Aged 35–84 Years, Stratified by Diabetes Status.

<table>
<thead>
<tr>
<th></th>
<th>All-cause mortality</th>
<th></th>
<th>Cardiovascular disease mortality</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths, n</td>
<td>Mortality, %</td>
<td>Log-rank p-value</td>
<td>Absolute difference, %*</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>1998–2001</td>
<td>257</td>
<td>27.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2006–2009</td>
<td>291</td>
<td>25.5</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>No diabetes</strong></td>
<td>1998–2001</td>
<td>536</td>
<td>14.5</td>
<td>−12.6</td>
</tr>
<tr>
<td></td>
<td>2002–2005</td>
<td>526</td>
<td>13.3</td>
<td>−14.9</td>
</tr>
<tr>
<td></td>
<td>2006–2009</td>
<td>410</td>
<td>12.1</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>1998–2001</td>
<td>185</td>
<td>34.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2002–2005</td>
<td>238</td>
<td>36.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2006–2009</td>
<td>201</td>
<td>36.1</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>No diabetes</strong></td>
<td>1998–2001</td>
<td>291</td>
<td>21.0</td>
<td>−13.9</td>
</tr>
<tr>
<td></td>
<td>2002–2005</td>
<td>290</td>
<td>19.2</td>
<td>−17.6</td>
</tr>
<tr>
<td></td>
<td>2006–2009</td>
<td>221</td>
<td>19.4</td>
<td>0.08</td>
</tr>
</tbody>
</table>

†Unadjusted 5-year mortality from Kaplan Meier survival curves.

*Absolute 5-year mortality difference between diabetic and non-diabetic patients.
TABLE 9.3. UNADJUSTED HAZARD RATIOS (95% CONFIDENCE INTERVALS) FOR 5-YEAR ALL-CAUSE AND CARDIOVASCULAR DISEASE MORTALITY IN PEOPLE WITH AND WITHOUT DIABETES, AND ADJUSTED HAZARD RATIOS AFTER STEPWISE ADDITION OF COVARIATES, STRATIFIED BY DIABETES STATUS AND PERIOD.†

<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>Unadjusted</th>
<th>Adjusted for:</th>
<th>+ age</th>
<th>+ Indigenous status</th>
<th>+ chronic kidney disease</th>
<th>+ hypertension</th>
<th>+ heart failure</th>
<th>+ stroke</th>
<th>+ prior coronary heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998–2001</td>
<td>2.03 (1.75, 2.36)</td>
<td>1.76 (1.52, 2.04)</td>
<td>1.69 (1.46, 1.97)</td>
<td>1.55 (1.34, 1.80)</td>
<td>1.50 (1.29, 1.75)</td>
<td>1.35 (1.16, 1.56)</td>
<td>1.33 (1.14, 1.54)</td>
<td>1.31 (1.13, 1.52)</td>
<td></td>
</tr>
<tr>
<td>2002–2005</td>
<td>2.35 (2.05, 2.70)</td>
<td>2.09 (1.82, 2.40)</td>
<td>1.85 (1.61, 2.12)</td>
<td>1.75 (1.52, 2.01)</td>
<td>1.62 (1.41, 1.86)</td>
<td>1.60 (1.39, 1.84)</td>
<td>1.59 (1.38, 1.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006–2009</td>
<td>2.37 (2.04, 2.75)</td>
<td>1.86 (1.60, 2.16)</td>
<td>1.53 (1.31, 1.79)</td>
<td>1.46 (1.25, 1.70)</td>
<td>1.34 (1.14, 1.56)</td>
<td>1.34 (1.14, 1.56)</td>
<td>1.31 (1.13, 1.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trend p-value</td>
<td>0.16</td>
<td>0.31</td>
<td>0.40</td>
<td>0.89</td>
<td>0.75</td>
<td>0.93</td>
<td>0.96</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Wome n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998–2001</td>
<td>1.80 (1.50, 2.17)</td>
<td>2.04 (1.69, 2.45)</td>
<td>1.93 (1.60, 2.32)</td>
<td>1.77 (1.47, 2.13)</td>
<td>1.76 (1.46, 2.12)</td>
<td>1.50 (1.24, 1.82)</td>
<td>1.47 (1.22, 1.78)</td>
<td>1.46 (1.21, 1.77)</td>
<td></td>
</tr>
<tr>
<td>2002–2005</td>
<td>2.15 (1.81, 2.56)</td>
<td>2.16 (1.81, 2.56)</td>
<td>1.89 (1.59, 2.25)</td>
<td>1.88 (1.58, 2.24)</td>
<td>1.64 (1.38, 1.96)</td>
<td>1.62 (1.36, 1.94)</td>
<td>1.61 (1.35, 1.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006–2009</td>
<td>2.09 (1.73, 2.53)</td>
<td>2.02 (1.67, 2.45)</td>
<td>1.70 (1.40, 2.06)</td>
<td>1.69 (1.39, 2.05)</td>
<td>1.45 (1.19, 1.77)</td>
<td>1.45 (1.19, 1.77)</td>
<td>1.43 (1.17, 1.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trend p-value</td>
<td>0.28</td>
<td>0.66</td>
<td>0.73</td>
<td>0.77</td>
<td>0.76</td>
<td>0.79</td>
<td>0.89</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease mortality‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998–2001</td>
<td>1.87 (1.52, 2.29)</td>
<td>1.61 (1.31, 1.98)</td>
<td>1.56 (1.27, 1.92)</td>
<td>1.40 (1.13, 1.72)</td>
<td>1.34 (1.09, 1.65)</td>
<td>1.15 (0.94, 1.42)</td>
<td>1.13 (0.92, 1.40)</td>
<td>1.12 (0.91, 1.38)</td>
<td></td>
</tr>
<tr>
<td>2002–2005</td>
<td>2.24 (1.84, 2.72)</td>
<td>2.02 (1.66, 2.47)</td>
<td>1.73 (1.42, 2.12)</td>
<td>1.61 (1.32, 1.97)</td>
<td>1.46 (1.19, 1.78)</td>
<td>1.44 (1.18, 1.76)</td>
<td>1.43 (1.17, 1.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006–2009</td>
<td>2.13 (1.69, 2.69)</td>
<td>1.67 (1.32, 2.11)</td>
<td>1.32 (1.04, 1.67)</td>
<td>1.24 (0.98, 1.57)</td>
<td>1.10 (0.87, 1.40)</td>
<td>1.10 (0.86, 1.39)</td>
<td>1.08 (0.85, 1.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trend p-value</td>
<td>0.39</td>
<td>0.55</td>
<td>0.62</td>
<td>0.77</td>
<td>0.20</td>
<td>0.82</td>
<td>0.90</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Wome n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998–2001</td>
<td>1.72 (1.34, 2.21)</td>
<td>1.99 (1.55, 2.55)</td>
<td>1.87 (1.46, 2.41)</td>
<td>1.74 (1.35, 2.24)</td>
<td>1.72 (1.33, 2.21)</td>
<td>1.43 (1.11, 1.86)</td>
<td>1.39 (1.08, 1.80)</td>
<td>1.38 (1.07, 1.79)</td>
<td></td>
</tr>
<tr>
<td>2002–2005</td>
<td>2.19 (1.70, 2.82)</td>
<td>2.21 (1.71, 2.85)</td>
<td>1.95 (1.51, 2.52)</td>
<td>1.93 (1.49, 2.50)</td>
<td>1.64 (1.27, 2.13)</td>
<td>1.61 (1.24, 2.09)</td>
<td>1.60 (1.23, 2.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006–2009</td>
<td>2.57 (1.93, 3.42)</td>
<td>2.50 (1.88, 3.33)</td>
<td>2.13 (1.60, 2.85)</td>
<td>2.10 (1.57, 2.81)</td>
<td>1.75 (1.31, 2.35)</td>
<td>1.76 (1.31, 2.37)</td>
<td>1.73 (1.29, 2.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trend p-value</td>
<td>0.03</td>
<td>0.11</td>
<td>0.12</td>
<td>0.25</td>
<td>0.57</td>
<td>0.27</td>
<td>0.20</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

† Derived from Cox regression models, adjusted for age (continuous) and age², Indigenous status, hypertension, chronic kidney disease, heart failure, stroke and prior coronary heart disease.
‡Based on standard definition of cardiovascular disease mortality.
CHAPTER 9. DIABETES AND TRENDS IN LONG-TERM MORTALITY FOLLOWING INCIDENT MYOCARDIAL INFARCTION

Figure 9.2. Hazard ratios from Cox regression models for people with versus without diabetes following incident myocardial infarction, for all-cause mortality in men (A) and women (B), and cardiovascular disease mortality in men (C) and women (D), stratified by period. Multivariable-adjusted models include age, indigenous status and comorbidities (hypertension, chronic kidney disease, heart failure, stroke and prior history of coronary heart disease).
9.5 DISCUSSION

Our study demonstrates three important findings. Firstly, there has been little change in the excess long-term all-cause mortality following incident MI in people with diabetes over the past decade. Secondly, people with diabetes continue to experience mortality rates nearly double that of their non-diabetic counterparts at 5-years' post-MI. Thirdly, despite major advances in the management of cardiovascular risk in people with diabetes, there has been no improvement in the CVD mortality differential by diabetes status in women, with a potentially widening gap over time, in contrast to the reduction in long-term CVD mortality in diabetic men.

The strength of this study lies in its use of high quality administrative health data. This allows capture of all incident MI cases during the study period, with accurate identification of first-ever events and complete capture of mortality status. Diabetes status was also identified from this data source. We have previously tested the accuracy of diabetes recording for CHD patients over time and found sensitivity of over 90% and positive predictive value of 92% for identifying diabetes status measured against hospital medical records [20]. Our method uses a lookback period of 13 years to identify diabetes status from hospital morbidity data which provides optimal ascertainment of diabetes status. We included patients aged up to 84 years, increasing the generalisability of results, but imposed the upper age limit because of decreasing reliability of MI recording with increasing age [21].

A limitation of our study is that comorbidity status is only ascertained from hospitalisation data, which may underestimate the prevalence of some conditions. The coding of underlying cause of death is influenced by changing standards. As a further sensitivity analysis, we also identified CVD death if coded in any cause of death field. This produced trends in CVD mortality in diabetic and non-diabetic patients similar to those seen for our standard and modified definitions. This, along with the modified definition analysis, demonstrates that any changes in cause of death coding are unlikely to have influenced the trend results in this post-MI cohort.

A number of studies have reported a temporal decrease in excess all-cause mortality in the broader diabetic population [8, 9, 12, 13, 22]. Studies confined to cohorts of MI patients have shown limited improvement in the excess long-term mortality associated with diabetes. These results have been reported from population-level registries, [6, 7]...
and single centre [5] and whole-population studies [14]. Even where the magnitude of decline in long-term mortality in people with diabetes has been substantial, for example, ~30% decline between 1985 and 2004 in a MI cohort from the Netherlands [5], the mortality differential between individuals with and without diabetes has not reduced. In contrast, a Swedish study using a whole-population MI registry reported a narrowing of this disparity out to 8 years following MI [23]. This result could be partly due to more marked declines in 30-day deaths in people with diabetes in that population. We have observed greater rates of decline in 30-day deaths after MI by diabetes status in our population [17], and exclusion of these patients from the study cohort provides a clearer picture of long-term mortality trends.

Favourable trends in MI incidence and subsequent 30-day case fatality in people with diabetes have been observed in the WA population during the current study period [16, 17]. Despite this, substantial improvements in long-term mortality in people with diabetes after a first MI are not evident. The disparity in use of evidence-based drugs and revascularisation in people with diabetes acutely following MI is likely to have reduced in recent years [17, 23, 24] contributing to observed short-term mortality improvements. Evidence from clinical trials suggests that control of LDL-C levels and blood pressure reduces the risk of death in people with diabetes [25–27]. While this is seen in the clinical trial setting, data on ongoing use in the real-world context is limited.

The limited change in all-cause mortality in people with diabetes may reflect the increasingly higher prevalence of CKD, hypertension and prior CHD hospitalisations in these patients [16]. Renal impairment imparts a high risk of mortality in diabetic patients [28] and the multivariable modelling in our study showed that CKD was increasingly associated with excess all-cause mortality. The Emerging Risk Factors Collaboration reported that in addition to vascular disease, diabetes is associated with substantial premature death from cancers and other diseases including renal disease, pneumonia and other infectious diseases [4]. Therefore, despite a decreasing severity of MI, partly mediated by increasing use of more sensitive troponin assays [29], lower total mortality rates in people with diabetes are not apparent.

An increasing proportion of deaths are attributed to non-vascular causes in people with diabetes [12, 13, 22]. This may reflect real changes in disease aetiology and comorbidity profile in this patient group. Changes in coding practices may also influence trends [15, 30]. Our study showed that the proportion of deaths with CVD as the underlying cause
decreased in men with diabetes and in non-diabetic men and women, perhaps indicating a real shift in cause of death. The fact that this pattern was not observed in women with diabetes, either for the standard or modified definition of CVD death, supports the trends reported in the current study, as any artefactual coding changes are likely to impact equally on coding practice in both genders.

Management of cardiovascular risk in people with diabetes has significantly improved during the past decade and this is likely to have contributed to reductions in CVD mortality [12, 13, 22]. In one of few studies reporting trends in CVD mortality after MI, rates fell similarly in diabetic and non-diabetic patients out to 1 year after first acute coronary syndrome presentation, with no gender differences observed [14]. These results also excluded early deaths. Our results out to 5-years demonstrate that these favourable trends continued in men with diabetes, but not in women.

The risk of CVD mortality in women with diabetes compared to those without diabetes remained elevated, despite adjustment for differences in baseline risk characteristics. This is consistent with other studies where further confounders, including dyslipidaemia and weight, have been adjusted for [31]. Absolute all-cause and CVD mortality rates remained 8–10% higher in women than men in the diabetic group in our study. The higher comorbidity burden in diabetic women is likely to contribute to the elevated mortality risk post-MI [32], especially in younger women [33]. Vascular mortality rates have shown less temporal improvement in women who are overweight or obese compared with lean women [34], which may be relevant given the greater relative increases in obesity in Australian women than men [35].

9.6 CONCLUSIONS

Our study shows that there has been no significant improvement in long-term all-cause mortality in people with diabetes following an incident MI in this whole-population setting, resulting in continued excess long-term mortality associated with diabetes. Encouragingly, there is some improvement over time in CVD mortality in men with diabetes, however a lack of improvement in CVD mortality in women with diabetes means that the gap for women may be widening. These results highlight an urgent need for addressing both cardiovascular and non-vascular risk in post-MI patients with diabetes, particularly in women, as improvements in MI incidence and short-term outcomes in people with diabetes are not reflected in current long-term outcomes.
9.7 REFERENCES


CHAPTER 10. GENERAL DISCUSSION AND CONCLUSIONS

The findings, implications and limitations for each of the studies in Chapters 4 to 9 have been presented and discussed in the relevant chapters. The discussion here focuses on the broader implications of these studies and an integration of the findings. The general discussion is presented in two sections — firstly, in relation to trends in CHD incidence in people with diabetes relative to those without and, secondly, in relation to mortality outcomes following hospitalisation for MI. Lastly, the broader limitations of the present studies and directions for future research arising from this program of work are outlined.

10.1 SUMMARY OF KEY FINDINGS

This thesis includes a collection of inter-related studies investigating epidemiological trends in CHD, including other elements of atherothrombotic disease, and focusing on adults with diabetes relative to trends in the non-diabetic population. It is unique in an Australian context and adds to the limited number of studies internationally where this full spectrum of epidemiological trends in diabetes and CHD has been investigated at a whole-population level. Understanding the trends in incidence of MI and CHD more broadly, early case fatality following MI, and very late outcomes provides important data regarding the potential population impacts of primary prevention, acute management and secondary prevention in the high-risk diabetic group.

This body of work has established that the incidence of MI and CHD more broadly has declined in people with diabetes in a whole-population setting although there remains an excess risk of MI associated with diabetes [1]. These trends have occurred in the context of a declining incidence of atherothrombotic vascular disease overall. In addition to a declining MI incidence, patients with diabetes who are hospitalised for a first-ever MI now have a similar risk of dying within 30-days of MI as people without diabetes. This is concurrent with increasing levels of acute coronary revascularisation and evidence-based medication use in MI patients with diabetes, although levels still remain below those seen for non-diabetic MI patients.

When long-term outcomes were analysed, the study results demonstrated that women have a higher risk of recurrent MI and CVD mortality than men following an incident
CHAPTER 10. GENERAL DISCUSSION AND CONCLUSIONS

MI [2]. This disparity is seen across all age groups and not just restricted to older age groups. In contrast to short-term mortality trends, temporal trend data demonstrated that longer-term mortality outcomes following MI have not improved significantly in people with diabetes. When the incident MI cohort was stratified by diabetes status, it emerged that the absolute difference in mortality following incident MI remained ~15% higher in diabetics than non-diabetics up to 5-years following MI and that this differential has not improved over recent decades.

10.2 TRENDS IN CORONARY HEART DISEASE INCIDENCE IN PEOPLE WITH DIABETES

10.2.1 MAJOR FINDINGS IN THE CONTEXT OF PUBLISHED LITERATURE

There are only a few populations where long-term incidence trends across the breadth of atherothrombotic vascular disease and specifically in people with diabetes are known. Our findings of declines in CHD, CeVD and PAD incidence based on hospitalisation data [3] are consistent with contemporary separate population studies on CHD [4] and CeVD [5], and also add to the limited PAD trend data [6]. Although the risk associated with the presence of polyvascular disease is well established, there is limited comparative data in terms of trends. Therefore, the declining incidence of polyvascular disease reported from the present study is important, as it has implications for primary and secondary prevention efforts across all vascular territories. This study also showed that declining incidence rates for all forms of atherothrombotic vascular disease occurred despite increasing age-adjusted prevalence of diabetes and hypertension.

Contemporary data on population trends in MI and CHD incidence in people with diabetes are emerging in the US and Europe, but in Australia, there has been no temporal trend data on these measures and thus the study in Chapter 6 fills a void in the national context.

The general perception has been that the ‘diabetes epidemic’ prevalent in many populations could drive CHD incidence upwards. This hypothesis was supported by studies which showed that the increasing prevalence of diabetes and obesity have negatively impacted on declines in CHD mortality rates in the US and England, although are still offset by improving trends in other cardiovascular risk factors [7, 8]. The increasing diabetes prevalence in Australia is therefore of concern because of its potential to attenuate the steadily declining CHD incidence and mortality rates observed since the 1960s in this country [9]. Previously published findings for the WA population
show an attenuation of long-standing downward trends in MI hospitalisation rates, a finding partly explained by the introduction of troponin assays in the late 1990s [10]. Despite these cumulative indications, the aggregated evidence thus far from the US [11–13] has shown declining CHD incidence in people with diabetes, and at a similar rate to that of non-diabetic people. European population data is less consistent, with no improvement in MI incidence in diabetic people in the Northern Sweden MONICA cohort [14] and disparate gender-specific trends in the German MONICA cohort [15].

Our findings in this Australian state-wide setting are therefore notable because of the marked falls in MI incidence in diabetic men and women, and the significant reduction in age-adjusted risk of a first-ever MI. It is likely that these results for the WA population are generalisable to most other Australian jurisdictions, given only small differences in population demographics and health system factors [16]. However, the higher proportion of Indigenous people in the Northern Territory population would likely mean that these WA results are less generalisable to their population because of the high prevalence of diabetes and other cardiovascular risk factors which occur at a younger age in the Indigenous population [17].

My previously published work has shown evidence of adverse trends in the incidence of MI in younger age groups in the WA population, particularly in women [18]. At the time, these findings were hypothesised to result from negative trends in risk factors, primarily diabetes and obesity. The study in Chapter 5 extended this analysis to include all hospitalised CHD [3] and showed small but significant increases in rates in 35–54-year-old women, but marginal declines in men in the same age group. A lack of improvement in rates also extended to CeVD incidence in this age group. A similar pattern in MI incidence has been reported in other whole-population settings [19, 20]. However, there is little comparative data for the age-specific results from the diabetes study in Chapter 6 [1]. These age-specific results were unexpected, as not only did the incidence of MI in diabetic 35–54-year-olds not improve, but rates in the non-diabetic 35–54 year age group (both men and women) increased significantly.

10.2.2 IMPLICATIONS OF RESULTS

Impact of changing primary prevention guidelines on CHD incidence

Understanding population level trends in CHD incidence in diabetic people is an important means of informing primary prevention effectiveness. Declining incidence of
CHAPTER 10. GENERAL DISCUSSION AND CONCLUSIONS

CHD in people with diabetes could reflect broad improvements in the management of cardiovascular risk in diabetic people. During the time covered by this thesis, the guidelines for the management of cardiovascular risk have evolved towards using absolute risk assessment; this is based on evidence that management of multiple risk factors is more effective than treating individual risk factors in lowering cardiovascular risk [21]. This shift may be particularly pertinent for people with diabetes given evidence of reductions in cardiovascular event rates associated with multifactorial management across risk factors [22].

The study findings, therefore, have important clinical implications for ongoing management approaches for people with diabetes in primary and specialist care. Improved management of risk factors, particularly blood pressure, lipids and glycaemic control, may have contributed to the decline in MI and CHD incidence [11, 13]. There are also suggestions of increasing levels of treatment for these conditions in diabetic patients in Australia [23]. Whether the approach to these risk factors has occurred via an absolute risk approach is unknown. Risk assessment algorithms with separate risk categories for diabetic people were introduced during and subsequent to the study period, and with specific targets for modifiable risk factors in this patient group [24, 25]. These changes are in line with the shift internationally towards integrated diabetes and CVD prevention and treatment [26].

However, indications are that the individual risk factor approach still dominates the management of CVD risk factors in primary care [27]. In addition, Australian data shows that general practitioners are less likely to treat people with diabetes to guideline-advocated targets for blood pressure and lipids [28]. Given that the findings of Chapter 6 showed a residual excess risk of incident MI for people with diabetes despite improving trends, further reduction of this risk may require not only better implementation of the risk assessment process, but more effective approaches for achieving risk factor targets in diabetic people. Modelling studies show that a reduction in mean population-level total cholesterol and SBP could result in a 24% to 30% reduction in the projected CHD death rate by 2020, even in the presence of increasing diabetes and obesity prevalence [29], and this highlights the importance of managing these risk factors in this patient group.


**Implications of prior vascular disease history**

The aim of investigating incidence across the vascular territories is to provide a more informed indication of collective prevention efforts, which is important given the shared pathophysiology and similar proposed risk factor approaches for CHD, CeVD and PAD. Falling incidence of polyvascular disease is a likely indication of declining burden of vascular disease as well as demonstrating cross vascular effects of preventive treatments. The presence of atherosclerosis in other vascular territories (cerebral and peripheral) is a major risk factor for the onset of CHD and vice versa. The study in Chapter 5 showed that rates of incident CHD in those with prior vascular disease history are decreasing significantly in the WA population. Although the data represents hospitalised cases only and can’t capture the full spectrum of vascular disease in the community, it may still be a proxy for decreasing severity of CVD as well as indicating the positive cross vascular effects of prevention treatments.

Classification of prevention as primary or secondary may be arbitrary in the context of these results. Falling rates of polyvascular disease in incident cases of CHD likely relate to secondary rather than primary prevention effects. In terms of diabetes, the thesis findings show that prior to the onset of a first-ever MI, around one-third of diabetic patients are managed in the context of established CHD, with this level increasing over the study period. It could be that the intensity of treatment of risk factors and diabetes may not be high enough to prevent the onset of MI in these patients, which would be consistent with the known under-treatment and reaching of targets in people with diabetes [30]. Alternatively, the patients who now experience an MI are an increasingly ‘higher-risk’ diabetic/CHD group, highlighted by double the level of prior CeVD and PAD, and increasing levels of CKD. If so, this has major implications for how prevention and management of these patients should be undertaken, particularly in regards to intensity of treatment.

**Impact of troponins on MI rates in diabetic versus non-diabetic patients**

The increasing proportion of incident MI cases labelled as NSTEMI is a phenomenon seen in many populations [31–34]. This increasing relative burden of lower severity MIs has been shown to attenuate overall downward trends in MI in WA and elsewhere [10, 31]. Interestingly this so-called ‘troponin effect’ was not markedly apparent in diabetic people in our study. However, the rates in the non-diabetic group could have been affected by this, as implied by the flat trends in incident MI but declining incidence of
all hospitalised CHD (Chapter 6). This study, therefore, raises the question of why a marked attenuation of trends is not seen for diabetic people. One hypothesis is that the markedly higher baseline risk of incident MI in diabetic people (4–6 times higher in 1998) means there is a greater likelihood of an absolute reduction in rates, even in the presence of increasing detection of NSTEMI cases. The ARIC study in the US also showed attenuation of downward trends in MI incidence directly associated with the introduction of troponin assays [35], yet a significant decline in CHD incidence in diabetic people in the recent decade [11]. However, in the non-diabetic population in that study, there was still a small reduction in CHD incidence which may be explained by the inclusion of a broader CHD grouping rather than MI separately.

Age-specific risk and trends

Whether the adverse trends in younger age groups, as indicated by levelling of CHD mortality and incidence rates in some countries including Australia [36–38], are real or artefactual has been the subject of conjecture. It could be argued that low event rates in younger people can only result in small reductions in absolute risk and thus difficulty in detecting trends of statistical significance. Therefore, whole population studies are particularly informative for this age group. The age-specific findings in Chapters 5 and 6 contribute to the data which has now accumulated internationally. For example, the pattern of flat trends in MI but significant reductions in CHD incidence in the younger diabetic group suggest a combination of increasing NSTEMI detection in younger people with diabetes but concurrent improvements in prevention and/or management of risk factors. The similar pattern in non-diabetic men in this age group is consistent with this supposition. Alternatively, decreasing CHD incidence could be driven by declining admissions for non-MI manifestations of CHD, which are often admissions for medical or procedural intervention for stable disease.

There is potential for misclassification of diabetes in younger people, both at a clinical level (possible lower propensity for doctors to diagnose diabetes) and at an administrative data level (younger people less likely to have prior hospitalisations to assist with identification of diabetes status). These factors may confound the trends in the diabetic and non-diabetic younger age group. Whether this misclassification of diabetes status occurs more in younger than older people is not clear. Additionally, hyperglycaemia may be present in people without a diagnosis of frank diabetes, therefore resulting in classification as non-diabetic in the present study. The significant
increases in both MI and CHD incidence in 35–54-year-old non-diabetic women may be in part associated with some degree of misclassification of diabetes status. However, adverse trends in incidence are also seen in this younger age group in other vascular disease manifestations, particularly CeVD [3], and this suggests that broader risk factor prevention and management issues also exist in this age group, and are not confined to diagnostic issues.

10.3 TRENDS IN MORTALITY AFTER MYOCARDIAL INFARCTION IN DIABETES

10.3.1 MAJOR FINDINGS IN CONTEXT OF PUBLISHED LITERATURE

Historically, early case fatality following MI in people with diabetes has been higher than in non-diabetic people [39–41]. In one of few Australian studies investigating trends in this measure, there was no improvement in case fatality in diabetic patients following incident MI between 1985 and 1994 in the Newcastle MONICA centre [39]. In contrast, the more contemporary data in this thesis showed marked downward trends in 30-day case fatality in people with diabetes, with little absolute difference between diabetic and non-diabetic patients at the end of the study period. These downward trends are consistent with other international findings during the same time period, although the similar levels of case fatality by diabetes status are only present in a few of these studies [11, 42, 43]. Our findings are also important in terms of relative risk because our multivariable results show that the adjusted relative risk is no longer elevated in diabetic versus non-diabetic patients.

In contrast, the long-term outcomes study (Chapter 9) showed that there was no improvement in the excess long-term mortality in diabetic versus non-diabetic people after incident MI over the same period and in the same population as the case-fatality findings (Chapter 7). Our results support much of the published work so far in this regard [44, 45]. However, the lack of reduction in excess mortality in other studies has generally been due to similar rates of decline in all-cause mortality in the diabetic and non-diabetic groups. Our results differ because all-cause mortality rates did not significantly decline in diabetic people after MI, and in the non-diabetic group, the decline was small, thus resulting in little change in the absolute difference between the two groups.

Our study also extended previous work by specifically investigating long-term trends in CVD mortality separately from all-cause mortality, for which there are limited
CHAPTER 10. GENERAL DISCUSSION AND CONCLUSIONS

comparative data for post-MI diabetic patients. The apparent shifts in the cause of death in people with diabetes from vascular to non-vascular causes in Australia contemporaneous to the present study [46] made this an important outcome to analyse. The improvement in CVD mortality in absolute and relative terms in men with diabetes supports the notion of a shift to non-vascular causes in light of the limited improvement in all-cause mortality. The contrasting findings for women with diabetes imply a lack of improvement in both cardiovascular and non-vascular mortality in diabetic women post-MI.

10.3.2 IMPLICATIONS OF RESULTS

The data on outcomes reported in this thesis highlight conflicting trends between early death rates and long-term mortality following MI in the same population. These data suggest that there may still be a significant gap in the long-term care and secondary prevention following MI in the diabetic group.

Impact of acute treatments

Acute management of patients presenting to hospital with suspected MI has changed markedly during the period of the current studies. Many studies showing reductions in early mortality after MI have also demonstrated concurrent improvements in the use of evidence-based therapies [40, 43, 47]. The drug data available for the studies in this thesis showed that dispensing of evidence-based in-hospital and discharge medications increased for diabetic people during the study period, with only small disparities existing between diabetic and non-diabetic patients in the later study period. However the use of coronary revascularisation, although increasing, remained around 10% lower in diabetic patients. The changing mix of STEMI/NSTEMI patients within the diabetic and non-diabetic groups may contribute to this disparity, particularly if a relatively greater increase in NSTEMI cases occurs in diabetic patients. Conversely, an Australia-wide registry study showed a consistently lower rate of invasive management in diabetic versus non-patients after acute MI regardless of MI type, indicating that this may not be the driver of lower revascularisation levels in people with diabetes [48]. In WA, an additional complicating factor is the centralisation of cardiac catheterisation facilities in Perth. This often necessitates extended transfer times for suspected ACS patients located outside the metropolitan area [49], which could affect treatment decisions, although whether this differentially affects diabetes patients is unclear.
Effect of increasing comorbidity levels

Diabetic patients generally have higher levels of comorbidities, and this was evident in the incident MI cohort, with higher baseline levels of hypertension, heart failure, CKD and other vascular disease manifestations compared with non-diabetic patients. However, the effect on trends in short and long-term mortality outcomes appears to differ. There was no longer an excess risk of 30-day mortality from unadjusted and age/sex adjusted models in diabetic patients by the end of the study period, and adjustment for comorbidities in diabetic patients did not weaken this effect. This appears to indicate that early mortality is falling despite the increasing levels of comorbidity. While the lower severity of MI presentation could potentially lead to lower case fatality rates, adjustment for MI type showed little effect on estimates, and other studies have shown relative reductions in case fatality or in-hospital mortality in people with diabetes for both STEMI and NSTEMI patients [43, 50].

In contrast, the excess risk of all-cause mortality out to 5 years following incident MI in diabetic patients remained around 1.5 to 2 times higher throughout the study period even after adjustment for comorbidities. Other studies have shown that high levels of comorbidity at baseline are significantly associated with poor long-term outcomes following MI and that this effect is pronounced in people with diabetes [51]. In particular, the presence of heart failure and CKD are strongly associated with the elevated risk of long-term mortality in diabetic people. The association of heart failure with mortality outcomes was reasonably constant over the study period. However, a greater attenuation of mortality risk was seen after adjustment for CKD. This combined with the increasing proportion of people with diabetes who have prevalent CKD at the time of incident MI is of concern because of the poor survival associated with CKD independent of diabetes and CHD.

Impact of secondary prevention

The falling rates of polyvascular disease in both incident and recurrent CVD cases (Chapter 5) imply broadly effective secondary prevention. However the use of follow-up methods and adjusted regression modelling to dissect these findings (Chapters 8 and 9) highlight that these trends may not apply across all population sub-groups. The study on age-specific gender differences showed that women have worse long-term cardiovascular outcomes after incident MI, a disparity seen across the age strata. When the population was stratified by diabetes status, CVD mortality did not improve in
diabetic women (in contrast to results in diabetic men). Therefore, the effectiveness of current secondary prevention approaches in women, in particular, should be considered in light of these findings.

It is known that there is under prescription and underutilisation of evidence-based medications and other prevention measures during hospitalisation and at discharge following MI in diabetic patients [52], although this gap has likely narrowed in the recent decade. These disparities are associated with poorer outcomes in the medium term following MI [48, 52]. Longer-term follow-up data from clinical trials has clearly demonstrated the efficacy of treatment of dyslipidaemia and hypertension in people with diabetes in the secondary prevention setting [53, 54]. However, population-level observational studies show that long-term adherence to cardiovascular medications following MI is poor [55]. In relation to diabetic patients, some studies have shown similar levels of dispensing of drugs and long-term adherence following MI across different comorbidities including diabetes [56] whereas cross-sectional data from the EUROASPIRE III survey indicates lower levels of drug use in diabetic patients with established CHD, particularly in terms of combination therapy [30], and importantly, that they are less likely to reach total cholesterol, blood pressure, smoking cessation and HbA1c targets compared with non-diabetics [57]. Notably, the same issues are observed in the primary prevention setting — undertreatment and lack of meeting treatment targets — which could provide a target for how to address these problems. Improved Australian data on longer-term medication use and persistence, and how well treatment targets are met may help to determine why long-term CVD mortality rates are not improving in diabetic women.

10.4 LIMITATIONS AND FUTURE DIRECTION OF RESEARCH

One of the limitations of this work is the lack of data on pre-hospital treatment and management and risk factor prevalence in the diabetic population. These data would improve our ability to draw inferences about the contribution of these factors to the downward trends in MI incidence and also in early deaths in people with diabetes. Obtaining these data often require prospective cohort studies in a community or primary care setting which were not available for this study. Consideration could be given to ongoing systematic audits in the community which supplement current self-report surveys for collection of risk factor prevalence data, including diabetes. Data at a person-based level collected in the primary care setting could be potentially linked with
the wider WADLS system, thus improving inferences which can be drawn from research such as in this thesis. Because there have been such marked reductions in MI and CHD incidence in diabetic people in WA, an improved understanding of the reasons for these trends would help to improve targeting of prevention resources. This is particularly important given that, despite these favourable trends, the risk of incident MI in people with diabetes remains significantly greater than in those without diabetes. The lack of pre-hospital data also meant an inability to adequately identify diabetes status in people who died out of hospital with no previous hospitalisations. Therefore, incidence and outcomes measures were restricted to hospitalised CHD cases.

The dichotomisation of diabetes status in observational studies, particularly with the use of administrative data, is an issue to consider in future work. Although the study in Chapter 4 demonstrated that diabetes status can be accurately determined from hospital morbidity data in this patient population when compared against hospital records, this method of identification does not account for glycaemic levels, glycaemic control or duration of diabetes. Concomitant with these issues are the difficulties associated with detecting diabetes in the setting of acute MI because of the impact of insulin-related stress response on glycaemic levels [58] and hence diabetes and pre-diabetes have been shown to be underdiagnosed in CHD patients in the acute setting [59, 60]. Conservative estimates are that 10% of ‘non-diabetic’ MI patients in the acute setting have diabetes, with only one-third of these patients recognised as diabetic at discharge [61]. The cumulative effect of these issues may be that an unknown proportion of the non-diabetic group in an observational administrative data study is incorrectly classified as non-diabetic at the time of MI hospitalisation. In the absence of widespread availability of data on blood glucose levels in such studies, further administrative data sources in Australia, such as drug and primary care data, could improve our ability to risk stratify patients. The linkage of pathology data to subsets of the population administrative data could also supplement this approach, and we are currently investigating this in relation to cardiac biomarker levels in MI patients (NHMRC grant #1078978). Such additional clinical data could potentially become a core dataset of any comprehensive data system such as the WADLS.

Additional to the issue of classification of diabetes status is that of classification of diabetes type. In the studies in this thesis, patients identified from the administrative data were not stratified by type. The proportion of diabetes classified as type 1 and type
2 based on hospitalisation data is similar to that seen in the broader diabetic population. Therefore, the study findings will be most generalisable to people with type 2 diabetes.

One of the limitations of focusing on mortality as the outcome of interest is that the risk of non-fatal cardiovascular events, including recurrent MI, onset or worsening of heart failure, and stroke, are not identified. This is particularly pertinent as improved early survival may leave a greater pool of patients at risk of non-fatal events and particularly so in diabetic patients. Ongoing work, which was presented at the EuroPRevent Congress in May 2015, is now being undertaken to explore this burden from an age-gender perspective (Appendix F) [62] thus building on the age-specific gender differences highlighted in Chapter 8. Recent attainment of state-wide data on outpatient drug prescription for cardiac patients will allow this work to be extended to investigate the impact of secondary prevention medications in this age- and gender-specific context [63]. Most studies investigating long-term outcomes after MI rely on hospital discharge drug data to investigate the association with long-term outcomes. The ongoing work will allow exploration of long-term prescription and persistence of prescribed medications (including cardiovascular and diabetic drugs) following MI, and the relationship with cardiovascular outcomes in diabetic people. This is particularly relevant given the lack of improvement in CVD mortality in women in the study in Chapter 9.

A better understanding of the reasons for the trends in younger people, both in diabetic and non-diabetic groups, is needed. There is now sufficient accumulation of population-wide trend data in this age group to warrant targeted examination of their risk factor prevalence and management, and the potential impact on the future incidence of CHD and MI. Administrative hospitalisation data alone may not be sufficient to address these questions and, therefore, a multi-population approach (because of the low number of events) combined with a community-based data collection approach may be needed. The interaction of age and gender should be considered in this context, given the adverse trends in incidence in women in the younger age group, even in the non-diabetic group. Further research needs to elucidate whether the increasing prevalence of obesity, or other risk factor changes, are driving these trends. The recent American Heart Association Scientific Statement on MI in women [64] notes the negative influence of an aggregation of cardiovascular risk factors in younger women, including
diabetes, and highlights the need for targeted guidelines for primary and secondary prevention of CHD in women, including younger women.

One of the issues which we were not able to address in detail in this thesis is the impact of Indigenous status on incidence and outcomes in this setting, as specific ethics approvals are required for analyses of this type. The association between a number of the factors raised by the findings of the thesis, including age-specific trends, the impact of CKD on outcomes (case fatality and longer-term) and the high proportion of Indigenous people in the diabetic cohort, require further analysis to determine their combined impact on trends in the younger age group.

10.5 FINAL CONCLUSIONS

The work in this thesis defines the spectrum of population-level CHD epidemiology in people with diabetes in the context of background population trends in CHD incidence, recurrence and mortality. These studies have filled a gap in contemporary CHD epidemiology in Australia, particularly with reference to cardiovascular risk in the diabetic population. The data highlight the potential for substantial improvements in CHD incidence in a high-risk group such as the diabetic population, even in the presence of increasing prevalence of this condition. It also highlights a concurrent shift away from the historical evidence of higher case fatality following an MI in people with diabetes. These favourable trends are not matched by improvements in excess long-term mortality in diabetic people, and the age- and gender–specific analyses help to elucidate underlying patterns. This study also underlines the need for improved long-term care and secondary prevention in diabetic people after acute MI as their excess long-term mortality has not improved substantially over the recent era.
10.6 REFERENCES


26. The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2013;34(39):3035–87.


APPENDICES

APPENDIX A.

Government of Western Australia
Department of Health

HUMAN RESEARCH ETHICS COMMITTEE AHEC ECO0422

Postal Address:
Executive Officer
DOHWA HREC
Level 1, C Block
189 Royal Street
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Prof Matthew Kuimian
Winthrop Professor
The University of Western Australia
School of Population Health
M431, 35 Stirling Highway
CRAWLEY WA 6009

Dear Prof Kuimian

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 Kuimian, Tom Briffa, Frank Sanfilippo, Elizabeth Geelhoed, Joe Hung, Paul Norman, Graeme Hankey, Anna Peeters, Danja Sarink, Lee Hedkoff, 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
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

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

9 October 2014
HUMAN RESEARCH ETHICS COMMITTEE (DOHWA HREC)  AHEC ECO0422

Postal Address:
Executive Officer
DOHWA HREC
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EAST PERTH WA 6004

A/Prof Tom Brittf
Research Associate Professor
School of Population Health
University of Western Australia
35 Stirling Hwy
CRAWLEY WA 6009

Dear A/Prof Tom Brittf

Project #2010/19
Uses of Linked Data in Studies of the Epidemiology of Vascular Diseases in Western Australia since 1978. [Short Title: The Linked Vascular File (LVF)]

Date of commencement: 14/04/2010
Date of completion: 09/06/2014

Research Team:
A/Prof Tom Brittf
Dr Pamela Broadbent
E/Prof Michael Hobbs
Dr Judy Kettelson
Ms Frances Green
Dr Jamie Rankin
Prof Elizabeth Geelhoed
Dr Kantz Gausia
Mr Steve Ridout

DOH data required: Yes
Data linkage required: Yes

Datasets to be accessed:
Emergency Department Mortality:
Hospital Morbidity: Electoral Roll

Ethics approval validity: 09/06/2014

CERTIFICATE OF APPROVAL - AMENDMENT
APPENDICES

Date of request: 20/01/2012
Date of next annual progress report: 09/06/2012
Date of approval: 08/02/2012
Requested Change/s:
Additional Researcher: Dr Tlow-Hiva (Katherine) Tong
Minimise access to identifying information - (URII and hospital codes) now kept in a separate file and only Dr Frank Sanfillippo, Steve Ridout and Judy Katzenellongbogen
Additional information and/or request: Nil

PROJ: Budget Allow
Chair
Department of Health WA Human Research Ethics Committee

09 February 2012

DOHWA HREC is constituted and operates in accordance with the National Health and Medical Research Council’s (NHMRC) ‘National Statement on Ethical Conduct in Human Research’. Applications are also reviewed for compliance with the Department of Health WA ‘Practice Code for use of personal health information’. 
Government of Western Australia
Department of Health

HUMAN RESEARCH ETHICS COMMITTEE (DOHWA HREC) AHEC E00422

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E/Prof Michael Hobbs
Honorary Research Fellow
School of Population
The University of Western Australia
35 Stirling Hwy
CRAWLEY WA 6009

Dear E/Prof Hobbs

Project #2011/62
Monitoring Acute Coronary Heart Disease in the Modern Era

Date of commencement: 01/03/2011
Date of completion: 30/06/2014
Research Team: E/Prof Michael Hobbs Prof Matthew Knulman
Dr Frank Santillipo Prof Tom Briffe
Dr Pam Bradshaw Dr Judy Katzenellenbogen
Ms Loo Hedoff Dr Kenzi Gaustra
Mr Steve Rideout

DOH data required: Yes
Data linkage required: Yes
Datasets to be accessed: Emergency Data; Hospital Morbidity;
NBS; PBS;
Hospital Pathology Reports

Date of Ethical Review: 10/08/2011
Ethics approval validity: 10/08/2015 (4yrs)

I am pleased to advise that the Committee has granted ethical approval for this project.

This letter constitutes Ethics Approval only; you will not receive the data requested for your project until approval for the release of these data is signed by the Department of Health WA Director General’s delegate.

This approval is subject to your continued compliance with the following conditions:

1. DOHWA HREC holds the Principal Investigator responsible for the ethical conduct of the project and the security of the personal health information therefore he/she must:
   a. Report anything which might warrant review of ethical approval of the project in the specified format including:
      - Any serious or unexpected adverse events; and
      - Unforeseen events that might affect the continued ethical acceptability of the project.

2. Submit for approval 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.
APPENDICES

3. Advise if the project is discontinued or withdrawn before the expected date of completion and give reasons for this action.
4. Provide an annual progress report to the HREC and a final report at the completion of the project.
5. Advise any changes of personnel in the research team, and provide a DOHWA Confidentiality Agreement/Confidentiality Acknowledgement form for any addition to the research team.

We wish you well with your project.

Yours sincerely

[Signature]

A/Prof Judith Allen
Chair
Department of Health WA Human Research Ethics Committee

12 August 2011

DOHWA HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) 'National Statement on Ethical Conduct in Human Research'. Applications are also reviewed for compliance with the Department of Health WA 'Practice Code for use of personal health information'.

Government of Western Australia
Department of Health

HUMAN RESEARCH ETHICS COMMITTEE (DOHWA HREC) AMEC E009422

Postal Address:
Executive Officer
DOHWA HREC
1st Floor “C” Block
189 Royal Street
EAST PERTH WA 6004

Prof Sandra Thompson
Director
Combined Universities Centre for Rural Health
PO Box 109
GERALDTON WA 6531

Project #2011/09
More Informed Action to Improve Aboriginal Heart Health in Western Australia

Date of commencement: 01/01/2012
Date of completion: 31/12/2015

Research team:
W/Prof Sandra Thompson
Dr Judy Katzonolllonbogon
E/Prof Michael Hobbs
Dr Frank Sanfilippo
Prof Elizabeth Goolhood
Prof Peter Thompson
Dr Karin Gausla
Dr Pam Bradshaw
Dr Angela Duray
A/Prof Dawn Bessarab
Dr Katherine Teng
Dr Derrick Lopez
Lee Hildick

DOH data required: Yes
Data linkage required: Yes
Datasets to be accessed: Emergency Department, Mortality, Hospital Morbidity, Electoral Roll
Ethics approval validity: valid to: 27/01/2016

CERTIFICATE OF APPROVAL - AMENDMENT

Date of request: 13/02/2012
Date of next annual progress report: 27/01/2013
Date of approval: 14/03/2012

Requested Change/s: Additional Researchers: Dr Tiaw-Hwa (Katherine) Teng, Dr Derrick Lopez and Lee Hildick.

Additional information and/or request: Approval for analysis to be conducted at both the Combined Universities Centre for Rural Health in Geraldton and at the Perth Office, H-Block, Sir Charles Gairdner Hospital Campus, University of Western Australia.

A/Prof Judith Allen
Chair
Department of Health WA Human Research Ethics Committee

19 March 2012
## APPENDIX B

### INTERNATIONAL CLASSIFICATION OF DISEASES CODES USED TO IDENTIFY THE STUDY COHORTS.

<table>
<thead>
<tr>
<th>Atherosclerotic disease</th>
<th>Sub-category</th>
<th>ICD-9/ICD-9-CM</th>
<th>ICD-10-AM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td>410</td>
<td>I21, I22</td>
</tr>
<tr>
<td></td>
<td>Unstable Angina</td>
<td>411.1, 413</td>
<td>I20.0</td>
</tr>
<tr>
<td></td>
<td>Angina pectoris/Stable angina</td>
<td></td>
<td>I20.1-I21.9</td>
</tr>
<tr>
<td></td>
<td>Certain current complications following acute myocardial infarction</td>
<td>411.0, 411.8, 411.89</td>
<td>I23</td>
</tr>
<tr>
<td></td>
<td>Other acute ischaemic heart disease</td>
<td>414</td>
<td>I24</td>
</tr>
<tr>
<td></td>
<td>Chronic ischaemic heart disease</td>
<td></td>
<td>I25</td>
</tr>
</tbody>
</table>

| Coronary heart disease  | Intra-arterial haemorrhage                       | 431                  | I61         |
|                         | Cerebral infarction                              | 433.x1, 434.x1       | I63         |
|                         | Stroke, not specified as haemorrhage or infarction | 436                  | I64         |
|                         | Occlusion and stenosis of precerebral or cerebral arteries not resulting in cerebral infarction | 433.x0, 434.x0       | I66         |
|                         | Sequelae of cerebrovascular disease              | 438                  | I69         |
|                         | Transient cerebral ischaemic attacks and other related syndromes | 435                  | G45         |

| Peripheral arterial disease | Atherosclerosis of aorta, renal arteries, and extremities | 440 | I70 |
|                            | Other peripheral vascular diseases               | 443.1, 443.9         | I73.1, I73.9 |
|                            | Other disorders of arteries and arterioles (Stricture of artery) | 447.1 | I77.1 |

ICD, International Classification of Diseases; CM, Clinical Modification; AM, Australian Modification.
APPENDIX C


<table>
<thead>
<tr>
<th>Year</th>
<th>3 years*</th>
<th>5 years*</th>
<th>10 years*</th>
<th>13 years*</th>
<th>15 years†</th>
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<tbody>
<tr>
<td>1996</td>
<td>11.24</td>
<td>8.28</td>
<td>3.17</td>
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</tr>
<tr>
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<td>7.01</td>
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<tr>
<td>1998</td>
<td>10.69</td>
<td>7.65</td>
<td>2.37</td>
<td>0.60</td>
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</tr>
<tr>
<td>1999</td>
<td>11.06</td>
<td>8.08</td>
<td>3.29</td>
<td>1.12</td>
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<tr>
<td>2000</td>
<td>9.57</td>
<td>7.01</td>
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<td>2001</td>
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<td>7.69</td>
<td>2.67</td>
<td>0.86</td>
<td>1.69</td>
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<tr>
<td>2002</td>
<td>10.60</td>
<td>7.87</td>
<td>2.70</td>
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<td>1.79</td>
</tr>
<tr>
<td>2003</td>
<td>10.93</td>
<td>8.35</td>
<td>3.06</td>
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<td>1.69</td>
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<tr>
<td>2004</td>
<td>9.52</td>
<td>7.25</td>
<td>2.79</td>
<td>0.96</td>
<td>1.55</td>
</tr>
<tr>
<td>2005</td>
<td>10.29</td>
<td>7.77</td>
<td>3.08</td>
<td>0.80</td>
<td>1.61</td>
</tr>
<tr>
<td>2006</td>
<td>9.42</td>
<td>6.81</td>
<td>2.61</td>
<td>0.78</td>
<td>2.02</td>
</tr>
<tr>
<td>2007</td>
<td>9.98</td>
<td>7.14</td>
<td>2.79</td>
<td>1.01</td>
<td>2.00</td>
</tr>
<tr>
<td>2008</td>
<td>8.49</td>
<td>6.09</td>
<td>2.54</td>
<td>0.95</td>
<td>1.57</td>
</tr>
<tr>
<td>2009</td>
<td>9.99</td>
<td>7.24</td>
<td>2.93</td>
<td>1.26</td>
<td>1.81</td>
</tr>
<tr>
<td>2010</td>
<td>9.58</td>
<td>6.42</td>
<td>2.13</td>
<td>0.76</td>
<td>1.80</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>10.09</strong></td>
<td><strong>7.38</strong></td>
<td><strong>2.76</strong></td>
<td><strong>0.89</strong></td>
<td><strong>1.27</strong></td>
</tr>
</tbody>
</table>

* Compared against a 15-year lookback period.
† Compared against a 20-year lookback period.
### APPENDIX D

**IDENTIFICATION OF UNCOMPLICATED HOSPITALISATION FOR RENAL DIALYSIS ADMISSION USING DISCHARGE DIAGNOSIS CODES FROM THE PRINCIPAL OR SECONDARY DIAGNOSIS FIELDS.**

<table>
<thead>
<tr>
<th>ICD-9</th>
<th>ICD-9-CM</th>
<th>ICD-10-AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>V56.0, V56.8</td>
<td>Z49.xx</td>
<td>403.xx, 404.xx, 585.9*</td>
</tr>
<tr>
<td>OR</td>
<td>V56.0, V56.8</td>
<td>Z49.xx</td>
</tr>
</tbody>
</table>

*In the presence of the relevant renal dialysis procedure code (8-853, 8-860).

ICD, International Classification of Diseases; CM, Clinical Modification; AM, Australian Modification.
APPENDIX E

Interpretation of comorbidities using hospital morbidity data: a methodological approach for analysing trends in diabetes admissions

I. Medoff, T. Della
Cardiovascular Research Group, School of Population Health, University of WA

INTRODUCTION

The increasing prevalence of diabetes nationally highlights the importance of measuring trends in diabetes. High-quality linked hospital morbidity data may be invaluable for epidemiological population trends in diabetes.

DATA SOURCE AND DEFINITION


CODING OF DIABETES

Prior to ICD-10-AM in WA (1999):
- In contrast to most other comorbidities, diabetes was coded even if active treatment not documented.
- Complications coded only if attributable to diabetes.

ANALYSING DIABETES TYPE

Classification type of diabetes for specific research questions may be required. However, the following issues should be noted:

1. 5th digit (denoting type) in ICD-9 is commonly missing in HMD.
2. In ICD-9-CM, Type 2 and unspecified type are grouped together (250.x0), unlike ICD-9 and ICD-10-AM.
3. 10% of patients with multiple admissions mentioning diabetes have >1 diabetes type coded.
4. Age is not sensitive for identifying type — e.g., using an age cut-off of ≤<40years at admission underestimates type 1 by up to 10%.

Recommended algorithms for determining diabetes type:

A. If multiple admissions with diabetes, code as diabetes type recorded on the most recent admission.
B. If one admission, code as in HMD, OR if type missing (960-67), code as unspecified diabetes.
C. For long term trends, categorise unspecified / other specified with Type 2 diabetes.

TRENDS IN HOSPITALISED DIABETES

- Incident admissions with diabetes had no hospitalisation with diabetes coded in the prior 15 years (Fig 4).
- Persons with prevalent diabetes had hospitalisation(s) with diabetes coded in the previous 15 years and alive at 30th June in each study year (Fig 5).
- Renal dialysis admissions excluded.
- Annual age-standardised incidence admission rates and prevalence were calculated.

ANALYSIS OF CODING CHANGES

- Excluding regular renal dialysis admissions, the increase in diabetes hospitalisations from 2003-07 was 37% (Fig 2).
- Regular dialysis admissions = dialysis coded in any diagnosis or procedure field and LOS ≥1day.
- After 2000, increasing proportion of diabetes admissions are for complications of diabetes (Fig. 3).

CONCLUSION

The rapid increase in diabetes hospitalisations over the past decade should be interpreted cautiously, including:

- Exclude regular renal dialysis admissions to improve reliability of diabetes trends
- Tailor algorithms to determine diabetes type from HMD.
- Further investigation of diabetes complications codes is required to determine the impact when using comorbidity indices.
- Where long term linked data is available, use of long lookback periods allows calculation of trends consistent with known evidence.
APPENDICES

APPENDIX F

Effect of diabetes on age-specific long-term cardiovascular outcomes following first myocardial infarction: a population-based study

L.Nedkoff,1 M Kuminman,1 J Hung,1 T Briffa2
1. School of Population Health, The University of Western Australia 2. School of Medicine and Pharmacology, The University of Western Australia

Methods

Study Cohort: All 30-day survivors of incident MI aged 35-84 years in WA from 2003 to 2010.

Data Source: Linked hospital mortality and death data (Western Australian Data Linkage System) with full population coverage.

Incident MI: Identified from principal discharge diagnosis within hospital mortality data. Classified as incident if no admissions for MI in the previous 13 years.

Diabetes status: Classified as having diabetes if recorded in any diagnosis field on a hospital admission in the 13 years prior to the incident MI.

Outcomes: Follow-up data available to 30th June 2015. Outcomes included hospitalization for re-MI, heart failure, and stroke, and CVD mortality (all-cause mortality following incident MI).

Statistical Analysis:

Multivariate hazard ratios in people with versus without diabetes were estimated from Cox regression models for each outcome (adjusted for 5-year age group; indigenous status; history of hypertension, heart failure, atrial fibrillation, peripheral arterial disease, chronic kidney disease, stroke, chronic lung disease, prior CVD/vascularisation, neoplastic heart disease, cancer, MI type).

Proportional hazards were found for diabetes status at time and no evidence of violation found.

Results

Mean follow-up time: 3.30 years. Non-diabetes 3.36 years.

Risk of cardiovascular outcomes in people with vs without diabetes after incident MI (adjusted hazard ratios, 95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Re-MI</th>
<th>Heart failure</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-days</td>
<td>1.51 (1.13, 2.03)</td>
<td>1.08 (0.47, 2.36)</td>
<td>1.38 (1.19, 1.63)</td>
</tr>
<tr>
<td>5-years</td>
<td>0.91 (0.38, 2.27)</td>
<td>1.26 (0.91, 3.70)</td>
<td>1.30 (1.05, 1.61)</td>
</tr>
<tr>
<td>10-years</td>
<td>1.12 (0.77, 1.63)</td>
<td>1.17 (0.86, 1.60)</td>
<td>1.12 (0.83, 1.50)</td>
</tr>
</tbody>
</table>

Conclusion

- The relative risk of adverse cardiovascular outcomes in diabetic versus non-diabetic patients after incident MI is greater in younger age groups.
- Risk is partly due to a higher proportion of Indigenous patients and prevalence of comorbidities such as chronic kidney disease.
- These data highlight the need for long-term secondary prevention efforts particularly in younger people with diabetes.

Characteristics of incident MI cohort, by age group (%)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>n=3017</th>
<th>n=311</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-49</td>
<td>14.8</td>
<td>11.8</td>
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<tr>
<td>50-59</td>
<td>31.2</td>
<td>29.2</td>
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<tr>
<td>60-69</td>
<td>35.8</td>
<td>36.1</td>
</tr>
<tr>
<td>70-84</td>
<td>18.2</td>
<td>12.9</td>
</tr>
</tbody>
</table>

Acknowledgements: We acknowledge the Data Linkage Board (Department of Health WA) for provision of the data. Ms Nedkoff is supported by a National Health and Medical Research Council / National Heart Foundation Postgraduate Scholarship.

Conflict of Interest: None to declare.