Myocardial infarction as the first manifestation of atherosclerotic disease

Emily Herrett

2013

Thesis submitted to the University of London in fulfilment of the requirements for the Doctorate of Philosophy

Faculty of Epidemiology and Population Health
London School of Hygiene and Tropical Medicine
Keppel Street
London WC1E 7HT

Statement of role

This project was supervised by Liam Smeeth (primary supervisor, London School of Hygiene and Tropical Medicine) and Harry Hemingway (secondary supervisor, University College London).

With guidance from my supervisors and advisory panel, I carried out the data management, performed the analysis and interpreted the results for all of the chapters in this thesis.

The analysis and results in Chapter 4 were performed on behalf of, and in collaboration with, Dr. Anoop Shah (UCL), Ms Rachael Boggon (Medicines and Healthcare Regulatory Agency), Dr. Spiros Denaxas (UCL), Professor Liam Smeeth, Professor Tjeerd van Staa (Medicines and Healthcare Regulatory Agency), Professor Adam Timmis (Barts and the London Hospital) and Professor Harry Hemingway (UCL).

Declaration of authorship

I, Emily Herrett, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed Date

_____ _____

Emily Herrett

Thesis abstract

Aim: To examine the occurrence of cardiovascular disease risk factors, previously diagnosed atherosclerotic disease, new ischaemic events and prescriptions issued in the period prior to first myocardial infarction (MI) and their association with outcomes at the time of and after MI.

Methods: This thesis describes studies using linked CALIBER data from four UK sources: the General Practice Research Database, Hospital Episode Statistics, the Myocardial Ischaemic National Audit Project and Office for National Statistics mortality data. Linkage of these sources created a large, rich longitudinal dataset, allowing reconstruction of the patient journey before and after first MI. Quality of MI recording across the four data sources was first assessed and three further studies examined atherosclerotic disease, risk factor and drug exposures in the period preceding MI.

Results: Despite an increased rate of ischaemic coronary presentations in the 90 days prior to MI, over half of first MI patients were unheralded by atherosclerotic disease diagnoses (56.5% (55.6-57.4%)). However, the great majority of people with no prior diagnosed atherosclerotic disease had identifiable vascular disease risk factors or had recent presentations with chest pain. Survival analysis showed that patients with new ischaemic presentations shortly before MI - possible clinical correlates of ischaemic preconditioning - had less severe infarcts and improved survival in the first seven days after MI (Hazard Ratio for coronary heart disease mortality 0.64 (0.57-0.73), $P<0.001$) compared to patients without previously recorded ischaemia. However, in the longer term ischaemic presentations shortly before MI were associated with poorer survival. Prescription of aspirin for primary prevention in the pre-MI period was also marker for attenuated MI severity, but with no effect on mortality or infarct size. There was no association between statin use for primary prevention and outcomes at MI.

Conclusions: The novel prospective data used in this thesis have provided the opportunity to obtain new insights into MI as the first manifestation of ischaemic heart disease.

Acknowledgements

Most of all I would like to thank my supervisors Liam Smeeth and Harry Hemingway, whose guidance and support have been invaluable throughout the past three years, and who have driven me to be better. Also thanks to my advisory committee members Krishnan Bhaskaran, Adam Timmis and John Whittaker.

You all promised me it would happen, and finally the end of the PhD has arrived! Thanks to all of my family and friends for their kind support. In particular I would like to thank Mum and Dad, Becky, Jemma, Kathryn, Rob, Zoe, Chen, Phil, Ruth, Katy, Sarah and Raphaelle who have pulled me through the hard days. And most recently thank you to Krishnan for helping me to maintain the PMA and for his endless proof reading!

Thanks also to Julie George, Spiros Denaxas, Anoop Shah, Ian Douglas, Caroline Minassian, Jenni Quint, and Sara Thomas for their support and advice.

Finally thanks to Andy, who has helped so much and always made things better.

Now let's have some fun!

Funding and ethics approval

This PhD was funded by a Medical Research Council Capacity Building Studentship. Ethical approval was granted by LSHTM (application number 5640).

CALIBER is funded by a Wellcome Trust project grant (086091/Z/08/Z) and a National Institute of Health Research (NIHR) programme grant (RP-PG-0407-10314) and has received Ethics approval (09/H0810/16).

Table of contents

List of figures

List of tables

List of abbreviations

ACS	Acute coronary syndrome
BNF	British National Formulary
CABG	Coronary artery bypass graft
CALIBER	Cardiovascular disease research using linked bespoke studies and electronic records
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cerebrovascular disease
ECG	Electrocardiograph
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
HR	Hazard ratio
ICD	International classification of diseases
IMD	Index of Multiple Deprivation
MI	Myocardial infarction
MINAP	Myocardial Ischaemic National Audit Project
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NSTEMI	Non ST-elevation myocardial infarction
ONS	Office for National Statistics
OPCS	Office for populations and censuses and surveys
OR	Odds ratio
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
QOF	Quality and outcomes framework
STEMI	ST-elevation myocardial infarction
TIA	Transient ischaemic attack

Chapter 1 Background

1.1 Introduction

This chapter describes the definition and burden of myocardial infarction in the UK, followed by a background to the topics covered in this thesis and the justification for this research project.

1.2 Myocardial infarction

1.2.1 Pathophysiology

Myocardial infarction (MI), commonly known as a heart attack, occurs when blood flow in the coronary arteries is severely restricted or completely blocked, leading to ischaemia manifesting as chest pain, and myocardial cell necrosis. Blockage of the arteries is usually the result of atherosclerosis and thrombosis (local coagulation of the blood) in the coronary artery. Atherosclerosis is the process by which fatty material is deposited on the arterial wall, reducing the lumen diameter and the flow of blood to the tissue of the heart. In some patients, atherosclerotic plaque rupture or erosion leads to thrombosis and sudden partial or complete occlusion of the artery. During MI, if the blockage is persistent and unresolved (either spontaneously or through clinical intervention), then myocardial cell necrosis continues, reducing the function of the heart and leading to higher risk of patient death.

1.2.2 The definition of MI in clinical care

In patients presenting with suspected MI, a range of clinical tools must be used that allow the clinician to distinguish between chest pain of non-cardiac origin, unstable angina and MI. The first standard definition in 1959[1] involved a typical history of chest pain, electrocardiogram (ECG) changes and the appearance of biochemical markers in the blood. In the subsequent fifty years, while these three basic components of the MI definition have been unchanged, the diagnosis of MI has been refined as more sensitive cardiac markers have been developed.[2] Table 1.1 describes the evolution of the MI diagnostic definition since the first definition in 1959.

In the late 1990s, troponins, were introduced as new biomarkers that were more specific and sensitive than any of the previous markers.[2] Its predecessor, creatine kinase-MB, has sensitivity of about 70% and a false positive rate of 3.4% compared to a troponin gold standard.[3] The heightened sensitivity of troponins means that even the smallest of infarcts can be identified.

In 2000, the advent of troponins and the need for precise definitions in both clinical care and research led to the redefinition of MI by the Joint European Society of Cardiology and American College of Cardiology Committee (Figure 1.1,[4]). Since troponins can be elevated in other disease settings and not just MI, the diagnosis of MI is based on both a rise and fall of troponin (or other biomarker), along with one other indicator of ischaemia.

In the UK, the increase in MI incidence resulting from the redefinition in 2000 has been estimated at between 26% and 58%,[3, 5] the latter representing an additional 160,000 MIs in the UK each year.[5]

Table 1.1 The changing definition of myocardial infarction (MI) from the first standard definition in 1959 to the latest revision in 2012.

Year	MI definition
1959[1]	First standard definition: typical history of chest pain, ECG changes and the appearance of biochemical markers in the blood.
1959-2000[2]	The definition remained largely unchanged, but with the addition of increasingly sensitive and specific biomarkers
2000[4]	Redefinition of MI: 1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a. Ischemic symptoms; b. Development of pathologic Q waves on the ECG; c. ECG changes indicative of ischemia (ST segment elevation or depression); or d. Coronary artery intervention (e.g. coronary angioplasty). Or pathologic findings of an acute MI.
2007[6]	Revised the 2000 definition, splitting the classification into different types (1-5), see Table 1.2.
2012[7]	Revised the 2007 definition, accounting for more sensitive biomarker assays and including the diagnosis of MI by imaging.

"Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1. *Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:*
    a. *Ischemic symptoms;*
    b. *Development of pathologic Q waves on the ECG;*
    c. *ECG changes indicative of ischemia (ST segment elevation or depression); or*
    d. *Coronary artery intervention (e.g. coronary angioplasty).*
2. *Pathologic findings of an acute MI."*

Figure 1.1 Criteria for acute, evolving or recent myocardial infarction (The Joint European Society of Cardiology/ American College of Cardiology Committee definition, 2000)

1.2.2.1 Types of MI: STEMI and NSTEMI

In a hospital setting, an ECG is used in the diagnosis of MI. The ECG trace is divided into segments, which are labelled alphabetically with the letters P to U (Figure 1.2). Assuming the other criteria for MI have been met (chest pain and rise and fall of a cardiac marker), MI can be separated into two types based on the appearance of the ST segment on the ECG (Figure 1.2). Elevation of the ST segment indicates 'ST-elevation MI' (STEMI) and absence of ST-elevation indicates a non ST-elevation MI (NSTEMI). ST-elevation suggests severe (full myocardial wall thickness) ischaemia and the diagnosis of STEMI must only be offered after a rise and fall of cardiac biomarkers.

STEMI and NSTEMI are thought to have different physiologies but since their classification was introduced only a decade ago, aetiological research is still ongoing. However, patients with STEMI tend to be younger, with fewer cardiac and non-cardiac co-morbidities[8] and some studies have shown a better long term prognosis than NSTEMI.[9, 10]

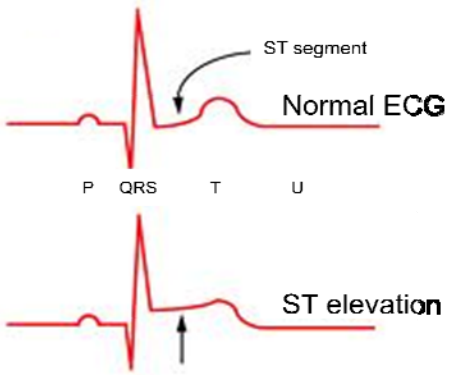
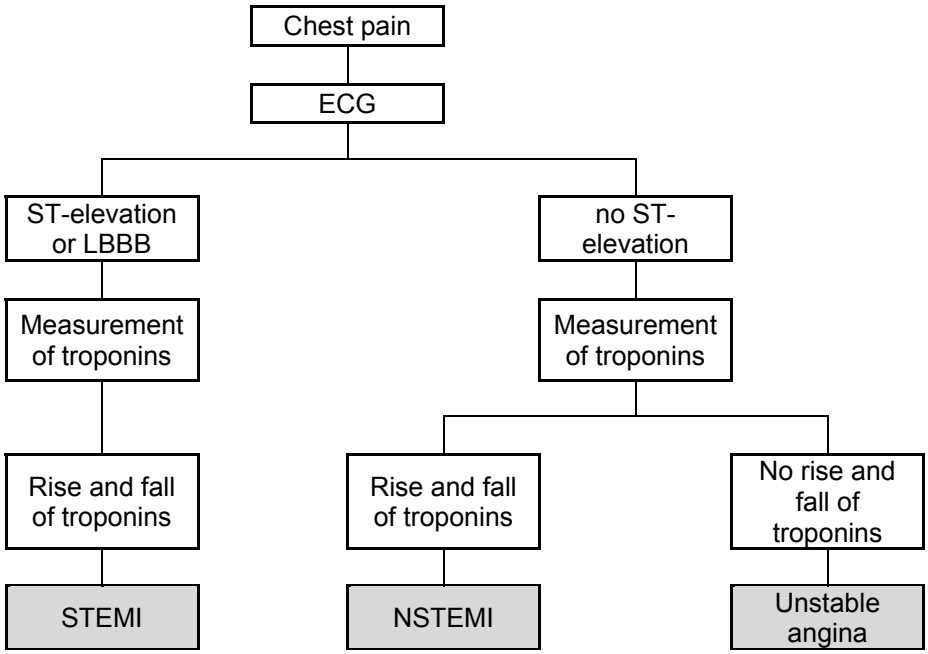


Figure 1.2 Two electrocardiogram (ECG) traces, with segments P to U labelled. Normal ECG (above) and with ST-elevation (below). Adapted from stemcellmx.com[11]

Figure 1.3 shows a scheme for the diagnosis of STEMI and NSTEMI. Briefly, patients with chest pain are given an ECG to identify the presence and severity of ischaemia. Based on these results and on a characteristic rise and fall in troponins (or another sensitive and specific cardiac marker), a diagnosis of STEMI or NSTEMI can be given. For patients without the rise and fall in cardiac markers, non ST-elevation acute coronary syndrome (ACS) (unstable angina) may be diagnosed.



LBBB: left bundle branch block, ECG: electrocardiogram; STEMI: ST-elevation myocardial infarction; NSTEMI: non ST-elevation myocardial infarction.

Figure 1.3 Simplified scheme of the classification of acute coronary syndromes, reproduced from White and Chew[12]

1.2.2.2 The new definition of MI in 2007 and 2012

In 2007, a revised version of the MI definition was published.[6] This updated the definition and separated MI into categories based on the circumstances leading to the infarct (Table 1.2).[6] This revision also acknowledged that different conditions can lead to low levels of myocardial necrosis, which, given the sensitivity of troponins, need to be accounted for when diagnosing MI.

In 2012, a third consensus document was published that further refined the diagnosis of MI based on more sensitive biomarker assays and the diagnosis of MI in specific disease settings. It also defines MI through the use of advanced imaging techniques such as echocardiograms, radionuclide, MRI and CT scans which can show new loss of viable myocardium or new regional wall motion abnormality.[7] This is of use in situations where the rise and fall of biomarkers cannot be observed.

Throughout all definitions, the requirement for chest pain, ECG and cardiac biomarker findings has been unchanged.

Table 1.2 Universal clinical classification of different types of myocardial infarction. Reproduced from the second consensus definition of myocardial infarction, 2007[6]

Type 1	Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/ or rupture, fissuring, or dissection.
Type 2	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST-elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
Type 4	Myocardial infarction associated with PCI, stent thrombosis as documented by angiography or at autopsy.
Type 5	Myocardial infarction associated with CABG.

LBBB: left bundle branch block; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft.

1.2.2.3 Implications for this thesis

The MI data analysed in this thesis are drawn from clinical care between 2003 and 2008. Throughout this period, the in-hospital diagnosis of MI was based on CK-MB or troponins and ECG results. The high sensitivity of the troponins to detect small amounts of myocardial necrosis means that small infarcts that would previously have been classified as unstable angina (pre-2000) are now labelled as MI. Therefore, the cohort of MIs analysed in this thesis may be different to historical studies of MI. The new consensus documents in 2007 and 2012 aimed to refine rather than alter the definition of MI, so were unlikely to have impacted the work in this thesis.

1.2.3 Incidence and prevalence of MI in the UK

While there has been a decline in both MI incidence and mortality over the past three to four decades,[13] the incidence of MI in the UK is still at 200-220 per 100,000 men and 80 to 90 per 100,000 women.[14] This corresponds to roughly 124,000 MIs in the UK per year. It is estimated that 23% of women and 26% of men with MI do not reach hospital[15] and of those who do, 11% do not survive the subsequent year.[16] In the UK, approximately one in five deaths in men is due to coronary heart disease, making it the second leading cause of death (behind cancer). In women, one in eight deaths are due to coronary heart disease, making it the third leading cause of death behind respiratory disease and cancer.

Reducing the incidence of MI would be beneficial in health terms, bringing a reduction in preventable long-term morbidity and mortality. It would also reduce the costs to the NHS, which currently spends over £4 billion on CHD care.[17]

1.3 Limitations of MI research

Traditionally, large studies of MI are retrospective in design, identifying patients at the time of MI and enquiring about pre-MI exposures. Therefore, detailed data occurring just before MI are not collected by most studies. Population-based cohort studies collecting data prospectively are often too small to capture sufficient MI patients to study subgroups, and often do not collect data frequently or in enough detail to study MI in detail.

1.4 Unprecedented opportunities for MI research offered by new data

Recent linkage of routinely collected records from primary care, hospitalisation, MI registry and cause-specific mortality data has presented unprecedented opportunities for coronary heart disease research in the UK. As well as providing enormous statistical power, the linkage of these different datasets greatly improves the quality of the data available and provides new opportunities to establish validity. The prospectively collected primary care data, combined with the detail collected in the MI registry in terms of timing, infarct size, type and treatment, and the incident outcomes gathered from hospital and mortality statistics, together provide a rich data source for CHD research which allows the patient journey to be reconstructed from primary care registration through to death. This is unique compared to the Scandinavian data linkages, which lack general practice data.[18] Linkage of these routinely collected data sources provides data with huge depth and breadth at a relatively low cost.

However, while the advantages of using routinely collected data for research make their use attractive, there are some key disadvantages that must be considered when undertaking research using such data. These include the lack of relevant data for some research questions (for example on lifestyle and behaviours in the datasets described above), missingness, and the potential of confounding by indication for studies of therapies. These limitations restrict the types of analyses that can be performed using routinely collected data. The analyses described in this thesis have therefore been

Given the wealth of research that has been made possible by the linkage of these data sources, the next section describes the aspects of MI research that are addressed in this thesis. The focus is on the unique data gathered prior to MI, an important period because it is a time when a patient may experience new symptoms or be treated with new drugs that might impact their subsequent MI and survival. The next two sections describe the importance of this period with regard to (i) atherosclerotic disease, risk factor and chest pain manifestations prior to MI, and (ii) pharmacological treatment.

1.5 The evolution of atherosclerotic disease prior to first MI

Reconstructing the patient journey from general practice registration through to MI allows the onset and evolution of atherosclerotic disease, risk factors and chest pain prior to

MI to be determined. This is important for two reasons, described in sections 1.5.1 and 1.5.2.

1.5.1 Does MI occur without warning?

Due to the lack of prospective research in MI overall, the onset, evolution and timing of atherosclerotic disease prior to first MI is not well described. Given the recent decrease in MI incidence and relative increase in angina incidence,[19, 20] the reduction in cardiovascular disease risk factors,[21] and the updated definition of MI,[22] an understanding of heralding of MI by disease, risk factors and chest pain would provide an understanding of where there may be missed opportunities for care. Better identification of patients who manifest with MI without the 'warning' of previous disease, risk factors or chest pain could enable improved prevention.

1.5.2 Effects on outcomes

There has been much interest in ischaemia occurring in the period prior to MI and its effects on outcomes. Patients experiencing previous atherosclerotic disease prior to MI have increased risk of events in other arterial beds[23] and worse atherosclerotic disease than MI patients unheralded by previous disease, with more diseased vessels and stenoses.[24] However, evidence from a large body of literature suggests that outcomes in MI patients unheralded by disease may be worse than for those with manifest disease.

1.5.2.1 Ischaemic preconditioning

In 1986, Murry showed that brief periods of ischaemia prior to a more prolonged insult could protect against cell death.[25] This phenomenon was termed 'ischaemic preconditioning' and was shown to reduce infarct size by 75%. This was hailed as "one of the most powerful and reproducible methods of delaying cell necrosis"[26] and these findings were successfully repeated in many *in vitro* studies.[27] Since these initial experiments, a large body of research has demonstrated the mechanisms by which ischaemic preconditioning acts. These have shown that there are two windows of protection conferred by an ischaemic stimulus, as described in Figure 1.4. The first is termed the classical phase, which was described by Murry and occurs in the twelve hours after the ischaemic stimulus

with strong but transient effects on infarct size. The second is slightly delayed, termed the "second window of protection" (SWOP), and occurs in the 12-96 hours after a preconditioning stimulus.[27]

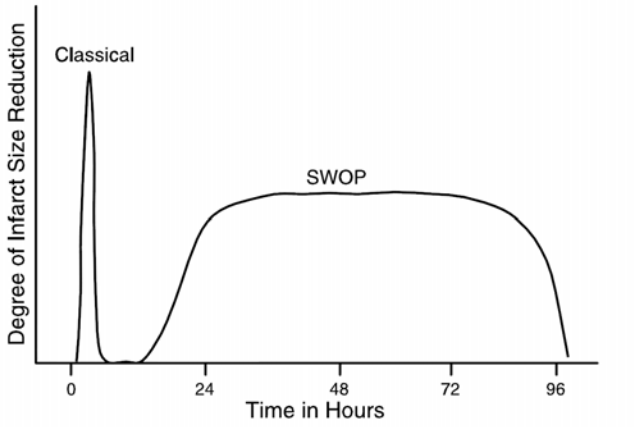


Figure 1.4 The two phases of ischaemic preconditioning. Reproduced from Yellon 2003: Preconditioning the Myocardium: From Cellular Physiology to Clinical Cardiology[27]

Ischaemic preconditioning can occur in clinical situations in addition to experimental in-vitro settings. Of particular interest here, coronary ischaemia occurring prior to MI has been suggested as a clinical correlate to ischaemic preconditioning.[28] This includes stable angina, unstable angina and chest pain occurring in the premonitory phase, i.e. the period shortly before MI. Such prodromal symptoms of MI represent partial occlusion of the artery and may have a preconditioning effect similar to those reported in experimental studies. The effects of these exposures have been studied retrospectively in hospitalised MI patients, in relation to in-hospital and longer term outcomes and have been associated with reduced infarct size,[29, 30] better outcomes at least in the short term,[31] and some evidence to suggest protection in the longer term.[32, 33]

1.5.2.2 Collateral circulation

Atherosclerotic disease diagnosed prior to MI may have other beneficial effects on survival compared to patients for whom MI is the first manifestation of disease. Myocardial ischaemia is one of the triggers of angiogenesis and arteriogenesis,[34] which allow collateral circulation to develop, compensating for reduced blood flow in major arteries due to atherosclerotic narrowing. Preinfarction angina has been described as a determinant of

collateral circulation,[34, 35] which has been associated with smaller infarct sizes.[36] However, not all studies have found developed collateral circulation in patients with previous myocardial ischaemia.[37, 38]

1.6 Pharmacological management of cardiovascular disease risk prior to MI

1.6.1 Prescription for primary prevention

Aspirin and statins have been shown to reduce cardiovascular morbidity and mortality in large randomised controlled trials, both in primary and secondary prevention, [39-44] although the effect of aspirin for primary prevention is currently under question.[45]

For patients *with* diagnosed atherosclerotic disease, these medications have a clear indication and should be prescribed after initial diagnosis according to guidelines from the UK National Institute of Health and Clinical Excellence.[46] Indication for aspirin and statins in patients *without* diagnosed atherosclerotic disease is less clear-cut. Guidelines currently recommend statins and until 2009 recommended aspirin to patients deemed to be at 'high' cardiovascular disease risk. Therefore, for all patients without diagnosed atherosclerotic disease, receipt of a prescription should be dependent on an assessment of cardiovascular disease risk and a decision by both general practitioner (GP) and patient. Due to (i) the uncertainties of risk prediction, (ii) the different risk prediction tools available, (iii) variation between GPs in their willingness to prescribe medications, and (iv) variation in patients' willingness to use them, there is likely to be variation in adherence to these guidelines.

Although MI events in patients without diagnosed atherosclerotic disease are unpredictable, it is these patients in particular for whom the medications should have been targeted. But, as described previously, the period prior to first MI has not been well-studied and so little is known about the initiation and duration of use of these medications in patients who go on to have MI.

1.6.2 Effects on outcomes at MI

While aspirin and statins are effective in reducing cardiovascular events in patients at high risk, they do not prevent all events. There is an emerging body of evidence suggesting that both aspirin and statins have effects on outcomes in patients who have MI despite these treatments. However, there is little evidence available for patients who are using these medications for primary prevention. Detailed data regarding risk factors and atherosclerotic disease diagnosis would be an important part of a study designed to explore outcomes at MI, due to confounding by indication, and the possibility that different effects of these medications might be seen for patients with different levels of cardiovascular disease risk. A beneficial or harmful effect of these medications could influence the decision to prescribe these medications.

1.7 Summary of thesis rationale

There are two main motivations for the work described in this thesis. First, there is a unique opportunity for new research into MI due to the linkage of primary care, hospitalisation, MI registry and mortality data. Second, the period preceding MI in patients without prior disease is of interest and is poorly understood. Many MIs occur in people with no previous manifestation of CHD but relatively little is known about the epidemiology of such MIs because, by definition, they are unexpected events.

While the linked data provide new opportunities, a first step in the use of such data is an assessment of its quality. Once the data have been shown to be of sufficient quality, the analyses in this thesis will be well placed to provide insight into MI as the first manifestation of disease at three levels; firstly to characterise the type of patients who experience MI as the first manifestation of atherosclerotic disease, secondly to characterize the effects of presentation with ischaemia prior to MI on subsequent mortality, and thirdly to characterize use of primary prevention medications and their effects of outcomes at MI. An understanding at these levels will be valuable for the future investigation of preventative strategies.

1.8 Aims and objectives

The aim of this thesis was to take advantage of the unique opportunities presented by the linkage of four data sources to investigate aspects of MI as the first manifestation of atherosclerotic disease. Specific objectives were as follows:

1.8.1 Objectives

I. To compare capture, risk factors, mortality and diagnostic validity of myocardial infarction in primary care, hospital discharge, disease registry and mortality statistics.

II. To examine the evolution of atherosclerotic disease and cardiovascular disease risk prior to first MI, cardiovascular disease risk factors and reported chest pain symptoms in first MI, including the timing of onset in relation to MI.

III. To examine the occurrence and timing of ischaemic presentations, including new atherosclerotic disease in different arterial beds and chest pain before non-fatal and fatal MI, and their associations with infarct size and coronary heart disease mortality.

IV. To examine the use of aspirin and statins prescribed prior to first MI for primary prevention and the effects on infarct severity, size and short term mortality.

1.9 Organisation of the thesis

This thesis is organised into seven further chapters. Chapter 2 introduces the data sources used in this thesis and discusses their strengths and limitations. Chapter 3 describes methods used through all analyses in identifying patients with MI and applying inclusion criteria. Chapters 4, 5, 6 and 7 address each of the four objectives in this thesis. Chapter 8 draws together and discusses the evidence gathered in this thesis and makes final conclusions.

Chapter 2 Data sources

2.1 Introduction

This chapter describes the data sources used in studies described in this thesis: the General Practice Research Database (GPRD), the Myocardial Ischaemia National Audit Project (MINAP), Hospital Episode Statistics (HES) and the Office for National Statistics (ONS) mortality register. Key characteristics of the four data sources are shown in Table 2.1.

The GPRD has now become the larger Clinical Practice Research Datalink (CPRD), "the new English NHS observational and interventional research service."[47] The CPRD continues to collect data in the same way as GPRD, and also holds several other NHS linked datasets.

Table 2.1 Key characteristics of the four data sources in this thesis

	GPRD	HES	MINAP	ONS mortality register
Type of data source	Longitudinal primary care data	National hospitalisation dataset	Acute coronary syndrome (ACS) register	National death census
Who is included?	Patients registered at primary care practices	Patients with hospitalisations for any cause	Patients hospitalised with acute coronary syndrome in NHS hospitals	People who die in England and Wales
Start of data collection	1987	1997	2000	Cause of death recorded since 1841, but since 2001 using ICD-10 codes,
Geographic regions covered	England, Wales, Scotland	England	England and Wales	England and Wales
Reason for dataset creation	Data are entered as part of routine clinical care, and the database was set up for research	To monitor hospital workload and outcomes of care	To compare performance of hospitals in meeting national standards for ACS management	To monitor trends in death
What is recorded?	Diagnoses, prescriptions, symptoms, lifestyle, vaccinations, test results etc	Diagnoses, procedures	Details regarding ACS diagnosis and management	Date and cause of death, including underlying and secondary causes.
How are data coded?	Read codes: a hierarchical coding system containing roughly 99,000 codes	International Classification of Disease, version 10 and Office of Population, Censuses and Surveys Classification of Surgical operations and procedures, version 4 codes	In 120 fields with multiple response categories as defined by the MINAP steering group.	International Classification of Disease, version 10

2.2 General Practice Research Database (GPRD)

2.2.1 Overview

The GPRD is a primary care database containing anonymised patient records for approximately eight percent of the UK population.[48] It was established in 1987 and is now one of the world's largest databases of anonymised longitudinal medical records from primary care.[49]

2.2.2 The data

2.2.2.1 Who is in the database?

About 630 general practices provide data to the GPRD[50] and all patients registered within these practices are included in the database until they die or transfer to another practice. Roughly half of GPRD practices consented to linkage with HES, MINAP and ONS at the time of this work. The practices chosen to participate in the GPRD are a representative sample of the UK, and since 98% of people in Britain are registered with a GP, patients within the GPRD are largely representative of the UK population.[51] At the time of this work (September 2012), there were 5.2 million actively registered patients in the GPRD.

2.2.2.2 How are data entered?

The GP records data using Vision Software. If a GP changes the software that is used in the practice, then they cannot contribute data to the GPRD. In order to enter computerized information, the GP types a descriptive term for the symptom or diagnosis and chooses the most appropriate entry from a drop-down list of possible choices, with corresponding Read codes (a hierarchical clinical coding system of over 80,000 terms that are used in general practice in the UK[52]). GPs are encouraged to use standardised recording practices for entering data. The data are uploaded to the GPRD daily, after they have been processed at the practice level.

2.2.2.3 What is measured?

A typical dataset from the GPRD contains information on a patient's sex, age, year of birth and registration details. Participating general practices are required to record (i) each episode of illness, or new occurrence of a symptom, and (ii) all significant morbidity events, for example all significant clinical contacts, all significant diagnoses and abnormal test results, referrals to outpatient clinics and hospital admissions.[50] Therapeutic information in the GPRD includes prescriptions using codes from the Prescription Pricing Authority, with the corresponding date, dosage and method of administration. Additional information is provided on vaccinations, weight and blood pressure measurements, laboratory test results and on some aspects of lifestyle. All information is entered by practice staff and is anonymised prior to central collection. The GP may also make comments about the patient consultation in a free-text section which can be linked to the codes for the consultation. This free text is not provided to researchers unless a specific request for it is made.

2.2.2.4 Data structure

The data are structured into ten file types, each containing specific information regarding the patient and/or practice. These are described in Table 2.2.

.

Table 2.2 General Practice Research Database file types and their contents

File type	What it holds	Example of contents
Patient	Demographic and registration status of patients	Patient identifier, month and year of birth, social deprivation†, registration status, death date, transfer out date
Practice	Practice administrative data	Practice identifier, geographical region, date practice became 'Up to standard', last data collection date
Staff	Information about the staff members entering data	Staff identifier, gender, role
Consultation	Administrative information about the consultation	Date of clinical event, date of data entry, type of consultation, staff identifier and duration of consultation
Clinical	Clinical data regarding medical history	Date of clinical event, date of data entry, GPRD medical code for the chosen Read code, additional details identifier*, entity type
Additional clinical details (ACD)	Specific data about a clinical event	Type of information held, called an 'entity', specific clinical details relating to that entity
Referral	Clinical data with relevant referrals to secondary care etc	The GPRD medical code for the chosen Read code, method of referral, referral specialty, urgency of referral
Immunisation	Data associated with immunisations	Reason for immunisation, type, stage, status and the compound used
Test	Test results	Type of test, result, normal range of result, unit of measure
Therapy	Information about therapies including medications and appliances	GPRD product code, British National Formulary code, quantity of product, dose, pack size, number of days prescribed

† Social deprivation measured using the Index of Multiple deprivation (see later).
*Allows a link to be made between a Read code in the 'clinical file' to additional details held in the 'additional clinical details' file.

The GPRD stores the majority of its data using Read codes. Some Read codes link to the 'additional clinical details' (ACD) file, which contains further details (usually) relating to that Read code, for example a Read code indicating smoking status may be linked to ACD file holding physician advice about smoking.

An 'entity' code recoded next to the Read code describes the kind of information stored in the ACD file (e.g. an entity code of 6 linked to any Read code indicates that the

ACD file holds smoking data). It is important to ensure that both Read codes and appropriate entity codes are searched when searching for data in the GPRD.

2.2.2.5 Patient identification

In general practice the NHS number, name, date of birth, address and postcode are used to identify patients. To protect patient identities these are removed before the data are centrally collected. Each patient is assigned a unique patient ID and each practice is assigned a practice ID to prevent identification of patients at any time. Although date of birth is removed, year of birth is retained so that analyses by age can be conducted.

2.2.3 Data quality

2.2.3.1 Quality measures undertaken by the GPRD

The GPRD has measures to ensure that the data it provides are research-quality. At the practice level, the GPRD implements 'up to standard' (UTS) dates for participating practices. The UTS date is deemed as the date at which the practice is considered to have continuous high quality data fit for use in research. This is calculated using an analysis on the total data in the practice, and is refreshed every time data are collected from the practice and processed into the database.

Up to standard criteria include a comparison of practice death and event rates to the general population. It also ensures that patients who have transferred out of the practice or have died are recorded correctly and "is based on an assessment of the completeness, continuity and plausibility of data recording in key areas, in accordance with the GPRD Recording Guidelines."[50]

When a practice is UTS, then its data are recommended for use by researchers. If a practice no longer meets the UTS criteria, then their records are still included in the database but should not be relied upon by researchers.

At the patient level, each patient in the GPRD is labelled as 'acceptable' or not based on a number of conditions including the validity of registration status, gender, age and year of birth (see Appendix A, section 10.1.1). If any of these conditions are violated, the patient's record is labelled as 'unacceptable' and is not recommended for research.

2.2.3.2 Quality measures assessed by independent researchers

In addition to the measures taken by the GPRD to ensure data quality, many independent, peer-reviewed publications have examined the validity of individual diagnoses. A systematic review of 357 validation studies of GPRD diagnoses estimated the median positive predictive value at 89%.[53] This means that for 100 diagnoses coded in the medical records, 89 can be verified using information from either inside or outside the database. A second validation study of diagnoses in the GPRD also found high positive predictive values for most diagnoses.[49] Some studies have also shown that GPRD data also have high sensitivity, high specificity and good completeness, although few studies have been able to assess this.[54-60] Most of the diagnoses and risk factors to be used in this project have undergone validation. Validation studies investigating atherosclerotic disease and cardiovascular disease risk factors are described below.

Validation of atherosclerotic disease

- MI has been validated in the GPRD several times and using a number of methods. Firstly the incidence of MI in the GPRD was found to be similar to that in other general practice data.[61] Secondly anonymised copies of paper medical records, hospital discharge summaries or death certificates were obtained to validate the MI diagnosis using further diagnostic criteria.[59, 61-64] The positive predictive values from these studies ranged from 85% to 100%. Thirdly, in three studies, a questionnaire investigating various aspects of the computerized diagnosis was sent to the GP. The positive predictive values in these studies ranged from 53% to 96%.[59, 61, 65] Finally, two studies carried out a manual review of the complete computer records (including the anonymised free text) for individuals with a diagnosis of MI. The records were assessed for confirmatory evidence of disease status; between 72% and 75% of individuals were confirmed as having MI.[66, 67] The estimates from these studies provide reliable evidence that the diagnosis of MI is valid within the GPRD. However, no studies have examined the validity of the timing of the MI code with respect to the true date of MI. These results, from many different designs and study populations within the GPRD, indicate that the positive predictive value of MI diagnosis in the GPRD is likely to be high.

- Coronary heart disease (CHD) was validated by Moser;[68] the prevalence of treated CHD in the GPRD in 1996 was "broadly comparable" to that from the 1994 Health Survey for England.[69] While the Health Survey for England is not necessarily an adequate 'gold standard' data source, the comparability of the two sources gives some indication of the accuracy of recording in both the GPRD and the Health Survey for England. However, the same result could also indicate that both sources are equally poor at detecting coronary heart disease.

- Two validations of stroke by GP questionnaire showed that the positive predictive value of a diagnosis of a cerebrovascular event was 86% and 93%.[59, 70] These studies used over a thousand patients with cerebrovascular accident and validated against a reasonable gold standard (GP questionnaire, and a review of the full medical record). However, a manual review of stroke diagnoses recorded 51% as 'probable' and the remaining patients as 'doubtful'.

- Peripheral arterial disease has been validated once and had a positive predictive value of 71%[59] when compared to a GP questionnaire and medical record review. However, this study was performed in the 1990s and recording of peripheral arterial disease may have changed over time. It was also performed in a relatively small number of patients (n=86), so the estimate may be imprecise.

Validation of cardiovascular disease risk factors

Hypertension and dyslipidaemia have been validated by comparing prevalence or incidence rates in the GPRD to those recorded in the Health Survey for England or Hospital Episode Statistics: rates were shown to be broadly comparable, again providing some indication of the accuracy of recording in these sources.[71-73] Diabetes has been validated many times using different methods and has shown to have high positive predictive value and similar rates to other sources.[51, 59, 68, 74-78]

Smoking was validated in patients with inflammatory bowel disease who had received an oral corticosteroid prescription. The researchers compared the electronic records to the GP's own records. This showed that the sensitivity of a current smoking diagnosis on a particular date was 78%, with a positive predictive value of 70%.[79] For behavioural factors that can change from one consultation to the next, these values are reasonable. However, in a group selected for a specific morbidity, the validity of a smoking record may be different to patients without the morbidity (for example those with inflammatory bowel

disease in this study may consult more frequently with the GP and have more opportunity to have an up-to-date smoking status recorded accurately). There is also likely to have been an improvement in recording of smoking since the introduction of the Quality and Outcomes Framework (see section below). Other cardiovascular disease risk factors (body mass index, family history) have not been validated in the GPRD.

2.2.3.3 Quality measures driven by the Quality and Outcomes Framework

For the past eight years, data quality in primary care has been driven by the Quality and Outcomes Framework (QOF), introduced to general practice in 2004. Over 99% of GPs are signed up to this voluntary scheme, which provides financial incentives to GPs to maintain good practice in four clinical domains and can contribute 25% of their income.[80] One of these four domains is the clinical domain, encouraging quality of care and recording of key chronic morbidities (including secondary prevention of CHD, primary prevention of cardiovascular diseases, heart failure, stroke and transient ischaemic attack, hypertension, diabetes, chronic obstructive pulmonary disease, epilepsy, hypothyroidism, cancer, palliative care, smoking mental health, asthma, etc).[81] There is some evidence to suggest that the scheme has led to an acceleration in the improvement of care for coronary heart disease, asthma and diabetes, although the improvements may now have reached a plateau,[80] and in fact the introduction of the QOF may actually lead to a reduction in the quality of care in areas not covered by the clinical indicators.[80]

2.2.4 Linkage to other databases

For this project, the GPRD will be linked with MINAP, HES and ONS mortality data. Details of this linkage are described in Appendix A, section 10.1.2. The GPRD has also been linked with cancer registry data and, with the recent creation of the Clinical Practice Research Datalink (CPRD), is set to be linked to many other datasets.

2.2.5 Publications

The GPRD has been widely used for observational studies, and has more publications than any other primary care database, with over 890 studies published to date in peer-reviewed journals.[50] Examples of important work based on GPRD include the findings that statins are associated with a decrease in the risk of dementia,[82] oral corticosteroid use is associated with an increase in risk of fractures,[83] the raised risk of MI in patients with psoriasis,[84] and the null association between the Measles, Mumps and Rubella vaccination and autism.[85]

2.2.6 Strengths

There are four key strengths of the GPRD as a research tool:

1. Size; there are 5.2 million currently registered patients in the database, but data are available for a total of 11 million patients (68 million person years of data).[86] This provides researchers with the power to investigate rare diseases and look at risk in sub-groups;
2. Representativeness of the UK population; and therefore the ability to generalise results from GPRD studies to the population;
3. Data quality; data are maintained to a high standard by GPRD checks and this is supported by independent validation studies of diagnoses;[53] and
4. Storage of the complete medical history of patients in the GPRD; this allows researchers to access detailed, prospectively collected data without recall bias.

2.2.7 Weaknesses

While the GPRD is an excellent source of data for research in primary care, researchers should be aware of the limitations of the data and consider ways of addressing these during analysis. These limitations are discussed in the following sections:

2.2.7.1 Missing data

While recording of data on key morbidities is now improved due to the introduction of the QOF,[80] GPRD does not routinely record some lifestyle factors (e.g. height, weight, diet, alcohol consumption). Additionally, any morbidity for which a patient does not require

a GP visit will not be recorded (e.g. minor respiratory infections). In addition, some medications are available over the counter, making it impossible to record all therapies used by patients.

Although recording of some key lifestyle factors and morbidities is poor, the missingness is unlikely to be at random. It is more likely that these factors are recorded if a patient is more at risk, for example smoking status is more likely to be recorded if the patient is a current smoker,[79] and blood pressure more frequently recorded in those who have high blood pressure.[87] Therefore, analysis using only non-missing data may lead to some bias in estimates using such lifestyle factors. This could be negated by use of multiple imputation, but imputing missing values in this way can only be done with extreme care due to the unknown mechanism of missingness.[88]

2.2.7.2 Frequency of consultation

For some registered patients there is no or very little follow-up data after initial registration with the practice. Patients who do not consult frequently are a problem for two reasons. First, if they have transferred out of the practice without informing the practice, then their inclusion in studies will introduce error, as their outcomes could never be recorded. Inclusion of these people in studies would lead to underestimation of incidence and outcomes. Second, if a patient attends only infrequently, then their chances of receiving a diagnosis or a treatment will be less than for a patient that consults more frequently. However, removing patients without frequent consultations runs the risk of removing real healthy people and biasing the study towards an unhealthier group.

2.2.7.3 Recording of existing morbidities

When a patient joins a practice and visits the GP for a 'new patient check-up', their medical history is recorded. This new coding of existing morbidities can be a problem for researchers wishing to calculate incidence. Inclusion of this new period of registration in calculations of incidence can therefore result in overestimates. To avoid any bias, the initial period of registration should therefore be excluded. Evidence suggests that after the first year of registration, the recording of most major acute and chronic conditions has reached the baseline levels.[89]

2.2.8 Summary and suitability of GPRD data for this project

The GPRD is a representative and valid source of data covering all aspects of primary care, from basic demographic data to diagnoses, therapies and hospital visits. Such a rich data source enables this project to investigate the occurrence of atherosclerotic disease, cardiovascular disease risk factors and the prescription of therapies for the primary and secondary prevention of MI; these prospective data before MI represent a unique strength.

2.3 The Myocardial Ischaemia National Audit Project (MINAP)

2.3.1 Overview

The Myocardial Ischaemia National Audit Project (MINAP) is the national registry of patients admitted to hospitals in England and Wales with acute coronary syndromes (ACS).[90] It was established by clinicians in 1998 to provide participating hospitals with a mechanism to audit their performance against standards defined in the National Service Framework (NSF) for coronary heart disease (CHD).[90, 91]

The NSF standards aimed to improve care and access to care for patients with CHD. MINAP relates to the framework's standards for treatment of ST-elevation MI (STEMI) patients, and those for the prescription, at discharge, of aspirin, beta blockers and statins in all ACS patients. However, data are also collected in MINAP on all other of forms of ACS (non ST-elevation infarctions (NSTEMIs) and troponin negative ACS) and their treatments (including primary angioplasty, prescription of clopidogrel etc). Users of MINAP are therefore able to examine these aspects of coronary care in addition to those relating to the NSF.

Data collection began in October 2000 and by mid-2002 all hospitals admitting emergency patients in England and Wales were participating in the registry. MINAP data are held by the Central Cardiac Audit Database (CCAD) Group,[92] which has developed a highly secure electronic system to collate, hold and analyse national cardiac data confidentially. CCAD provides the National Institute for Clinical Outcomes Research (NICOR) with a dataset stripped of identifiers for audit and research purposes. MINAP is currently funded by the Health Quality Improvement Partnership.[93]

2.3.2 The data

2.3.2.1 Who is in the database?

MINAP collects a wealth of information regarding the care and outcomes of patients with ACS who attend one of over 225 participating National Health Service (NHS) hospitals in England and Wales. Each year the database accrues approximately 85,000 episodes of care. Hospital staff are encouraged to enter data, using the MINAP data application software, for all ACS patients admitted to hospital.

2.3.2.2 What is measured?

Data are collected for each patient from ambulance paramedic crews, accident and emergency departments and cardiac care wards. The MINAP dataset holds 123 fields[94] under the following categories; patient demographics, admission method, the timing of care given, clinical features and investigations (e.g. ECG result, cardiac biomarkers), past medical history (including prior cardiovascular disease risk factors, atherosclerotic disease and procedures, family history), drug treatment prior to admission, detail of primary reperfusion treatment, drug treatment in hospital, clinical complications, interventional treatments, hospital outcome, discharge diagnosis and discharge (secondary prevention) treatment (e.g. referral to specialist units).[90] Importantly, MINAP records MI type: ST-elevation MI and non ST-elevation MI (defined in Chapter 1).

The dataset is revised every two years to meet the requirements of users and to respond to changes in management of patients. For example, the dataset was updated to incorporate data items which reflect the National Institute for Health and Clinical Excellence guidelines for secondary prevention of MI (e.g. to record the provision of smoking cessation and dietary advice). Revisions are also made in response to changes in the definition of acute coronary syndrome.

2.3.2.3 Patient identification

Patients are identified by their unique NHS number, which is stored in pseudonymised format and used to link the data to subsequent events or procedures undergone by the patient. Names and addresses, including post code of residence, are collected by the hospitals but are not stored centrally or available to researchers. Patient age is supplied to researchers rather than date of birth because this is considered too strong an identifier. The NHS number and local patient case record number are encrypted before the data are uploaded to the secure central database.

2.3.3 Data quality

2.3.3.1 Accuracy

MINAP provides detailed guidelines and technical advice for data entry and makes recommendations to staff entering the data in order to maintain data quality and ensure continuity of data collection. There is also a dedicated MINAP helpdesk for problems

regarding data entry and clinical definitions. The MINAP data entry program is designed to minimise common errors that arise in entering data, with range and consistency checks to improve accuracy. Staff are asked to enter data concurrently with the patient's hospital stay to improve accuracy and efficiency.

2.3.3.2 Validation

An annual MINAP validation exercise requires each hospital to re-enter 20 items of data from the original medical records of 20 randomly selected MINAP patients, using a specially designed data validation tool. These 20 items are set by MINAP and include NHS number and variables regarding diagnosis, treatment, outcome and discharge. Agreement between the original and re-entered data is assessed for each of these variables. Areas in which agreement is inadequate (Measure of reliability Kappa value below 0.5) are identified and the underlying cause is resolved where possible. Reports are sent to hospitals identifying areas of weakness and advice is available to improve performance. Agreement varies between fields (high in key fields, slightly lower elsewhere) but in the 2008 validation, the median level of agreement between MINAP data and re-audit data (across all hospitals) was 89.5%.[95] This exercise has been compulsory since 2004 and allows hospitals to compare their performance with others and maintain the quality of their data.

2.3.3.3 Completeness within the dataset

Thirty six key fields are mandatory within the dataset including NHS number, date and time of arrival at hospital, discharge diagnosis, time to reperfusion therapy (if given), hospital mortality and secondary prevention medication prescribed at discharge. Annual checks for completeness are made in 20 other key variables and in 2007/8 these were 98% complete.[96] The completeness of variables that were not intended for audit use (e.g. family history of coronary heart disease, height, weight, blood pressure, previous MI or angina) is slightly lower but is improving with time (unpublished findings). There are some data items which are incomplete because the data are not available, for example if a patient is sent to another hospital for intervention, and that intervention is not known, the field will be left blank.

2.3.3.4 Studies assessing validity of MINAP

To date, there have been no peer-reviewed studies examining the validity of MINAP data, including its completeness.

2.3.4 Linkage to other data

The Central Cardiac Audit Database Group facilitates mortality tracking for MINAP records using the Office for National Statistics, which provides vital status and date of death for patients in the database, although cause of death cannot be determined. The MINAP dataset has been linked to other databases and national registries using NHS number as a unique identifier. For example, MINAP has been linked with the coronary interventional database held by the British Cardiovascular Interventional Society (BCIS), and the surgical data held by the Society of Cardiothoracic Surgeons.[97, 98] Linkage of MINAP with other datasets offers a unique opportunity to validate individual cases of STEMI and NSTEMI recorded in MINAP.

2.3.5 Research published using MINAP data

The original purpose of MINAP was to provide contemporary analyses to hospitals so that they were able to relate their performance to the nationally agreed targets outlined in the NSF CHD.[91] For example, a NSF target for England was for 68% of "heart attack" patients to receive thrombolytic treatment within 60 minutes of calling for help. MINAP data showed that this target was exceeded in 2008/09 with an average of 72%. The performance of each hospital is summarised in an annual public report "How the NHS manages Heart Attacks" (e.g.[96]).

The MINAP Academic Group, based at NICOR at University College London, encourages use of the MINAP data for research. This group ensures that any research conducted using MINAP data is of a high standard and that researchers adhere to the guidelines for use of the data.

One of the first publications using MINAP showed data in relation to the original NSF CHD targets, focusing on access to treatment for patients with acute MI.[99] This showed that speed of treatment had improved with time and that the proportion of acute MI patients given thrombolysis had increased during the study period (1993-2002). Analyses of data from 2004-2005 by Birkhead[100] showed that the outcome and management of MI

was partly dependent on the specialty of the physician admitting the patient. Weston et al[101] used MINAP data to identify a reduction in mortality in non-diabetic hyperglycaemic patients who are treated with insulin when presenting with ACS.

Ben-Shlomo[102] analysed data from 2002-2003 to assess ethnic differences in both healthcare-seeking behaviour and the in-hospital management of acute chest pain. This revealed that people of South Asian origin are less likely to use ambulance services and are managed differently to other ethnic groups in hospital. Gale et al[103] used the MINAP data to examine predictors of hospital outcome in patients with ST-elevation infarctions, finding that aspirin use and pre-hospital thrombolysis predicted survival, while increasing age, systolic blood pressure and heart rate predicted mortality. Most recently, Birkhead et al[104] showed that angiography in NSTEMI patients has a beneficial effect on mortality, which was not modified by age, sex or co-morbidity.

These publications highlight the potential of the database for answering a diverse range of questions about acute coronary syndromes. The ability of MINAP to adapt over time and the continuous improvement in completeness will further add to its utility as a database fit for research.

2.3.6 Strengths

MINAP's strengths are its size and population coverage. Data are collected from every acute hospital in England and Wales even though participation is not compulsory. Therefore, the data should be representative of all ACS patients hospitalised in England. Data have now been collected for over 800,000 ACS events from across England and Wales, giving users of the data unprecedented power to answer research questions relevant to small subsets. Additionally, with 123 variables describing exact timings of the events, prior morbidity, treatment, diagnosis and follow-up, the detail of the data represents another great strength. Importantly, MINAP holds data on MI type, distinguishing between STEMI and NSTEMI. Data regarding MI type are not available in HES or ONS data and are infrequently recorded in GPRD.

2.3.7 Weaknesses

There is uncertainty in the completeness of patient capture. While some participating hospitals do record all patients admitted with suspected ACS, other hospitals

predominantly record only those with STEMI, which leads to under-reporting of NSTEMI. This may be to the lack of an agreed national standard of care for NSTEMI and other ACS, so hospitals with limited resources for data entry might choose to record STEMI preferentially, where their results can be measured against targets. In addition, where patients with non ST-elevation ACS are not exclusively admitted to cardiology wards, patient ascertainment is likely to be less complete. Many patients (with both STEMI and NSTEMI) are now transferred between hospitals during the index event, which makes data capture more difficult. The threat to data capture of inter-hospital transfers is however, being addressed by linking MINAP records between hospitals.[90] There have been no formal investigations to look at the capture of patients within each hospital and some hospitals are more rigorous with data collection than others.

Incomplete patient capture within hospitals raises concerns about the representativeness of MINAP data. This concern is amplified because a proportion of ACS patients die before, or soon after reaching hospital, or are admitted to private hospitals (although in England and Wales the number of patients admitted to private hospital will be negligible). These people will be omitted from the database.

Missingness needs to be addressed in some data fields. For example, for the 444,519 events recorded in the years 2003-2007 inclusive, 26,032 had either age or sex missing (5.9%). Removing events with incomplete data (in the variables of interest) leaves a reasonable number of events for analysis because the database is so large. However, patients with missing data may be different to patients with complete data, so removing them from the analysis may lead to a selection bias. Cattle et al[105] demonstrated that patients who have missing data in a field relating to angioplasty are more likely to have died than those with complete data.

The cost of local data entry is not covered by MINAP's funding. Each hospital must therefore make a financial contribution to the project to support data entry, and this contribution is subject to variability. As a consequence, those responsible for data entry may not have clinical expertise, which could lead to variability in data accuracy.

2.3.8 Summary and suitability of MINAP for this project

The MINAP database is a unique and valuable resource for researchers interested in the risk factors, treatments and outcomes of ACS. The detailed information recorded in the database creates scope for a wide range of research using MINAP data alone; linkage to

other sources creates an even more valuable and versatile resource. Within its first decade MINAP has gathered information on almost 800,000 events, which provides unprecedented power to investigate subgroups of risk.

2.4 Hospital Episode Statistics (HES)

2.4.1 Overview

Hospital Episode Statistics (HES) is a data warehouse of hospital discharge coding data, established in 1987 to facilitate the collection and use of hospital data in England.[106] Its main purposes are:

- To monitor hospital workload and outcomes of care;
- To compare workloads between different geographical areas and hospital trusts;
- To study lengths of hospital stay and other measures of efficiency with which care is delivered;
- To monitor waiting lists; and
- To study the epidemiology of hospitalised disease.[107]

Prior to the creation of HES (since 1950), data on a smaller sample of hospital admissions were collected[107] but HES now undertakes data collection from all NHS trusts in England by the department of Health and are held by Northgate Information Solutions on behalf of the NHS Information Centre for health and social care (NHS IC).

2.4.2 The data

2.4.2.1 Where do the data originate?

HES data are input by clinical coders based on patient notes at the end of the admission. These data are submitted to the Secondary Uses Service (SUS) (part of the NHS Information Centre), which has a dual role of providing the data to the Department of Health and copying it into a database. Monthly, the SUS data are extracted and sent to HES. Staff at SUS then validate and clean the data extract according to a set of rules before making it available to researchers.[106]

2.4.2.2 Who is in the database?

Data are collected "for each episode of admitted patient care delivered in England by NHS hospitals or delivered in the independent sector but commissioned by the NHS."[106] This means that data are collected for in-patients (since 1989), outpatient appointments (since 2003), accident and emergency (A&E) (since 2007) and adult critical

care (since 2008). Data from admitted patients comprises over 16 million episodes of care per year and the addition of outpatient data provides a further 60 million new records per year. A&E data add 12 million records per year.

2.4.2.3 What is measured?

Each HES record contains information in the following four areas:[106]

1. Information about the patient, for example age, gender, ethnicity, socioeconomic status;
2. Clinical information about diagnoses and operations (one main diagnosis and up to 13 secondary diagnoses and twelve operation fields);
3. Administrative information (admission and discharge dates, time waited on waiting list, date of admission, length of stay and the specialty of the consultant); and
4. Geographic information (e.g. where the patient lives, where they are treated, the NHS trust providing care).

HES collects data using three sets of codes: the World Health Organisation's International Classification of Diseases Tenth Revision (ICD-10), the Office of Population, Censuses and Surveys Classification of Interventions and Procedures fourth revision (OPCS-4), and A&E Clinical Codes.

ICD-10 collects data on conditions being investigated or treated at the hospital admission, OPCS-4 records the procedures and interventions performed, while the A&E clinical codes record diagnoses, investigations and procedures that are undertaken during A&E attendance.

Since the start of data collection in 1989, changes have been made to the data that are collected in response to updated coding systems (ICD and OPCS). ICD-10 codes are now used to code the 'primary' diagnosis, defined by HES as "the main condition treated or investigated during the relevant episode of healthcare".[106] There is also space in the database for up to 13 additional secondary diagnoses to collect data on other conditions or co-morbidities that are relevant to patient care. Similarly, the OPCS-4 codes are used to code a main procedure or intervention, with space for up to 12 secondary procedures or interventions.

2.4.2.4 Episodes, spells and patient identification

The unit of measure in HES is the 'Finished consultant episode' (FCE), which is defined by HES as "a period of admitted patient care under a consultant or allied healthcare profession within an NHS trust". FCEs are grouped together in 'spells', which represent all FCEs in a single hospital admission. Therefore, each 'spell' can have many FCEs as patients are often transferred between specialties and treated by more than one consultant during their stay. Around 8% of hospital admissions have more than one episode of care.[108]

NHS numbers are collected and individual patients are given a unique HES identifier during data cleaning, which allows researchers to identify multiple hospital admissions for the same patient. NHS number, date of birth, address and postcode are not distributed by HES in order to maintain confidentiality.

2.4.3 Data quality

The nature of data recording in HES means that quality can be affected in one of three stages. First, the clinician must recognise and make a correct diagnosis in the patient, second the clinician must document that diagnosis in the clinical notes, and third the coders must receive the notes and classify the diagnosis correctly using ICD-10 or OPCS-4 codes.

While HES has procedures and checks to maintain quality, hospital data quality was cited as a concern by the Audit Commission in 2002,[109] and the report made several recommendations for improvement. More recent assessments of data quality by the audit commission have shown improvements in quality,[110] but as discussed below, several independent studies undertaken by researchers have shown that quality is still poor in some areas.

2.4.3.1 Data quality procedures in HES

A HES data quality team monitors the data. Following receipt of the data, cleaning takes place in a four stage process:[106]

1. Provider mapping, which ensures that the hospital codes are correct and usable, mapping old codes to new ones where appropriate;

2. Automatic cleaning, which uses a predefined list of rule to deal with common errors in the dataset, for example the removal of extra characters in the codes (spaces, ampersands, full stops);
3. Manual cleaning, which removes duplicated data and removes episodes outside the required date range;
4. Derivation, which allows HES to add certain fields that SUS does not store (e.g. Primary Care Trust fields, age group, descriptions of codes, and HES identifiers).

Throughout this process, the data quality team produces reports to ensure that the processes are occurring correctly and to identify any novel issues that have not been dealt with. HES also publishes reports that list known issues of data quality. The data quality team also feeds back information to the data providers themselves, encouraging them to take responsibility for the data that they provide and preventing problems arising in the next extract. There are also regular audits of coding in each hospital.

2.4.3.2 Independent studies of HES data quality

Several small studies have assessed the quality of data in HES. Some have focused on the reproducibility of codes: a study comparing locally entered diagnostic codes with codes entered by external coders showed that *exact* agreement was 43%- 60% for general diagnoses but was higher for acute diagnoses (appendicitis 51%-65%). *Approximate* agreement was higher for general diagnoses and was yet higher (78-80%) for appendicitis.[111] This indicates that although subtypes of a diagnosis may be recorded poorly, the overall diagnosis is likely to be correct.

Other studies have focused on completeness: in 2002, Williams and Mann[112] conducted a review of validation studies looking at completeness of hospital discharge coding since 1990. This showed that hospitals were failing to capture all in-patient and day-case episodes; completeness was between 66% and 84% for diagnoses. Accuracy of procedure recording was also low. The authors attributed the inaccuracy and missingness in the data to the time of coding, which occurs after the spell is complete (i.e. the patient is discharged). This evidence is now old and completeness is likely to have improved over time after the Audit Commission recommendations and the introduction of the government 'Payment by Results' scheme,[113] which offers financial rewards for accurate and complete coding. Evidence of an improvement with time is shown by Hodgson et al,[114] who compared hospital discharge coding of type 1 diabetes with a diabetes register and found the concordance was 91% in 2000-2006, but only 52% in 1992-1999.

A study of the coding of abdominal aortic aneurysm (AAA) showed good consistency (95%) between the presence of a repair code and a concurrent diagnostic code for AAA.

While evidence from Welsh hospital-based data suggest that serious, acute diagnoses such as MI are only 10% under-recorded,[115] a more recent study of MI outcomes (2009) has shown that recording remains suboptimal in England.[116] In a comparison of hospital discharge coding (on which HES is based) to the Oxford Vascular Study (OXVASC), the authors identified 820 incident MI cases in OXVASC. Of these cases, only 53% were captured in hospital discharge data as acute MI (ICD-10 I21, I22). A further 25% had less specific ischaemic heart disease codes, but 21% had no coronary codes at all.[116] This suggests that improvements are still needed in recording of hospital data.

2.4.4 HES data for academic purposes

HES was designed for use in epidemiological studies and has been used as such, resulting in several hundred publications focusing on diverse outcomes including MI[117, 118] and other atherosclerotic disease,[119, 120] cancer,[121] pregnancy[122] and mental health.[123]

2.4.5 Strengths

HES data are collected by the hospital providers as part of routine care and as such form a rich dataset for researchers interested in the primary diagnosis or cause for hospitalization, and also in secondary or complicating conditions. HES is nationwide in England and is therefore a representative source of data for patients in England. It collects information on over 16 million episodes of in-patient care each year; this wealth of information allows researchers to assess the burden of rare conditions and allows subgroup analyses for more common conditions. The Payment by Results scheme encourages coding of incident and relevant prevalent diagnoses of the patient, so important co-morbidities should be recorded.[113] Data quality is improving with time and HES cleans and validates the data, thus ensuring that the data are of the best possible quality given the restraints of time and cost.

2.4.6 Weaknesses

As a routine source of data, HES is subject to missingness, duplicated data and incomplete records. Concerns have been raised about the quality of the data, and in particular for the completeness of recording of MI. However, there have been no large-scale, peer reviewed studies to examine all aspects of the data quality and highlight the strengths and weaknesses of the data.

2.4.7 Summary and suitability of HES for this project

The focus of this project is patient with MI. While HES classifies diagnoses according to ICD-10, which does not distinguish between STEMI and NSTEMI, the types of MI, it has strong data on co-morbidities. Linkage with MINAP provides additional data on type of MI, admission and diagnostic test characteristics.

The lack of in-depth, large validation studies of the HES data highlight the importance of the new linkage of HES with GPRD, MINAP and ONS. This linkage provides a new platform in which to assess the validity of acute coronary syndromes in HES.

2.5 Office for National Statistics (ONS) mortality records

2.5.1 Overview

The Office for National Statistics (ONS) mortality records are a complete database of death records for England and Wales. Registration of death has been a legal requirement since 1837, after the introduction of the Births and Deaths Registration Act, and they have been recorded with a cause of death since 1841. The government have collected statistics on cause of death from the late 19th century in order to monitor public health, allocate resources and evaluate public health policies.[124]

2.5.2 The data

As death registration is mandatory in the UK, any person who dies in England and Wales should be included in the database. Data are entered by a local registrar. In three quarters of deaths, the registrar refers directly to the Medical Certificate of Cause of Death (MCCD), which is completed by the doctors involved in the patient's care and includes information on the underlying and other causes of death. Learning how to fill in this form correctly is part of training for doctors. One quarter of deaths are referred to a coroner (e.g. if patient was not seen by a doctor, cause is unclear, unnatural or suspicious) and in most cases the coroner confirms the information written on the MCCD. If the cause of death remains unclear, data from a post-mortem or inquest are used in death registration.

The MCCD has two parts. Part I contains the underlying cause, which is the most frequently used data in routine health statistics, and is defined as either "the disease or injury which initiated the train of events directly leading to death", or "the circumstances of the accident or violence which produced the fatal injury".[125] Part II records details of associated conditions "that contributed to the death but are not part of the causal sequence". In the coding of death certificates, rules are applied to ensure that the most useful information regarding the cause of death is recorded in the appropriate place, and that data are comparable.

Classification systems used to record mortality statistics have evolved over time to reflect new knowledge on the causes and types of diseases, and the World Health Organisation (WHO) is now responsible for maintaining the coding system: the International Classification of Diseases, now in its tenth revision (ICD-10) and used across much of the world to record both fatal and non-fatal disease. ONS mortality data have been coded using

ICD-10 since 2001.[124] Patients are identified in the ONS mortality database using their unique NHS number.

2.5.3 Data quality

Registrars at Local Registration Services enter data into an online system, which has validation checks to ensure that data are correct. ONS performs regular diagnostic tests on data to identify problems: local registrars are contacted if any problems are identified.

When the data have been uploaded to the ONS database, they are subject to a series of further validation processes that are designed to identify inconsistencies in the data, for example to ensure that all fields are complete, to check that the conditions on the death certificate are compatible with the gender and age of the deceased, cross-field internal comparisons and plausibility checks.[126]

2.5.4 Summary and suitability of ONS for this project

ONS mortality data are a complete source of death data for England and Wales. They hold data on the date and underlying cause of death, which is important in this project to identify patients dying from MI who do not reach hospital and may not be captured in any of the other data sources.

2.6 Linkage of GPRD, MINAP, HES and ONS mortality

2.6.1 Purpose of the linkage

The Cardiovascular disease Research using Linked Bespoke studies and Electronic Records (CALIBER) group established the linkage of the GPRD, MINAP, HES and ONS, combining the rich data from each source into a single dataset. Using such a dataset, researchers can address questions on the sequence and progression of cardiovascular disease events and investigate their association with a range of risk factors.[127] In creating this dataset, CALIBER has allowed reconstruction of the longitudinal patient journey from GP registration through to death (Figure 2.1). These four data sources were linked by a trusted third party on behalf of the CALIBER group. Details regarding the linkage are described in Appendix A, section 10.1.2.

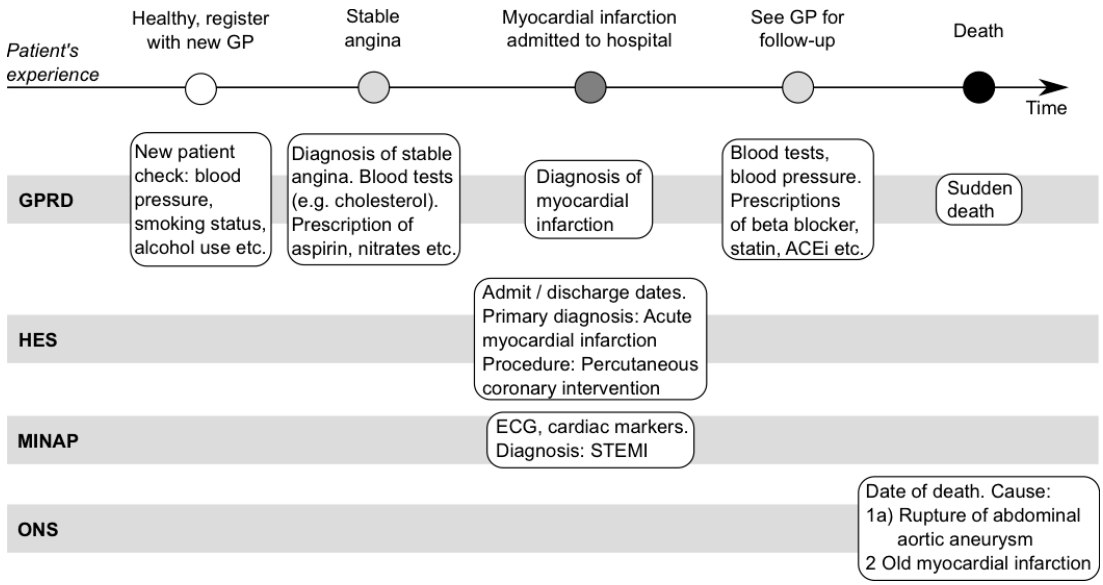


Figure 2.1 Linked data from CALIBER and the longitudinal patient journey (reproduced from Denaxas et al, 2012[127])

2.7 Chapter summary

- This chapter described the data sources to be used in this thesis: GPRD, HES, MINAP and ONS.

- Each data source was created for a different purpose and each has important strengths and weaknesses.

- Linkage of the national audit of MI with general practice records, hospital admissions data and mortality data from the Office for National Statistics provides major advances in terms of data quality and validity, and offers new opportunities for research with unprecedented power, ability to distinguish types of MI, and ability to follow patients prospectively through their medical record to death.

Chapter 3 General methods

3.1 Introduction

This chapter describes how the linked GPRD, MINAP, HES and ONS data were used to identify patients with first MI and identify morbidities, risk factors and prescriptions of cardiovascular medications.

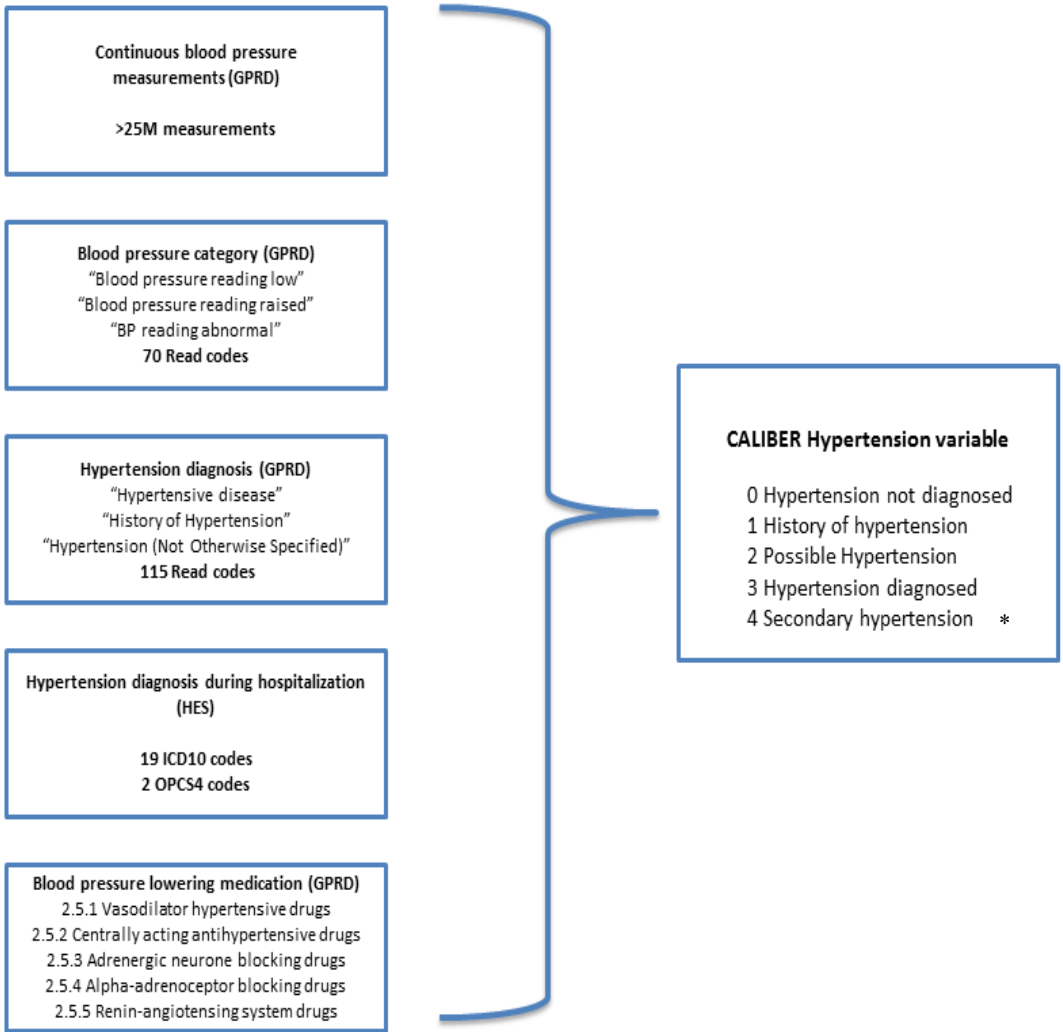
3.2 CALIBER data

3.2.1 Converting raw data to research-ready data

Following linkage of the four data sources by the Trusted Third Party, six billion records of raw data were available for research.[127] However, these data were not in a usable form and required extensive processing to make them ready for researchers.

I played a key role in developing a transparent, reusable approach to convert the data from their raw form to a research-ready dataset. For each data source, this involved identifying where usable data may be held within the dataset and developing a strategy to extract and code it in a useful way that could be modified to suit researcher needs. As discussed in the following sections, this involved developing a good working knowledge of the structure of each data source, an understanding of how each of the risk factors and morbidities in this thesis could be diagnosed, monitored and treated, and generating lists of codes for use in GPRD, HES and ONS. Following identification of appropriate codes in each source, the data had to be brought together to create variables for use in the analyses for this PhD, for example as in Figure 3.1, which describes the way in which data are used from GPRD and HES to define patients with hypertension.

This work culminated in the creation of a CALIBER data manual, see Appendix B. This work was a vital step in ascertaining good quality data for this thesis and the data manual is now being used by other researchers using CALIBER data.



*Secondary hypertension indicates hypertension induced by an underlying secondary cause, such as renal or endocrine disorders. This category was only used when Read or ICD codes stating 'secondary hypertension' were used and was not inferred from any other morbidity. Primary hypertension did not have specific Read codes and therefore was not defined here.

Figure 3.1 CALIBER hypertension variable creation from multiple electronic health records sources, a combination of a) repeat continuous blood pressure measurements b) categorical data on measured blood pressure c) hypertension diagnosis in primary care d) hypertension diagnosis during hospitalisations and e) prescription of blood-pressure lowering medications. Reproduced from Denaxas et al, 2012[127]

3.3 Using GPRD data

3.3.1 Creating variables using GPRD data

As discussed in Chapter 2, the GPRD stores the majority of its data using a set of 100,000 Read codes that represent terms for diagnoses, symptoms, tests, procedures, behavioural and demographic information, in addition to the GP's management of conditions. There are usually several Read codes that indicate a single diagnosis or procedure (e.g. to describe subtypes, synonyms or complications of a diagnosis). To capture all patients with a particular condition, researchers can choose to do one or more of the following:

- Develop a list of Read codes to indicate the diagnosis, specific symptoms, management, treatments and procedures used for the condition;
- Develop a list of Read codes that indicate clinical tests, the results of which (available in the additional clinical details (ADR) file) can define disease (e.g. HbA1c and diabetes);
- Develop a list of relevant Entity codes, which indicate further specific information held in the additional clinical details file, (e.g. there are specific Entity codes for various disease registers, to indicate the results of height and weight measurements, to indicate smoking status etc); and
- Develop a list of medications specific to the diagnosis so that the diagnosis can be inferred from prescriptions (e.g. insulin prescription indicates diabetes).

Variables for conditions in this thesis were therefore created based on a combination of some or all of the above information in the GPRD.

3.3.2 Generating Read code lists in the GPRD

The GPRD does not provide a standard protocol for creating lists of Read codes to represent a certain condition. There are also few widely available code lists for commonly studied conditions. Therefore, the CALIBER group created a standard operating procedure (SOP) for code list development and implemented the SOP to generate the lists of codes for the diagnoses, procedures, symptoms and tests used in this thesis. I was part of a four

person team that developed the SOP. The list of code lists used in this thesis to identify patients with cardiovascular disease and cardiovascular disease risk factors in the GPRD are shown in Table 3.1 and Table 3.2. The steps in the SOP are shown in Figure 3.2. The SOP was designed to maximize both the sensitivity of the initial search of Read codes, and the specificity of the final list by removing incorrect codes at the rating stage.

3.3.2.1 Rating Read codes according to variable definitions

For all diagnoses, procedures, symptoms and tests, Read codes were rated against agreed definitions (see CALIBER manual) by two independent raters, both of whom were clinicians (including one general practitioner). Codes were categorized as follows:

- Not indicative of the diagnosis (presence of the code did not indicate that the patient had the diagnosis);
- Reliant on test result to indicate presence or absence of diagnosis (e.g. a code indicating a glucose tolerance test would be linked to a result in the additional clinical details file, the results of which might confirm a diabetes diagnosis);
- 'Possible';
- 'Definite'; or
- 'History of' the diagnosis (where the code indicated that a diagnosis had been made in the past and did not indicate incident morbidity).

For some variables, categories were more specific. See the CALIBER data manual for the classification of each variable. Discrepancies between raters for all codes were resolved by discussion.

For test results to confirm or refute diagnoses, raters assigned a cut-off, based on national standards or clinical guidelines. Abnormal test results (defined by either categories in the data or by cut-offs) were considered as 'definite' indicators of the diagnosis; potentially abnormal test results (or borderline results) were considered as 'possible' indicators of disease.

The Read code lists produced using this method were compared to the code lists of other researchers (where available) to check the validity of raters' coding. If any terms were missing, the search terms were updated and new codes were rated.

3.3.2.2 GPRD conflicting codes

Where more than one code was recorded to indicate the presence or absence of a diagnosis, in the event of a conflict arising, the 'worst case scenario' was assumed, increasing the sensitivity of the code search.

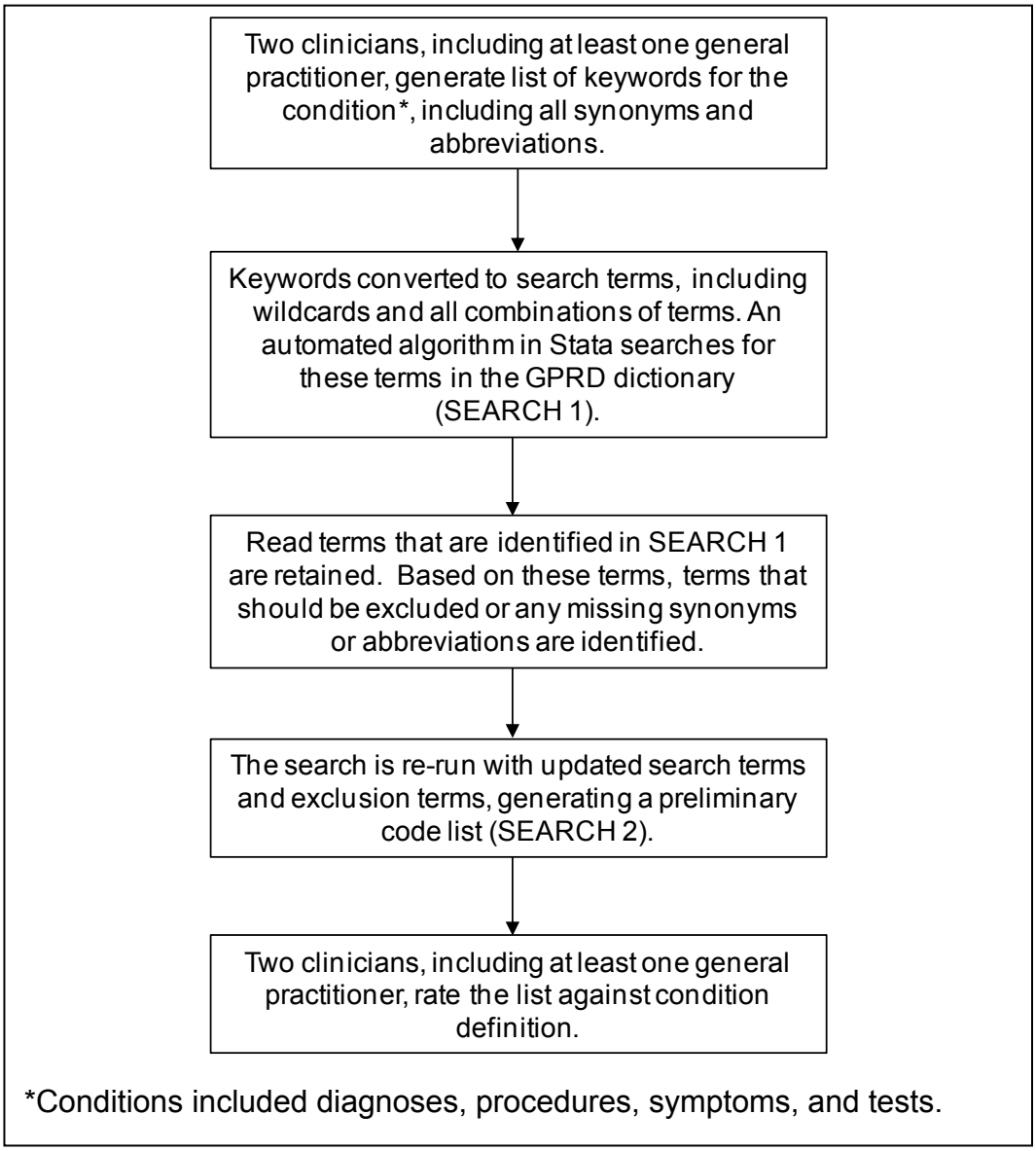


Figure 3.2 Standard operating procedure: method of Read code list creation in the GPRD

Table 3.1 GPRD cardiovascular disease Read codes lists and the number of codes included

GPRD cardiovascular disease Read code lists	N Read codes in list
Coronary disease and its tests	
Acute coronary syndrome	1
Stable angina	26
Unstable angina	14
Coronary artery bypass graft	66
Percutaneous coronary intervention	30
Cardiac arrest	37
Cardiac markers NOS	7
CK-MB	3
Troponins	6
Resting ECG	123
Exercise ECG	12
Coronary angiogram, modality NOS	12
Coronary angiogram results	3
Coronary CT angiogram	1
Coronary invasive angiogram	14
Coronary MRI angiogram	1
Stress echocardiogram	1
Radioisotope scan	15
CHD NOS	10
Heart failure	93
Echocardiogram	19
Myocardial infarction, type NOS	62
ST-elevation MI	1
Non ST-elevation MI	1
Thrombolysis	21
Angiography, anatomy NOS	5
Cerebrovascular disease and its tests	
Cerebral haemorrhage	50
Ischaemic stroke	11
Stroke NOS	43
Transient ischaemic attack	9
Carotid angiogram	6
Carotid ultrasound	4
Cerebral CT	3
Cerebrovascular disease procedures	30
Ischaemic cerebrovascular disease NEC	87
Peripheral arterial disease and its tests	
Peripheral arterial disease	73
Peripheral arterial angiogram	16
Peripheral arterial ultrasound	6
Abdominal aortic aneurysm	14
Abdominal aortic angiogram	6
Abdominal aortic ultrasound	2
Peripheral arterial disease procedures	152
Abdominal aortic aneurysm procedures	82
Atherosclerotic disease NEC	31
Sudden cardiac death	1
Chest pain	38

NOS: not otherwise specified; NEC: not elsewhere classified; CHD: coronary heart disease; MI: myocardial infarction; ECG: electrocardiogram.

Table 3.2 GPRD Read code lists for cardiovascular disease risk factors and the number of codes included

GPRD cardiovascular disease risk factors Read code lists	N Read codes in list
Diabetes and its tests	
Diabetes diagnosis	513
120 minute glucose tolerance test	2
Fasting plasma glucose	1
Fasting serum glucose	3
Glucose tolerance test	19
HbA1c	17
Hyperglycaemia	9
Hypoglycaemia	28
Plasma glucose	4
Post-prandial glucose	4
Serum glucose	36
Glucose problems	16
Dyslipidaemia	51
Obesity and surgery	
Obesity	78
Bariatric surgery	30
Hypertension and its tests	
Blood pressure categories	69
Hypertension	114
Smoking	
Smoking	124
Family history	
Family history of cardiovascular disease	43
Family history of coronary disease	29
Ethnicity	167

3.4 Using HES data

3.4.1 Creating variables using HES data

As described in Chapter 2, HES stores morbidity and mortality information using a set of 15,000 ICD-10 codes. These are separated into a primary diagnosis for each episode within a hospitalisation, and thirteen additional secondary diagnoses. In HES, the primary diagnosis for the first episode within the admission is usually the reason for admission, so is often used in research. ICD-10 codes were hand-searched based on relevant search terms as defined in the Read code list search. This produced a sensitive list of ICD-10 codes, which was rated by two clinicians and categorised according to the variable definitions, as described in section 3.3.2. The list of code lists created for use with ICD-10 data in this thesis is shown in Table 3.3. The code lists themselves are in Appendix B.

3.4.2 OPCS-4 procedure codes in HES

HES data regarding the procedures, operations and interventions performed during a hospitalisation are coded using the OPCS Classification of Interventions and Procedures, version 4 (OPCS-4). For each condition, the complete list of 11,000 OPCS-4 codes was hand-searched using the search terms defined in the Read code list search. Codes were rated according to variable definitions as described above in section 3.3.2. The list of code lists for use with OPCS code are shown in Table 3.4 and the code lists are in Appendix B.

3.5 Using MINAP and ONS data

MINAP data contains morbidity data that were recorded in hospital. No data manipulation was required to use these variables in defining atherosclerotic disease, risk factors or medication use.

Use of ONS data was to define a date and cause of death only. Any contributing causes of death that were listed alongside the underlying cause were not used to define previous comorbidity, as the timing of these morbidities is unknown.

Table 3.3 ICD-10 code lists created and the number of codes included

ICD-10 code lists for HES and ONS data	N ICD-10 codes in list
Coronary disease	
Acute ischaemic heart disease	4
Angina	4
Unstable angina	1
Cardiac arrest	5
CABG	1
CHD NOS	9
Heart failure	8
Myocardial infarction	23
Cerebrovascular disease	
Cerebral stroke	26
Ischaemic stroke	11
Ischaemic cerebrovascular disease (non-stroke)	28
Stroke NOS	11
Transient ischaemic attack	2
Peripheral arterial disease	
Peripheral arterial disease	4
Abdominal aortic aneurysm	6
Cardiovascular disease risk factors	
Diabetes	65
Dyslipidaemia	10
Family history of cardiovascular disease	2
Hypertension	18
Obesity	6
Smoking	2
Atherosclerotic disease NEC	6
Sudden cardiac death	1

Table 3.4 OPCS-4 code lists created and the number of codes included

OPCS-4 code lists	N ICD-10 codes in list
Coronary disease	
Cardiac arrest procedures	16
CABG	50
PCI	20
Other coronary procedures	2
Thrombolysis	2
Cerebrovascular disease	
Stroke NOS procedures	1
Other cerebrovascular procedure	23
Peripheral arterial disease	
Peripheral arterial disease procedures	77
Abdominal aortic aneurysm procedures	66
Cardiovascular disease risk factors	
Hypertension drug prescribing	2

3.6 Myocardial infarction case definitions

This section describes how MI was defined in each of GPRD, HES, MINAP and ONS. Patients with MI in any of the four sources were considered to be potential cases. Inclusion criteria were then applied to generate the final cohort of patients.

3.6.1 Myocardial infarction in GPRD

Any patient with a code included in one of these seven lists was included as a potential case in the dataset (See Appendix A, section 10.2.1 for code lists):

- Diagnosis of ST-elevation MI;
- Diagnosis of non ST-elevation MI;
- Diagnosis of MI of unspecified phenotype;
- ST segment elevation or Q waves indicating MI on ECG;
- Cardiac markers of unspecified type, shown to be potentially abnormal or abnormal;
- CK-MB, shown to be potentially abnormal or abnormal; or
- Troponins, shown to be potentially abnormal or abnormal.

The date of MI was the date recorded by the GP. If the event date was missing, it was imputed using the system date (the date that the data are entered by the practice staff), which is complete for all records.

3.6.2 Myocardial infarction in HES

HES MI was defined as ICD-10 codes I21 to I23 recorded as the primary diagnosis in the first episode of hospitalisation (see code lists in Appendix A, section 10.2.1). The date of MI in HES was the date of admission. Where this was incomplete, date of admission was imputed based on the date of discharge and median duration of stay in hospital for all MI patients. Where both date of admission and discharge were missing, the patient's record was excluded.

3.6.3 Myocardial infarction in MINAP

MINAP MI was defined by an algorithm (as shown in Figure 3.3) based on the international definition of MI[6] using three MINAP variables: (i) discharge diagnosis, (ii) raised cardiac enzymes, and (iii) the ECG that determined treatment. This algorithm was developed by the CALIBER group. Patients given a discharge diagnosis of any acute coronary syndrome (ACS) were included in the study. This included:

- STEMI;
- NSTEMI;
- troponin positive ACS;
- troponin negative ACS; or
- ACS with unknown troponin.

Patients with these discharge diagnoses were then re-categorised into STEMI, NSTEMI or unstable angina based on:

1. The presence of absence of recorded raised cardiac markers, and
2. ST-elevation or left bundle branch block (LBBB) on their ECG, as shown in Figure 3.3.

A comparison of the discharge diagnosis and the CALIBER diagnosis is shown in Chapter 4.

MINAP date of admission was considered to be the date of MI. However, this variable was not complete (see Chapter 4). Twelve remaining date variables, holding data regarding patient admission and quality of care, can provide a reasonable proxy for date of admission. An algorithm was developed using these variables to impute missing date of admission (where incomplete) in the order shown in Figure 3.4. This provided a near-complete date of admission. Patients without any information regarding the timing of MI were excluded from analysis. Only the first admission for a CALIBER diagnosis STEMI or NSTEMI was included.

3.6.4 Myocardial infarction in ONS

ONS MI was defined based on an underlying cause of death coded as I21, I22 or I23. The date of death was taken as the date of MI.

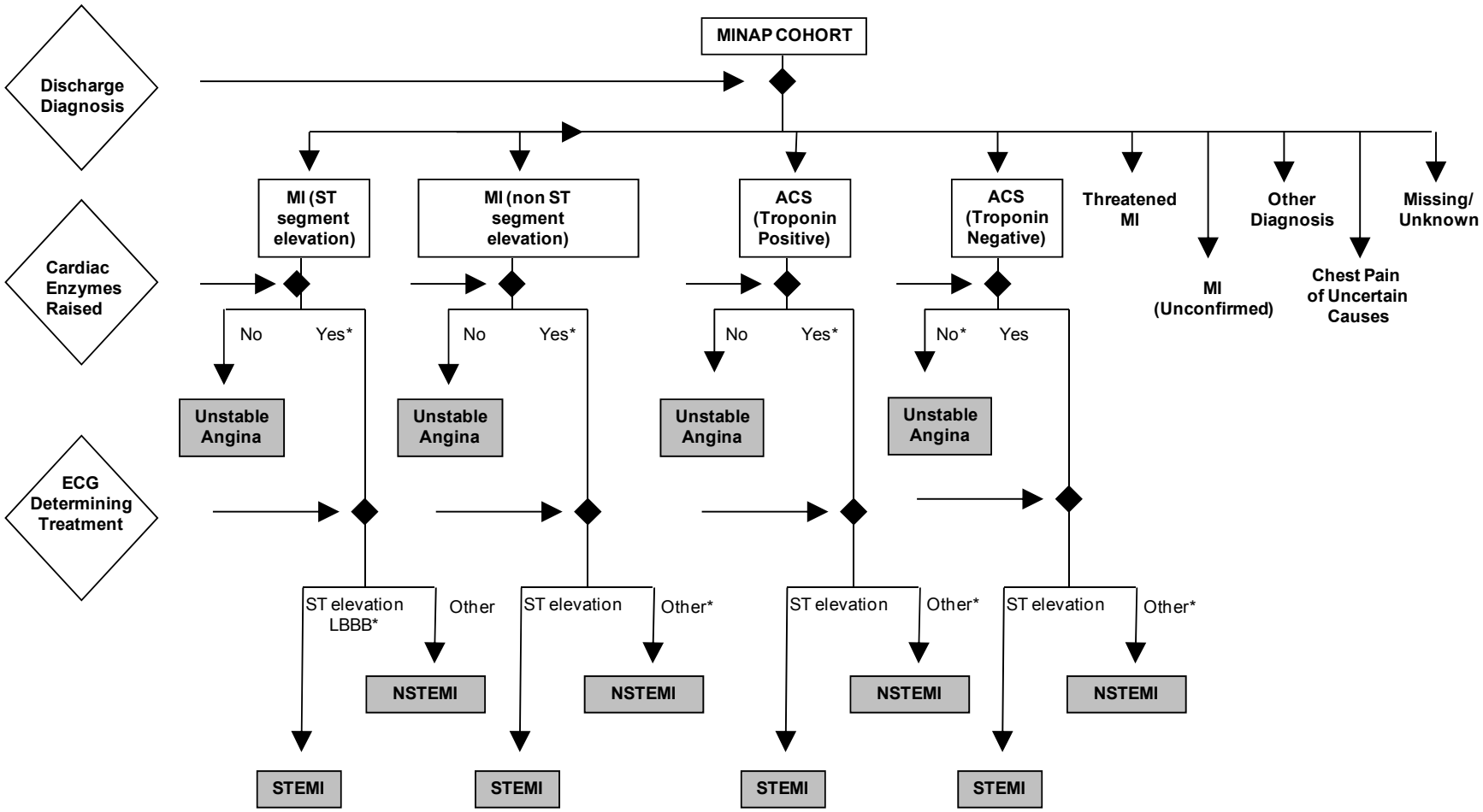


Figure 3.3 CALIBER algorithm to define MI phenotype in MINAP data using discharge diagnosis, cardiac enzymes and ECG data. Developed by McNamara, in collaboration with the CALIBER group

1. Date of admission
2. Date of arrival of emergency services
3. Date of call for help
4. Date of symptom onset
5. Date of reperfusion
6. Date of cardiac arrest
7. Date of referral for investigation
8. Date of daycase transfer
9. Date of local angio
10. Date of first local intervention
11. Date of return referral
12. Date of death or discharge
13. Date of discharge*

* Date of discharge alone is not a good proxy for date of admission as patients may remain in hospital for several days or weeks. Median length of stay was calculated for patients with a complete date of admission and discharge (median 6 days, IQR 3-10 days). The median duration was then subtracted from the date of discharge to impute date of admission.

Figure 3.4 MINAP variables holding date and time data

3.7 Inclusion criteria

Patient inclusion in the study was based on the criteria described below. A chart describing the flow of data losses is described in Appendix A, Section 10.2.3.

3.7.1 Time period of interest

To obtain the maximum information for each patient in the study, the time period of interest was constrained to the time when all four data sources were collecting data. This was between 1st January 2003 and 31st March 2009, although MINAP data in 2009 were not complete. Therefore, for the majority of analyses the data were cut at the end of 2008. This also allowed for up to 18 months of post-MI follow-up for each patient, as GPRD and ONS data were available until mid-2010. This was considered sufficient time in which to assess outcomes in the MI patients.

3.7.2 First MI across the linked patient record

To identify patients with their first MI, data from potential cases across all data sources were combined and the earliest record of MI was taken to be the patient's first (Figure 3.5). For patients whose MI was recorded in more than one database, a record in another data source within 30 days of the first was considered to represent the same MI event. Records after 30 days were considered to be recurrent MI (Figure 3.6). A 30 day cut-off was used as this was considered a reasonable time in which different data sources should capture a record of MI, after which any recording is likely to indicate recurrent MI. The validity of this assumption was tested in the analyses of Chapter 4.

Patients with a recorded history of MI in GPRD, HES or MINAP were excluded. In HES, a history of MI was defined with a more sensitive list of codes, including any patient previously receiving coronary thrombolysis, as recorded in the OPCS-4 dataset, with Dressler's syndrome (ICD-10 code I24.1) and those with a code indicating history of MI (I25.2).

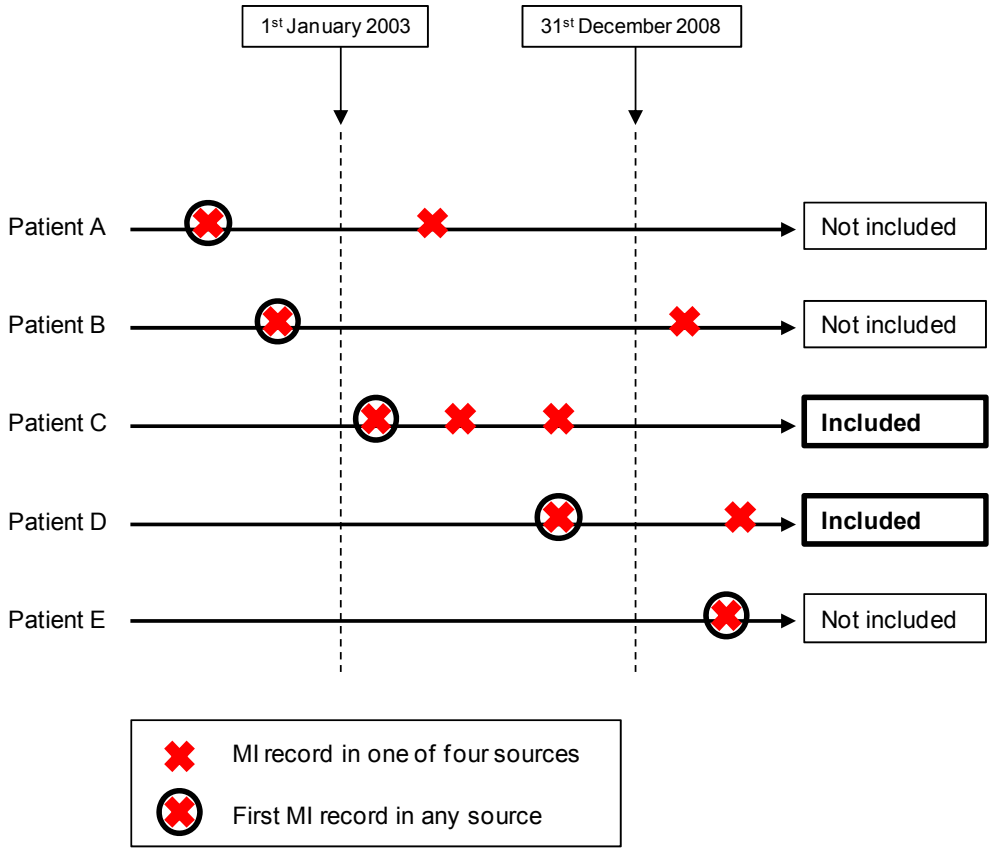


Figure 3.5 Identifying patients with first MI across the linked data sources who were included in this study

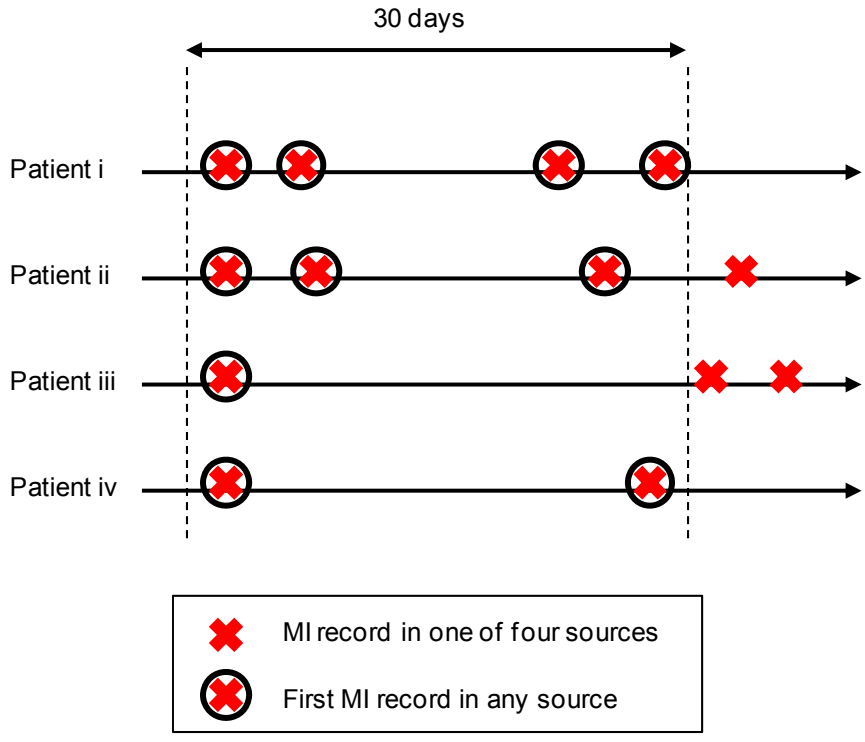


Figure 3.6 Identifying MIs across more than one data source. If a record is recorded within 30 days of the earliest record, it represents the same event

3.7.3 Patient registration with a GPRD practice at the time of first MI

Within the GPRD practices that consented to the linkage, any patient ever registered was linked with MINAP, HES and ONS data. However, the date of hospital admission in MINAP or HES did not necessarily overlap with the period of GPRD registration. GPRD is the major source of risk factor and cardiovascular disease data in this study and therefore patients who registered with a GPRD practice after their MI or transferred out of the practice before their MI were excluded.

3.7.4 At least twelve months of up to standard registration before first MI

Patients with less than a year of up to standard follow-up before their MI were removed from the analysis (definition of UTS in Data Sources Chapter 2). Evidence shows that one year of registration should provide sufficient time for prevalent and historical diagnoses to be made and risk factors to be measured.[89]

3.7.5 At least one consultation in the UTS registration period before first MI

After registering with a general practice, a change in patient circumstances (e.g. emigration, or moving into a nursing home) can mean that a patient never visits their GP. These patients, even if they were unwell, would not consult with the physician at their registered practice. To avoid including such patients in the analysis, any patients without consultations prior to MI were excluded.

The application of this inclusion criterion could have resulted in overestimation of the proportion of patients with previous atherosclerotic disease or cardiovascular disease risk factors through the exclusion of truly healthy patients (those who are more unwell are more likely to consult more frequently). The number of patients who were excluded by this criterion was recorded and its impact on the final result was assessed.

3.7.6 At least 18 years of age at the time of MI

The focus of this thesis is in atherosclerotic cardiovascular disease and risk factors before MI occurring in adults. Therefore, any MIs occurring in patients under 18 years old were excluded.

3.8 Identification of demographic variables

3.8.1 Year of birth and sex

Year of birth and sex in GPRD were likely to be more accurate than those recorded in an acute hospital setting in MINAP or HES. Therefore, year of birth and sex were taken from GPRD data.

3.8.2 Ethnicity

Ethnicity data in each of the sources were not complete so data were drawn from GPRD, MINAP and HES, where recorded. Ethnicity was classified as (i) white, (ii) south Asian, (iii) black or other, or (iv) unknown.

In GPRD, ethnicity is recorded in the Read codes. In MINAP there are two ethnicity variables, which were combined to reduce missingness. For patients admitted to MINAP more than once, data from admissions before their MI were used to assess ethnicity. In HES, there is an ethnicity field. Where there was discordance within or between data sources in the recording of these broad categories of ethnicity, the patient ethnicity was set to missing.

3.8.3 Social deprivation

Social deprivation data were provided by the Office for National Statistics and were provided as a score based on the Index of Multiple Deprivation (IMD) 2007.[128] This measures deprivation in England using information from seven domains (income, employment, health deprivation and disability, education skills and training, barriers to housing and services, crime and the living environment). Measures are provided at the level of the lower-layer super-output area (SOA). There are 32,482 SOAs in England with mean population size of 1500. SOA data are therefore a suitably precise measure of deprivation at a local level. Data from the IMD were divided into quintiles for analysis.

3.8.4 Duration of pre-MI registration

The duration of registration prior to MI was calculated as the time between the date of MI and the current patient registration date with the GPRD practice.

3.8.5 Number and rate of consultation prior to MI

An inclusion criterion in this study was for patients to have at least one consultation after registration. Additionally, the rate of consultation is an indicator of the general health of patients. Every patient contact within general practice is recorded in the GPRD against a specific consultation type (e.g. doctor/nurse appointment, telephone consultation, acute visit, out of hours visit). A list of relevant consultation types is shown in Appendix A, section 10.2.2. The rate of consultation prior to MI was calculated as follows:

$$\textit{Rate of consultation} = \frac{\textit{N consultations in medical history prior to MI}}{\textit{N years of pre-MI registration}}$$

3.9 Identification of atherosclerotic disease prior to MI

Atherosclerotic disease was categorized into cardiac disease, cerebrovascular disease, peripheral arterial disease (including abdominal aortic aneurysm) and atherosclerotic disease of unspecified site. MINAP, HES and GPRD data were used to identify patients with any of these subtypes. Any morbidity recorded in the GPRD or HES up to the day prior to MI was considered to have occurred prior to MI. Morbidities recorded in the medical history section of the MINAP hospital record were considered to have occurred prior to MI. Data from MINAP were combined from the record of the case admission for MI in addition to previous non-MI admissions.

All morbidities were classified as binary variables: present or not. Only patients with 'definite' diagnoses (including abnormal test results) were defined as having atherosclerotic disease. A sensitivity analysis was conducted in each analysis to examine the extent to which this decision affected results.

Each of the following variables, including their definitions, units, and data files used, plausible ranges for continuous values, and implementation instructions are described in the CALIBER data manual (Appendix B).

3.9.1 Cardiac disease

3.9.1.1 Stable angina

Patients with stable angina were identified in the GPRD using a combination of Read codes for diagnoses and procedures, test results and prescription data. Patients with Read codes for a diagnosis of stable angina (not including vasospastic angina or cardiac syndrome X), symptoms of ischaemic or exertional chest pain, or procedural codes for coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) were classified as having stable angina. Also included were those with diagnosed one, two or three vessel coronary disease, those with an abnormal result following an ambulatory or exercise ECG, invasive, CT or MRI angiogram, radioisotope scan or stress echocardiogram and those with at least two prescriptions for an anti-anginal medication (BNF chapters 2.6.1 (Nitrates: glyceryl trinitrate, isosorbide dinitrate and isosorbide mononitrate) and 2.6.3 (Other anti-anginal drugs: ivabradine, nicorandil and ranolazine)). One prescription alone could not define angina as patients may have been given nitrates to rule out an angina diagnosis; a subsequent prescription indicates that the nitrates worked and the patient is likely to have stable angina. In HES, patients with angina were identified based on ICD-10 diagnostic codes or OPCS-4 procedural codes for angina, CABG or PCI. In MINAP, patients with angina were identified based on a recorded history on admission to MINAP.

3.9.1.2 Unstable angina

Patients were defined as having unstable angina if they had a previous admission for unstable angina in MINAP (as assessed using the CALIBER phenotype definition algorithm) or a diagnostic code for unstable angina, acute coronary syndrome, or acute ischaemic heart disease in the GPRD or HES.

3.9.1.3 Heart failure

This included patients with a recorded history of heart failure on admission to MINAP, severe left ventricular systolic dysfunction (ejection fraction <30%), a diagnostic code for heart failure of any cause in the GPRD or HES (categorized as valvular, hypertension or unknown), or an abnormal echocardiogram in the GPRD. Patients with a left ventricular ejection fraction of <55% were categorised as 'possible' heart failure. Sensitivity analyses were performed to determine whether the inclusion of patients with 'possible' in addition to 'definite' heart failure affected the key results.

3.9.1.4 Cardiac arrest

Patients with cardiac arrest were identified based on a list of diagnostic and procedure codes in the GPRD and HES. Patients were categorised as experiencing:

- Ventricular tachycardia;
- Ventricular fibrillation;
- Implanted cardiac defibrillation device; or
- Asystole, electromechanical death, cardiac arrest or resuscitation.

3.9.1.5 Coronary heart disease not otherwise specified

In the GPRD and HES, there are several unspecific codes that do not indicate a particular subtype of coronary disease, but are commonly used in patients with CHD. Therefore, these codes were assigned to a variable of their own.

3.9.2 Cerebrovascular disease

Cerebrovascular disease was identified based on a combination of diagnostic Read codes, abnormal test results and relevant procedures in the GPRD, a record of previous stroke at MINAP admission, or diagnostic and procedure codes in HES. In the GPRD, relevant diagnostic Read codes included those indicating ischaemic stroke, stroke of unspecified subtype, transient ischaemic attack and non-stroke ischaemic cerebrovascular disease. An abnormal cerebral CT, carotid angiogram or carotid ultrasound from GPRD data also indicated cerebrovascular disease.

3.9.3 Peripheral arterial disease (PAD)

PAD, including abdominal aortic aneurysm, was identified based on a combination of diagnostic Read codes, abnormal test results and procedures in the GPRD, or a record of PAD at MINAP admission, or diagnostic and procedure codes indicating peripheral disease in HES. Relevant Read and ICD-10 codes for AAA were only those deemed by the CALIBER group raters to be of atherosclerotic origin. Abnormal abdominal or peripheral artery ultrasound scan, aortogram or peripheral artery angiography were defined as PAD. Finally, patients with procedures to repair AAA or the peripheral arteries identified patients with PAD.

3.9.4 Atherosclerotic disease of unknown phenotype

This category included Read or ICD-10 terms such as “Atherosclerosis”, which do not indicate a subtype or site of atherosclerotic disease.

3.10 Identification of cardiovascular disease risk factors prior to MI

Records of cardiovascular disease risk factors were considered to be prior to MI if they occurred any time in a patient's record up to one day prior to MI. Except where noted, risk factors were categorised as binary variables: present or not.

3.10.1 Systolic and diastolic blood pressure measurements

Each record of blood pressure in the GPRD is entered as a systolic and/or diastolic measure. After range and consistency checks of these values (implausible values were excluded –see CALIBER data manual for values, Appendix B), all of the systolic records in a patient's pre-MI follow-up were averaged using the mean. Systolic blood pressure measurements are available at admission in MINAP, but since these are occurring during MI, they were not used to indicate pre-MI coronary risk. Blood pressure measurements are not recorded in HES. Mean systolic blood pressure was used to calculate Framingham risk scores (see below).

3.10.2 Hypertension

Patients with hypertension were identified based on data from GPRD, HES and MINAP. In GPRD, hypertension was defined in three ways. Firstly by a diagnosis of hypertension, secondly patients with a series of three consecutive systolic or diastolic blood pressure measurements above the standard cut-offs for raised blood pressure (>140mmHg systolic, >90mmHg diastolic) within one year, and thirdly patients with three or more consecutive Read codes indicating 'high/raised blood pressure' within one year. The cut-offs for high blood pressure were lower in non-diabetic patients to reflect NICE guidelines. Patients with a definite code for diabetes had a cut-off of diastolic blood pressure of >80mmHG, and for systolic >130mmHg. In MINAP, hypertension was defined based on a recorded medical history of hypertension. In HES, hypertension was identified based on OPCS codes for anti-hypertensive drug treatment or an ICD-10 diagnostic code for hypertension.

3.10.3 Dyslipidaemia

Patients with dyslipidaemia were identified based on Read codes in the GPRD, ICD-10 codes in HES or a medical history of dyslipidaemia in MINAP. Due to the common prescription of lipid-regulating drugs even in patients without dyslipidaemia, these drugs were not included in the definition. Due to the lack of consensus in the literature with respect to cholesterol measures, measures of total, HDL and LDL cholesterol were not assigned cut-points. Where these individual risk factors were relevant to analysis as confounders, they were included as continuous variables.

3.10.4 Total serum cholesterol and HDL cholesterol

All total serum and HDL cholesterol measurements recorded in a patient's pre-MI follow-up were extracted from the GPRD, based on code lists. These were averaged using the mean to generate a single measure each for total and HDL cholesterol.

3.10.5 Overweight and obesity

Body mass index (BMI) was calculated for all patients based on GPRD and MINAP data. Range and consistency checks were in place for these values (as sometimes weight is recorded in stones, and height in feet); implausible values were excluded (see CALIBER data manual). Patients were categorised as underweight (BMI<18.5kg/m^2), normal weight BMI≥18.5kg/m^2 and <25kg/m^2) overweight or obese (BMI≥25kg/m^2) according to the World Health Organisation definition.

In GPRD, BMI is recorded many times during patient follow-up. The measure closest to the MI date was considered to be the most accurate BMI for the patient.

Patients who were overweight or obese were identified using a code list indicating obesity in the GPRD and HES, or by a BMI of ≥25 recorded in MINAP or GPRD. Patients prescribed bariatric surgery or anti-obesity drugs (Orlistat or centrally acting appetite suppressants, from GPRD data) were also considered to be obese. Patients without any BMI data or Read codes indicating weight categories were defined as unknown.

3.10.6 Smoking

In GPRD data, smoking is often recorded many times during patients follow-up to reflect and monitor changes over time in patient behaviour. An algorithm was applied to the data to deduce the most likely smoking status for the patient at the time of MI. This is based on one or more measures prior to MI and (sometimes) after MI. If this was different to the MINAP record, then by default the MINAP record was used as the smoking status at MI, as it was considered to be the most up to date record. Smoking status is not recorded in HES. Smoking status was defined as current, ex, or non. Patients without any record of smoking status were defined as unknown.

3.10.7 Diabetes

A definite diagnosis of diabetes was identified based on a MINAP record of diabetes at admission, a HES code for diabetes, or one of the following from the GPRD data:

1. Read codes indicating diagnosis of diabetes, its complications or hyperglycaemia;
2. At least two prescriptions of anti-diabetic drugs (insulin or oral anti-diabetics);
3. Abnormal blood glucose or HbA1c levels (≥ 48 mmol/mol or ≥ 6.5%),
4. Abnormal glucose tolerance test (based on a GP recorded result);
5. Abnormal plasma or serum glucose (≥11.1mmol/l) or fasting plasma glucose (≥7.0 mmol/l); or
6. Abnormal post-prandial glucose (≥11.1mmol/l).

Where tests or Read codes were potentially abnormal or borderline, diabetes was coded as possible. Women prescribed metformin who were under 50 years of age were not considered to be diabetic based on this prescription alone, as metformin is used to treat polycystic ovary syndrome.

3.10.8 Family history of CHD

Patients with a family history of CHD were identified based on code lists in the GPRD and HES data, and on a recorded family history in MINAP.

3.10.9 Framingham risk score

The Framingham risk score for ten year hard CHD (MI or coronary heart disease death) endpoints[129] was calculated using the information derived for age, sex, average total and HDL cholesterol, smoking, systolic blood pressure and use of blood pressure lowering drugs. For total cholesterol, HDL cholesterol and systolic blood pressure, the mean of all values recorded prior to MI was taken for each patient, and these composite measures were used in calculation of the Framingham score. The rationale for using mean measures, rather than the last value prior to MI (or e.g. the mean in the year prior to MI), was to maximise the use of the longitudinal data available. Additionally this strategy may have captured raised cardiovascular disease risk more accurately in patients with historically raised cholesterol or blood pressure, which had subsequently been brought to normal levels by cardiovascular medications. The consequences of this decision are discussed in Chapters 6 and 7, where Framingham scores and their components are used in regression models.

The score was categorised into patients with <10% risk, 10-20% risk and >20%. This score is intended for use in patients 30-79 years of age; patients older than 79 were considered to have the same risk as those who were 79. Due to missingness in some of the components of the risk score, Framingham risk could not be calculated for all patients, and this is discussed further in the subsequent analysis chapters (4-7).

3.11 Identification of cardiovascular drug use prior to MI

MINAP holds records of selected cardiovascular drug use at admission. As discussed in Chapter 2, prescription drugs are well-recorded in the GPRD. Cardiovascular drugs were categorised by BNF chapter. Any patient with two or more prescriptions issued by the GPRD and from the same BNF chapter were considered as having received the drug. The main drugs of interest in this thesis were:

- blood pressure lowering drugs, including:
  - diuretics,
  - beta-adrenoceptor blocking drugs,
  - calcium channel blockers,
  - vasodilators,
  - centrally acting antihypertensive drugs,
  - adrenergic neurone blocking drugs,
  - alpha-adrenoceptor blocking drugs,
  - angiotensin-converting enzyme inhibitors;

- lipid lowering, including
  - statins,
  - bile acid sequestrants,
  - ezetimibe,
  - fibrates,
  - nicotinic acids;

- antiplatelets, including
  - aspirin,
  - clopidogrel,
  - dipyridamole.

For each of these three drug categories, patients were defined as ever/never users, and additionally as users/ non-users in the 90 days prior to MI.

3.12 Identification of chest pain prior to MI

Chest pain recorded as 'coronary' or 'exertional' in nature by the GP was used to define stable angina. Two other categories of chest pain were defined in the GPRD data: 'unattributed by the GP to any cause' and 'attributed to a non-coronary cause'. These two chest pain types were explored in MI cases. A record of chest pain in MINAP was defined as a previous admission for chest pain of unknown cause. HES data were not used to identify chest pain.

3.13 Consistency within and between data sources

It was not uncommon for the sources to differ in their assessment of atherosclerotic disease, cardiovascular disease risk factors and use of medications. Concordance is described in Chapter 4. It was also not uncommon for patients to be recorded, for example, with several different smoking statuses on the same day. The most sensitive approach was used where codes were discrepant: if any data source categorised a patient as having a condition, an elevated risk factor or using a drug, then the patient was categorised with that positive result.

3.14 Post-MI follow-up

ONS mortality data were used to follow-up patients after MI. The primary outcome for each study is described in each of the analysis chapters (Chapters 4-7).

3.15 Missing data

In the GPRD, usual researcher practice is to take the absence of *codes* for morbidity in a patient's record to indicate absence of that morbidity in the patient. As discussed in Chapter 2, many validation studies have been performed that have assessed the positive predictive value of diagnoses, but few have examined their sensitivity. Researchers must assume that if disease is symptomatic, then it will be recorded in the data. For this reason, there is no 'missing' data for most morbidities and only misclassification of disease status. The validation study undertaken in Chapter 4 gives some indication of the extent of misclassification in the recording of MI.

However, the same does not apply to measurements of smoking status, blood pressure, cholesterol and smoking (for example), for which the absence of data is not informative. Subsequently, there is some missingness in these variables. However, the reasons for missingness of cardiovascular disease risk factors are not straightforward. They are usually missing due to a lack of opportunity for the GP to take the measurements; patients who fail to visit their GP may be anywhere on a scale from very healthy (no need to visit GP) to having a large number of cardiovascular disease risk factors (but which are not causing symptomatic disease). In reality, missingness is likely to be due to a combination of reasons and may not be related to any measured variables within the dataset.

Due to the complexity of the missingness, multiple imputation was not explored as an option to deal with the missingness in these analyses. Multiple imputation requires the data to be missing at random (i.e. the missingness depends on the observed data), which is not necessarily applicable in this setting. This requires further exploration, beyond the scope of this thesis. Indeed, the missingness of these measurements is somewhat informative in terms of quality of care provided by GPs. The consequences of missing data are discussed further in Chapter 7.

3.16 Chapter summary

- This chapter described the methods used to identify patients with MI in each of the four sources. In GPRD this was with Read codes, in HES and ONS using ICD-10 codes, and in MINAP using discharge diagnosis, cardiac markers and ECG results.
- Data on other morbidities, symptoms and drugs were extracted from GPRD, HES and MINAP.
- Death was identified using ONS mortality data.
- Inclusion criteria common to all analyses in this thesis were also discussed.

Chapter 4 Data quality

4.1 Summary

This chapter describes the quality of the data used in this thesis. The first half of this chapter (section 4.2) is a paper to be submitted to the British Medical Journal (with some minor modifications to place it in the context of this thesis), describing the capture, risk factors, mortality and diagnostic validity of acute MI in GPRD, HES, MINAP and ONS. The second half (section 4.3) contains further details relating to the quality of the linked data, including the representativeness and quality of each linked source.

4.2 Capture of acute myocardial infarction events in primary care, hospital admissions, registry data and national mortality statistics

4.2.1 Introduction

'Collect once, use many times' is fundamental to electronic health records which support patient decision making, healthcare policy and public health. Electronic health record systems with comprehensive population coverage across whole countries are rare (Singapore) and the UK has opportunities because of its single health system, the National Health Service (NHS). Even within the NHS a single major disease event is still separately recorded in diverse clinical and administrative systems. Thus acute myocardial infarction (MI) is recorded in primary care (for example in the General Practice Research Database, GPRD), at hospital discharge (Hospital Episode Statistics (HES)), in the national registry of acute coronary syndromes (Myocardial Ischaemia National Audit Project, MINAP) and in the Office for National Statistics (ONS) mortality data. Establishing the validity of recording in these data sources is important because these individual (unlinked) sources are widely used to inform care and policy, and in ascertainment of outcomes in trials[130-132] and cohorts[133-135] as a cheaper alternative to active follow-up.

What we do not know is how these different systems overlap, and to what extent risk factors and mortality are similar in MI recorded in different sources. Previous cross referencing studies of acute MI have (i) compared coding of hospital discharges and cause of death to case note review,[116, 136] compared recording in two national registers of MI,[137] compared hospital discharge and death records in fatal MI, and compared primary care coding to results from case review.[61]

To our knowledge, there are no studies comparing the recording of MI across linked sources from primary care, hospital discharge, registry data and mortality data. Furthermore, data linkage provides the opportunity to validate the diagnosis of MI in the subset of patients who have MI recorded in primary care or hospital discharge coding and also have a MINAP record, where MINAP is the gold standard in recording hospital discharge diagnosis, ECG findings and cardiac markers. Since the four data sources originate from different settings (hospital-based, primary care, death registration), we expect to observe differences in the populations that they capture. However, the extent of the differences and the characteristics of patients who are captured in each source are poorly understood.

4.2.2 Aim and objectives

To compare the capture and diagnostic validity of acute myocardial infarction in primary care, hospital discharge, national ACS registry and national mortality statistics. Specific objectives are as follows:

1. To establish the consistency of characteristics (risk factors, all-cause mortality) between cohorts of patients who are recorded with MI in each of the data sources, i.e. are the same kinds of patients captured?;

2. To describe and compare capture of MI between data sources;

3. To assess the validity of MI recorded in each source (And to establish whether MIs recorded in each source are of adequate validity to use in this thesis).

4.2.3 Methods

4.2.3.1 Data sources

The GPRD is a primary care database containing anonymised patient records for roughly eight percent of the UK population. Data are collected as part of patient care, including demographic details, symptoms, diagnoses, treatments, hospitalizations and death. Diagnoses are coded by general practitioners using the Read Clinical Terminology system.[52]

HES is a database of hospital discharge coding data for all inpatient and outpatient care in English NHS hospitals. It contains information from admitted patients on demographics, symptoms, clinical diagnoses and treatments and comprises over twelve million episodes of care per year. Diagnoses are coded using the International Classification of Diseases, tenth revision (ICD-10).

MINAP is the national registry of patients admitted to hospitals in England and Wales with acute coronary syndromes (ACS). All NHS hospitals that treat ACS patients contribute data to MINAP. Information in MINAP includes admission characteristics, demographics, co-morbidities, diagnostic tests, treatment and outcomes.

ONS collects data on date and cause of mortality for the UK, where death registration is a legal requirement. Causes of death are coded using ICD-10.

Of the 630 participating GPRD practices in 2010, 244 from England consented for their data to be linked to further data sources. In October 2010, the identifiers of patients in these practices were sent to a Trusted Third Party, who performed linkage with HES, MINAP and ONS. This linkage was based on a deterministic match between NHS number, date of birth and gender; 96% of patients with a valid NHS number were successfully matched.

4.2.3.2 Study population

The initial cohort comprised all eligible, registered GPRD patients whose practice consented to the linkage. Start of follow-up was defined as the latest of: (i) the start of MINAP data collection (1st January 2003), (ii) one year post registration with GPRD practice, (iii) one year post GPRD practice 'up to standard' date (a measure defined by the GPRD whereby the practice meets data quality criteria), or (iv) 30 days after the start of HES-GPRD linkage period. The end of follow-up was defined as the earliest of (i) the end of MINAP data linkage period (31st March 2009), (ii) the end of the HES linkage period, (iii) the last collection date from the GPRD practice, (iv) the transfer out date, or (v) the date of the last ONS mortality update. Using these criteria, we restricted our period of interest to the time when all data sources were actively collecting MI data.

(Note: In this analysis, the three months towards the end of the linkage period was included (January to March 2009), but this was excluded from the remaining analyses in this thesis.)

4.2.3.3 Identifying patients with myocardial infarction

In each data source, we identified a group of patients experiencing MI within the follow-up period (2003-2009), according to 'researcher usual practice' MI definitions. Patients with MI in GPRD were those who had a Read code indicating MI (Appendix A, section 10.3.1). (Note: the Read code list used in this study was a modified version of the list used in the rest of the thesis, to reflect usual researcher practice in the current study, while being as sensitive as possible in the rest of the thesis). The date of MI was the event date recorded by the general practitioner. In HES data, MI was defined as ICD-10 codes I21-I23 as a primary diagnosis in the first episode of a hospital spell. In MINAP, ST-elevation MI and non ST-elevation MI were identified using hospital discharge diagnosis, markers of myocardial necrosis and the ECG. Hospital admission date in MINAP and HES was classified as the date of MI. Patients with MI in ONS were identified using ICD-10

codes I21, I22 and I23 as an underlying cause of death. Patient demographic and risk factor characteristics, defined using GPRD data, were compared between patients with MI identified using any of the four data sources in isolation.

4.2.3.4 Agreement between data sources

Patient records of MI from GPRD, HES, MINAP and ONS were pooled and the earliest date of MI (within our time period of interest) across each patient's record was identified. MIs were categorised as 'fatal' or 'non-fatal' according to whether the patient died of any cause within 7 days. This separation was required in order to assess agreement: fatal events would not necessarily be hospitalised and therefore would not be expected to be recorded in HES and MINAP, and by definition non-fatal events would not be recorded in ONS mortality data. Therefore, assessing agreement of fatal and non-fatal events separately provided a more realistic estimate of MI capture in each source.

Records of MI between data sources were considered to agree if the time difference from the earliest date and the date recorded in another data source was less than 30 days. MIs recorded more than 30 days after the earliest date were considered as new events and were not included in the analysis. Further MI events recorded at any later date in any of the data sources were not included, ensuring that only each patient's first MI in follow-up was included and that each patient only appeared once in the analysis.

4.2.3.5 Statistical analysis

For patients who survived seven days after MI, agreement between data sources was established for GPRD, HES and MINAP in a three-way Venn diagram. Capture by ONS was not assessed in this non-fatal group.

The proportion of 'fatal MI' patients (who died of any cause within seven days) captured by each source was examined, but agreement of records across all four sources was not compared as we would not expect hospital data to capture patients who died before reaching hospital.

Where more than one database recorded an MI (based on the 30 day definition), the number of days between recording was described. Differences in agreement between health authorities were also examined. Agreement was then redefined based on a 90 day definition

to test our assumption that 30 days was an adequate time window for MI to be recorded across all sources.

In patients where MI was recorded in one source but not another, we looked for other codes that may have been used to describe the MI. In MINAP, we looked for unstable angina or admission diagnoses of any acute coronary syndrome. In GPRD and HES we looked for other acute coronary syndrome, coronary disease, chest pain or cardiac codes that may have been used to represent the MI, and in GPRD we additionally examined codes indicating contact with secondary care. Where none of these codes was recorded, we tabulated all recorded Read and ICD-10 codes in the 30 days before and after the date of MI to ascertain any evidence of MI in the patient record.

MINAP records detailed diagnostic criteria of MI (such as ECG findings and cardiac markers) that are not captured by other sources; therefore we expect the classification of suspected ACS in MINAP (STEMI, NSTEMI, unstable angina) to be accurate. Considering the MINAP definition as the 'gold standard', we calculated the positive predictive value of GPRD or HES diagnoses of MI among patients who also had a MINAP record within 30 days (i.e. the proportion in which the MINAP diagnosis was MI rather than something else). We also calculated the sensitivity of GPRD and HES for detection of MINAP MI.

We performed a logistic regression analysis to establish whether age, sex, deprivation, rate of GP consultation, year of MI and mortality at 30 days explained suboptimal recording of MI.

This analysis was completed using pseudo-anonymised linked data. Approval was obtained from the Independent Scientific Advisory Committee (ISAC), the MINAP Academic Group (MAG) and the CALIBER Oversight Committee. The study is registered on clinicaltrials.gov (unique identifier NCT01569139).

4.2.4 Results

We identified 21,302 patients with MI in any of the four data sources. There were 558 (2.6%) patients recorded in ONS only, while 15,291 were recorded in GPRD, 13,344 in HES and 10,087 in MINAP. Overall, 20,744 were recorded in at least one of these three sources.

4.2.4.1 Agreement in 'fatal' and 'non-fatal' MI

Of the 21,302 patients, 17,825 (83.7%) were non-fatal (defined as alive at seven days). The agreement in recording of MI in this group was assessed in GPRD, HES and MINAP. Across all patients, 75% were captured by GPRD, 68% by HES and 53% by MINAP.

Figure 4.1 describes the agreement in recording for non-fatal MI. Overall, 31% of patients were identified with MI in all three data sources and 64% in at least two data sources within 30 days. When our time period of interest was extended to 90 days, the proportion with complete agreement rose to 32%, indicating that most MIs are recorded close to the date of MI recorded in other data sources. The GPRD accounted for the largest number of MIs that could not be identified in the other sources. Examining variation by strategic health authority revealed no major disparities.

For the 3,477 'fatal MI' patients who died of any cause within seven days, 82.9% were captured in ONS with MI recorded as the underlying cause of death, and 57.8% had a MI code recorded in GPRD. As expected, HES and MINAP captured fewer of the fatal events (35.9% and 17.9%, respectively).

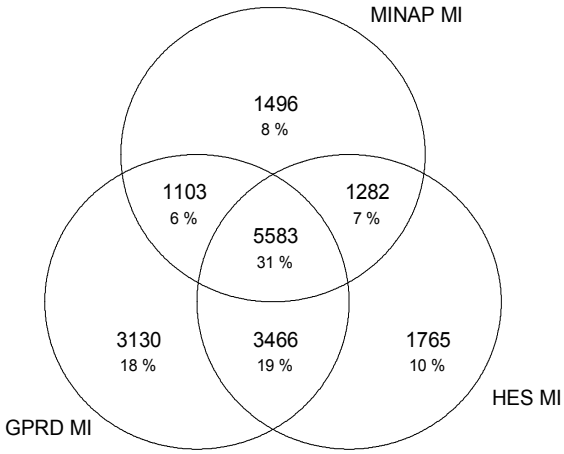


Figure 4.1 Overlap in recording of non-fatal MI in GPRD, HES and MINAP, within 30 days of the first record of MI across the three sources (N patients=17,825)

4.2.4.2 Agreement in timing between data sources

For HES and MINAP, date of admission agreed in over 80% of patients who had MI recorded in both sources (Figure 4.2). When comparing GPRD with HES, or GPRD with MINAP, 51.2% and 52.4% of patients' MIs were recorded in GPRD on the date of hospital admission, respectively. There was a smaller peak in GPRD recording between five and seven days after admission, probably reflecting GPRD recording of discharge date rather than admission date, followed by a 'tail' with smaller numbers of diagnoses in GPRD recorded up to 20 days after admission.

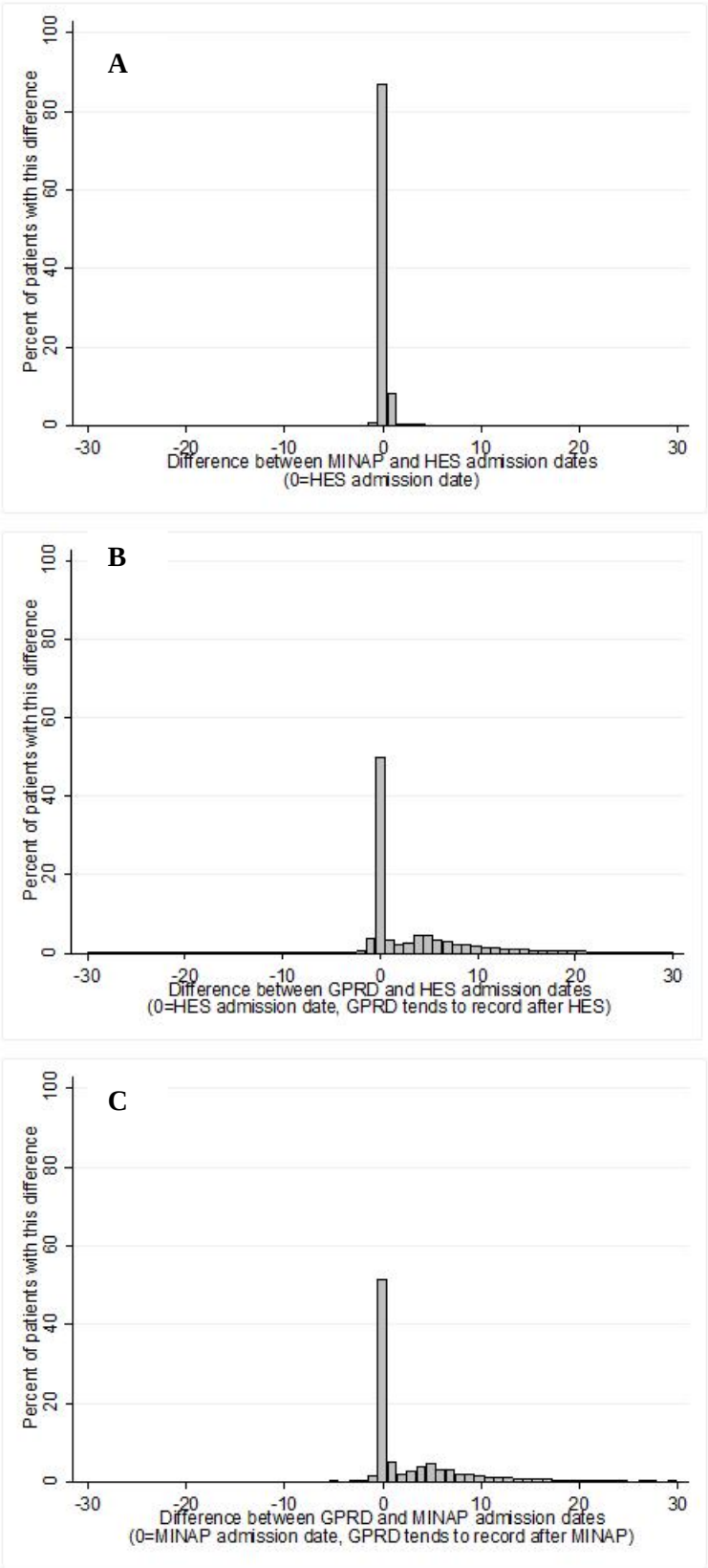


Figure 4.2 Histograms showing the number of days' interval between nearest matched MI records in each pair of data sources: (A) MINAP and HES (N=7,288), (B) GPRD and HES (N=9,531), (C) GPRD and MINAP (N=6,919)

4.2.4.3 Agreement in diagnosis between data sources

Non-fatal MI

GPRD captured over two thirds of non-fatal hospitalised MIs (identified in either HES or MINAP) with a Read code of MI. A further 10 to 15% of patients were recorded with ACS or other cardiac diagnoses, including stable angina and revascularization, a further 3% had a record of chest pain, but roughly 10% of hospitalized MIs were not recorded in the Read coded data with any cardiac diagnosis (Appendix A, Table 10.8). The most commonly used Read codes in these patients indicated contact with secondary care, for example codes for discharge letters, hospital accident and emergency attendance, or consultations with a cardiologist.

HES captured 68% of MI events identified in GPRD and 73% of those identified in MINAP with a primary diagnosis of MI in the first episode of hospital admission. A further 5% were captured as primary diagnoses after the first episode, indicating that the patient was admitted for another reason (or initially given a different diagnosis) and experienced MI while in hospital. For 14% of GPRD MIs and 6% of MINAP MI patients, HES recorded no cardiovascular disease codes. Common ICD-10 codes in these patients within 30 days of the GPRD MI date included those for renal failure.

MINAP captured roughly half of GPRD and HES MIs as STEMI or NSTEMI, but there were no records for most of the remaining patients (45% of GPRD MIs and 40% of HES MI patients had no MINAP record).

Fatal MI

MI patients identified by ONS mortality data (with underlying cause of death I21, I22 and I23 only, N=2,882) were unlikely to be captured in hospital sources; 37% were captured as MI by HES and 17% by MINAP. Just over half (56%) were captured by the GPRD within 30 days of the death date; in the majority of patients without a GPRD MI code, contact with secondary care or transfer out of practice were recorded. Of the 2,009 patients who were identified with MI in the GPRD and died within seven days, 24% were recorded in HES with MI, 12% in MINAP and 81% in ONS with MI as the underlying cause of death. Of the 1,248 HES MI patients and 623 MINAP MI patients who died within seven days, MI was recorded as the ONS underlying cause of death in roughly 80% of patients.

95% of patients with MI identified in GPRD, HES or MINAP and dead within seven days were captured with an underlying or *secondary cause of death* as coronary by ONS mortality register. When the time window was extended to 90 days, there was very little change in the proportions described here.

4.2.4.4 Comparison to MINAP gold standard MI definition

For GPRD and HES MI patients with an associated MINAP record, the positive predictive value of the MI diagnosis (probability that the diagnosis recorded in MINAP was MI rather than unstable angina or a non-cardiac diagnosis) was over 90%. The sensitivity of GPRD or HES in detecting MINAP MI was 70.6% and 72.6%, respectively (Table 4.1).

Table 4.1 Comparison with MINAP cardiologist gold standard in the subset of patients recorded in primary care (GPRD) or hospital admission (HES) with a record in the acute coronary syndrome register (MINAP), N=7146 and 7402, respectively

		MINAP cardiologist gold standard MI				
		Yes	No*	Total	Sensitivity (95% CI)	Positive predictive value (95% CI)
Primary care MI (GPRD)	**Yes**	6,612	534	7,146	70.6 (69.7-71.5)	92.5 (92.0-93.0)
	No	2,750				
	Total	9,362				
Hospital admission MI (HES)	**Yes**	6,797	605	7,402	72.6 (71.7-73.5)	91.8 (91.3-92.4)
	No	114				
	Total	6,911				

*MINAP recorded event as unstable angina or 'other' diagnosis. The number of patients who did not have GPRD MI and did not have HES MI were not quantified in this analysis.

4.2.4.5 Logistic regression analysis

In a multiple logistic regression analysis, compared to patients who were only recorded in one data source, those who were recorded in multiple sources were younger, more likely to be male, with a lower rate of GP consultation prior to MI, alive at 30 days after MI, and more likely to have experienced MI in one of the later years of the time period of interest (Table 4.2).

4.2.4.6 Comparison of characteristics and outcomes for MI patients recorded in different data sources

To give some measure of the validity of events across each of the data sources, the demographic, risk factor characteristics and mortality experience of cohorts of MI identified in each sources were compared.

Cardiovascular disease risk factors

Demographic and pre-MI cardiovascular disease risk factor prevalences were consistent across MI patients captured by primary care (GPRD), ACS registry (MINAP) and hospital admissions (HES) (Table 4.3); MI patients captured by national mortality records (ONS) were older than patients recorded in the other sources and had a higher risk factor burden reflecting their age.

One year mortality

Figure 4.3 describes the all-cause one year post-MI mortality of patients captured by each source; primary care (GPRD) records capture patients who die before reaching hospital, indicated by the high initial mortality in this group compared to the two hospital sources. At one year all-cause mortality was similar across GPRD, HES and MINAP (20.9%, 24.3% and 19.3% respectively).

Table 4.2 Results of logistic regression analysis to examine the predictors of capture in more than one source

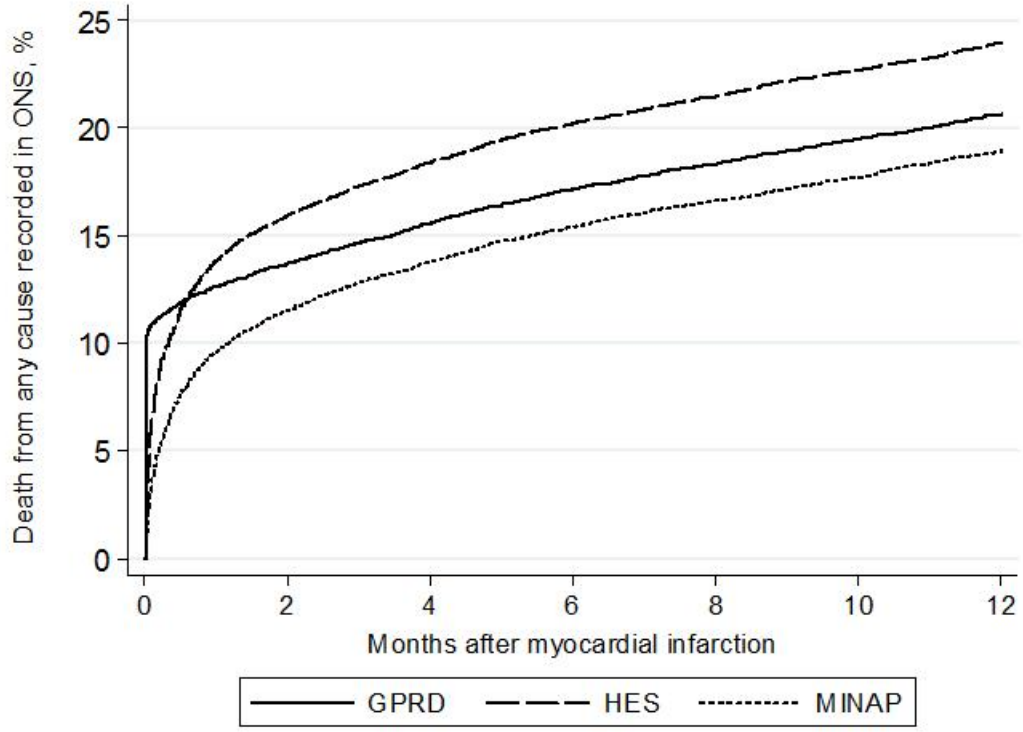
	Primary care (GPRD) only versus any combination‡, odds ratio (95% CI)	Hospital admission (HES) only versus any combination‡, odds ratio (95% CI)	ACS register (MINAP) only versus any combination‡, odds ratio (95% CI)
N patients	13,071	11,927	9,400
Age group			
<65	1 -	1 -	1 -
65-74	0.71 (0.63-0.79) ***	0.73 (0.63-0.85) ***	0.50 (0.42-0.59) ***
75+	0.71 (0.64-0.79) ***	0.56 (0.49-0.65) ***	0.40 (0.34-0.46) ***
Sex			
Male	1 -	1 -	1 -
Female	0.86 (0.79-0.94) ***	0.83 (0.74-0.93) ***	0.83 (0.73-0.93) **
Social deprivation quintile			
1 (least deprived)	1 -	1 -	1 -
2	1.10 (0.96-1.25)	1.03 (0.87-1.22)	1.07 (0.90-1.28)
3	1.05 (0.93-1.20)	1.01 (0.85-1.19)	1.06 (0.89-1.26)
4	1.06 (0.93-1.21)	0.88 (0.75-1.04)	0.90 (0.75-1.07)
5 (most deprived)	0.96 (0.85-1.09)	1.03 (0.87-1.22)	1.17 (0.97-1.41)
Primary care consultation rate per year$^{\alpha}$	0.85 (0.82-0.88) ***	0.87 (0.83-0.91) ***	0.85 (0.80-0.89) ***
Mortality at 30 days$^{\beta}$	2.20 (1.61-3.00) ***	0.31 (0.26-0.38) ***	0.41 (0.33-0.50) ***
Calendar year, per one year increase	1.17 (1.14-1.19) ***	1.12 (1.08-1.15) ***	1.01 (0.98-1.04)

*P<0.05, **p<0.01, ***p<0.001; α for an increase of 10 consultations per year; β based on ONS mortality data;
‡ Outcome; an odds ratio above 1 indicates that the risk factor increases the odds of the MI being captured in more than one data source; an odds ratio below 1 indicates that the risk factor decreases the odds of the MI being captured in more than one data source.

Table 4.3 Prior risk factors among patients with MI recorded in primary care, hospital admission, ACS registry and death registry sources from 1st January 2003 to 31st March 2009

	Primary care: GPRD		Hospital admissions: HES		ACS registry: MINAP		Cause specific mortality: ONS†	
Nature of coding	Read codes		ICD-10 codes I21, I22, I23 as primary diagnosis		Clinical diagnosis STEMI and NSTEMI		ICD codes I21, I22, I23 underlying cause of death	
N patients	16,668		14,319		15,479		5,698	
Age, median (IQR)	73	(61-81)	73	(61-82)	71	(59-81)	81	(73-87)
Sex, n female (%)	6,123	(36.7)	5,261	(36.7)	5,391	(34.8)	2,491	(43.7)
Social deprivation, most deprived IMD quintile, n (%)	3,320	(19.9)	2,883	(20.1)	2,911	(18.8)	1,010	(17.7)
Ethnicity, n (%)*								
White	12,805	(76.8)	11,721	(81.9)	12,119	(78.3)	3,755	(65.9)
South Asian	205	(1.2)	207	(1.4)	205	(1.3)	42	(0.7)
Black or other	202	(1.2)	191	(1.3)	204	(1.3)	53	(0.9)
Unknown	3,456	(20.7)	2,200	(15.4)	2,951	(19.1)	1,848	(32.4)
Smoking, n (%)								
Current	4,382	(26.3)	3,745	(26.2)	4,320	(27.9)	982	(17.2)
Ex	9,863	(59.2)	8,352	(58.3)	8,252	(53.3)	3,483	(61.1)
Non	2,045	(12.3)	1,887	(13.2)	2,085	(13.5)	735	(12.9)
Unknown	378	(2.3)	335	(2.3)	822	(5.3)	498	(8.7)
Systolic blood pressure mmHg, mean (SD)	145	(15.5)	145	(15.7)	144	(15.4)	146	(16.9)
Use of blood pressure lowering drugs, n (%)	9,545	(57.3)	8,127	(56.8)	6,574	(42.5)	3,413	(59.9)
Total serum cholesterol mmol/L, mean (SD)	5.4	(0.9)	5.4	(0.9)	5.4	(0.9)	5.3	(0.9)
HDL cholesterol mmol/L, mean (SD)	1.3	(0.3)	1.3	(0.3)	1.3	(0.3)	1.3	(0.3)
Use of lipid lowering medications, n (%)	5,793	(34.8)	4,809	(33.6)	4,064	(26.3)	2,011	(35.3)
Framingham risk score* n (%)								
<10%	2,893	(17.4)	2,438	(17)	3,160	(20.4)	615	(10.8)
10-20%	9,171	(55)	7,909	(55.2)	8,901	(57.5)	3,280	(57.6)
>20%	4,604	(27.6)	3,972	(27.7)	3,418	(22.1)	1,803	(31.6)
Diabetes, n (%)	3,002	(18)	2,552	(17.8)	2,504	(16.2)	1,221	(21.4)
Charlson index, mean (SD)	2.5	(1.7)	2.4	(1.6)	2.4	(1.6)	3.2	(1.9)
Primary care consultation rate per year, median (IQR)	3.7	(1.6-7.9)	3.7	(1.6-8.2)	2.5	(0.7-6.7)	4.5	(1.8-9.9)

Note: all demographic and risk factor data, except where noted, are based on GPRD data.
Note: individual patients may be captured in more than one source and therefore be represented in more than one column. *Data from HES. †Patients in the cause specific mortality column (ONS) are those who were recorded with myocardial infarction (ICD-10 codes I21, I22 or I23) as the underlying cause of death on their death certificate.
*Where components of the score, these were imputed using the population median.



GPRD: General Practice Research Database; HES: Hospital Episode Statistics; MINAP: Myocardial Ischaemia National Audit Project; ONS: Office for National Statistics mortality data.

Figure 4.3 Kaplan Meier curve showing crude all-cause mortality, stratified by data source (GPRD N=16,668, HES N=14,319, MINAP N=15,479). ONS data not shown as they are fatal on the date of MI, by definition

4.2.5 Discussion

4.2.5.1 Principal findings

Just one third of non-fatal MIs were captured in all three of GPRD, HES and MINAP, and two thirds were captured by at least two. None of the four sources used in this study captured all MI events and therefore complete ascertainment of MI requires use of multiple sources.

The groups of MI patients captured by each data source had similar demographic and cardiovascular disease risk factor profiles and, with the exception of the cohort identified by national mortality statistics, had similar mortality in the year after MI. The positive predictive value of MI records in primary care and hospital admission were over 90% compared to the MINAP gold standard based on the international definition of MI.[4] While many patients did not have a MINAP record, these figures offer some evidence for the validity of MI records across the sources.

4.2.5.2 Strengths

The UK government has created the Clinical Practice Research Datalink (CPRD, www.cprd.com) which aims to maximize use of linked electronic healthcare data. Evaluating the quality of the data available in these linked data sources is therefore a priority but there has been only one four-source comparison of primary care, hospital, registry and cause-specific mortality data for cancer,[138] and none for MI.

Our study is the first to examine four major data sources for MI recording in England, with coverage from over six years of data collection and over 20,000 MI patients, more than any previous validation study of the GPRD or HES. Our period of interest was restricted to a time when all data sources were collecting information on patients, so in the absence of error, hospitalized MI should have been recorded in hospital admission data, ACS registry and primary care. All patients in our study were registered with a GPRD practice, providing several years of prospectively collected pre-MI data regarding demographics, cardiovascular disease risk factors and morbidity, allowing detailed comparisons to be made between patients captured by each data source.

4.2.5.3 Weaknesses

Some patients in this study may have been included based on MI codes that were non-acute or incorrect. These would not be associated with records in the other sources. For example, overestimation of MI in the GPRD can result from repeated entry of MI codes by the general practitioner (GP) to indicate a history of MI. We excluded the first year after practice registration to avoid inclusion of these old MIs but we cannot rule out some miscoding. Additionally, in the GPRD, MI may be captured in the non-coded free text section of the data. Studies are currently underway to encode this text to make is more easily accessible to researchers, but these data were not used in the current study.

In the HES MI data, we excluded patients whose diagnosis at first hospital admission was not MI (e.g. to exclude patients with post-operative MI) and we did not apply this criterion to cases identified in the GPRD, MINAP or ONS. This contributed to some of the discordance in the main analysis, but non-first episode MI accounted for only 5% of GPRD, MINAP and ONS MIs.

4.2.5.4 Reasons for non-capture of MI

There are several possible explanations for non-coding of MI in each source:

- In the GPRD, GPs may receive limited information about a patient's hospital admission, administrative problems may mean that a GP does not receive a letter, or diagnoses may be recorded only in the free text or paper notes rather than as Read codes;

- In HES and MINAP, the diagnosis of MI may be unclear in the patient notes and be misinterpreted by a non-clinician coder or data entry clerk. Alternatively, the patient may attend a private hospital where HES and MINAP data are not collected;

- In MINAP, patients not admitted to cardiology wards tend not to be recorded; and

- For patients who die within seven days of MI, the underlying cause of death may not be MI and therefore our study would have classified this as discordant.

4.2.5.5 Comparison with other literature

Non fatal MI

Our analysis showed that positive predictive values of MI diagnoses in GPRD and HES were high when compared to a gold standard based on the international definition of MI. To our knowledge, there have been no previous studies examining the positive predictive value of a HES MI diagnosis, but our results are consistent with the results from several smaller validation studies of GPRD MI data, which set out to confirm the diagnosis of MI in the electronic record using further diagnostic criteria from within the GPRD such as anonymised copies of paper medical records, hospital discharge summaries, death certificates, [59, 61-64] or questionnaires to the general practitioner.[59, 61, 65-67] We also showed that - where recorded - the timing of a GPRD code compared to hospital admission date was accurate.

Due to time, cost and logistical difficulties, the sensitivity of MI records in any of these data sources (i.e. the proportion of those with a true MI who are captured by the source) has not previously been assessed. Here we estimated sensitivity compared to a gold standard MINAP MI and have shown that GPRD fails to record approximately 30% of hospitalized cases of non-fatal MI. Additionally we have shown that the GPRD does not capture one quarter, HES one third and MINAP nearly half of non-fatal MI cases. Therefore, MI recording in each of the sources is incomplete.

This is consistent with a recent study showing that recording of acute MI was suboptimal in hospital data.[116] In a comparison of hospital discharge coding (on which HES is based) to the Oxford Vascular Study (OXVASC), the authors identified 820 incident MI cases in OXVASC. Of these cases, only 53% were captured in hospital discharge data as acute MI (ICD-10 I21, I22).[116] We found slightly better results; 62% of GPRD MIs and 72% of MINAP MIs were captured by HES.

Incomplete records in each of these data sources suggest that the incidence of MI, calculated based on any of these sources, is underestimated. A two-source study of MI in the UK compared the incidence based on primary care records with the incidence based on hospital data and showed that in combination they provide the highest estimates of incidence.[139] Further two source comparisons of MI in Australia,[140] Denmark[137] and the Netherlands[141] have shown that hospital records alone underestimate true MI incidence. With the three sources used in the current study to identify non-fatal MI, we have shown that even using two sources will result in underestimates of incidence.

The relatively low completeness of MINAP is unsurprising; MINAP data are not collected as part of patient care and often only for patients in coronary care units. The strengths of MINAP lie in its detailed treatment data and diagnostic accuracy, which other data sources are unable to provide.

Fatal MI

We estimate that for the hospitalized 'fatal' patients who died within seven days, 85.4% and 79.6% in HES and MINAP, respectively, had MI recorded as their underlying cause of death. These figures are concordant with results from the Oxford Record Linkage Study, where the mortality records of 5,686 patients with hospitalized MI who died within 30 days were examined and 85.2% were recorded with MI as the underlying cause of death.[138]

4.2.5.6 Implications for clinicians and policymakers

Whether captured in GPRD, HES or MINAP, patients with MI have the same risk factor distribution and post-MI survival experience. This indicates that each data source is likely to provide a source of 'true' MI patients which researchers can be confident is not heavily biased in terms of patient selection.

Our study shows that there is no single gold standard source of MI that captures all events and diagnoses. The 'collect once, use many times' ideal is a strategic goal and not likely to be realizable in the medium term given the financial and resource constraints placed upon the NHS. Therefore, as an alternative to such a gold standard data source, we suggest use of linked data in healthcare commissioning and estimating disease burden. Here we have shown that by combining data from primary care, hospital admissions, ACS registry and mortality data, there is a vastly improved picture of MI morbidity and mortality in England.

Other researchers should choose their data source carefully, bearing in mind the strengths and weaknesses of each source, to meet the needs of their individual research questions. For example, the detailed recording in MINAP on timing, diagnostic accuracy and treatment make it useful for examining treatment effects at the time of MI. GPRD contains longitudinal primary care information over many years of follow-up, making it useful for pharmacoepidemiological research requiring detailed drug exposures. HES documents

morbidity for patients in NHS hospitals in England and is therefore useful for health services research, but as with MINAP it does not record hospitalizations abroad or in the private sector. ONS mortality records contain information on all death registrations in England and Wales, which is an almost complete source for fatal events. The linkages between MINAP, GPRD, HES and ONS require the patient to be registered with a GP have a valid NHS number, so linkage may fail for people such as refugees, prisoners, members of the armed forces and those without a permanent address.

4.2.5.7 Future research

Our descriptive and post-MI survival data show that cohorts of MI in each data source are similar and are all likely to represent true MI patients. However, for epidemiological studies with MI as an exposure or outcome, it would be worthwhile to compare the results based on different sources for MI recording. Further case record review can also take place for patients included in the UK Biobank cohort, based on multiple sources of patient health records, including self-reported data.[135]

Based on the results from the current study, it may be possible to refine MI definitions in each source to improve sensitivity or specificity depending on individual study requirements. Other established data linkages will provide opportunity to compare recording of other diseases, which may have different levels of agreement between data sources. Further data linkages are also being established by CPRD, with some already complete and validated,[142] and the number of primary care practices involved is also set to increase.

4.2.6 Conclusion

Complete ascertainment of MI requires multiple sources. Previous estimates of incidence based on single data sources are underestimates. However, where recorded, the quality of MI diagnosis in each of the sources compared to a gold standard is high. Policy makers and researchers can be assured that the data are valid.

4.2.7 Implications for this thesis

Each of the databases has been shown to be a valid source of MI patients in terms of patient characteristics and mortality experience. Timing of MI in the GPRD, HES and MINAP was also comparable for non-fatal events. Therefore, in this thesis any source can be used to identify MI patients with confidence that the MIs are real events and recorded in a timely way.

While capture of MI is suboptimal in each of the sources, none of the objectives in this thesis estimate incidence and so the implications of the low sensitivity of each source are minimal.

4.3 Further analyses of data quality

In addition to the assessment of MI validity in section 4.2, further analyses were performed to give an indication of the quality of data used in this thesis. The objectives of these analyses were:

1. To assess the representativeness of the linked portion of each data source to its source (a comparison of linked to non-linked GPRD, HES, MINAP and ONS data): this will highlight any bias in patient selection introduced by the linkage;
2. To consider overall data quality in GPRD, HES and ONS, and briefly describe data quality in MINAP.

In addition, Appendix A, section 10.3.2 describes a comparison of the concordance of GPRD, HES and MINAP with respect to their recording of atherosclerotic disease diagnoses prior to MI.

4.3.1 Previous analysis to compare linked with non-linked GPRD data

The GPRD have performed analyses to assess the representativeness of patients included in the linked data compared to those that were not linked.[143] At a randomly selected index date, the mean age of patients was the same in linked and non-linked practices. The proportion of females, the mean BMI and duration of follow-up was also the same in linked and non-linked patients.

The proportion of current smokers was slightly more in the linked practices than the non-linked and the linked practices tended to be from more deprived areas. The analysis also showed slight variation in the geographical areas of practices in the linkage: practices in London were less likely and those in the South West of England were more likely to participate. The authors concluded that "patients in linked practices were representative of the whole GPRD population."[143]

4.3.2 New analysis to compare linked with non-linked HES data

In this analysis, data from the *whole* of HES were compared to those in the *linked* HES data. Data from the whole of HES were freely available online data for primary diagnoses for finished consultant episodes.

4.3.2.1 Number of linked finished consultant episodes

The number of records in HES increased by roughly 30% between 1998/99 and 2007/08, from 11.9 million to 15.4 million. The proportion of linked episodes increased by roughly 80% during this time, from 0.5 million to 0.9 million (Figure 4.4). The proportion of HES episodes that were linked rose from 4.5% to 5.9%.

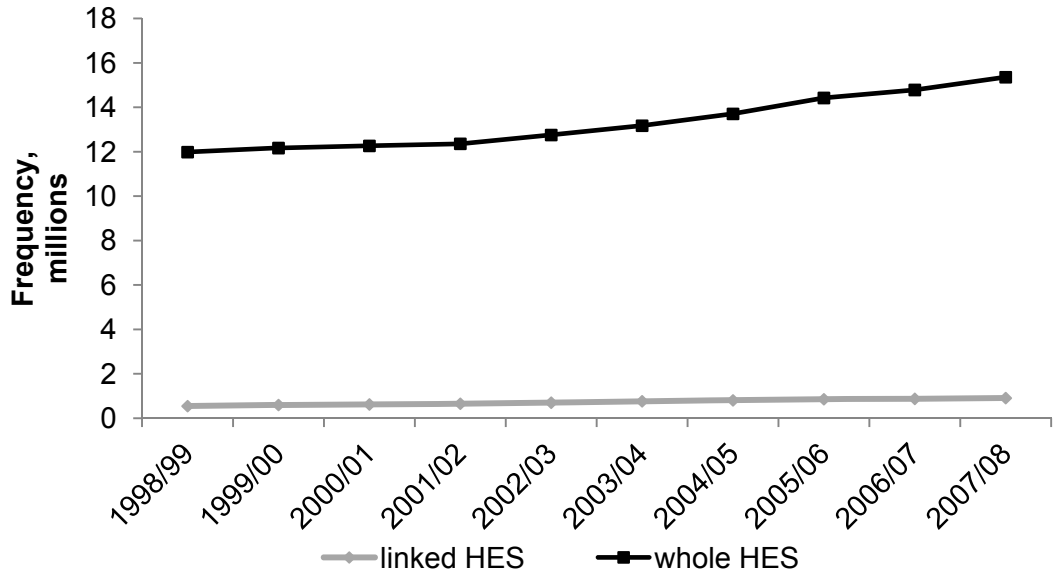


Figure 4.4 Frequency of primary diagnoses in finished consultant episodes, by financial year in linked HES and for all of HES data, for the period 1998-2008

4.3.2.2 Age and sex

The mean age in the linked records was similar to the mean age for all records (47 and 48, respectively). The proportion of male patients was slightly lower in the linked data compared to the whole dataset (41% and 44%, respectively).

4.3.2.3 Top ten diagnoses

The frequency of primary diagnoses within finished consultant episodes in the whole of HES was compared to the linked data. Table 4.4 shows the top ten primary diagnoses in over 7 million finished consultant episodes in the linked data, and in over 132 million episodes in the whole of HES. Concordance between the linked HES and the whole of HES was high. There was roughly the same distribution of codes.

4.3.2.4 Conclusion

Aside from the small differences in the distribution of men and women between the linked dataset and the whole of HES, the data used in this thesis are largely representative of the whole of HES. This provides further evidence of the representativeness of the patients in this study compared to the population of England.

Table 4.4 Top ten diagnoses over the period 1997/98 to 2007/08 in the linked HES data, and in all of HES

	Linked HES				Whole HES			
	ICD code	Term	Frequency	In top 20 whole HES?	ICD code	Term	Frequency	In top 20 linked HES?
1	R10	Abdominal and pelvic pain	158,471	Yes	Z38	Liveborn infants according to place of birth	4,072,251	Yes
2	Z38	Liveborn infants according to place of birth	148,502	Yes	R10	Abdominal and pelvic pain	2,629,827	Yes
3	R69	Unknown and unspecified causes of morbidity	137,179	Yes	R69	Unknown and unspecified causes of morbidity	2,601,403	Yes
4	R07	Pain in throat and chest	128,693	Yes	R07	Pain in throat and chest	2,362,904	Yes
5	O70	Perineal laceration during delivery	93,429	Yes	H26	Other cataract	1,768,687	Yes
6	O26	Maternal care for other conditions predominantly related to pregnancy	88,862	Yes	J44	Other chronic obstructive pulmonary disease	1,497,346	Yes
7	H26	Other cataract	87,267	Yes	N39	Other disorders of urinary system	1,410,763	Yes
8	N39	Other disorders of urinary system	81,113	Yes	I25	Chronic ischaemic heart disease	1,393,717	Yes
9	I20	Angina pectoris	69,905	Yes	I20	Angina pectoris	1,371,772	Yes
10	I25	Chronic ischaemic heart disease	68,963	Yes	J18	Pneumonia, organism unspecified	1,340,080	Yes

4.3.3 Analysis to compare linked with non-linked MINAP data

At the time of this work, the complete MINAP datasets contained 740,454 records and 26,885 (3.63%) of these were linked to other data sources. The sections below describe the distribution of admission dates, age, sex, mortality and discharge diagnosis of patients who were linked compared to those that did not link.

4.3.3.1 Number of linked MINAP admissions

The MINAP data used for this thesis are for the period 1st January 2003 until 8th August 2011. The total number of MINAP admissions and the number that are linked are shown in Figure 4.5 by calendar year up to the last complete year (2010); the number of linked patients drops in 2009 as the linkage period ends. The few patients who are in the linked dataset after the end of the linkage period in 2009 are likely to be those whose NHS number was linked via a previous admission during the linkage period. In 2003, 4.0% of MINAP admissions were linked and in 2008 this had risen to 4.9%.

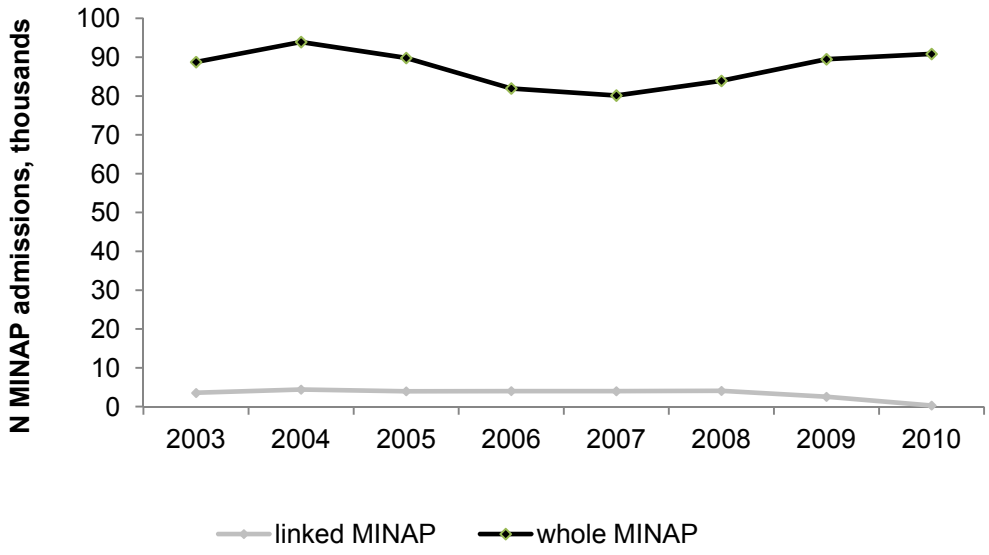


Figure 4.5 Frequency of all and linked MINAP admissions by year

4.3.3.2 Age and sex distributions

The age and sex distributions were comparable in the linked and unlinked patients. Figure 4.6 describes the age distribution. The median age in the non-linked group was 71 (IQR 59-80), and in the linked group it was 70 (IQR 58-80). Table 4.5 describes the sex distribution. There was more missingness in the unlinked group. This is likely to be because a valid NHS number was required for the linkage; age in those without valid NHS numbers may not be recorded as well as in those with NHS numbers. After removing patients with missing sex, there was no difference in the distribution of sex between linked and unlinked patients (Chi squared P=0.77).

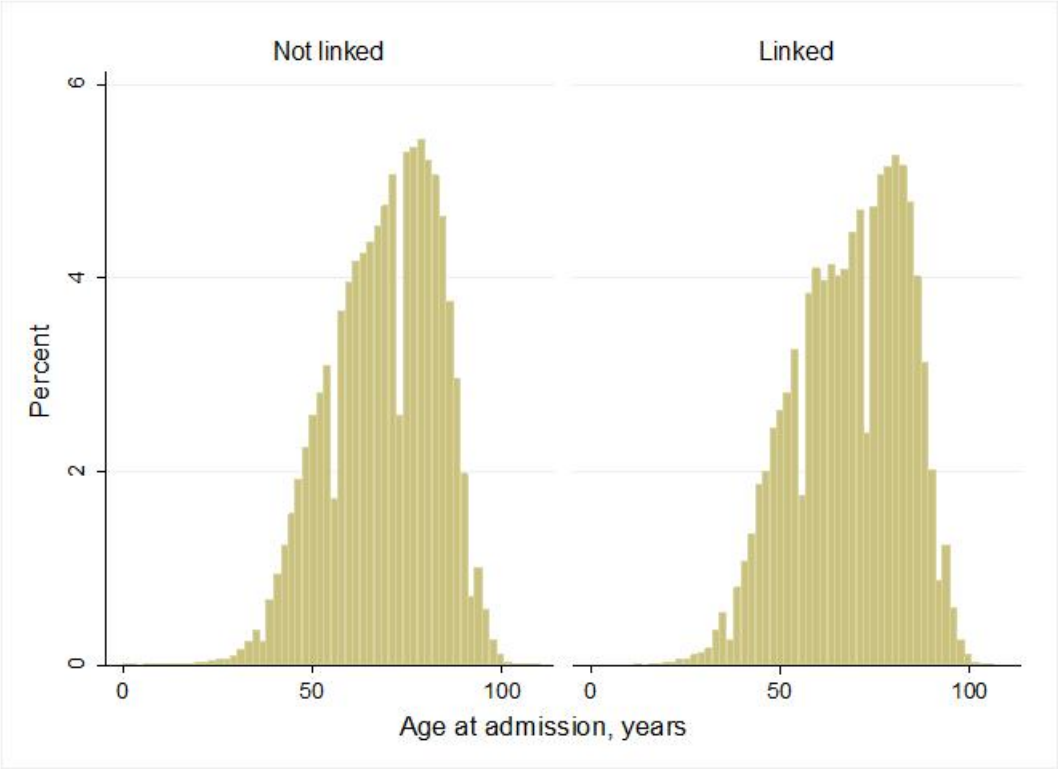


Figure 4.6 Histograms describing the age at admission to hospital in linked (N=26,885) and unlinked (N=713,569) MINAP patients

Table 4.5 Sex distribution in linked and unlinked patients

	Not linked		Linked		Total	
	n	(%)	n	(%)	n	(%)
Male	459,409	(64.4)	17,402	(64.7)	476,811	(64.4)
Female	250,626	(35.1)	9,457	(35.2)	260,083	(35.1)
Missing	3,534	(0.5)	26	(0.1)	3,560	(0.5)
Total	713,569	(100.0)	26,885	(100.0)	740,454	(100.0)

4.3.3.3 Discharge diagnosis

The distribution of discharge diagnoses in the linked and unlinked groups were very similar (Table 4.6).

Table 4.6 Discharge diagnoses in linked and unlinked admissions

Final diagnosis	Not linked		Linked		Total	
	n	(%)	n	(%)	n	(%)
Myocardial infarction (ST-elevation)	227,096	(31.8)	8,533	(31.7)	235,629	(31.8)
Threatened MI	2,102	(0.3)	98	(0.4)	2,200	(0.3)
ACS troponin positive	355,417	(49.8)	12,951	(48.2)	368,368	(49.8)
ACS troponin negative	40,862	(5.7)	1,657	(6.2)	42,519	(5.7)
Chest pain of uncertain cause	20,818	(2.9)	769	(2.9)	21,587	(2.9)
Myocardial infarction unconfirmed	4,181	(0.6)	152	(0.6)	4,333	(0.6)
Other diagnosis	38,918	(5.5)	1,549	(5.8)	40,467	(5.5)
ACS troponin unspecified	5,672	(0.8)	297	(1.1)	5,969	(0.8)
Missing	18,503	(2.6)	879	(3.3)	19,382	(2.6)
Total	713,569	(100)	26,885	(100)	740,454	(100)

ACS: acute coronary syndrome.

4.3.3.4 Mortality

Thirty day mortality was the same in linked and unlinked patients at 30 days (8.6% in linked and 8.7% in unlinked, chi squared P=0.55). Subsequent mortality cannot be compared due to high amounts of missingness in the unlinked group (6.8% missing in unlinked, 0.5% in linked).

4.3.3.5 Conclusion

The patients from the MINAP dataset who were linked to other sources are representative of those from the whole of MINAP. Those who were linked have a low level of missingness in age, sex, and vital status, which indicates that patients who were linked may have been recorded better in the dataset overall.

4.3.4 Analysis to compare linked with non-linked ONS data

In this analysis, freely available ONS cause-specific mortality data for the whole of England and Wales in 2004 (N=510,332) were compared to the linked dataset in 2004 (N=25,725). The frequency of mortality by ICD-10 chapter was similar in the linked and the whole datasets (Table 4.7), so there is no evidence to suggest that the patients in the linked ONS dataset were not representative of those in all of England and Wales.

4.3.4.1 Conclusion

Although the data were only assessed for one of the years in which the study took place, we assume that the data in the remaining years were not of a similar quality. The results indicate that the patients in this study are representative of all individuals who died during the study period.

Table 4.7 Comparison of the underlying cause of death of 510,332 patients in all of England and Wales in 2004 to 3,474 patients with recorded death in the linked data in 2004

ICD chapter	Underlying cause	N in whole dataset	% in chapter: whole dataset	N in linked dataset	% in chapter: linked dataset
A00-B99	Certain infectious and parasitic diseases	5,009	1.0	218	0.9
C00-D48	Neoplasms	138,062	27.1	6,647	25.8
D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1,014	0.2	60	0.2
E00-E90	Endocrine, nutritional and metabolic diseases	7,519	1.5	407	1.6
F00-F99	Mental and behavioural disorders	14,299	2.8	1,074	4.2
G00-G99	Diseases of the nervous system	14,606	2.9	891	3.5
H00-H59	Diseases of the ear and mastoid process	39	0.01	2	<0.1
I00-I99	Diseases of the circulatory system	190,603	37.4	9,231	35.9
J00-J99	Diseases of the respiratory system	69,213	13.6	3,399	13.2
K00-K93	Diseases of the digestive system	24,912	4.9	1,224	4.8
L00-L99	Diseases of the skin and subcutaneous tissue	1,670	0.3	79	0.3
M00-M99	Diseases of the musculoskeletal system and connective tissue	4,393	0.9	199	0.8
N00-N99	Diseases of the genitourinary system	9,397	1.8	509	2.0
O00-O99	Pregnancy, childbirth and the puerperium	46	<0.1	2	<0.1
P00-P96	Certain conditions arising in the perinatal period	213	<0.1	5	<0.1
Q00-Q99	Congenital malformations, deformations and chromosomal abnormalities	1,274	0.3	59	0.2
R00-R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	11,566	2.3	771	3.0
V01-Y89	External causes of morbidity and mortality	16,497	3.2	948	3.7
Total N		**510,332**	**100.00**	**25,725**	**100.00**

4.3.5 Quality of GPRD, HES and ONS data

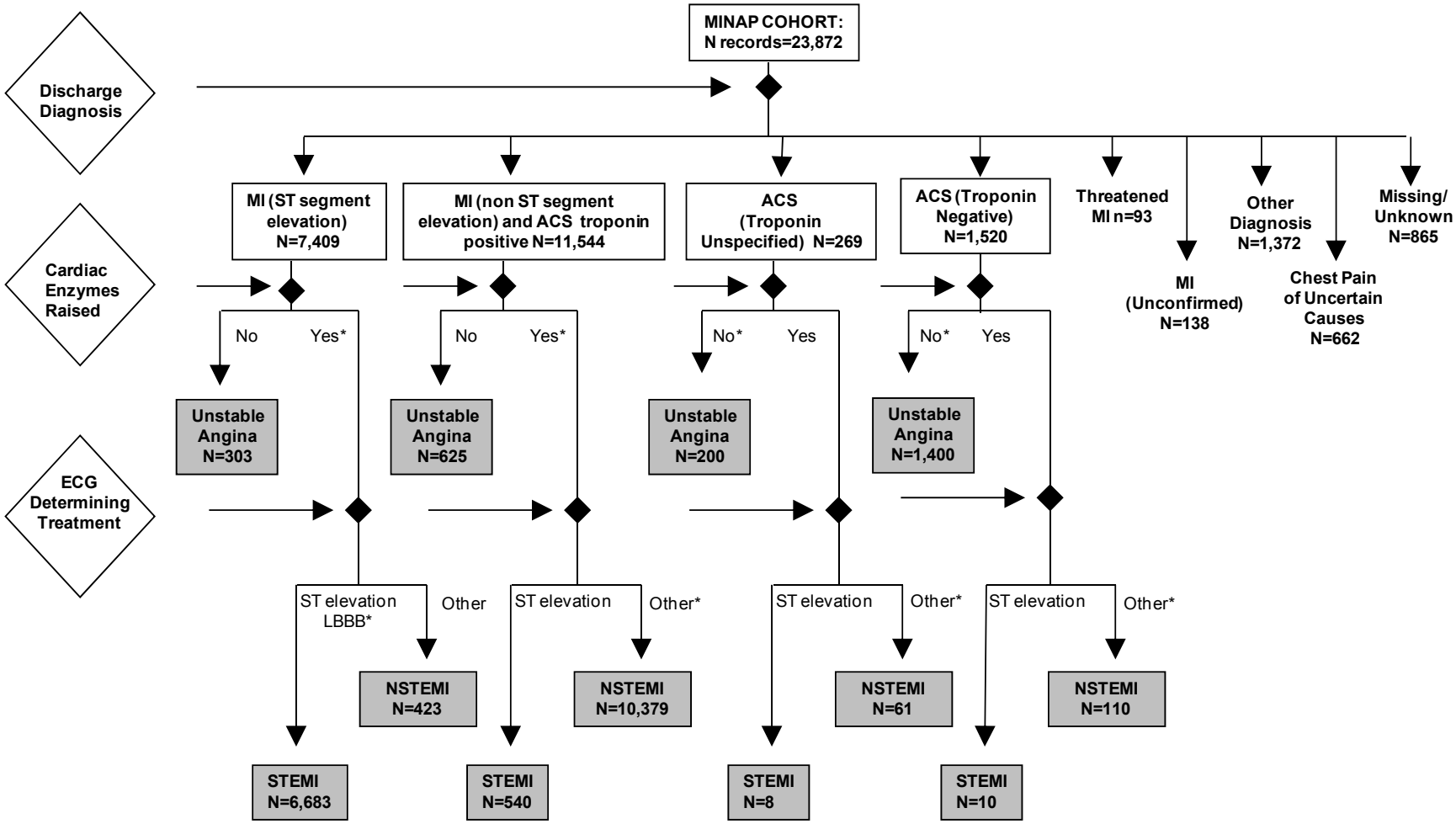
The quality of GPRD and HES data has been assessed in a number of validation studies, as described in Chapter 2 (Data sources). While these validation studies are for non-linked data, the previous analysis showed that the linked subsets were representative of the whole data sources. Additionally, GPRD data are monitored continually to identify inconsistencies, and HES and ONS data are cleaned before release. Therefore, it was decided not to make any further assessment of data quality in GPRD, HES and ONS within this thesis.

4.3.6 Quality of MINAP data

There have been no formal validation studies of MINAP data and the data are not fully cleaned before release (as individual researchers should choose their strategy to deal with missingness and data inconsistencies). Therefore, some brief analyses were conducted to examine the quality of the data and to assess the validity of our methods.

4.3.6.1 Diagnosis of STEMI and NSTEMI: applying the CALIBER algorithm

Our case definition of MI in MINAP was based on re-categorisation of discharge diagnosis using cardiac markers and ECG results, based on the international definition of MI,[6] as shown Figure 4.7. Comparison between the original MINAP discharge diagnoses and the CALIBER-assigned diagnosis is shown in Table 4.8. Roughly 10% of patients with a discharge diagnosis of STEMI and NSTEMI were recategorised, but 90% of all ACS discharge diagnoses were concordant with results of cardiac markers and ECG results.



*In unimputed data, missing and unknown fall into this category.

Figure 4.7 CALIBER MI phenotype algorithm, from McNamara

Table 4.8 Comparison of MINAP discharge diagnosis and the CALIBER assigned diagnosis based on discharge diagnosis, raised cardiac markers and ECG results, based on 20,742 patients with acute coronary syndrome

		CALIBER diagnosis							
		STEMI		NSTEMI		Unstable angina		Total	
		n	(%)	n	(%)	n	(%)	n	(%)
Original discharge diagnosis	STEMI	6,683	(90.2)	423	(5.7)	303	(4.1)	7,409	(100)
	NSTEMI/ troponin positive ACS	540	(4.7)	10,379	(89.9)	625	(5.4)	11,544	(100)
	ACS troponin unspecified	10	(0.7)	110	(7.2)	1,400	(92.1)	1,520	(100)
	Troponin negative ACS	8	(3)	61	(22.7)	200	(74.3)	269	(100)
	All ACS	7,241	(34.9)	10,973	(52.9)	2,528	(12.2)	20,742	(100)

STEMI: ST-elevation myocardial infarction; NSTEMI: non ST-elevation myocardial infarction; ACS: acute coronary syndrome.

4.3.6.2 Missingness in key MINAP variables

Missingness in MINAP is low in the key variables that are used for audit, and in those required for the linkage (NHS number, age, sex). Missingness in the variables used in this thesis is shown in Table 4.9. Missingness is high for variables recording cardiovascular disease history, cardiovascular disease risk factors and drug use at admission. While the MINAP data are weaker in this area, this is compensated by linkage to GPRD, where these data are recorded more completely. Range checks were performed for continuous variables: values outside the plausible range (as defined by the CALIBER data manual) were re-coded to missing (<1%).

4.3.6.3 Conclusion

MINAP discharge diagnosis data were shown to be internally consistent in 90% of patients with ACS. While there was high missingness (>50%) in some variables, the demographic variables used in the linkage and the variables used to validate MI type were well-completed. Missingness in risk factor and co-morbidity data will be compensated with data from other sources.

Table 4.9 Missingness in variables used in this thesis, for 8,059 cases recorded in the Myocardial Ischaemic National Audit Project (MINAP)

	n missing (%)	
NHS number	0	(0)
Age	0	(0)
Gender	4	(<0.1)
Ethnicity	741	(9.2)
Date of admission (before imputation)	199	(2.5)
Date of discharge	644	(8.0)
Previous morbidity		
Myocardial infarction	5,479	(68)
Angina	6,169	(76.5)
Peripheral arterial disease	6,001	(74.5)
Cerebrovascular disease	6,250	(77.6)
Heart failure	6,446	(80)
PCI	6,476	(80.4)
CABG	5,901	(73.2)
Cardiovascular disease risk factors		
Diabetes	3,677	(45.6)
Hypertension	4,774	(59.2)
Hypercholesterolaemia	2,545	(31.6)
Smoking	940	(11.7)
Family history	13,796	(53.5)
Height	6,304	(78.2)
Weight	5,619	(69.7)
Cardiovascular medications before admission		
Antiplatelet	716	(8.9)
Beta blocker	3,727	(46.2)
ACEI	3,759	(46.6)
Statin	3,683	(45.7)
Thienopyridin	3,677	(45.6)
Admission characteristics		
Peak troponin	1,810	(22.5)
Heart rate at admission	1,796	(22.3)
Systolic blood pressure at admission	1,173	(14.6)
ECG record	795	(9.9)
Cardiac markers	831	(10.3)
Left ventricular ejection fraction	5,357	(66.5)

NHS: National Health Service; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; ECG: electrocardiogram; ACEI: angiotensin converting enzyme inhibitor.

4.3.7 Implications for this thesis

These analyses of data quality have shown that the linked data are representative of their respective sources, and therefore it is unlikely that selection bias has been introduced by using the linked data.

4.4 Chapter summary

- Each of the data sources used in this thesis (GPRD, MINAP, HES and ONS) record MI events that are similar in terms of their demographic and risk factor characteristics, and with similar one year survival. This indicates that each source is capturing similar cohorts of MI patients and gives some indication about the validity of each source. The timing of MI was also consistent for MIs recorded in multiple sources.

- A record of MI was captured by GPRD, MINAP and HES in about a third of patients and captured by at least two sources in two thirds of patients. Therefore, using multiple sources to capture MI patients is ideal, and combining MI events from GPRD, MINAP, HES and ONS would provide a more complete picture of MI incidence in the UK.

- The subsets of each data source used in the linkage were representative of the source data in terms of median age, sex and diagnoses, so it is unlikely that selection bias has arisen by using linked data.

- Data quality in each of the four sources is adequate for the analyses in this thesis.

Chapter 5 Heralding of myocardial infarction

5.1 Summary

This chapter describes an analysis to assess the type and timing of atherosclerotic disease diagnoses, cardiovascular disease risk factors and chest pain prior to first myocardial infarction.

5.2 Literature review

5.2.1 Introduction

The extent to which first acute myocardial infarction (MI) is heralded by previous symptomatic atherosclerotic disease, major risk factors or symptoms has important implications for understanding MI aetiology, as well as the provision of optimal services. Therefore, a literature review was undertaken to assess heralding of myocardial infarction.

This literature review focused on studies estimating (i) the proportion of patients with first MI with previously diagnosed atherosclerotic disease (coronary, cerebrovascular or peripheral arterial disease), or previously elevated cardiovascular disease risk factors, and (ii) the timing and onset of atherosclerotic disease in relation to MI.

5.2.2 Methods

5.2.2.1 Search strategy

A search was conducted in the MEDLINE and EMBASE databases to find relevant literature. Search terms are described in Appendix A, Table 10.16. The searches were restricted to titles only to increase the specificity of the search, given the broad nature of the terms.

5.2.2.2 Inclusion criteria

Studies were included only if they fulfilled the following criteria:

1. Included patients with first MI;
2. Examined a specific objective regarding the prevalence of atherosclerotic disease and risk factors prior to MI;
3. Study in humans;
4. Manuscript written in English language.

Titles and abstracts were reviewed to identify potentially relevant studies. For those that indicated that they had focused on identifying the proportion of patients with atherosclerotic disease or cardiovascular disease risk factors, or examining the timing of atherosclerotic disease diagnosis in relation to MI, full text was sought to assess whether the study met the inclusion criteria.

5.2.3 Results

5.2.3.1 Studies reporting heralding by atherosclerotic disease and risk factors

The initial search generated 2,658 studies. The titles and abstracts were reviewed to identify studies whose main aim was reporting the prevalence of patients heralded by atherosclerotic disease and risk factors prior to MI. No studies were identified that estimated both the proportion of patients heralded by atherosclerotic disease and the proportion heralded by cardiovascular disease risk factors. However, some studies provided estimates of the proportion heralded by disease and others estimated the proportion heralded by cardiovascular disease risk factors and the duration of symptoms prior to MI. These are briefly summarised below.

5.2.3.2 Studies reporting heralding by atherosclerotic disease

Just one study was identified that examined the proportion of patients with different pre-MI manifestations of atherosclerotic disease in patients with first MI. This was in the Framingham study, which began in 1948, with follow-up through to 1984 and during this time identified 532 men and 296 women with MI. In this study 68.6% of men and 60.5% of women with MI were unheralded by prior angina, intermittent claudication, stroke/TIA or congestive heart failure.[144] The prevalence of disease of each subtype was as follows:

- Angina: 20.9% in men, 24.7% in women;
- intermittent claudication: 9.4% in men, 10.5% in women;
- Stroke or TIA: 5.3% in men, 8.1% in women;
- Congestive heart failure: 3.4% in men, 9.8% in women.

However, the data collected in this study is now old due to changes in the incidence of angina[13] and the redefinition of MI in 2000.[4]

A more recent study (in 2009) based on patients with non ST-elevation acute coronary syndromes examined the presence of peripheral arterial disease, cerebrovascular disease and coronary artery disease prior to the event, and the occurrence of polyvascular disease.[145] The CRUSADE study enrolled over 95,000 patients with NSTEACS from 484 sites in the US; 48.9% had no prior atherosclerotic disease, 38.3% had disease in one territory, 11.2% in two and 1.6% in three. Of those without prior atherosclerotic disease, 91.8% were NSTEMI and the remaining 8.2% were ACS. The prevalences of each major

cardiovascular disease risk factor were described for patients without prior atherosclerotic disease, but an estimate of the number of patients without either disease or risk factors was not reported. While this study was large and in recently collected data, it focused on NSTEACS, so an estimate of heralding by atherosclerotic disease in MI overall is not available.

Yawn reported both the proportion of patients with prior coronary disease and the proportion with previously elevated risk factors, but did not combine the two estimates.[146] In 298 patients, 52% of men and 30% of women had CHD diagnoses prior to their first MI. This study also measured the duration of coronary disease prior to first MI, showing that the average duration was 5 years prior to MI. No studies were identified that aimed to assess the duration of diagnosed atherosclerotic disease prior to MI. However, this was a relatively small study and did not estimate the occurrence of peripheral or cerebrovascular disease prior to MI.

5.2.3.3 Studies reporting angina prior to MI and ischaemic preconditioning

There were many studies reporting the proportion of patients with angina prior to MI. The majority of these focused on the prevalence and effects of prodromal angina prior to MI, i.e. angina of very short duration, and none reported the proportion of patients with and without longstanding atherosclerotic disease. This is the subject of Chapter 6. However, six studies were identified that reported the prevalence of angina prior to first MI (Table 5.1). These studies show that the proportion of first MI patients with previous angina (or chest pain likely to be angina) is likely to lie between 21% (in men only)[144] to 63%.[147] These studies varied widely in their timing, study designs, setting and definition of angina. Four of these were retrospective and therefore relied on patient recall for exposure identification. One was based on the prospective Framingham study,[144] but this followed patients up biennially and detailed data on the onset and evolution of disease were unavailable. The other prospective study was based on just 150 women with MI, but was able to assess the timing of onset.[148]

Importantly, the most recent of these studies is over a decade old and given (i) the recent decrease in MI incidence and relative increase in angina incidence,[19, 20] (ii) the reduction in cardiovascular disease risk factors,[21] and (iii) the updated definition of MI,[22] there is scope for an updated estimate of previous angina.

Table 5.1 Studies examining the proportion of patients with angina prior to first myocardial infarction

Author, year	Country	Years of data collection	Number of MI patients	Study design	Angina definition	% with preinfarction angina
Anzai, 1995[149]	Japan	1994-1995	291	Retrospective, hospital-based	New onset <1 month duration, Chronic & worsening pattern <1 month duration, Chronic stable angina >1 month duration	*Anterior Infarction*: 39% new onset angina, 15% chronic & unstable, 10% chronic & stable. *Inferior infarction*: 26% new onset angina, 12% chronic & unstable, 17% chronic & stable.
Behar, 1992[150]	Israel	1981-1983	4,166	Retrospective, hospital based	Chronic angina >1 month	43%
Cupples, 1993[144]	USA	1948-1982	828	Prospective, Framingham study	Physician diagnosed angina	20.9% in men, 24.7% in women
Kobayashi, 1998[147]	Japan	1980-1995	1,637	Retrospective, hospital-based	Typical chest pain at any time before MI.	63%
Pierard, 1988[151]	Belgium	1977-1980	732	Retrospective, hospital-based	Chronic angina > 1 month. New onset angina <1 month	27% chronic angina, 34% new onset
Yawn, 2004[148]	USA	1996-2001	150	Prospective, based on medical records	Any CHD diagnosis	52% in women

CHD: coronary heart disease

5.2.3.4 The prevalence of atherosclerotic disease in key MI registries

While MI registers usually include patients with recurrent MI in addition to first events, they do give an indication of the frequency of disease in MI patients (Table 5.2). The proportion of MI patients in these studies, including over 500,000 MI patients, who had previous angina was between 10.1% in STEMI patients in the National Register of MI and 74.8% in patients with non ST-elevation acute coronary syndromes in the EuroHeart Survey. The prevalence of cerebrovascular disease was between 5 and 13% and the prevalence of peripheral arterial disease between 7 and 13%.

Table 5.2 The prevalence of prior atherosclerotic disease in patients recorded in key myocardial infarction registries

	GRACE [152]		NRMI [153]		MONICA Scotland[15]		Euro Heart Survey [154]		SWEDEHEART 2004-2006 [155]		REGICOR [156]
	STEMI (n=3,419)	NSTEMI (n=2,893)	STEMI (n=153,486)	NSTEMI (n=337,192)	Men (n=3,991)	Women (n=1,551)	STEMI (n=4,431)	NSTEMI/UA (n=5,367)	Men (n=9,386)	Women (n=4,994)	All MI (n=3,849)
MI, %	19	33	21.5	28.3	32	25.6	22.3	35.6	11.3	10.6	0
Angina, %	49	67	10.1	14.2	41.6	41.5	56.4	74.8	n/s	n/s	43.9
Stroke/TIA, %	6	10	9.1	12.9	5.9	5.7	5.9	8.1	n/s	n/s	n/s
Peripheral disease, %	8	13	n/s	n/s	n/s	n/s	7	10.6	n/s	n/s	n/s
Heart failure, %	7	14	13.8	24	n/s	n/s	8.2	11.9	4.3	9.1	n/s
PCI, %	6	13	10.1	11.3	n/s	n/s	7.3	15.2	4	2.2	n/s
CABG, %	5	13	9.8	16.8	n/s	n/s	3.4	11	3.3	1.7	n/s

Abbreviations: STEMI: ST-elevation MI; NSTEMI: non ST-elevation MI; UA: unstable angina; n/s: not stated; GRACE: Global Registry of Acute Coronary Events; NRMI: National Register of Myocardial Infarction; MONICA: Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; SWEDEHEART: the Swedish cardiac registry; REGICOR: the coronary heart disease register in Spain.

5.2.3.5 Studies reporting heralding by elevated cardiovascular disease risk factors

Several studies have reported the prevalence of 'optimal' risk factor profiles in patients with MI with respect to the four 'major' cardiovascular disease risk factors: smoking, diabetes, hypertension and total cholesterol.[157] These studies, using a range of designs, have shown that most patients with MI have at least one cardiovascular disease risk factor. However, no estimates have been published in patients with their first MI and without prior atherosclerotic disease.

In the UK, 2% (5/202) of patients with ischaemic heart disease in the British Regional Heart Study were normotensive, with normal cholesterol and were non-smokers.[158] However, for the same set of risk factors, 13% of MI cases recorded in the MONICA Augsberg dataset (including fatal and non-fatal) had optimal levels. This higher figure is in line with other studies; a cross sectional study of 122,000 clinical trial patients with MI showed that 15% of women and 19% of men had no major risk factors at the time of MI,[159] although if family history of CHD and obesity were considered as risk factors, then this fell to 8.5% of women and 10.7% of men. In a large US study of patients with NSTEMI (>74,000 patients),[160] 10.5% had no recorded major risk factors. Yawn reported that 98% of women with MI had at least one CHD risk factor identified before MI, and 84% had at least two identified.[146]

Greenland assessed the prevalence of risk factors in fatal and non-fatal CHD events in three large observational studies; for non-fatal MI in the Framingham Study, over 85% of young men and over 90% of older men had at least one recorded risk factor;[161] 70% of younger women with MI and 87% of older women also had at least one elevated risk factor. In fatal coronary heart disease, the number of patients with at least one elevated risk factor in the MRFIT cohort, the Chicago Heart Association project and the Framingham study were over 90%. When borderline results were also included, nearly 100% of MI patients had unfavourable risk factor profiles. Risk factors included in these analyses were smoking, diabetes, hypertension and high cholesterol.[161]

5.2.4 Strengths of previous research

There were two studies that reported the proportion of patients with and without prior atherosclerotic disease, and several that reported the proportion with and without elevated traditional cardiovascular disease risk factors. They have done so in varied geographical populations, in large samples and at different time points. They provide good

estimates of the proportion of patients with and without prior atherosclerotic disease or with and without cardiovascular disease risk factors.

5.2.5 Limitations of previous research

No studies were identified that reported the proportion of first MI patients who have no prior atherosclerotic disease and cardiovascular disease risk factors, which was the focus of this review.

5.2.6 Limitations of this review

The search strategy used in this review limited the search to the titles only. Inclusion of terms to indicate heralding of MI in the abstract produced over 30,000 articles. Inclusion of specific atherosclerotic disease diagnoses such as 'angina', 'coronary disease', 'cerebrovascular disease' or 'peripheral arterial disease' (and their synonyms) would also have generated an unmanageable number of results. Therefore, this search was required to be more specific. Despite the high specificity and low sensitivity of the search, any relevant studies would have been identified as reference lists were scanned and cited reference searches of any papers described in the review were also performed.

5.2.7 Conclusion

This literature review indicates that there are no current studies investigating heralding of MI by atherosclerotic disease in all arterial beds, cardiovascular disease risk factors, cardiovascular medications and chest pain.

5.3 Objectives

Using prospectively collected primary care data linked to detailed hospital data on acute coronary syndromes:

1. To describe the initial manifestation, distribution and timing of different atherosclerotic presentations prior to MI;

2. To describe the cardiovascular disease risk in patients without diagnosed atherosclerotic disease prior to MI;

3. To describe the proportion of MIs that occur without any previously diagnosed atherosclerotic disease, cardiovascular disease risk factors or chest pain.

5.4 Methods

5.4.1 Identification of patients with MI

Analysis of the current objective was performed before the recording of MI in the linked data was validated (results in Chapter 4). Therefore, a pragmatic and conservative approach was used to identify MI in this analysis, using the assumption that recording of acute MI in HES and MINAP was more accurate than recording in GPRD or ONS (due to prevalent coding of MI and failure to record MI in the primary care record, and concern about the validity of a record of fatal MI in ONS). Therefore, the analyses in this objective were based on hospitalized cases of first MI identified in MINAP and HES, as described in Chapter 3. Patients with any evidence of previous MI in HES, MINAP or the GPRD were excluded from the analysis.

Table 5.3 Definition of acute myocardial infarction in Hospital Episode Statistics (HES) and the Myocardial Ischaemia National Audit Project (MINAP)

Data source	MI definition
HES	ICD-10 code I21, I22 or I23 as the primary diagnosis in the first hospital episode.
MINAP	ST-elevation MI or non ST-elevation MI following the joint American Heart Association / European Society of Cardiology definition.[6]

5.4.2 Exclusion criteria

Exclusion criteria are described in Chapter 3. Briefly, patients were excluded if they had a recorded history of MI (n=7,163), were under the age of 18 at MI (n=1), had not been registered with the primary care practice for at least one year before MI (n=769), whose MIs occurred outside the period where all databases were collecting data (outside 1st January 2003 to 31st December 2008, n=4,446), and patients without any primary care consultations in their record prior to MI (n=3).

5.4.3 Heralding by atherosclerotic disease

Atherosclerotic disease diagnoses in GPRD, MINAP and HES were identified using the methods described in Chapter 3. Disease diagnosed in GPRD and HES up to one day before the date of admission for MI was considered to 'herald' MI. Those recorded on the

date of MI in MINAP were also considered to herald MI. Codes recorded in the GPRD or HES on or after the date of admission were considered to be new diagnoses made at the time of MI or post-MI, and were not included in the analysis. Atherosclerotic disease was categorised into the following phenotypes:

- Coronary heart disease (CHD), including:
    - stable angina, including patients with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG),
    - unstable angina,
    - cardiac arrest*,
    - heart failure*,
    - CHD of unspecified type;
- Peripheral arterial disease (PAD), including abdominal aortic aneurysm (AAA);
- Cerebrovascular disease, including:
    - stroke,
    - transient ischaemic attack (TIA),
    - other non-stroke ischaemic cerebrovascular disease;
- Atherosclerotic disease of unspecified type.

*although these were not necessarily coronary in nature, these were categorized as coronary diagnoses for this analysis.

5.4.4 Duration of atherosclerotic disease before first MI

The duration of each diagnosed disease phenotype was calculated based on the time between the earliest recorded code in the GPRD or HES and the date of MI. MINAP does not record dates of previous atherosclerotic disease and therefore if MINAP data alone indicated heralding, the date of onset was recorded as unknown. In addition, the date of onset was recorded as unknown if the earliest GPRD Read code indicating disease in the GPRD indicated a 'history of' the disease rather than an incident diagnosis.

5.4.5 Initial manifestation of atherosclerotic disease before first MI

The initial manifestation of disease was determined based on the phenotype of longest duration. If two phenotypes were recorded on the same day (i.e. with the same

duration) then the following hierarchy (created by CALIBER collaborators, unpublished), was used to determine which phenotype should be classed as the initial manifestation:

1. Heart failure (most severe)
2. Unstable angina
3. PCI or CABG
4. Stable angina
5. CHD of unknown subtype
6. Atherosclerotic disease of unknown type
7. PAD
8. Cerebrovascular disease
9. Cardiac arrest
10. TIA (least severe)

5.4.6 Polyvascular atherosclerotic disease

The presence of polyvascular atherosclerotic disease (i.e. disease in more than one arterial bed) was based on the number of arterial beds affected (coronary, peripheral, cerebrovascular) at the time of MI.

5.4.7 Cardiovascular disease risk factors before first MI

Smoking status (categorised as current, ex, non and unknown), diabetes, dyslipidaemia, hypertension (each categorised as binary variables, present or absent), BMI (classified as underweight, normal, overweight, obese or unknown) and family history of CHD were recorded in the GPRD and HES up to one day before MI. Identification of these risk factors is described in Chapter 3.

5.4.8 Cardiovascular drugs before first MI

Prescriptions of lipid lowering, blood pressure lowering and antiplatelets medications (as described in Chapter 3) were assessed based on GPRD prescription dates and MINAP recording of use at admission. A binary variable was created for each medication to describe use in the six months before MI.

5.4.9 Chest pain before first MI

Experience of chest pain in patients without diagnosed atherosclerotic disease was explored. As discussed in Chapter 3, two types of chest pain were of interest:

- Chest pain attributed to a non-coronary cause; and
- Chest pain unattributed to any cause.

Consultations for either of these types of chest pain up to the day before MI were extracted from GPRD records, as described in Chapter 3. Admissions to MINAP hospitals, with discharge diagnoses of 'other' were also recorded as chest pain.

5.4.10 'Unheralded' MI

This chapter describes heralding of MI by atherosclerotic disease diagnoses, cardiovascular disease risk factors and chest pain. However, patients without these factors recorded in their medical record are not termed 'unheralded'. This is for two reasons: firstly, the term 'unheralded' is misleading when used out of context because it implies that disease, risk factors and chest pain are the only signs that may precede MI (which is not the case), and secondly, such symptoms may have been experienced by the patient but not been reported or recorded in the medical record. However, the term unheralded may be used in conjunction with a qualifying factor (e.g. "unheralded by atherosclerotic disease", or "unheralded by disease or cardiovascular disease risk factors").

5.4.11 Statistical analysis

In the main analysis, the proportions of patients with each type of atherosclerotic disease were reported. The initial manifestation was also reported, and the onset and median duration of disease prior to MI were described for coronary, cerebrovascular and peripheral arterial disease. The proportion of patients with diagnosed disease in one, two or three arterial beds was calculated. The prevalence of each risk factor was then compared in patients with and without atherosclerotic disease diagnosed prior to MI. The frequency and rate of consultations were assessed monthly in the five years leading to MI, and daily in the year prior to MI. Finally, the occurrence of MI without previous disease, risk factors, cardiovascular medications and chest pain was examined and described by age and sex.

5.4.12 Sensitivity analyses

Various analyses were undertaken to assess the sensitivity of the results to analytic decisions and assumptions. First, the sensitivity of the rating of Read and ICD-10 codes was assessed. The analysis was repeated including codes rated as 'possible' indicators of atherosclerotic disease in addition to the 'definite' codes used in the main analysis. Due to the uncertainty of its effects, a minimum consultation rate was not applied to this analysis. To assess how this would have affected the results, the patients were stratified by consultation rate and the proportion of patients with atherosclerotic disease in each stratum was examined. The third sensitivity analysis addressed the assumption that one year of pre-MI follow-up was sufficient for prevalent atherosclerotic disease to be identified by the GP. This was increased to three years and the proportion of patients with diagnosed disease was compared to the results of the main analysis. The final sensitivity analysis assessed the effect of including patients with atherosclerotic disease diagnosed prior to the UTS date. It is possible that the date of diagnosis prior to UTS was inaccurate. Therefore, the prevalence and pattern of onset of each subtype diagnosed only inside the UTS period was compared to the results in the main analysis.

5.5 Results

5.5.1 Description of cases

There were 11,255 patients with MI who met all eligibility criteria. They had a median age of 72 and 38.2% were female (Table 5.4). Detailed clinical data were unavailable in HES but of the 8,059 patients recorded in MINAP, 48.1% were STEMI and 51.9% were NSTEMI.

Table 5.4 Demographic characteristics of patients with myocardial infarction (N=11,255)

	N=11,255	
Age in years, median (IQR)	72	(60-81)
Female, n (%)	4,294	(38.2)
Ethnicity, n (%)		
White	9,129	(81.1)
South Asian	82	(0.7)
Other	207	(1.8)
Unknown	1,837	(16.3)
IMD quintile, n (%)		
1 (Least deprived)	2,229	(25.5)
2	1,911	(21.9)
3	1,812	(20.8)
4	1,644	(18.8)
5 (Most deprived)	1,135	(13)
Consultations per year, median (IQR)	6.4	(3.4-10.8)
Years of pre-MI GPRD registration, median (IQR)	8.6	(5.5-13.4)
MI type*, n (%)		
STEMI	3,304	(48.1)
NSTEMI	3,567	(51.9)

*In 6,871 MINAP patients only. MI: myocardial infarction; GPRD: General Practice Research Database; IQR: inter-quartile range; STEMI: ST-elevation myocardial infarction; NSTEMI: non ST-elevation myocardial infarction

5.5.2 Atherosclerotic disease before MI

Of the 11,255 first MI patients, 4,897 (43.5%, (95% CI: 42.6-44.4%)) were heralded by previously diagnosed atherosclerotic disease. Table 5.5 shows the atherosclerotic disease manifestations of these patients. The most common manifestation was stable angina and the coronary arteries were most frequently diseased. The annual proportion of heralded patients varied between 41.5 and 46.1% during the study period but with no evidence of a time trend (p=0.1) (Appendix A, Figure 10.3). Appendix A, Table 10.17 describes the initial manifestations in these patients; 16.1% of patients first manifested with cerebrovascular or peripheral disease, and while many of these patients subsequently developed symptomatic coronary disease before MI, a fifth (1,053 patients) of patients heralded by disease had peripheral or cerebrovascular disease only.

When the prevalence of previous disease was examined by MI types (restricting the analysis to MINAP patients, in whom MI type was known, N=6,871), there were striking differences. The proportion of patients with any prior disease in NSTEMI patients was 50.4% compared to 29.4% in STEMI patients. The differences in heralding between STEMI and NSTEMI patients are explored in paper 1 (Appendix A, section 0).

5.5.2.1 Polyvascular disease before MI

Of the 44% of patients with diagnosed atherosclerotic disease prior to MI, the majority had just one arterial bed with manifest disease; 31.1% of patients had disease in one arterial bed, 10.4% in two and 2.0% of patients had disease diagnosed in all the coronary, cerebrovascular and peripheral arteries. Polyvascular disease was strongly related to older age (P<0.001). Figure 5.1 shows that the majority of single and double vascular disease was in the coronary circulation.

Table 5.5 Manifestations of atherosclerotic disease before first myocardial infarction (MI), and the duration between manifestation and MI (N=11,255)

	n	(%)	Median duration before MI, years (IQR)	
Any atherosclerotic disease	**4,897**	**(43.5)**	**6.7**	**(2.5-11.9)**
Coronary disease	**3,836**	**(34.1)**	**3.4**	**(0.7-7.7)**
Stable angina	2,902	(25.8)	6.1	(1.8-11.6)
Unstable angina	562	(5.0)	2.1	(0.1-5.6)
PCI or CABG	519	(4.6)	5.7	(1.3-11.1)
Heart failure	1,122	(10.0)	3.3	(1.0-6.5)
Cardiac arrest	108	(1.0)	2.4	(0.2-5.3)
CHD not otherwise specified	2,265	(20.1)	6.8	(2.5-12.1)
Other atherosclerotic disease	**2,356**	**(20.9)**	**4.9**	**(1.9-8.9)**
Cerebrovascular disease	1,256	(11.2)	5.7	(2.3-10.6)
Peripheral arterial disease	1,204	(10.7)	5.1	(2.1-9.0)
Atherosclerotic disease of unknown subtype	**117**	**(1.0)**	**3.0**	**(1.3-6.0)**

PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CHD: coronary heart disease; IQR: inter-quartile range. *Patients with atherosclerotic disease of unknown subtype were those with unspecific Read codes recorded in the GPRD (see methods). Patients appear more than once if they are diagnosed with more than one type of atherosclerotic disease before MI.

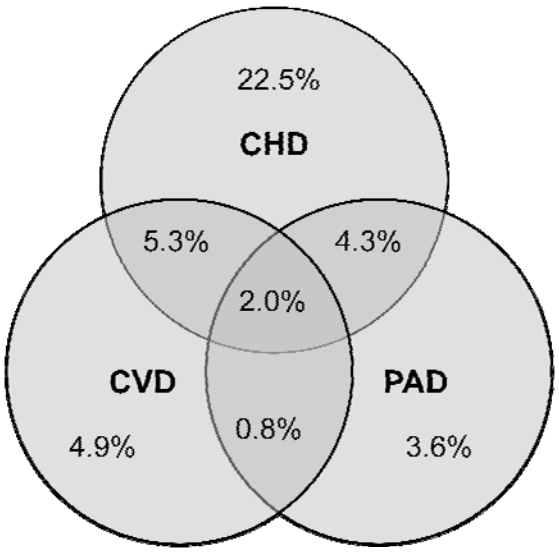


Figure 5.1 Proportion of all patients with coronary heart disease (CHD), cerebrovascular disease (CVD) and peripheral arterial disease (PAD) and combinations of each of these in 11,255 patients with first myocardial infarction
(56% of patients had no previously diagnosed atherosclerotic disease, 31% had disease at one site, 10% had two and 2% at three sites.)

5.5.3 Onset and duration of atherosclerotic disease before MI

Of the 4,897 patients who had previously diagnosed disease, 4,540 (92.7%) had a reliable date of onset (i.e. were first recorded with atherosclerosis in the GPRD or HES with a code which indicating incident disease). Table 5.5 shows the median duration between first ever diagnosis of atherosclerotic disease and MI, and the median duration between first diagnosis of *specific phenotypes* of atherosclerotic disease and MI. The median duration between first diagnosis and MI was 6.7 years. The median duration of cerebrovascular and peripheral disease was 4.9 years, slightly more than for coronary disease (median 3.4 years). Of patients heralded by disease, 6.6% were diagnosed twenty years or more before MI, 33.0% ten years or more, 59.7% five years or more and 84.9% one year or more (Table 5.6). There was a long duration of heralding in most patients with previously diagnosed disease.

The rate of atherosclerotic disease onset in the ten years prior to MI was relatively stable (shown in Figure 5.2) until the year prior to MI when there was a large increase in the rate. To examine this pattern further, the rate of disease onset was described by arterial site (Figure 5.3). This showed that the rapid increase in disease diagnosis before MI was restricted to coronary heart disease presentations. The rate of coronary disease in the year before MI was 4.6 times higher than in the remaining nine years before MI (95% CI 4.16-5.01) P< 0.001. No such rise was seen in cerebrovascular of peripheral disease presentations. The rate of coronary diagnoses in the last year of pre-MI follow-up is displayed in more detail in Figure 5.4, showing that the rapid rise in the onset of coronary disease was restricted to the 90 days before MI.

Table 5.6 Cumulative onset of atherosclerotic disease before MI, in patients with a complete date of onset (N=4,540)

Duration of atherosclerotic disease	Cumulative n (%) with atherosclerotic disease before MI	
≥20 years	301	(6.6)
≥15 years	643	(14.2)
≥10 years	1,497	(33)
≥5 years	2,711	(59.7)
≥2 years	3,566	(78.5)
≥1 years	3,853	(84.9)
≥0.5 years	4,053	(89.3)
≥1 day	4,540	(100)

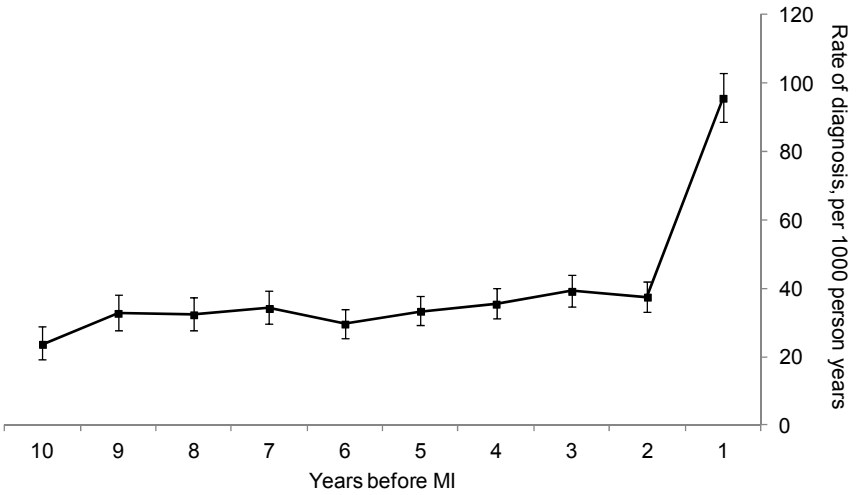


Figure 5.2 Rate of atherosclerotic disease onset in the ten years prior to first myocardial infarction (MI), per 1,000 person years (95% confidence intervals) in 11,255 patients

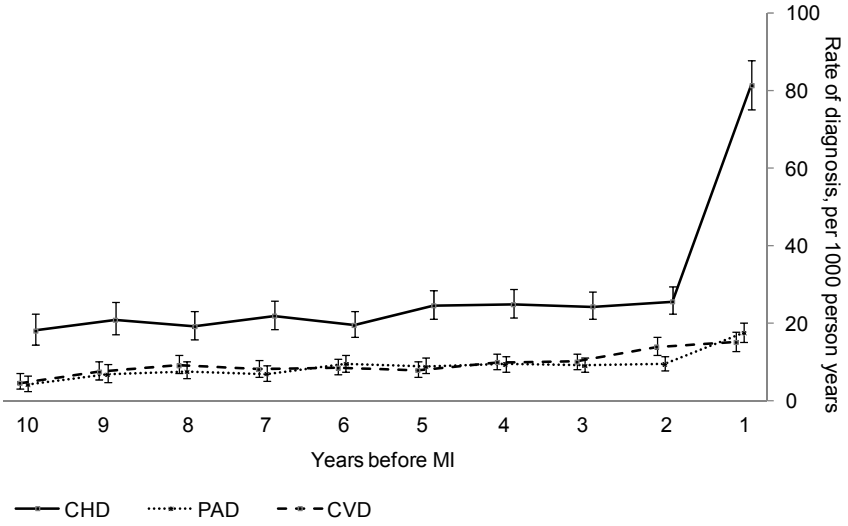


Figure 5.3 Rate of coronary heart disease (CHD), peripheral arterial disease (PAD) and cerebrovascular disease (CVD) onset in the ten years prior to first myocardial infarction (MI), per 1,000 person years (95% confidence intervals) in 11,255 patients

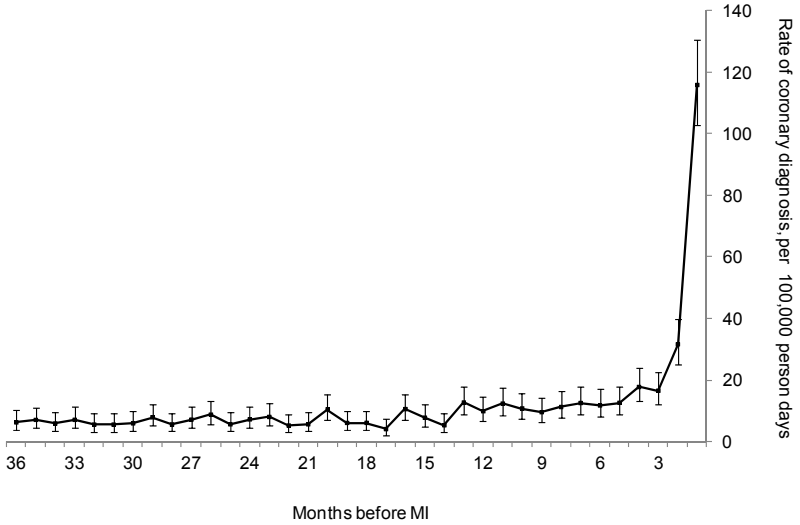


Figure 5.4 Monthly rate of coronary diagnosis in the three years prior to first myocardial infarction (MI), per 100,000 person days (95% confidence intervals) in 11,255 patients.

5.5.3.1 The premonitory period

The weeks or months preceding MI is often called the 'premonitory' or 'prodromal' period, where patients experience chest pain or other symptoms that, retrospectively, can be described as associated with the patient's subsequent MI. Based on the data from this analysis, the premonitory period was defined as the 90 days prior to MI.

Diagnoses of coronary disease in the 90 days before MI were stable angina (n=272), unstable angina (n=96), CABG or PCI (n=34), CHD not otherwise specified (n=107). In total, 344 (3.1%) patients were first diagnosed in these three months; for comparison, only 83 patients were diagnosed with the same disease outcomes in the three to six months before MI, and 61 from six to nine months before MI.

In addition to the patients with diagnosed coronary disease in the 90 days before MI, a further 403 (6.3%) patients *without* diagnosed atherosclerotic disease consulted their GP with chest pain that was recorded as non-coronary (n=15) or that was not attributed to any cause (n=396). One patient was admitted to hospital and had a MINAP discharge diagnosis of 'other' (i.e. not acute coronary syndrome) in the 90 days before MI. The monthly frequency of consultation for chest pain in patients without atherosclerotic disease diagnosis was stable until the month before MI, when a large increase in consultations was seen (Figure 5.5). Examining the daily consultation rate for chest pain in only the year prior to MI, the increase in consultations begins in the 30 to 50 days before MI and the largest rise is in the week before MI.

The monthly and daily rate of consultation for all causes were also calculated for all patients (N=11,255) (Figure 5.6 and Figure 5.7). The rate of consultation increased steadily over the three years prior to MI, but then exponentially in the five months prior to MI. A closer examination of this pattern describes the largest increase in the thirty days prior to MI. In the 11,255 patients included in this analysis, the number of all-cause consultations doubles from approximately 400 per day (roughly 4% of future MI patients per day) in the ninety to thirty days before MI, to nearly 1400 (roughly 12%) the day before MI.

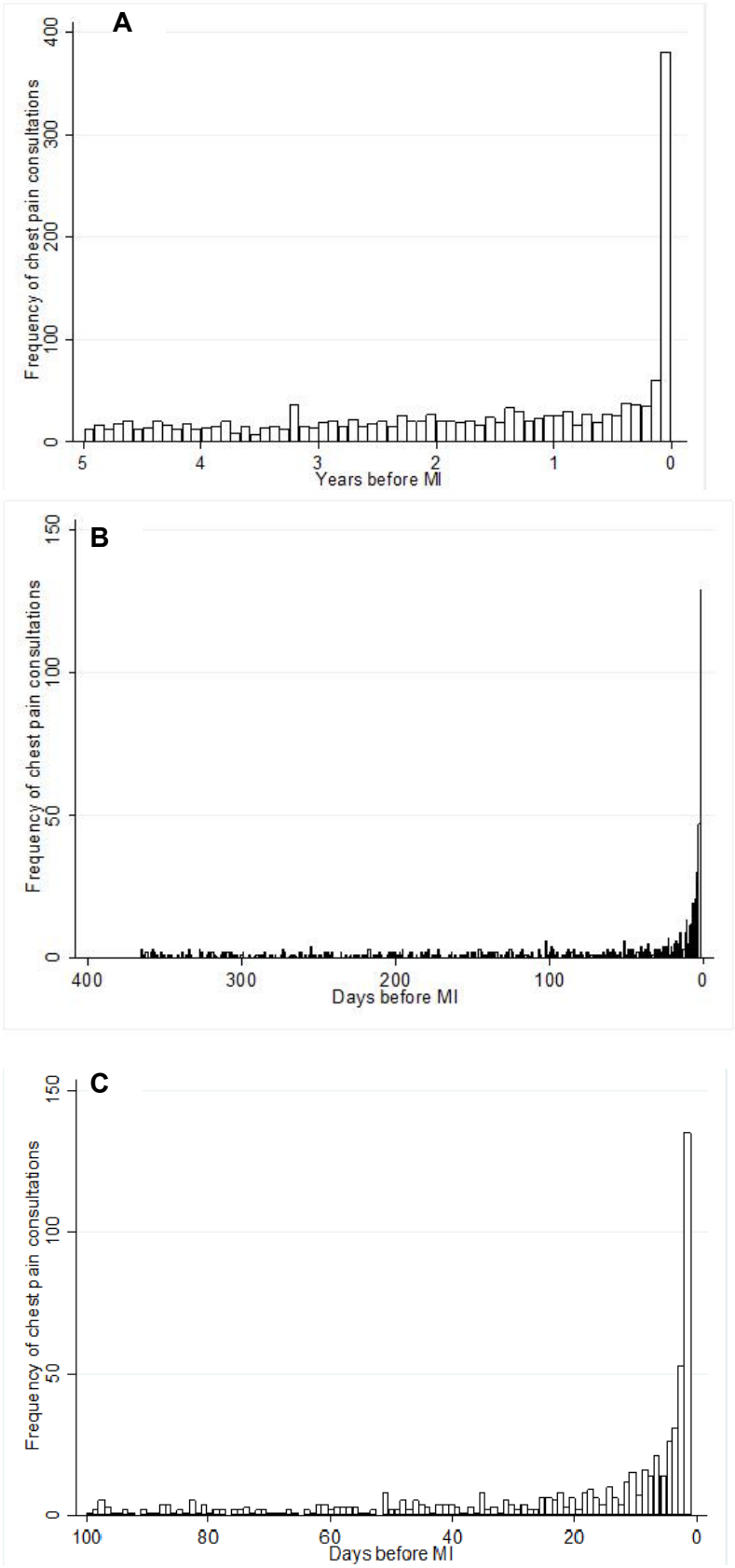


Figure 5.5 Frequency of chest pain consultations in patients without diagnosed atherosclerotic disease, in (A) five years before myocardial infarction (MI), (B) one year before MI and (C) 100 days before MI (N=7,325)

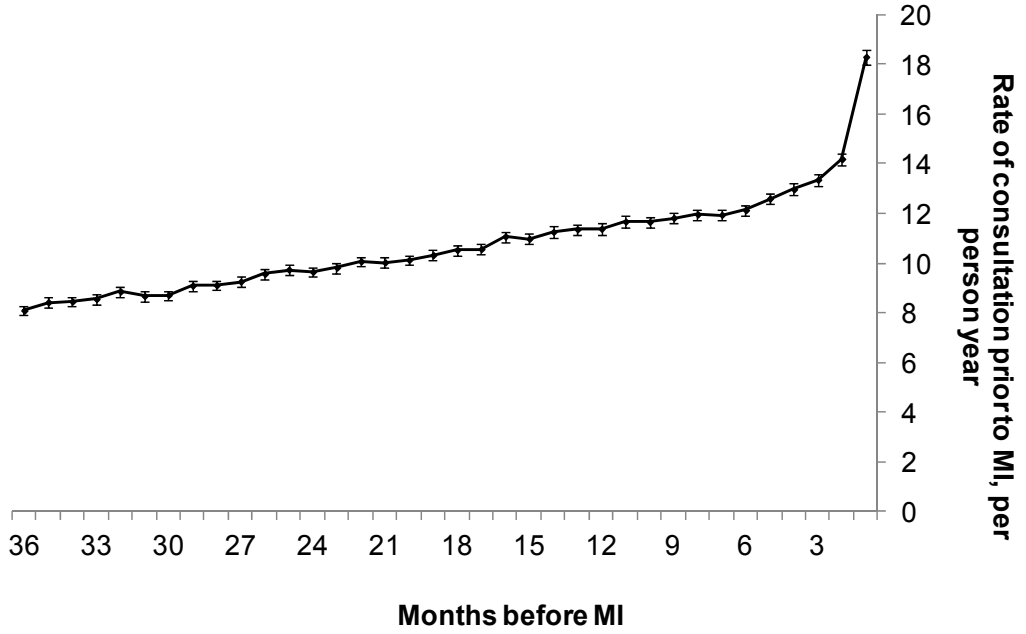


Figure 5.6 Monthly rate of consultation for any cause in primary care for 11,255 patients with MI, in the three years leading up to MI

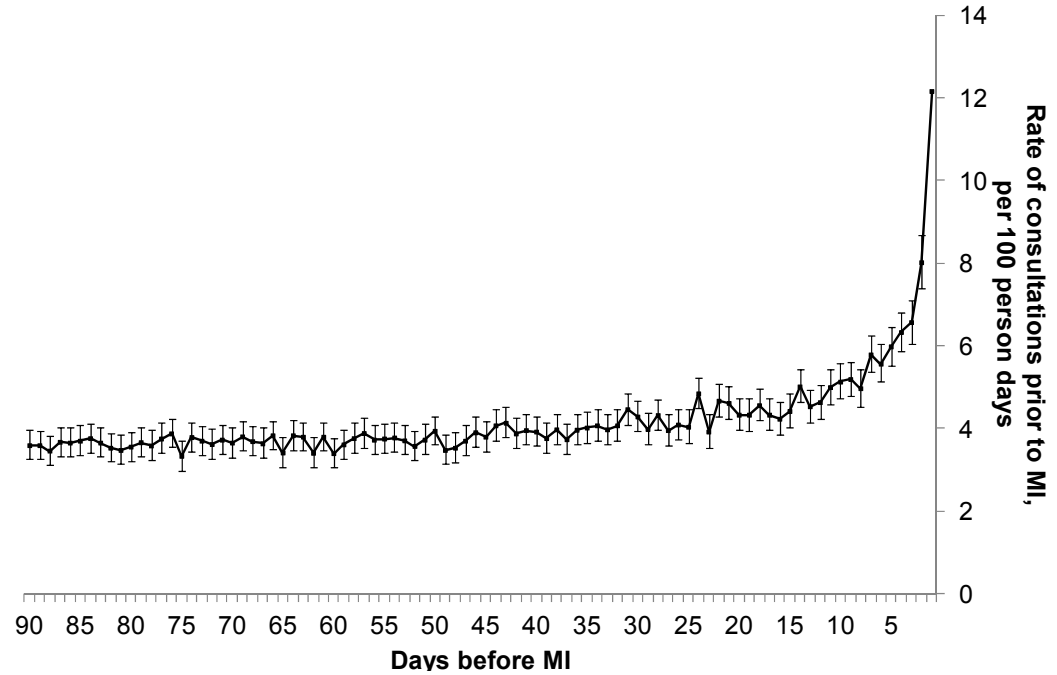


Figure 5.7 Daily rate of consultation for any cause in primary care for 11,255 patients with MI, in the 90 days leading up to MI

5.5.4 Demographic characteristics of patients with and without previously diagnosed atherosclerotic disease

Overall, patients with prior atherosclerotic disease tended to be older, were more likely to be female and with more social deprivation than patients unheralded by disease (Table 5.7). The peak in MI without previous disease was younger for men than women (age group 50-59 age group for men, but 70-79 group for women) (Figure 5.8). Patients with prior atherosclerotic disease had a higher rate of consultation before MI, reflecting their increased disease burden and need for services, but were registered with the GPRD practice for a similar duration before MI.

Table 5.7 Demographic variables in 11,255 myocardial infarction patients with and without previously diagnosed atherosclerotic disease

	No previous diagnosed atherosclerotic disease N=7,325		Previously diagnosed atherosclerotic disease N=5,950		Total N=11,255	
Median age, years (IQR)	66	(56-77)	78	(69-84)	72	(60-81)
Female, n (%)	2,166	(34.1)	2,128	(43.5)	4,294	(38.2)
Ethnicity, n (%)						
White	5,087	(80)	4,042	(82.5)	9,129	(81.1)
South Asian	49	(0.8)	33	(0.7)	82	(0.7)
Other	124	(2.0)	83	(1.7)	207	(1.8)
Unknown	1,098	(17.3)	739	(15.1)	1,837	(16.3)
IMD quintile, n (%)						
1 (Least deprived)	1,322	(26.8)	907	(23.8)	2,229	(25.5)
2	1,092	(22.2)	819	(21.5)	1,911	(21.9)
3	1,029	(20.9)	783	(20.6)	1,812	(20.8)
4	875	(17.8)	769	(20.2)	1,644	(18.8)
5 (Most deprived)	607	(12.3)	528	(13.9)	1,135	(13.0)
Primary care consultations per year, median (IQR)	4.7	(2.4-8.3)	8.8	(5.4-13.6)	6.4	(3.4-10.8)
Years of pre-MI GPRD registration, median (IQR)	8.4	(5.3-13.2)	8.8	(5.6-13.7)	8.6	(5.5-13.4)

IMD: index of multiple deprivation; GPRD: General Practice Research Database; IQR: inter-quartile range.

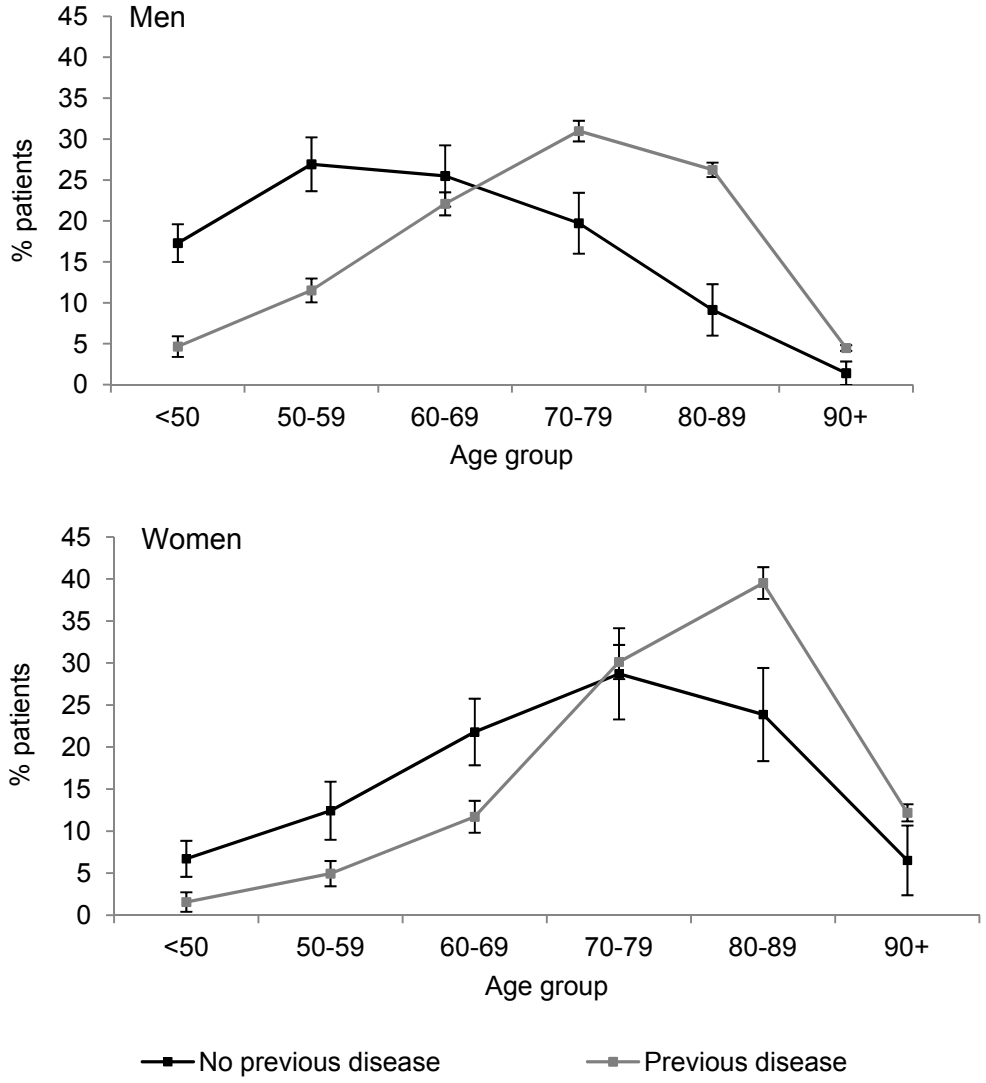


Figure 5.8 Demographic distribution of patients with myocardial infarction, with and without previously diagnosed atherosclerotic disease, with 95% confidence intervals, in men (N=6,961) and women (N=4,294)

5.5.5 Cardiovascular disease risk factors and medication prescriptions in patients with and without previously diagnosed atherosclerotic disease

The prevalences of hypertension, diabetes and dyslipidaemia were higher in patients heralded by atherosclerotic disease diagnoses. However, current smoking and family history of coronary disease were more prevalent in those unheralded by disease. Levels of overweight and obesity were similar between the groups. The pre-MI prevalence of cardiovascular disease risk factors is shown in Table 5.8.

The risk factor burden in patients without diagnosed atherosclerotic disease (Figure 5.9) was on average slightly lower than in patients with diagnosed atherosclerotic disease; the median number of traditional cardiovascular disease risk factors in patients with previous disease diagnoses was 2 (IQR 1-3) compared to 1 (IQR 1-2) in those without. In patients heralded by diagnosed atherosclerotic disease, 459 patients (9.4%) had no recorded elevated risk factors and in unheralded patients 979 (15.4%) had no recorded elevated risk factors.

Prescribing of blood pressure lowering, lipid lowering and antiplatelet medications in the six months before MI is also shown in Table 5.8. Prescribing was higher in those with diagnosed atherosclerotic disease, but even in those without established disease, 15.9% of patients were prescribed antiplatelets, 35.4% were prescribed blood pressure lowering and 15.0% were prescribed lipid lowering medications, indicating known raised risk among this group. Prescription of one, two or three of lipid lowering, blood pressure lowering and antiplatelets drugs is shown in Figure 5.10. In patients with diagnosed atherosclerotic disease, it was most common to be receiving all three drug classes. In patients without diagnosed disease, it was most common to be receiving none, although 5.9% of such patients were prescribed all three medications in the six months before MI.

Table 5.8 Cardiovascular disease risk factors and prescription of cardiovascular medications in patients with and without previously diagnosed atherosclerotic disease

	No previously diagnosed atherosclerotic disease N=6,358		Previously diagnosed atherosclerotic disease N=4,897		TOTAL N=11,255	
	n	(%)	n	(%)	n	(%)
Hypertension	2,857	(44.9)	3,566	(72.8)	6,423	(57.1)
Diabetes	758	(11.9)	1,188	(24.3)	1,946	(17.3)
Dyslipidaemia	1,161	(18.3)	1,675	(34.2)	2,836	(25.2)
Family history CHD	2,421	(38.1)	1,655	(33.8)	4,076	(36.2)
Weight						
Underweight	18	(0.3)	27	(0.6)	45	(0.4)
Normal weight	356	(5.6)	259	(5.3)	615	(5.5)
Overweight or obese	1,360	(21.4)	980	(20.0)	2,340	(20.8)
Weight unknown	4,624	(72.7)	3,631	(74.1)	8,255	(73.3)
Smoking status						
Non-smoker	906	(14.2)	641	(13.1)	1,547	(13.7)
Ex-smoker	3,116	(49)	3,213	(65.6)	6,329	(56.2)
Current smoker	2,274	(35.8)	1,007	(20.6)	3,281	(29.2)
Unknown	62	(1.0)	36	(0.7)	98	(0.9)
Blood pressure lowering	2,250	(35.4)	3,592	(73.4)	5,842	(51.9)
Lipid lowering	954	(15)	2,272	(46.4)	3,226	(28.7)
Antiplatelets	1,013	(15.9)	2,976	(60.8)	3,989	(35.4)

CHD: coronary heart disease.

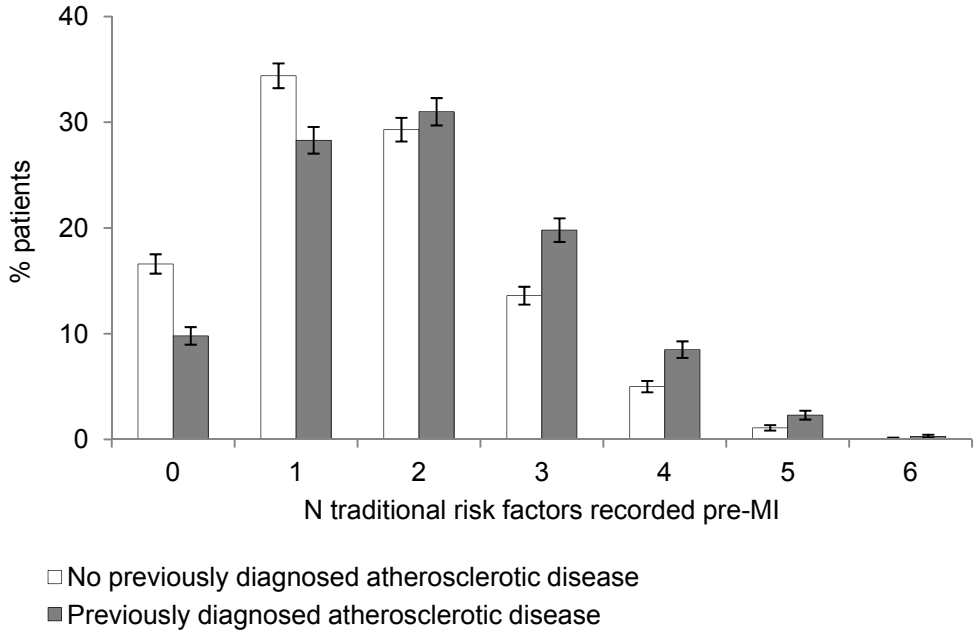


Figure 5.9 Number of traditional cardiovascular disease risk factors in 11,255 myocardial infarction (MI) patients with and without previously diagnosed atherosclerotic disease (hypertension, dyslipidaemia, overweight or obese, family history coronary heart disease, diabetes, current smoking), with 95% confidence intervals

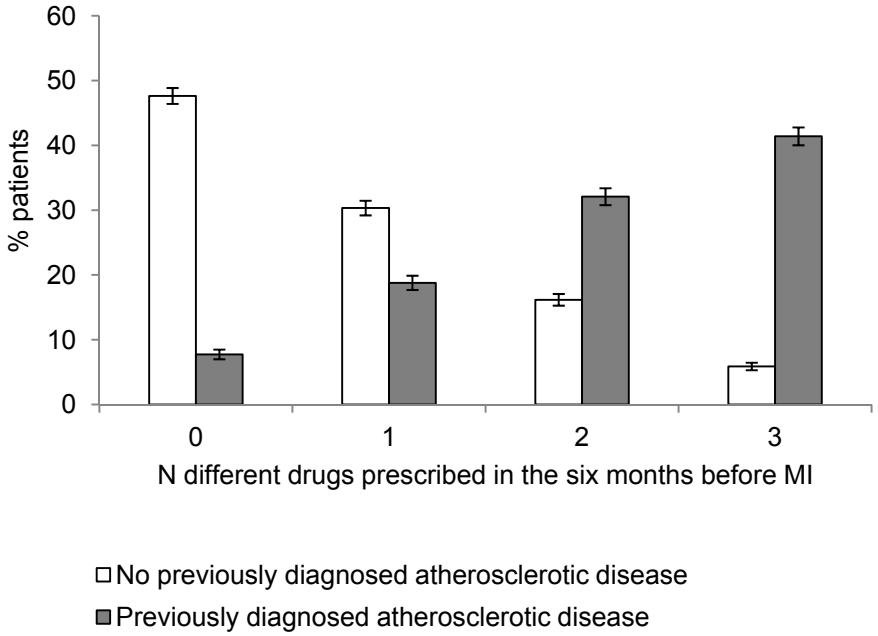


Figure 5.10 Number of different drugs prescribed in the six months prior to myocardial infarction (MI), in 11,255 patients with and without previously diagnosed atherosclerotic disease (lipid lowering, blood pressure lowering, antiplatelets), with 95% confidence intervals

5.5.6 MI without warning

810 of 11,255 (7.2% 95% CI (6.7-7.7%)) first MI patients experienced no previous atherosclerotic disease diagnoses before their MI, had no elevated cardiovascular disease risk factors and had not been prescribed any of the three key cardiovascular drugs in the six months before MI. In the eyes of the general practitioner, these are healthy patients whose MIs are without warning. If cardiovascular drug use was extended to ever-use rather than use in the six months prior to MI, then 736 patients (6.5%) occur without warning. If consultation for chest pain is also included, 703 (6.2%) occur without warning.

The distribution of this subset of patients by age and sex is shown in Figure 5.12. Men were most likely to experience MI without warning (N=540 versus 270 in women) and most frequently in age groups 60 to 80. Women who had MI without warning tended to be older (peak in age group 80-89). In both men and women, patients who had their MI without warning tended to older than patients with known elevated cardiovascular disease risk (Figure 5.13).

The consultation rate preceding MI was lower in patients who had MI without warning compared to those with elevated cardiovascular disease risk (median 3.5 consultations per year (IQR 1.7-6.6) and 5.0 (IQR 2.6-8.5), respectively, Kruskal Wallis P=0.0001 for a comparison of medians). When the total number of consultations in the year prior to MI was assessed, the median number of consultations for patients with elevated cardiovascular disease risk (but without known atherosclerotic disease diagnoses) was 7 (IQR 3-13), and was lower in patients who had MI without warning (median 5 (IQR 2-9)).

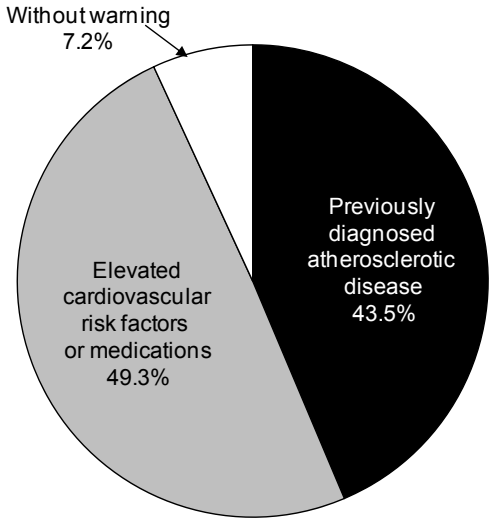


Figure 5.11 Distribution of 11,255 myocardial infarction patients by previous atherosclerotic disease and cardiovascular disease risk factors

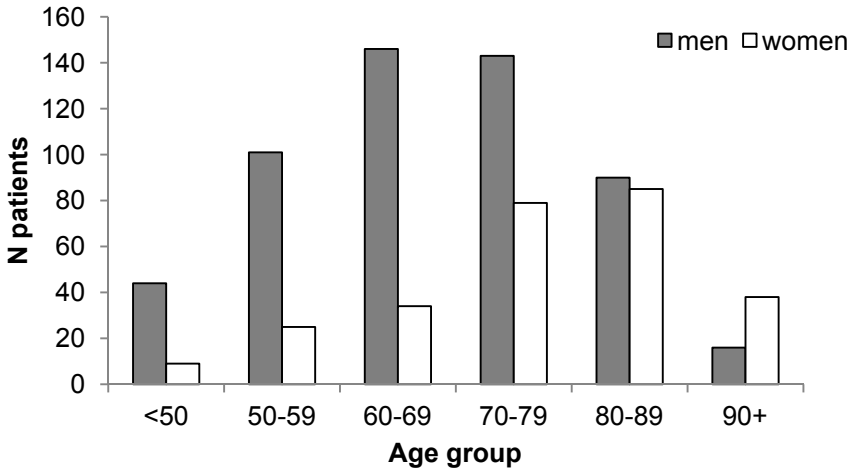


Figure 5.12 Number of men and women who had myocardial infarction without warning (total N=810)

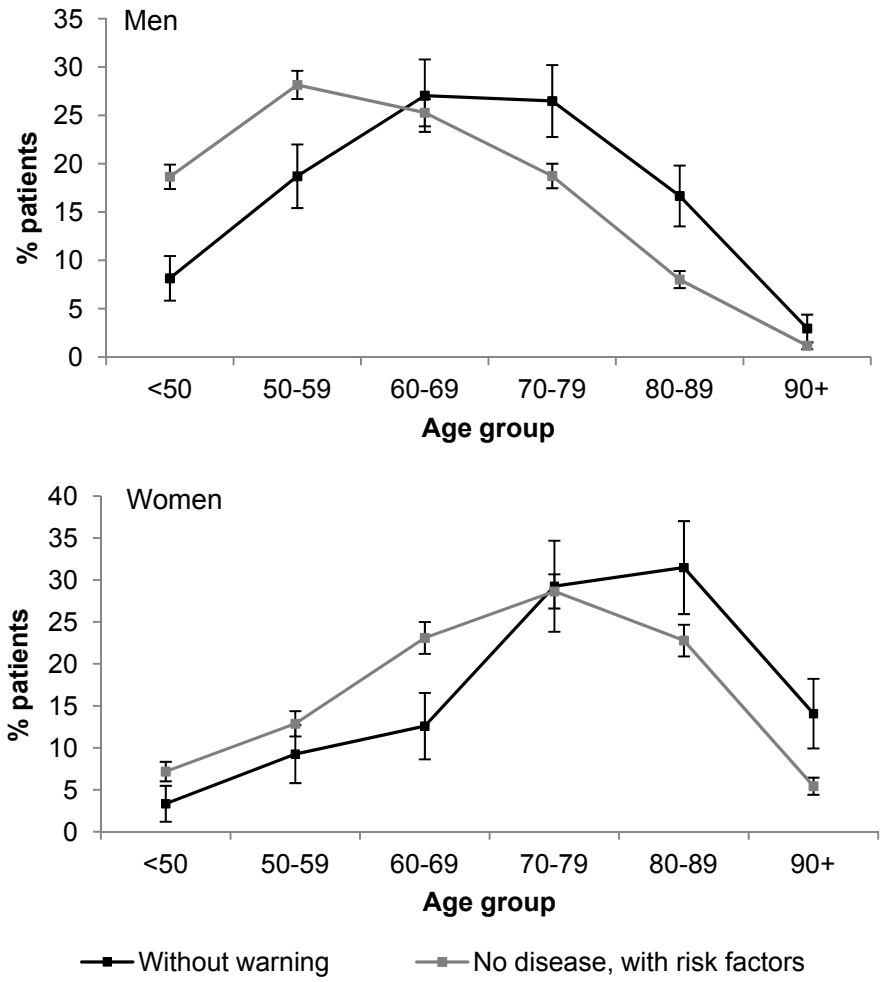


Figure 5.13 Demographic distribution of patients (5,159 men, 2,166 women) with myocardial infarction, with no previously diagnosed atherosclerotic disease, with and without elevated risk factors or cardiovascular medication prescriptions, with 95% confidence intervals

5.5.7 Sensitivity analyses

5.5.7.1 'Possible' diagnostic codes to define atherosclerotic disease

The codes used to define atherosclerotic disease in this thesis were rated as 'definite' indicators of atherosclerotic disease by two independent raters, including one general practitioner. However, many Read codes were rated as 'possible' indicators of disease. In the main analysis, only definite codes were used. In this sensitivity analysis, the possible codes were included. This made very little difference to the overall estimate of the proportion of patients with prior atherosclerotic disease (46.4% compared to 43.5% in the original analysis) or to the prevalences of specific atherosclerotic disease phenotypes (Table 5.9). This indicates that the list of 'definite' rated codes was sensitive.

5.5.7.2 Variation in the proportion heralded with atherosclerotic disease, by consultation rate

The proportion of patients with atherosclerotic disease varied between percentiles of consultation rate (Appendix A, Figure 10.4). Patients with the lowest consultation rates had the lowest prevalence of atherosclerotic disease diagnosis at MI and those with the highest consultation rate had the highest prevalence. However, a low rate of consultation may be due either to good health or to a reluctance to visit the GP despite symptomatic disease. When the analysis was restricted to patients with a high consultation rate (top 25th percentile), the prevalence of atherosclerotic disease rose from 43.5% in the original analysis to 66.1%. When the analysis was restricted to patients with low consultation rate, just 19.3% of patients were heralded (see Table 5.9). This suggests that introducing a minimum consultation rate would have changed the results of the study.

5.5.7.3 Excluding patients with less than three years of pre-MI UTS follow-up

In the main analysis, all MI patients were required to have at least one year of up to standard (UTS) follow-up prior to MI (where the UTS date is defined by the GPRD as the date when the practice starts to provide continuous good quality data). This was to allow adequate time for GPs to record prevalent conditions after patient registration with the practice and was shown by Lewis et al to be a sufficient time period.[89] However, some authors using GPRD data exclude patients who do not have at least three years of registration. When patients with less than three years of registration were excluded, the proportion heralded by atherosclerotic disease overall was increased by less than half a percent. The proportion of patients with prevalent atherosclerotic disease, stratified by disease subtype, showed very similar results (Table 5.9). This indicates that the criterion to include only patients with at least one year of pre-MI follow-up was adequate to identify prevalent atherosclerotic disease.

5.5.7.4 Patients diagnosed with atherosclerotic disease within the UTS period only

In this analysis, only MI events that occurred within the UTS period were included, when GPRD data are marked as being of good quality. However, atherosclerotic disease diagnoses were allowed to occur beforehand. Of the 4,897 patients with diagnosed atherosclerotic disease, 1,346 (27.5%) were first diagnosed with atherosclerotic disease

before the practice UTS period began. Excluding these patients in a sensitivity analysis gives us a similar (albeit lower) pattern of prevalence of the different types of atherosclerotic disease, and a similar pattern of onset. (Appendix A, Figure 10.5).

Table 5.9 Prevalence of atherosclerotic disease in sensitivity analyses

	Original analysis N=11,255		Possible Read codes in addition to definite N=11,255		Top 25% of consultation rates N=2,814		Bottom 25% of consultation rates N=2,814		Excluding patients without at least three years of pre-MI UTS follow-up N=10,302		Atherosclerotic disease diagnosed within UTS only N=9,909	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any atherosclerotic disease	**4,897**	**(43.5)**	**5,224**	**(46.4)**	**1,859**	**(66.1)**	**544**	**(19.3)**	**4509**	**(43.8)**	**3,551**	**(35.8)**
Coronary disease	**3,836**	**(34.1)**	**4,242**	**(37.7)**	**1,501**	**(53.3)**	**411**	**(14.6)**	**3540**	**(34.4)**	**2,680**	**(27)**
Stable angina	2,902	(25.8)	2,908	(25.8)	1,175	(41.8)	274	(9.7)	2673	(25.9)	1,912	(19.3)
Unstable angina	562	(5)	586	(5.2)	253	(9)	54	(1.9)	511	(5)	360	(3.6)
PCI or CABG	519	(4.6)	519	(4.6)	229	(8.1)	45	(1.6)	464	(4.5)	291	(2.9)
Heart failure	1,122	(10)	1,194	(10.6)	576	(20.5)	71	(2.5)	1031	(10)	771	(7.8)
Cardiac arrest	108	(1)	109	(1)	56	(2)	8	(0.3)	100	(1)	81	(0.8)
CHD not otherwise specified	2,265	(20.1)	2,921	(26)	936	(33.3)	201	(7.1)	2101	(20.4)	1,361	(13.7)
Other atherosclerotic disease	**2,356**	**(20.9)**	**2,407**	**(21.4)**	**999**	**(35.5)**	**194**	**(6.9)**	**2172**	**(21.1)**	**1,638**	**(16.5)**
Cerebrovascular disease	1,256	(11.2)	1,315	(11.7)	571	(20.3)	85	(3)	1160	(11.3)	834	(8.4)
Peripheral arterial disease	1,204	(10.7)	1,235	(11)	515	(18.3)	107	(3.8)	1116	(10.8)	823	(8.3)
Unknown atherosclerotic disease	**117**	**(1)**	**155**	**(1.4)**	**58**	**(2.1)**	**9**	**(0.3)**	**106**	**(1)**	**78**	**(0.8)**

MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CHD: coronary heart disease; UTS: up to standard.

5.6 Discussion

5.6.1 Main findings

Over half of first MIs represent the first clinical manifestation of atherosclerotic disease. The majority had at least one elevated cardiovascular disease risk factor or were being treated with a cardiovascular medication in the six months before MI; 7% of all MI patients had no previously diagnosed atherosclerotic disease or elevated risk factors in their medical record. Ours is the first study to quantify this proportion of MIs, which are completely without warning or unheralded by disease or cardiovascular disease risk factors.

There was also identified a clear premonitory period before MI, during which there was a rapid increase in the rate of coronary disease diagnosis and GP consultations for chest pain (in the group without diagnosed atherosclerotic disease). There were no increases in the rate of cerebrovascular or peripheral arterial disease during this time.

5.6.2 Comparison with other literature

5.6.2.1 Previous atherosclerotic disease

Previous estimates of the proportion of MI patients with previous angina or coronary disease were between 21% and 63%. The estimates of heralding by stable angina and coronary disease prevalence generated in the current study are comparable with these estimates (25.8% and 34.1%, respectively). The wide range of estimates in the literature reflects differences in timing of studies, their setting, the local prevalence of angina and risk factors, inclusion criteria and study design. The most comparable study to ours in terms of design was Yawn et al,[148] where the prevalence of physician-diagnosed pre-MI coronary disease was estimated in women. This was based on prospectively collected medical records in the US (1996-2001) and generated an estimate of 52% heralding by coronary disease. The estimate of heralding by coronary disease in women in the current study was 42%, but was based on several thousand more patients than Yawn's study, which included only 150 cases.

A comparison with studies reporting the baseline results of MI registry data showed equally wide-ranging estimates. For example, the Global Registry of Acute Coronary Events (GRACE) found 49% of STEMI patients and 67% of NSTEMI patients had previous angina,[152] compared to this study's estimates of 16% and 33%, respectively. Even the estimates of heralding by any coronary disease in this study are still far below the

prevalences described in GRACE patients. The difference may have been due to the retrospective nature of the data from GRACE and the definition of previous angina. However, a Scottish register of 2,887 MI patients[162] showed more similar results to the current study; 21.4% with angina compared to 26.4%.

The estimates generated for PAD and cerebrovascular disease are also comparable to those of GRACE (GRACE PAD prevalence: 8% in STEMI, 13% in NSTEMI, our estimates: 7% and 13%, respectively. GRACE cerebrovascular disease prevalence: 6% in STEMI, 10% in NSTEMI, our estimates: 7% and 13%, respectively).[152] Our overall results for all MI are also comparable to the Scottish study,[162] which found 7.6% with PAD and 10.4% stroke in their MI patients, which compares well to our prevalences of 11.1% and 11.7%, respectively.

This study extends these findings and is the first to estimate the proportion of patients with any form of pre-MI atherosclerotic disease and examine the onset and duration of specific disease subtypes before MI. Our estimate of 45% with previous atherosclerotic disease is comparable with the 51% of hospitalised patients with non ST-elevation acute coronary syndromes (unstable angina and MI) without any evidence of atherosclerotic disease in the CRUSADE registry.[145]

The results from this study regarding polyvascular disease are also in line with other published findings. In over 95,000 patients with unstable angina and NSTEMI in the CRUSADE registry, Bhatt and colleagues estimated the prevalence of disease in one vascular territory to be 38.3%.[163] Our estimate was slightly lower, at 31.1%. They found 11.2% of patients with disease at two sites and 1.6% at three sites; our estimates were 10.4% and 2.0%, respectively. Since the analyses in this thesis have shown that patients with STEMI have a lower atherosclerotic burden, and our estimates were for STEMI and NSTEMI combined, this could explain our lower estimates than those from CRUSADE, which was in NSTEMI alone.

Quantifying the burden of atherosclerotic disease before MI represents a step forward in our understanding of unheralded MI and in elucidating whether MIs truly occur in some patients without warning. It also highlights the importance of secondary prevention of cardiovascular disease. This study showed that a large proportion of patients with MI had previously diagnosed atherosclerotic disease and should have been receiving lipid lowering drugs and antiplatelets to reduce their risk of further vascular events, but only a third were in receipt of all three. The MIs included in these studies can be seen as ‘failures’ of secondary prevention.

5.6.2.2 Prodromal symptoms of MI

Prodromal chest pain symptoms before MI were described in the 1970s by Harper[164] and Stowers & Short,[165] who both showed a steep increase in ischaemic symptoms in the four weeks before MI. These studies were based on retrospective data from MI survivors and therefore ours is the first study to quantify, in detail and without recall bias, the increase in coronary disease diagnosis and chest pain before MI. We also showed the increase in all-cause consultations in the prodromal period, and that this was equivalent to 4% of patients consulting per day in the years prior to MI, with an increase only to 12% in the day before MI.

As this was a case-only analysis, the results cannot show whether such patients are identifiable from the large numbers of patients who consult with chest pain (or for any cause) or are newly diagnosed with coronary disease in general practice every day, and there are few public health implications of this analysis. However, Ruigomez[166] examined the incidence of ischaemic heart disease (IHD) in the year following a first chest pain consultation in the GPRD and found that patients with unspecific chest pain were eighteen times more likely to develop IHD than control patients without chest pain. Patients with chest pain who developed IHD were older, more likely to be male and had a worse cardiovascular disease risk profile. These findings suggest that further investigation is warranted in MI patients who have previously presented with chest pain or recent angina to characterise the short term risk of coronary events in such patients. Further research could also identify patients for whom this is a remediable premonitory period.

Many studies have examined whether coronary symptoms occurring shortly before MI confer a survival advantage.[29, 31, 33, 167] The ischaemic preconditioning theory suggests that pre-MI coronary symptoms may condition the myocardial tissue to ischaemia, so that during MI the myocardial tissue is preserved leading to smaller infarcts and better outcomes.[30, 168] This was the subject of investigation in Chapter 6.

5.6.2.3 Risk factor burden

Our estimate of the risk factor burden in MI patients is consistent with other studies, showing that MI patients overall tend to have one or more elevated traditional cardiovascular disease risk factors.[159, 169, 170] In this study the recorded burden of risk factors in patients unheralded by diagnosed atherosclerotic disease was lower than for those heralded. However, those without diagnosed atherosclerotic disease tended to be younger than those

without disease, providing less time for increased cardiovascular disease risk and while the prevalence cardiovascular disease risk factors was lower in this group, over a third were current smokers, nearly half were hypertensive and many also had diagnosed diabetes or dyslipidaemia. These are key cardiovascular disease risk factors, which indicate raised risk and show that there are targets for prevention in most patients, not least for smoking.

There could be some bias in the recording of cardiovascular disease risk factors in patients with and without prior atherosclerotic disease. Patients with diagnosed disease consult more frequently in general practice and have known atherosclerotic disease, and so the opportunity and motivation exist for close monitoring of risk factors. Conversely, those without disease have fewer opportunities for risk factor measurement. In this analysis, the frequency with which individual risk factors were measured in patients with and without disease was not examined. Further still, the levels of management and treatment of cardiovascular disease risk between both groups were not compared. Therefore, patients without prior atherosclerotic disease could represent a group in which there are many missed opportunities for care either due to:

(i) Fewer GP consultations and less opportunity for identification of raised risk;
(ii) Differences in frequency of vascular disease risk factor measurement; or
(iii) Differences in intensity of treatment.

A comparison with healthy controls is required to understand if and why risk factors are not measured and to find ways of identifying patients at high risk of unheralded MI. Given the large proportion of patients in this study whose first atherosclerotic disease manifestation was MI, this highlights the need for assessment and good quality management of vascular disease risk in primary care. However, such patients must be identified by the GP from all of the patients without atherosclerotic disease, which represents a challenge. Therefore, further work to identify patients at high risk, based on other characteristics or levels of cardiovascular disease risk, is essential in reducing the burden of MI.

5.6.2.4 Out of the blue MI

7.2% of first MI patients had no previously recorded diagnosed atherosclerotic disease or raised cardiovascular disease risk. To our knowledge, no studies have previously estimated this proportion. Patients who had MI without warning were more likely to be men between 50 and 70 years of age. Fewer women had MI without warning and those who did tended to be older.

It is widely thought that patients experiencing MI without warning are men who fail to visit their GP despite having truly elevated risk or symptomatic disease. To some extent this may be true: the rate of consultation in patients with MI without warning was lower than in those with diagnosed disease or known elevated cardiovascular disease risk, and was lower in men than women. Although there were *fewer* opportunities for measurement of risk prior to MI without warning, the median number of consultations in the year prior to MI was just 2 fewer than in patients with elevated cardiovascular disease risk (5 in MI without warning versus 7 in those with known raised risk). This shows that in the majority of patients, there were likely to be opportunities for cardiovascular disease risk to be measured. However, in this study the measurement of cardiovascular disease risk in primary care and the reasons that these patients consulted in the year prior to MI were not examined. This is an important area of further research: to identify patients who are at risk of MI without warning could add aid risk prediction.

5.6.2.5 Non-atherosclerotic causes of MI

While it is thought that few MIs occur in patients with normal coronary arteries,[171] various non-atherosclerotic causes of MI have been suggested,[172-174] including clotting abnormalities, coronary vasospasm, dissection, emboli, infections and inflammatory disorders. These cannot be explored in the current data, but may be responsible for a proportion of MIs occurring without warning.

5.6.3 Strengths

Our study was large and based on over 11,000 cases of MI. The confidence interval for our estimate was small and indicated that the true proportion of hospitalised MI patients with previously diagnosed atherosclerotic disease lay between 43.9 and 45.6%. Most large studies of MI recruit patients at the time of MI and enquire retrospectively about previous atherosclerotic disease and risk factors. A major strength of this study is that the data were collected prospectively for many years prior to MI. This provided the detail to examine the onset and type of atherosclerotic disease and its treatment before MI. It also had the benefit of avoiding errors in recall.

The three databases used in this analysis have been validated and shown to be of high quality (Chapter 2, Chapter 4). MINAP data are subject to annual checks in data

quality; the most recent assessments showed that completeness and validity were high in key fields.[175] HES also undergoes extensive validation of codes and checks for completeness.[176] The GPRD has been used extensively in research and a wide range of diagnoses, including MI and other atherosclerotic disease outcomes, have undergone validation.[53, 59, 62, 64, 65, 68, 177-182] As discussed in Chapter 2 (Data sources), the GPRD has stringent data quality controls at the patient and practice level, and provides researchers with UTS dates within which the data are of suitable quality for research. Additional quality improvement in the GPRD has been driven by the Quality and Outcomes Framework[183] (QOF) introduced in 2004, which aimed to improve the quality of care in general practice and has improved collection of data, particularly regarding cardiovascular disease.

Aspects of the linkage quality are examined in Chapter 4 but showed that the patients included in these linked data are representative of the sources from which they came.[143] Our cases were therefore representative of all hospitalised MIs in the UK and were based on the international definition of MI in MINAP[6] and on widely used ICD-10 codes in HES. MINAP data hold information from all NHS hospitals in England and Wales and HES collects data from all English hospitals. In addition, the GPRD has been shown to be representative of the UK population.

All of our MI cases had at least one year of pre-MI UTS follow-up. Some studies have indicated that one year is insufficient for the GP to record prevalent diagnoses in new patients. A sensitivity analysis extending this criterion to three years had no effect on the overall atherosclerotic disease prevalence before MI. Therefore, one year was sufficient time in which to record prevalent diagnoses in the majority of patients. Indeed, the median duration of follow-up was 8.7 years (IQR 5.5-13.5), which far exceeds even this more stringent three year requirement. Additionally the duration of primary care registration was very similar in patients heralded and unheralded by diagnosed disease, indicating that the absence of atherosclerotic diagnoses in unheralded patients was not due to inadequate time in follow-up.

Over a quarter of the patients with atherosclerotic disease were first diagnosed before the GPRD UTS period began. To examine the possibility that this introduced error into our description of the onset of disease, a sensitivity analysis was performed excluding these patients. The patterns in the onset of different types of atherosclerotic disease were unchanged in this analysis.

Our estimates of heralding were based on GPRD Read codes rated as 'definite' indicators of atherosclerotic disease. A sensitivity analysis was performed to examine whether the addition of codes rated as 'possible' would affect our estimates. The proportion heralded increased only by a few percent, indicating that the codes rated as 'definite' had high sensitivity. Use of ICD-10 codes in defining HES MI was also examined: nearly all were recorded with I21 ("Acute MI"), and of those recorded with I22 ("Subsequent MI") or I23 ("Certain current complications following acute MI"), most were also recorded as acute MI in MINAP. Therefore, the rating and choice of MI codes were adequate.

5.6.4 Weaknesses

This study only included cases that reached hospital. Approximately one third of MI cases die before reaching hospital[184] and our study was therefore biased towards patients who survived. Our results are therefore not generalisable to patients who die before reaching hospital. The four source comparison of the capture of MI across GPRD, HES, MINAP and ONS has subsequently shown that each of the four data sources contributed valid MI events. However, this study was performed before those data were analysed, when it was considered that including cases recorded only in ONS or GPRD would bring concerns about the acute nature of the MIs and of their exact timing. This would have affected our interpretation of the duration and onset of heralding diagnoses and chest pain consultations prior to MI.

Patients in this study were followed up through the electronic health records from primary care. Therefore, diagnoses could only be made if patients attended the practice or a hospital and disclosed symptoms or underwent tests. Despite a similar time in follow-up, patients with and without atherosclerotic disease had widely different average annual consultation rates (heralded by atherosclerotic disease 8.8 consultations per year, unheralded 4.8 consultations per year). Some researchers choose to implement a minimum consultation rate to reduce the chances of misclassification in patients who consult less frequently (as infrequent consulters are less likely to receive diagnoses). In our study, this would have a large effect on the results. A sensitivity analysis showed that the proportion heralded was 19.3% in the low consultation rate group and 66.1% in the higher consultation group. These results can be interpreted in two ways: either some symptomatic atherosclerotic disease was missed in those who consulted less frequently, or they were a truly healthier group of patients with no cause to consult. Due to the seriousness of atherosclerotic disease, patients are likely to consult if they are symptomatic, and therefore a minimum consultation rate was

not introduced in this analysis. The exclusion of patients without any consultations prior to MI would have made little impact on the results (n=14).

The GPRD does not routinely collect data on behavioural factors including diet, alcohol intake and exercise which, if measured, may have indicated increased cardiovascular disease risk and reduced the proportion of patients who had MI 'without warning'. This is a limitation of the data but these factors are not routinely incorporated into cardiovascular disease risk scores and so are likely to contribute less to a patient's overall cardiovascular disease risk than the risk factors included. Additionally, identifying patients with only poor diet or exercise alone is of limited use as GPs are unlikely to intervene unless a more traditional cardiovascular disease risk factor was raised (e.g. patient became overweight, hyperlipidaemic or hypertensive). The absence of lifestyle data is a drawback to using routinely collected records rather than data from researcher-led studies, but the opportunities for research on a large scale and the relevance of these results to routine clinical care outweigh this disadvantage.

5.6.5 Implications

The British Heart Foundation estimates that there are 124,000 MIs in the UK per year.[14] If 70% of these are first MIs,[15] and 56% of these are unheralded by previous atherosclerotic disease, then there may be up to 50,000 unheralded MIs per year. This represents a significant burden, both financially and in terms of morbidity, and strengthens the need for primary prevention in primary care. The results in this study also emphasise the need for secondary prevention after diagnoses in the coronary, cerebrovascular or peripheral arteries.

5.6.6 Further research

A research priority is a comparison of patients who experience MI without prior atherosclerotic disease (or without warning) to the general population. This may elucidate novel risk factors for MI. Over half of first MIs occur without previous disease and these contribute significant morbidity and financial burden to the healthcare system. Understanding why some patents with or without elevated risk factors have MI and others do not is of importance in reducing this burden. Further research into the prodromal period before MI and the possibility of reducing the risk of MI in patients who consult for new

coronary disease or chest pain could also be of value. A second priority is determining whether the premonitory symptoms experienced shortly before MI represents a period potentially of remediable risk.

5.6.7 Conclusion

This aim of this thesis was to gain an improved understanding of MI that occurs as the first manifestation of disease; the first step was therefore to examine the evolution, prevalence and timing of different atherosclerotic disease subtypes and risk factors before MI. This was the first study to prospectively evaluate the onset of coronary, cerebrovascular and peripheral arterial atherosclerotic disease, risk factors and chest pain symptoms before first MI.

Nearly half of first MIs were preceded by diagnosed atherosclerotic disease and for most patients this has been recognised for many years. This implies that there is often a long period during which the GP can intervene with effective secondary prevention measures.

For the other half of first MI patients, the MI was the first manifestation of atherosclerotic disease. Nearly all of these patients had recognised elevated cardiovascular disease risk, but very few reported symptoms to the GP prior to MI. The challenge now remains to characterize differences between these MI patients and the general population who do not have MI, and to identify any missed opportunities in the management of patients with recorded raised risk.

5.7 Chapter summary

- No large study has previously evaluated the occurrence of atherosclerotic disease, cardiovascular disease risk factors and cardiovascular medication prescription prior to first MI using prospectively collected data.

- Patients with first MI were identified in MINAP and HES. The prevalence and timing of previous atherosclerotic disease, major cardiovascular disease risk factors and cardiovascular drug prescriptions were assessed.

- Half of MI patients had a previous diagnosis of atherosclerotic disease and there was a prodromal period prior to MI in which the rate of coronary diagnoses and chest pain consultation was increased.

- MI occurring without prior coronary, cerebrovascular or peripheral arterial disease, risk factors or symptoms was uncommon, in just 7% of patients.

Chapter 6 Effect of ischaemic manifestations prior to myocardial infarction

6.1 Summary

This chapter describes an investigation into new and existing ischaemic atherosclerotic disease presentations and chest pain prior to first MI and their effects on MI type and mortality.

6.2 Literature review

6.2.1 Introduction

Ischaemic preconditioning describes the phenomenon by which brief episodes of ischaemia prior to a prolonged ischaemic insult can lead to smaller infarct size, first described in 1986 by Murry[25] under experimental conditions. Since this groundbreaking study, ischaemic preconditioning has been hailed as the "most powerful experimental method of delaying the onset of myocardial necrosis known so far"[33] and has been shown beyond doubt to occur in humans.[185] There is a substantial body of published research investigating the occurrence, mechanisms and outcomes of ischaemic preconditioning and the topic has been extensively reviewed. As discussed in Chapter 1, many studies have investigated naturally occurring angina prior to MI as a clinical correlate to ischaemic preconditioning.[27, 186]

The following sections review the evidence to date regarding the effects of atherosclerotic disease and chest pain prior to MI on infarct size, presentation and clinical outcomes. Since the focus of this thesis is MI as the first manifestation of atherosclerotic disease, the review focused on studies assessing the effects of angina prior to first infarction.

6.2.2 The evidence to date

6.2.2.1 Search strategy

There have been several published reviews of the occurrence and effects of preinfarction angina. A brief search was conducted in the MEDLINE database to identify review articles examining the natural ischaemic preconditioning effect of preinfarction angina. Search terms for this were "Ischemic preconditioning" (as an exploded Medical Subject Heading), but restricting to review articles in humans and written in the English language. This search, performed in September 2010, generated 783 results. Titles were reviewed and full text of potentially relevant papers was sought.

None of these reviews were systematic and none focused on patients with first MI. Therefore, a systematic literature search was performed to identify studies examining outcomes of patients with first MI.

A literature search was completed in the English language medical literature (MEDLINE and EMBASE) for studies examining ischaemic preconditioning and

preinfarction angina. Search terms are described in Appendix A, Table 10.20. The search was initially conducted in January 2011 and repeated in September 2012 to identify any recently published studies. Studies were included if they fulfilled the following criteria:

1. Naturally occurring ischaemia exposure (experimentally-induced ischaemia as an exposure was excluded) prior to first MI;
2. Study in humans;
3. Manuscript written in English language;
4. Outcomes investigated included: infarct size, severity, post-MI cardiac or all-cause mortality.

Titles and abstracts of the 1017 studies identified in the initial search were screened for relevance. Any studies deemed to be relevant were obtained as full text and were assessed with respect to the inclusion criteria. To ensure that no relevant studies were missed, the reference lists of all included studies were examined.

6.2.3 Results

Twenty eight studies were identified that examined the effects of previous angina on MI size, severity or subsequent mortality. These were published between 1998 and 2011, with between 22 and 4,166 first MI patients and a total of 11,703 patients. The prevalence of 'preinfarction angina' ranged from 21%[187] to 67%,[188] (median 49%). The studies came from a large range of geographical regions, including Europe, North America, South America, the Middle East and Asia.

6.2.3.1 The effect of preinfarction angina on infarct size

There is good overall evidence for a protective effect of preinfarction angina on infarct size, as measured by peak creatine kinase (CK) and other techniques. This was the conclusion of several review papers of preinfarction angina and ischaemic preconditioning[186, 189] and has been reported in eighteen studies of patients with first MI (Table 6.1). Key studies reporting these effects are described below, by the type of angina exposure that was examined (chronic angina versus new onset angina).

Chronic angina

Three studies reported effects of chronic angina and all described a protective effect of angina on infarct size.[147, 149, 187] Romero-Farina identified 131 patients with a history of MI and reported a smaller necrotic zone in patients with chronic angina (of more than a month's duration) prior to their MI (% necrosis 4.5 ± 8.8% in those with angina, 11.4 ± 11.9% in those without angina, P=0.002).[187] However, this analysis was performed in patients who had survived for one to ten years after their MI and who had reduced systolic function. It therefore represents a highly selected group of patients who are unlikely to be representative of MI patients overall.

Anzai reported the effects of chronic or prodromal angina on infarct size, and found a beneficial effect of this combined exposure on peak creatine kinase levels in patients with anterior and inferior MI (peak CK level lower in angina, P<0.03).[149] This was a slightly larger study (N=291) and the only inclusion criteria were (i) reaching hospital with a MI diagnosis and (ii) the ability to provide a detailed clinical history. While this study population is much less selected than the smaller study described above, these criteria would have excluded patients who died before reaching hospital or in the emergency room and therefore are unlikely to be representative of the general population experiencing their first

MI. Kobayashi also reported lower peak CK levels in patients with previous chronic or prodromal angina prior to MI compared to patients with no previous angina, in a much larger study of 1,637 patients.[147]

In all of these studies, baseline characteristics of patients with and without previous angina were tabulated. In the studies of Anzai and Romero-Farina, there were no differences in baseline characteristics, indicating that the differences shown in infarct size were unlikely to be driven by differences in cardiovascular disease risk factors or use of beta blockers, angiotensin converting enzyme inhibitors (ACEI) or calcium channel blockers prior to MI.[149, 187] However, these two studies may have been too small to show differences in baseline characteristics - in Kobayashi's larger study, there were differences in sex, hypertension, and hypercholesterolaemia between those with and without previous angina. Since infarct size was not an outcome of interest, an adjusted analysis was not performed and the observed differences in infarct size may have been due to differences in vascular disease risk. Additionally, each of these studies was based on retrospective angina data and therefore subject to error in recall.

New onset prodromal angina

Fifteen studies investigated the effects of new onset or prodromal angina shortly before MI, with exposure definitions ranging from angina in the 24, 48 or 72 hours before MI, to new onset angina in the one month before MI. Thirteen of these studies described a beneficial effect of prodromal angina on infarct size; two showed no effect. The studies described below are those in which the main focus of the analysis was to report the effects of previous angina on infarct size.

Ottani (1995) reported infarct size as a primary outcome, and showed that of 25 hospitalised first MI patients, the 12 with prodromal angina, defined as angina within 24 hours or infarct, had lower CK-MB release indicating smaller infarcts (86.3 ± 66 IU/L in those with angina, 192.3 ± 108 IU/L in those without angina, $P<0.01$).[37] The investigators estimated that angina afforded a protection of 33% on infarct size (95% CI 7.1-58.9%). However, this study was performed in a small and highly selected group of patients, who had undergone thrombolysis, were reperfused within 90 minutes and had a patent infarct-related artery. These inclusion criteria were chosen to mimic experimental conditions, so the effect of angina on MI shown here is unlikely to be representative of that in a general population.

In a second study published a decade later, Ottani (2005) reported a beneficial effect of prodromal angina in 22 hospitalised first MI patients undergoing primary percutaneous coronary intervention (PPCI).[190] The twelve patients who experienced angina in the 24 hours before infarct had a lower QRS score (measure of infarct size) at 7 days than those without angina (score=4.5 ± 2.5 in those with angina, 6.5 ± 2.4 in those without angina, P=0.07). This was a small study restricting to patients undergoing PPCI and investigated whether the beneficial effect observed in thrombolysed patients (in the 1995 study) was due to ischaemic preconditioning rather than faster thrombolysis in patients with previous angina. Nevertheless, this study lends support to the body of evidence that angina prior to MI has a protective effect on infarct size.

Yamagishi (2000) analysed the effect of preinfarction angina occurring in the 72 hours before MI on subsequent myocardial injury, as measured by resting ^{123}I-BMIPP and ^{201}TI myocardial SPECT up to one month after MI. Peak CK levels were lower in patients with angina (P=0.02), and previous angina was associated with a decreased necrotic area.[38] Baseline characteristics of patients with and without prior angina were compared and shown to be similar between the groups, so were unlikely to confound the associations observed. This was one of the larger studies assessing infarct size (n=136) but was conducted in hospitalised patients who had survived the acute phase of MI.

In a study of hospitalised MI patients in Japan, there was no effect of prodromal angina occurring in the 2 to 48 hours prior to infarct, as measured by peak CK (22.1 ± 9.2 UI/L in patients with angina, 40.0 ± 33.3UI/L in patients without angina, P=0.1). However, there was a trend towards smaller infarct size in the group with angina, but the study may have been underpowered: despite data collection from 26 sites in Japan, just 25 patients were included in this study because the inclusion criteria were so extensive, leading to a small and highly selected group of patients.[191]

Finally, Iglesias-Garriz reported the effect of angina in the 24 hours before MI on infarct size in 116 hospitalised patients without diabetes who had undergone angioplasty.[192] This study showed a beneficial effect of angina on the necrotic region, but no effect on peak CK-MB concentrations. Baseline cardiovascular disease risk factors in the groups with and without angina were tabulated and shown to be similar. Therefore, differences in infarct size are unlikely to be confounded by cardiovascular disease risk factors. However, no assessment was made of prior cardiovascular drug use, which may have been different in patients with and without previous angina, and could have affected infarct size.

All of these studies used retrospectively collected exposure data and therefore may be subject to error and recall bias. None of these studies were designed to show the effect of prodromal or chronic angina on outcomes in a general population setting, but to prove the concept of ischaemic preconditioning and identify possible mechanisms through which preinfarction angina might act. Nearly all of the studies had strict inclusion criteria and therefore what the effect would be in an unselected cohort is unclear. Additionally, none of these studies compared the effects of angina at different times prior to MI.

Table 6.1 Effects of previous angina on infarct size, as measured by peak creatine kinase, size of necrotic area or QRS score at risk in patients with first MI

Author, year	Country	MI patients included	Angina definition	N MI patients	N (%) exposed	Peak CK (IU/l) in patients +/- angina*	Effect of angina on infarct size
Anzai, 1995[149]	Japan	Hospitalised first Q wave anterior wall MI	Chronic and prodromal; new onset <1 month, chronic & worsening pattern <1 month, chronic stable angina >1 month	291	117 (61%)	Anterior infarct + 1824 ± 1458 - 2819 ± 2515 Interior infarct: + 1315 ± 1230 - 1934 ± 1303	Smaller infarct, P<0.016 for anterior, P=0.028 for inferior
Ottani, 1995[37]	Italy	Hospitalised MI patients with thrombolysis	Prodromal; typical angina occurring at rest within 24 hours of infarct, or complete absence of symptoms	25	12 (48%)	+ 86.3 ± 66 - 192.3 ± 108	Smaller infarct, P<0.01
Kobayashi, 1998[147]	Japan	Hospitalised first MI	Chronic and prodromal; stable or unstable angina	1637	1032 (63%)	+ 2790 ± 2842 - 3288 ± 3037	Smaller infarct, P<0.01
Napoli, 1998[193]	Italy	Hospitalised first Q wave MI with thrombolysis <65 years	Prodromal; new onset angina in the 48 hours preceding MI	90	48 (53%)	+ 976 ± 168 - 1612 ± 328	Smaller infarct, P<0.05
Noda, 1999[191]	Japan	Hospitalised first MI in left anterior descending artery with PTCA	Prodromal; new onset angina 2-48 hours before onset	25	11 (44%)	+ 22.1 ± 9.2 - 40.0 ± 33.3	NS, P=0.10
Inoue, 1999[194]	Japan	Hospitalised inferior MI, total occlusion of right branch and successful angioplasty within 24hrs	Prodromal; angina pectoris in 24 hours prior to MI	75	18 (24%)	+ 1294 ± 188 - 1836 ± 136	Smaller infarct, P=0.04
Yamagishi, 2000[38]	Japan	Hospitalised MI undergoing imaging	Prodromal; chest pain in 72 hours before onset of MI	136	48 (35%)	+ 2504 ± 1745 - 3518 ± 2550	Smaller infarct, P=0.02
De Felice, 2001[195]	Italy	Hospitalised first Q wave MI with thrombolysis	Prodromal; chest pain in 7 days prior to MI	90	Not stated	+ 1865 ± 1562 - 2630 ± 1360	Smaller infarct, P=0.002
Abe, 2002[188]	Japan	Hospitalised first anterior wall MI	Prodromal; angina within 48 hours	36	24 (67%)	+ 2747 ± 1939 - 4891 ± 2639	Smaller infarct, P<0.05
Colonna, 2002[196]	Italy	Hospitalised first MI	Prodromal; angina in the 7 days preceding MI	51	25 (49%)	+ 5994 ± 2820 - 9831 ± 5859	Smaller infarct, P=0.005
Papado-poulos, 2003[197]	Greece	Hospitalised NSTEMI patients without known history of CHD, < 75 years	Prodromal; angina in the last 48 hours before MI - separated into those occurring <12 hours	40	22 (55%)	+ 48 ± 28 - 116 ± 81	Smaller infarct, P<0.003
Tomoda, 2004[198]	Japan	Hospitalised STEMI	Chronic and prodromal; ≥1 occurrence of chest pain in 24 hours before MI, or angina >24 hours before MI	613	166 (27%)	+ 3500 ± 2625 - 3937 ± 2727	NS, P=0.30
Iglesias-Garriz, 2005[199]	Spain	Hospitalised first STEMI patients treated with primary coronary angioplasty, no valvular disease, post infarct angina,VF/VT, diabetes	Prodromal; angina in the 24 hours prior to infarct	78	32 (41%)	+ 343 ± 256 - 353 ± 256 P=0.859	Smaller infarct as measured by % necrotic area, P=0.033
Ottani, 2005[190]	Italy	Hospitalised first anterior MI, treated with PCI	Prodromal; new onset angina in the 24 hours prior to infarct	22	12 (55%)	QRS score at 7 days*: + 4.5 ± 2.5 - 6.5 ± 2.4	Smaller infarct, P=0.07
Tamura, 2006[200]	Japan	Hospitalised first anterior wall ST-elevation MI	Prodromal; typical chest pain within 48 hours of onset of MI	142	70 (49%)	+ 3652 ± 2440 - 5507 ± 3058	Smaller infarct, P=0.0002
Mladenovic, 2008[201]	Serbia	Hospitalised first uncomplicated single vessel MI	Prodromal; History of angina within 2 months, except for within 24 hours	46	27 (59%)	+ 193.6 ± 108.8 - 281.8 ± 171.4	Smaller infarct, P=0.039
Romero-Farina, 2008[187]	Spain	Patients with a history of MI	Chronic; chronic angina prior to MI	131	27 (21%)	% necrosis* + 4.5 ± 8.8 - 11.4 ± 11.9	Smaller infarct, P=0.002
Takeuchi, 2011[202]	Japan	Hospitalised first anterior STEMI undergone successful reperfusion therapy, imaging within a week, total or subtotal occlusion of left anterior descending artery	Prodromal; typical chest pain episodes within 48 hours	125	60 (48%)	Normotensives: + 2904 ± 1693 - 4979 ± 2471 Hypertensives: + 2885 ± 2215 - 5278 ± 2801	Smaller in normotensives, P<0.05, not smaller in hypertensives, P>0.05

*Peak CK was used to measure infarct size, except where noted. MI: myocardial infarction; CHD: coronary heart disease; PTCA: percutaneous transluminal coronary angioplasty; VF: ventricular fibrillation; VT: ventricular tachycardia; STEMI: ST-elevation MI: NSTEMI: non ST-elevation MI; PCI: percutaneous coronary intervention.

6.2.3.2 The effect of preinfarction angina on infarct severity

The effect of preinfarction angina on infarct severity as measured by ST-elevation and the appearance of Q waves at ECG have been reported in six studies of first MI (Table 6.2), although no studies focused their analysis on these outcomes and none performed multivariate analyses.

One study examined the effect of chronic angina alone on the appearance of Q waves at MI.[150] Over 4,000 patients who survived to seven days and were eligible for recruitment into the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) were included in the study. A history of chronic angina was associated with more Q waves at MI ($P<0.001$). However, this was in a crude analysis and the study reported important differences between patients with and without previous angina in terms of age, sex, diabetes and hypertension prevalence, so the association may be confounded by background vascular disease risk.

Two further studies examined the effect of chronic angina and new onset angina on the appearance of Q waves. In a Belgian study of 732 hospitalised, unthrombolysed first MI patients, there were no differences in the proportion of patients with non-Q wave MI in those with and without angina.[151] In a subsequent study a decade later in 1,637 first MI patients, findings were similar, although important differences were reported between the angina groups with respect to cardiovascular disease risk.[147] Based on the different associations described here and the absence of multivariate analysis, the effects of previous chronic angina on MI severity are unclear. These studies suggest that the *new onset* angina may be driving benefits in infarct severity and that *chronic angina* alone is associated with poorer outcomes. However, in studies of only *new onset* angina in the 7 days or 24 hours before infarct, the reported effects are also inconsistent, with effects in different directions.

In a small study of 25 highly selected MI patients (described in section 6.2.3.1), Ottani (1995) showed a trend towards fewer Q waves in patients with prodromal angina in the 24 hours prior to MI, but no effect on ST-elevation. This study may have been too small to show a real effect of prodromal angina because as in a slightly larger study of 75 MI patients, there was good evidence for a beneficial effect of prodromal angina in the same time period on ST-elevation.[194] Similarly, in a study of 90 patients, chest pain in the seven days prior to MI was associated with fewer Q waves ($P=0.002$).[195] This evidence, along with evidence from review articles suggest that preinfarction angina is associated with fewer Q waves and less ST-elevation in patients with MI.[168]

Table 6.2 Studies reporting the effect of previous angina on infarct severity, as measured by ST-elevation or appearance of Q waves at electrocardiogram (ECG)

Author, year	Country	MI patients included	Angina definition	N MI patients	N (%) exposed	Effect of exposure
Pierard, 1988[151]	Belgium	Hospitalised first MI, no thrombolysis	Chronic and prodromal; chronic >1 month or new onset <1 month	732	447 (61%)	No effect
Behar, 1992[150]	Israel	Trial population of hospitalised first MI who survived 7 days	Chronic; angina >1 month	4,166	1,801 (43%)	More Q wave MI, P<0.0001
Ottani, 1995[37]	Italy	Hospitalised first MI patients with thrombolysis	Prodromal; angina ≤ 24 hours prior to MI	25	12 (48%)	No effect on ST-elevation, trend towards fewer Q waves P=0.1
Kobayashi, 1998[147]	Japan	Hospitalised first MI	Chronic and prodromal ; stable or unstable angina	1,637	1,032 (63%)	More non-Q wave MI in angina group, P<0.01
Inoue, 1999[194]	Japan	Hospitalised first inferior MI with total occlusion of right branch and successful angioplasty within 24 hours	Prodromal; angina ≤ 24 hours prior to Mi	75	18 (24%)	Less ST segment elevation, P<0.01
De Felice, 2001[195]	Italy	Hospitalised first Q wave MI with thrombolysis	Prodromal; chest pain ≤7 days prior to MI	90	Not stated	Fewer Q waves, P=0.002

Table 6.3 In-hospital cardiac mortality in patients with first myocardial infarction (MI)

Author, year	Country	MI patients included	Timing of angina exposure before MI	Exposure assessment	N MI patients	N (%) exposed	Outcomes assessed	Was multivariate analysis performed?	Effect of exposure
Anzai, 1995[149]	Japan	First Q wave MI only	Chronic or prodromal	Retrospective	291	189 (61%)	In-hospital cardiac death	Yes - beta adrenergic and calcium antagonists	Protective on in-hospital cardiac mortality RR=1.56 p=0.049
Kobayashi, 1998[147]	Japan	Hospitalised MI	Chronic or prodromal	Retrospective	1,637	1,032 (63%)	In-hospital death due to: • cardiogenic shock/CHF • arrhythmias, • cardiac rupture	No	No crude effect seen for cardiogenic shock/CHF or arrhythmias. Angina was protective on death due to cardiac rupture, P<0.01

RR: rate ratio; CHF: congestive heart failure.

6.2.3.3 The effect of preinfarction angina on in-hospital mortality

Studies examining in-hospital mortality were separated into those reporting effects on cardiac death and those reporting effects on all-cause mortality. If preinfarction angina were to have any effect on mortality through ischaemic preconditioning or collateral channels, it would most likely be restricted to (or stronger in) cardiac mortality.

In-hospital cardiac mortality

In patients hospitalised with first MI, two studies examined the effects of preinfarction angina on in-hospital cardiac death (Table 6.3). In a study of 291 patients with Q wave MI, the 189 who had ever experienced previous angina were protected against cardiac mortality at multivariate analysis: those without angina were at increased risk (RR=1.56, P=0.049).[149] This analysis was adjusted for cardiovascular disease risk factors and the use of beta blockers, ACEI and calcium channel blockers prior to MI. Cardiovascular medications given in response to chest pain symptoms or high cardiovascular disease risk may negate the effect of ischaemic preconditioning and the effects of these have not been addressed in most other studies.

In a larger study of 1,637 patients, no effect of previous angina was seen for in-hospital death due to cardiogenic shock, congestive heart failure or arrhythmias, although there was some crude effect of previous angina on death due to cardiac rupture ($P<0.01$),[147] which alone drove an association with overall in-hospital mortality. No adjusted analysis was performed to examine independent predictors of cardiac mortality in this study.

Both of these studies were based on hospitalised MI patients who were not highly selected for inclusion, and therefore are more representative of all hospitalised MI patients in their respective countries. However, as above, angina data were collected retrospectively and therefore may be subject to error.

In-hospital all-cause mortality

Six studies examined all-cause in-hospital mortality (Table 6.4). Behar examined the effects of chronic angina alone compared to no angina in a large group of hospitalised MI patients (n=4,166), and showed an adverse effect on mortality in a crude analysis (OR=1.30 (95% CI 1.10-1.53)); no multivariate analysis was performed and this effect may

have been attenuated if it had been adjusted for the substantial differences observed between patients in terms of cardiovascular disease risk. This study was in a highly selected population of patients who survived for seven days and were recruited into a trial. Therefore, the effects of chronic angina in general populations are unclear.

Two studies assessed the joint effects of chronic and prodromal angina. Pierard reported no differences in in-hospital mortality compared to patients with no angina in a crude analysis of 732 patients. A larger and more recent study in 1637 patients, which performed a well-adjusted analysis (including demographic variables, cardiovascular disease risk factors and previous atherosclerotic disease), reported lower mortality in the group with angina (OR=0.665, P=0.014). The differences observed for chronic angina compared to chronic &/or prodromal angina may be the result of the different exposure definitions, but could also be related to use of thrombolysis in the studies. It has been suggested that the beneficial effects of ischaemic preconditioning only occur in reperfused myocardium; Behar and Pierard both performed studies in the pre-thrombolytic era, which could explain the lack of beneficial effects.

Of the three studies examining the effect of prodromal angina on mortality, only one performed a multivariate analysis[203] and found some evidence for lower mortality in the group with angina, although this failed to reach significance (OR=0.44 (95% CI 0.16-1.17) p=0.09). The two other studies showed no effect but the low numbers of fatalities in these studies meant that they were likely to be underpowered to demonstrate an effect.

Table 6.4 In-hospital all-cause mortality in patients with first myocardial infarction (MI)

Author, year	Country	MI patients included	Timing of pre-MI angina exposure	Exposure assessment	N MI patients	N (%) exposed	Outcome assessed	Was multivariate analysis performed?	Effect of exposure
Pierard, 1988[151]	Belgium	Hospitalised first MI, unthrombolysed	Chronic and new onset; chronic >1 month, new onset <1 month	Retrospective	732	200 chronic, 247 new onset (61%)	In-hospital all-cause	No	No effect of chronic and new onset angina.
Behar, 1992[150]	Israel	Hospitalised first MI surviving to seven days, included in the SPRINT trial	Chronic; angina for >1 month	Retrospective	4,166	1791 (43%)	In-hospital all-cause	No	Worse mortality in angina group OR=1.30 (95% CI 1.10-1.53)
Kobayashi, 1998[147]	Japan	Hospitalised MI	Chronic and new onset	Retrospective	1,637	1032 (63%)	In-hospital all-cause	Yes - age, sex, risk factors, previous atherosclerotic disease	Lower mortality in the angina group: adjusted OR=0.665, P=0.014.
Papadop-oulos, 2003 275[204]	Greece	Hospitalised first NSTEMI aged ≤75, without prior CAD, CHF, collateral circulation	Prodromal; 'Late' angina ≤12 hrs, 'early' angina within 12-48 hours of admission	Retrospective	66	12 'early' (18%) 16 'late' (24%)	In-hospital all-cause	No	No effect of 12 hour or 48 hour angina.
Tomoda, 2004[198]	Japan	Hospitalised first STEMI undergoing primary PCI <6hrs after onset	Prodromal; angina in 24 hours of infarct	Retrospective	202	59 (29%)	In-hospital all-cause	No	No effect of previous angina, mortality in patients with angina: 8.5% and without angina: 8.4%, P=0.85
Ishihara, 2005 150[203]	Japan	Hospitalised first anterior MI undergoing angiography within 12 hours	Prodromal; angina within 24 hours of infarct	Retrospective	598	206 (34%)	30 day all-cause	Yes - demographics, risk factors, collateral circulation, reperfusion, multivessel disease	Some evidence for lower mortality in angina group : Adjusted OR=0.44 (95% CI 0.16-1.17) p=0.09

NSTEMI: non ST-elevation MI; STEMI: ST-elevation MI; PCI: percutaneous coronary intervention; OR: odds ratio; CAD: coronary artery disease; CHF: congestive heart failure

6.2.3.4 The effect of preinfarction on post-hospital outcomes

Post-hospital cardiac mortality

Two studies compared long term cardiac mortality after first MI in patients with and without previous angina (Table 6.5).[144, 149] Patients with and without previous angina in the Framingham study were followed up for up to 34 years after MI. Men with angina had significantly higher mortality than those without angina after adjusting for cardiovascular disease risk factors (RR=1.49 (95% CI 1.12-2.00)) although no evidence for an effect was seen in women (RR=1.12 (95% CI 0.76-1.65)).[144] This study also examined the effect of non-coronary exposures (stroke and peripheral arterial disease) on post-MI mortality. In both men and women at multivariate analysis, there were higher rates of mortality (coronary and all-cause) in patients with either cerebrovascular or peripheral ischaemia, although these did not reach significance.[144] The prospectively collected exposure data and representativeness to the general population are strengths of this study, but due to the biennial follow-up, misclassification of angina was possible. Additionally, the study began in 1948, and the data are now somewhat outdated due to changes in the MI definition, MI incidence and angina incidence in the last fifty years.

The second study examining cardiac mortality did so in patients with chronic or new onset angina compared to patients without angina. This study showed that patients *without* angina had higher one year cardiac mortality than those with angina, after adjusting for demographic, risk factor and cardiovascular drug use (RR=1.85 p=0.003).[149] The reason for the discrepancy compared to the Framingham study are likely to be due to the substantial difference in follow-up duration (34 years versus 1 year) but may also be due to the differences in the definitions of angina or proportion of patients who had previous angina (22% in Framingham, 65% in the Japanese study).

Post-hospital all-cause mortality

Due to the logistical difficulties of doing so, the majority of studies did not assess long-term follow-up, and even fewer were able to examine cause-specific mortality after hospitalisation. Three studies described all-cause mortality during long term follow-up (Table 6.6). Pierard, who reported no effect on in-hospital mortality, showed that long term survival was adversely affected by previous chronic and prodromal angina.[151] Similarly, Behar, who initially showed poorer mortality in those with chronic angina, showed that this was maintained at one and five years.[150] Both studies adjusted for demographics,

cardiovascular disease risk factors and some cardiovascular drugs. These studies imply that chronic angina is associated with worse mortality in long term follow-up after MI. Studies including recurrent MI have also examined coronary heart disease mortality and have tended to show worse mortality in patients with chronic angina than in those without.[205, 206]

In 202 hospitalised STEMI patients in Japan, Tomoda assessed various outcomes with respect to prodromal angina in the 24 hours prior to infarct.[198] The 59 patients with prodromal angina had worse all-cause mortality than the group without, but this did not reach significance (P=0.39). In this analysis, only ten patients died during longer term follow-up, so there was insufficient power to find any effects or to perform multivariate analysis. Therefore, the effects of prodromal angina on longer term mortality are unclear.

Table 6.5 Longer term cardiac mortality in first myocardial infarction (MI) patients with and without previous angina

Author, year	Country	MI patients included	Timing of angina exposure before MI	Exposure assessment	N MI patients	N (%) exposed	Outcomes assessed	Was multivariate analysis performed?	Effect of exposure
Cupples, 1993[144]	United States	First MI	Chronic	Prospective	828	184 (22%)	34 years coronary heart disease mortality	Cardiovascular disease risk factors	In men: previous angina RR1.49 (95% CI 1.12-2.00). In women: 1.12 (95% CI 0.76-1.65)
Anzai, 1995[149]	Japan	First Q wave MI	Chronic and prodromal	Retrospective	291	189 (65%)	One year cardiac mortality	Yes – demographics, risk factors, beta adrenergic and calcium antagonists	At multivariate, absence of angina predicted mortality RR=1.85 p=0.003

RR: rate ratio

Table 6.6 Longer term all-cause mortality in myocardial infarction (MI) patients with and without previous angina

Author, year	Country	MI patients included	Timing of angina exposure before MI	Exposure assessment	N MI patients	N (%) exposed	Outcomes assessed	Was multivariate analysis performed?	Effect of exposure
Pierard, 1988[151]	Belgium	Hospitalised first MI, un-thrombolysed	Chronic and prodromal; chronic >1 month, new onset <1 month	Retrospective	732	200 chronic, 247 new onset (61%)	3 year all-cause	Yes - beta blockers, admission delay, age, sex, smoking, diuretics	Angina related to higher mortality p=0.008.
Behar, 1992[150]	Israel	Hospitalised first MI survivors to 7 days, included in SPRINT trial	Chronic >1 month	Retrospective	4,166	1,791 (43%)	One year, five years all-cause	Yes – demographics, previous disease, cardiovascular disease risk factors	Adjusted OR=1.29 (95% CI 1.16-1.44) higher mortality in angina group
Tomoda, 2004[198]	Japan	Hospitalised first STEMI with PCI <6 hours after onset	Prodromal; angina in 24 hours before infarct	Retrospective	202	59 (29%)	Follow-up all-cause, duration not stated.	No	No effect, P=0.39

OR: odds ratio; PCI: percutaneous coronary intervention.

6.2.3.5 Age, diabetes, reperfusion and BMI

There is debate in the literature regarding the effects of ischaemic preconditioning and preinfarction angina in the elderly. Experimental studies of ischaemic preconditioning showed that it was ineffective in elderly animal hearts, and early clinical studies showed similar results. However, more recent studies have shown effects in elderly patients and there is a suggestion that this might be affected by physical activity.[207-209]

In addition to the possibility of differing effects by age, there have also been studies examining effect modification by hypertension,[202] type of reperfusion,[210, 211] gender,[212] and diabetes.[213] Few studies have examined these effects and the results have been inconsistent. Even in some of the larger studies, the ability to detect effects in subgroups is likely to have been low. Therefore, the effects in patients with and without diabetes, hypertension, BMI and by gender have not been well-characterised.

6.2.3.6 Mechanisms for improved survival in patients with preinfarction angina

The mechanisms for the observed beneficial effects of preinfarction angina on infarct size and (possibly) in-hospital mortality are not fully understood. Three mechanisms have been suggested. First, patients with chronic angina may have developed collateral channels, so that when flow is occluded in the main artery, it is compensated by flow in collateral channels. However, Kloner (2001) postulated that for patients with new onset angina in the week or days before MI, there is no opportunity for the development of these vessels.[214] Additionally, some studies have shown that collateral vessels do not occur more frequently in patients with preinfarction angina. Second, Andreotti suggested that preinfarction angina was associated with faster reperfusion times, therefore preventing myocardial necrosis.[215] This was also shown by Evrengul (2005) but no evidence of faster reperfusion was shown by Ottani (1995).[216, 217] Finally, ischaemic preconditioning may be delaying necrosis in this subgroup of patients. Brief episodes of ischaemia prior to the final insult may have triggered the cascade of chemical reactions that prevent subsequent cell necrosis (as described in Chapter 1).

6.2.4 Strengths of previous research

The effects of preinfarction angina, defined in a number of different ways, have been extensively evaluated in a number of geographical regions and in different patient populations.

6.2.5 Limitations of previous research

There are a number of limitations to the current body of literature investigating preinfarction angina and the possible effects of ischaemic preconditioning. These were discussed in the previous sections and include:

- widely differing exposure definitions, from 24 hours in many studies,[37, 194, 198, 201, 203] to 48 hours,[188, 191, 193, 202] 72 hours,[38] 7 days,[195, 196] 30 days[147, 149] or chronic angina of more than 30 days.[144, 147] This heterogeneity is likely to have contributed to some of the discrepancies observed, although no systematic differences in outcomes were noted between the shorter 'prodromal' exposure times and the longer term exposures;

- lack of prospectively collected data on symptoms and events. Retrospective data on the main exposure and potential confounders or explanatory variables are potentially problematic, particularly for the onset and duration of angina, medication use and diagnosed morbidities prior to MI. Any misclassification of the main exposure or confounding variables may result in residual confounding, bias and incorrect effect measures;

- most studies were in hospitalised or trial patients, highly selected for specific research questions. The results of these studies are therefore not generalisable to all hospitalised patients due to strict inclusion criteria such as restriction to specific types of MI (Q wave, STEMI, NSTEMI, anterior or interior MI), requirement to survive for several days, undergo PCI or angiography shortly after MI, or have certain morbidities. The results are also not generalisable to the general population because a substantial proportion of people with MI do not reach hospital. This means that the extent of ischaemic presentations prior to MI in general populations is unclear;

- poor adjustment, or no adjustment, for baseline characteristics in assessing the in-hospital and post-hospital effects of previous angina on mortality. Some of the beneficial effects seen may be due to poor adjustment for risk lowering medications;

- low power to detect effects in many of the smaller studies and low numbers of fatalities in assessing mortality effects. Iglesias-Garriz published a meta-analysis of six studies examining the effect of angina in the 24 hours before MI on post-MI in-hospital mortality.[192] Pooling these studies provided the power to demonstrate an effect, which the individual studies were unable to achieve. This showed a reduced risk in the 1217 of 3497 patients with prodromal angina (OR=0.61 (95% CI 0.48-0.78));

- changes in the definition of MI[6] and in treatment practices over the past sixty years over which these studies spanned. While there is some evidence to suggest that the likelihood of ST-elevation is decreased in patients with preinfarction angina, this effect has not been well-characterised. No studies have assessed infarct severity as the main focus of the study and none have adjusted for differences in baseline covariates in multivariate analysis;

- all but one[144] of the included studies restricted their exposure definitions to either chest pain or angina. Given recent interest in the ischaemic preconditioning effects of ischaemia in other arterial beds based on experimental studies and randomised trials,[218, 219] naturally occurring ischaemia in the peripheral or cerebrovascular arteries may have some effect in observational clinical studies, but these have not been assessed.

One final limitation was also identified, which was not discussed in the review above. This relates to the timing of exposure. The timing of ischaemic symptoms with respect to MI is important due to the cellular mechanisms involved in ischaemic preconditioning and the possible development of collateral channels. Most studies of preinfarction angina have focused on the 24 to 72 hours before MI. These time periods fit with theories of ischaemic preconditioning and the second window of protection in the 12-72 hours after the ischaemic stimulus, as discussed in Chapter 1.[27]

Two studies (not included in this review as they included recurrent MI) have compared angina occurrence in different time periods on MI outcomes. Kloner compared angina occurring in the 24 hours prior to MI with angina at other times (48h, 72h, 1 week, 1 month >1 month). There was no effect of angina beyond 24 hours on in-hospital re-infarction, severe congestive heart failure or death.[220] Similarly, Hirai[221] found a protective effect of angina in the 7 days before MI on left ventricular ejection fraction, but no effect of angina occurring more than 7 days prior to MI.

These studies imply that the preconditioning effect is short-lived. However, this review has identified studies showing beneficial effects of chronic angina on in-hospital outcomes. Additionally, Herlitz (1993) reported that patients with chronic angina had smaller infarcts than those with new onset angina in the three months prior to MI.[222] Therefore, the effects of timing of angina are uncertain.

6.2.6 Limitations of this review

There are two main limitations of this review. The first is the possibility that not all studies were identified by the literature search. However, the search strategy was broad and the reference lists of all included studies were searched. Therefore, I am confident that I have identified the key studies in the field.

The second limitation is the possibility of publication bias. Although several studies were identified showing no effect of preinfarction angina on outcomes, there is a possibility that further studies showing no effects were not published.

6.2.7 Conclusion

There appears to be a real effect of preinfarction angina on some clinical outcomes at the time of MI. While the mechanisms for this are not fully understood, there is a strong possibility that ischaemic preconditioning has some effect at MI. This includes an association with reduced infarct size, attenuated severity in presentation, and a possible association with lower in-hospital mortality. However, various aspects of the effect of preinfarction angina are unclear: first, the effects on clinical presentation with ST-elevation or non ST-elevation MI; second, the effects of ischaemic exposures at different times prior to MI and third the effects of ischaemia in non-coronary arterial beds. Additionally, characterising the preinfarction experience of patients who do not reach hospital may provide further insight into the effects of this exposure.

To address these limitations a large, prospective study was performed examining the occurrence, timing and effect of different types of symptoms and disease manifestations in different arterial beds before MI. The population-based data will allow the effects in the general population to be characterised. The size of the study and the detail of the prospective data will allow adjustment for well-measured risk factors and cardiovascular prescriptions provided to these patients. Additionally, it will allow subgroup analysis,

assessment of effect modification by age, reperfusion or hypertension, as suggested above, and examination of the effects by MI type.

6.3 Objectives

1. To describe the ischaemic coronary, cerebrovascular and peripheral arterial clinical presentations and chest pain consultations recorded in primary care in the 90 days before admission with first acute MI.

2. To compare the characteristics of patients admitted with acute MI with and without new presentations of ischaemia before MI, including peak troponin, MI type (STEMI, NSTEMI), heart rate, in-hospital treatment, time to presentation and reperfusion (MINAP cases only).

3. To examine the association between pre-MI ischaemic presentations and post-MI coronary heart disease mortality, and whether associations are modified by previously diagnosed atherosclerotic disease, age, sex, diabetes, hypertension, reperfusion strategy or use of cardiovascular medications before MI.

4. To examine the association between timing of the ischaemic presentation and coronary heart disease mortality (split time into days before infarction: 1-2, 3-7, 8-30, 31-90 days).

6.4 Methods

The prospectively collected medical records of a cohort of MI patients were reviewed to assess the occurrence of chest pain and new onset ischaemic atherosclerotic disease in any arterial bed in the 90 days prior to MI. Those with and without these presentations were compared in terms of their MI characteristics and subsequent coronary heart disease mortality.

6.4.1 Definition of acute myocardial infarction

Patients with MI were identified based on a record in any one of the four data sources. MI definitions are described in detail in Chapter 3 (Methods) and briefly in Table 6.7.

Table 6.7 Definition of acute myocardial infarction in each of the four data sources: GPRD, HES, MINAP and ONS

Data source	MI definition
GPRD	Read code for MI, raised markers of myocardial necrosis, or ECG result indicative of MI.
HES	ICD-10 code I21, I22 or I23 as the primary diagnosis in the first hospital episode.
MINAP	ST-elevation MI or non ST-elevation MI following the joint American Heart Association / European Society of Cardiology definition.[6]
ONS	ICD-10 code I21, I22 or I23 as the underlying cause of death.

6.4.2 Categorisation of ischaemia before MI

Patients were initially categorized into three groups based on their pre-MI experience of ischaemic atherosclerotic disease and chest pain, according to the scheme in Figure 6.1. Atherosclerotic disease diagnoses were split into coronary, cerebrovascular and peripheral arterial and were based on codes in the GPRD, MINAP and HES patient records (as described in Chapter 3 Methods). Coronary disease included stable and unstable angina, coronary heart disease (CHD) not otherwise specified, receipt of percutaneous coronary intervention or coronary artery bypass graft; cerebrovascular disease included

ischaemic stroke and transient ischaemic attack; peripheral arterial disease included symptoms of intermittent claudication and new diagnoses of peripheral arterial disease.

- Patients with '*no prior ischaemic presentations*' had no atherosclerotic disease diagnoses in their electronic health record prior to MI and no consultations for chest pain in the 90 days before MI.

- Patients with '*new ischaemic presentations*' had either a new atherosclerotic disease diagnosis in the 90 days before MI (either first ever diagnosis or diagnosis in a new arterial bed, for example new coronary disease diagnosis in the presence of longer term cerebrovascular disease) or a chest pain consultation in the 90 days before MI.

- Patients with '*existing ischaemic diseases*' had no new atherosclerotic disease diagnoses or chest pain consultations in the 90 days before MI but had long-standing atherosclerotic disease (>90 days' duration).

Atherosclerotic disease diagnoses in different arterial beds and chest pain consultations were based on codes in the GPRD, MINAP and HES patient records as set out in Chapter 3 and the CALIBER manual (see Appendix B). The codes used to define diagnosis of atherosclerotic disease were those rated by two clinicians as definitely indicative of disease (a sensitivity analysis was conducted to assess whether inclusion of 'possible' codes in addition to 'definite' codes affected the results). The assumption that presentation with chest pain had the same effect as presentation for ischaemic atherosclerotic disease was tested in a sensitivity analysis.

In the second part of analysis, the timing of the closest ischaemic presentation prior to MI was split into categories (1-2 days, 3-7 days, 8-30 days and 31-90 days before MI). This categorisation is based on definitions of pre-infarction angina used in the body of literature that examines natural ischaemic preconditioning.

The timing of onset of atherosclerotic disease was taken as the date of the first code indicating disease in the patient's GPRD record (except where the code indicated prevalent disease, where the timing of onset was set to missing).

6.4.3 Exclusion criteria

Patients were excluded if they had a recorded history of MI (n=6,337), were under the age of 18 at MI (n=2), had not been registered with the primary care practice for at least

one year before MI (n=8,516), whose MIs occurred outside the period where all databases were collecting data (outside 1st January 2003 to 31st December 2008, n=23,804), and patients without any primary care consultations in their record prior to MI (n=12).

Patients were also excluded if they had diagnosed abdominal aortic aneurysm, heart failure or cardiac arrest (i.e. non-ischaemic cardiovascular disease) at any time before MI but with no ischaemic diagnoses in their medical records (n=676). A sensitivity analysis was performed including these patients to assess the effect of this exclusion on the results of the main analysis.

6.4.4 Cardiovascular disease risk factors and risk lowering medication prior to MI

Age, sex, deprivation, duration of registration and primary care consultation rate were taken from primary care (GPRD) records. Ethnicity was taken from GPRD, HES and MINAP. Cardiovascular disease risk factor data were derived from GPRD and HES (recorded at any time up to the day before MI) and MINAP. Risk factors included in this analysis were smoking (categorized as non, ex, current or unknown at the time of MI), hypertension (either diagnosed hypertension or three consecutive raised (>140/90mm Hg) measurements), total serum cholesterol (mean of all total serum cholesterol measurements prior to MI), HDL cholesterol (mean of all total serum HDL measurements prior to MI) and diabetes (diagnosed diabetes or insulin prescription) (all described in Chapter 3).

Risk lowering medication use in the six months prior to MI was based on prescriptions issued in primary care up to the day before MI and reported use of these drugs at hospital admission (available in MINAP data). Specific drug categories of interest were blood pressure lowering, lipid lowering and antiplatelets,

The Framingham risk score for ten year 'hard' CHD (MI or coronary heart disease death) endpoints[129] was also calculated as described in Chapter 3.

6.4.5 Follow up after MI and primary outcome

Patients with MI were followed for up to 7.6 years after MI (median 2.6 years). The primary outcome was death with an underlying cause of coronary heart disease (ICD-10 codes I20-I25), as recorded in ONS mortality data. As recording of cause of death may be inexact, a sensitivity analysis was conducted using all-cause mortality as an outcome.

6.4.6 Statistical analysis

The type and timing of new and existing ischaemic presentations in the 90 days before MI were described. Characteristics of MINAP patients with no prior ischaemic presentations, new ischaemic presentations and existing ischaemic diseases, for whom there were data on MI type and severity, were compared in terms of admission heart rate, systolic blood pressure, ECG, raised markers of myocardial necrosis, time to hospital admission and time to reperfusion. Groups were compared using chi squared tests for categorical variables, Kruskal Wallis tests for comparing medians, and t tests for comparing means.

Cox regression analysis was used to compare the post-MI coronary heart disease mortality of patients with new and existing ischaemic presentations to patients with no prior ischaemic presentations. Tests for proportional hazards, based on Schoenfeld residuals, were performed on all models and interactions with time were fitted where there was non-proportionality. In the first instance, interactions with time were fitted based on follow-up time categories of 0-7 days, 8-30 days, 31-90 days, 91 days to one year and one to two years, which were considered to be the time points at which the mortality effects may change. Time periods were combined where the effects of previous ischaemic presentations were similar based on similar effect measures and assessed using likelihood ratio tests comparing models with combined versus separate time periods. Regression analyses were adjusted for age, sex, hypertension, total serum cholesterol, diabetes, smoking, blood pressure lowering, lipid lowering and antiplatelet medication prescription in the six months before MI. A directed acyclic graph (DAG) describes the associations between ischaemic presentations, coronary heart disease mortality and these variables in Appendix A, Section 10.5.2. Likelihood ratio tests were used to assess interactions between any of these explanatory variables and the main exposure.

Cox regression analysis was also used to compare the coronary heart disease mortality of patients with presentations at different times before MI to patients without any prior ischaemic presentations.

6.4.7 Further analyses and sensitivity analyses

MI type was available in the subset of patients recorded in MINAP. The main analysis (examining the effect of new ischaemic presentations on coronary heart disease mortality) was repeated in this subset only, and was adjusted for MI type to examine its confounding effect.

In another analysis the effects on MI outcomes of previously consulting with a GP for reasons other than ischaemia were examined.

The new ischaemic presentations exposure was split into its constituent components (chest pain, new and established CHD, cerebrovascular disease, peripheral arterial disease) to assess differences between these presentations.

To align our results with the literature examining 30 day mortality, the analysis was repeated using a pre-specified cut point at 30 days post-MI.

All analyses were performed in Stata version 11. The study details are registered online at clinicaltrials.gov (NCT01604486, May 2012) and a time-stamped detailed analytic protocol is shown in Appendix B.

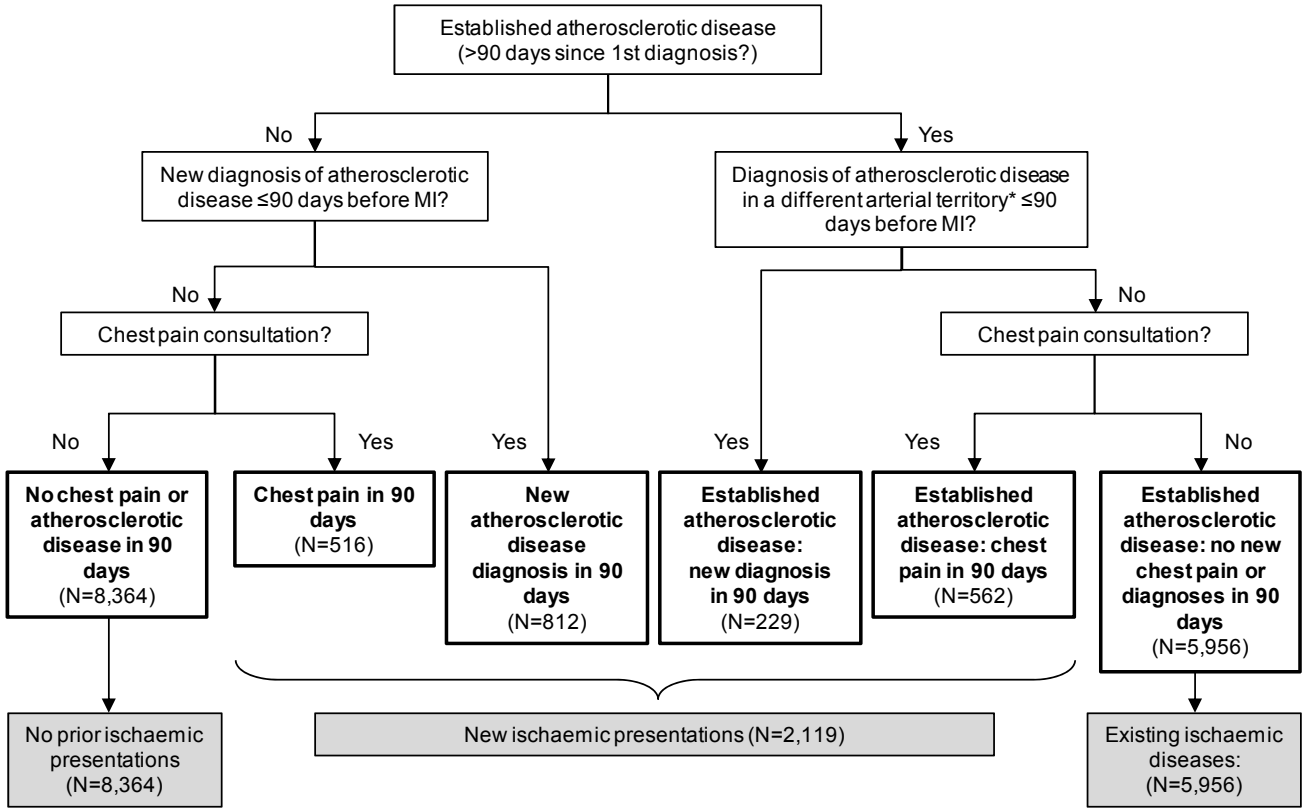


Figure 6.1 Categorisation of patients with acute myocardial infarction, according to prior atherosclerotic disease and chest pain consultations Atherosclerotic disease, defined as myocardial ischaemia (stable or unstable angina, percutaneous coronary ischaemia, coronary artery bypass graft), cerebral ischaemia (ischaemic stroke, transient ischaemic attack) and new peripheral arterial disease diagnoses including intermittent claudication.

*Patients with diagnoses in a different arterial territory include those with new coronary, peripheral arterial or cerebrovascular disease against a background of existing disease in a different territory. Note: new atherosclerotic disease included a single first prescription of nitrates before MI.

6.5 Results: new ischaemic presentations prior to MI

6.5.1 Atherosclerotic disease diagnoses in the 90 days before MI

There were 16,439 patients with first MI between 1st January 2003 and 31st December 2008 and who met all inclusion criteria. Table 6.8 describes the different subtypes of ischaemic atherosclerotic diseases and chest pain that patients presented with in the 90 days before MI. Overall 2,119 (12.9%) patients presented to their family physician with new ischaemic presentations in the 90 days before MI, 8364 (50.9%) had no prior ischaemic presentations, and 5,956 (36.2%) had existing ischaemic diseases with no new presentations in the 90 days before MI. As shown in Chapter 5, coronary disease was the most common atherosclerotic disease presentation in the 90 days before MI. Figure 6.2 shows the proportion of MI patients presenting with chest pain and new ischaemic atherosclerotic disease in the 90 days prior to MI, broken down by timing of presentation

6.5.2 Demographic and cardiovascular disease risk factor distribution

Table 6.9 describes the demographic distribution of patients, according to new or existing ischaemic presentation before MI. Those with new ischaemic presentations in the 90 days prior to MI were older than those with no prior presentations (P<0.001). They had a similar proportion of women and distribution of social deprivation. They were more likely to have a higher Framingham risk score, and higher prevalence of diabetes and hypertension (P<0.001 for each comparison). They had been registered in the primary care practice for a similar duration but had a higher rate of primary care consultation compared to patients without new ischaemic presentations (median 7.4 consultations per year, IQR (4.2-12.4), compared to (4.7 (2.4-8.3), P<0.001).

Those with existing ischaemic diseases (>90 days' duration) were older, more likely to be female and had a higher prevalence of high Framingham risk (risk greater than 20%), (P<0.001 for each comparison). They had the highest primary care consultation rate prior to MI (median 9.0 consultations per year, IQR (5.6-14.0)) and had been registered with their primary care practice for longer than those without prior ischaemic presentations (P<0.001).

Differences in ethnicity between the groups were driven by differences in the 'unknown' group and due to the high proportion of patients with unknown ethnicity, ethnicity was not included in the main analysis.

6.5.3 Prescription of cardiovascular medications

The number and proportion of patients with a first or repeat prescription of blood pressure lowering, lipid lowering, and antiplatelet medications in the 90 days before MI are shown in Table 6.9 and Figure 6.3. Patients with new ischaemic presentations were more likely to be initiated on blood pressure lowering, lipid lowering or antiplatelet medications compared to those with no prior ischaemic presentations ($P<0.001$ for each). They were also more likely to obtain a repeat prescription in the 90 days prior to MI ($P<0.001$). However, in those with no prior ischaemic presentations, 34.3% were already prescribed blood pressure lowering medications, 11.0% lipid lowering and 9.9% antiplatelets, suggesting that increased cardiovascular disease risk was acknowledged by the primary care physician.

For patients with existing ischaemic diseases, fewer patients were newly initiated on these medications in the 90 days prior to MI than those with new ischaemic presentations, but a larger proportion had repeat prescriptions written in the 90 days prior to MI.

Table 6.8 New atherosclerotic disease diagnoses and chest pain consultations in 16,439 patients with and without 'established' disease (>90 days' duration)

	No established disease N=9,692		Established disease >90 days' duration N=6,747		Total N=16,439	
	n	(%)	n	(%)	n	(%)
Any atherosclerotic disease	796	(8.2)	225	(3.3)	1,021	(6.2)
Coronary disease	671	(6.9)	126	(1.9)	797	(4.8)
Stable angina	525	(5.4)	92	(1.4)	617	(3.8)
Unstable angina	209	(2.2)	34	(0.5)	243	(1.5)
CHD not otherwise specified	234	(2.4)	49	(0.7)	283	(0.6)
PCI or CABG	77	(0.8)	14	(0.2)	91	(1.7)
Cerebrovascular disease	107	(1.1)	65	(1)	172	(1)
Peripheral arterial disease	42	(0.4)	35	(0.5)	77	(0.5)
Presentation of unknown type†	2	(0)	22	(0.3)	24	(0.1)
Single nitrate prescription	16	(0.2)	4	(0.1)	20	(0.1)
Chest pain	516	(5.3)	562	(8.3)	1,078	(6.7)

PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CHD: coronary heart disease

† where the only code indicating atherosclerotic disease in a patient's record was of unknown type

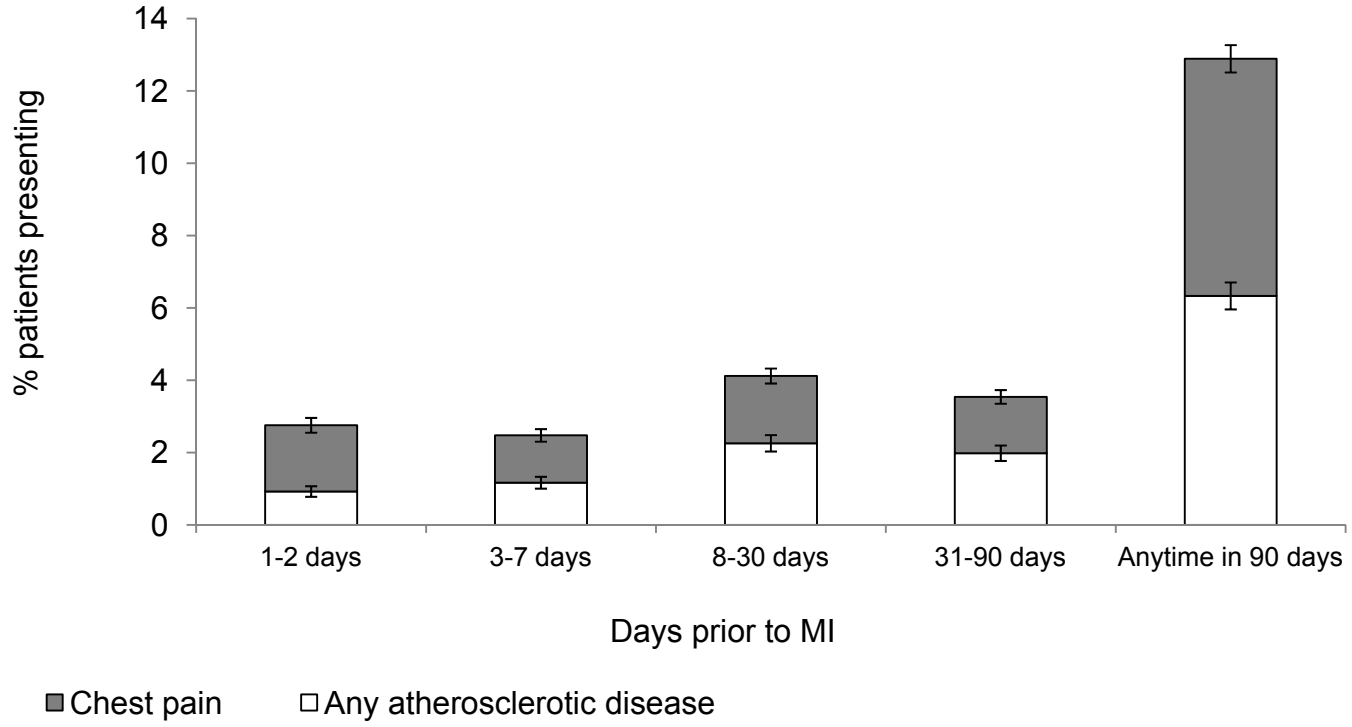


Figure 6.2 Proportion of all myocardial infarction (MI) patients (N=16,439) with new ischaemic presentations in the 90 days period prior to MI, stratified by those consulting for chest pain and those with new ischaemic atherosclerotic disease, with 95% confidence intervals

Table 6.9 Demographic and cardiovascular disease risk factor distribution in patients in each exposure group

	No new ischaemic presentations		New ischaemic presentations		Existing ischaemic diseases	
N patients	8,364		2,119		5,956	
Age, median (IQR)	68	(57-79)	72	(61-81)***	79	(70-85)***
Sex, n female (%)	3,030	(36.2)	803	(37.9)	2,652	(44.5)***
IMD quintile, n (%)						
1 (least deprived)	1,773	(21.3)	485	(23)	1,045	(17.6)***
2	1,680	(20.1)	418	(19.8)	1,168	(19.6)
3	1,688	(20.2)	422	(20)	1,171	(19.7)
4	1,596	(19.1)	389	(18.4)	1,282	(21.6)
5 (Most deprived)	1,603	(19.2)	399	(18.9)	1,281	(21.5)
Ethnicity, n (%)						
White	5,799	(69.3)	1,562	(73.7)***	4,552	(76.4)***
South Asian	66	(0.8)	20	(0.9)	34	(0.6)
Black or other	184	(2.2)	51	(2.4)	122	(2)
Unknown	2,315	(27.7)	486	(22.9)	1,248	(21)
Smoking, n (%)						
Non-smoker	1,225	(14.6)	282	(13.3)***	792	(13.3)***
Ex-smoker	4,055	(48.5)	1,262	(59.6)	3,876	(65.1)
Current smoker	2,830	(33.8)	554	(26.1)	1,186	(19.9)
Unknown	254	(3)	21	(1)	102	(1.7)
Hypertension, n (%)	3,725	(44.5)	1,264	(59.7)***	4,320	(72.5)***
Total serum cholesterol in mmol/L, mean (SD)	5.6	(0.8)	5.6	(0.9)	5.3	(1)***
HDL cholesterol in mmol/L, mean (SD)	1.3	(0.3)	1.3	(0.3)	1.4	(0.3)***
Diabetes, n (%)	1,026	(12.3)	377	(17.8)***	1,505	(25.3)***
Framingham risk, n (%)						
<10%	1,940	(22.9)	390	(17.7)***	639	(11.1)***
10-20%	4,776	(56.3)	1,181	(53.6)	2,973	(51.7)
>20%	1,763	(20.8)	633	(28.8)	2,134	(37.1)
Blood pressure lowering, n (%)						
First prescription in 90d	82	(1)	130	(6.1)***	51	(0.9)
Any prescription in 90d	2,867	(34.3)	1,220	(57.6)***	4,261	(71.5)***
Lipid lowering, n (%)						
First prescription in 90d	103	(1.2)	158	(7.5)***	132	(2.2)***
Any prescription in 90d	918	(11)	668	(31.5)***	2,601	(43.7)***
Antiplatelets, n (%)						
First prescription in 90d	79	(0.9)	253	(11.9)***	72	(1.2)
Any prescription in 90d	825	(9.9)	883	(41.7)***	3,283	(55.1)***
Nitrates, n (%)						
First prescription in 90d	0	(0)	419	(19.8)***	45	(0.8)***
Any prescription in 90d	0	(0)	680	(32.1)***	1,654	(27.8)***
Consultation rate per year, median (IQR)	4.7	(2.4-8.3)	7.4	(4.2-12.4)***	9.0	(5.6-14)***
Years of pre-MI GPRD registration, median (IQR)	8.2	(5.2-12.9)	8.3	(5.1-13.4)	8.7	(5.4-13.5)***

IQR: inter-quartile range; SD: standard deviation; IMD: index of multiple deprivation; HDL: high density lipoprotein. *P<0.05, **p<0.01, ***p<0.001, compared to the group with no ischaemic presentations, from Chi squared test for categorical variables, Kruskal Wallis test for comparing medians, T test for comparing means

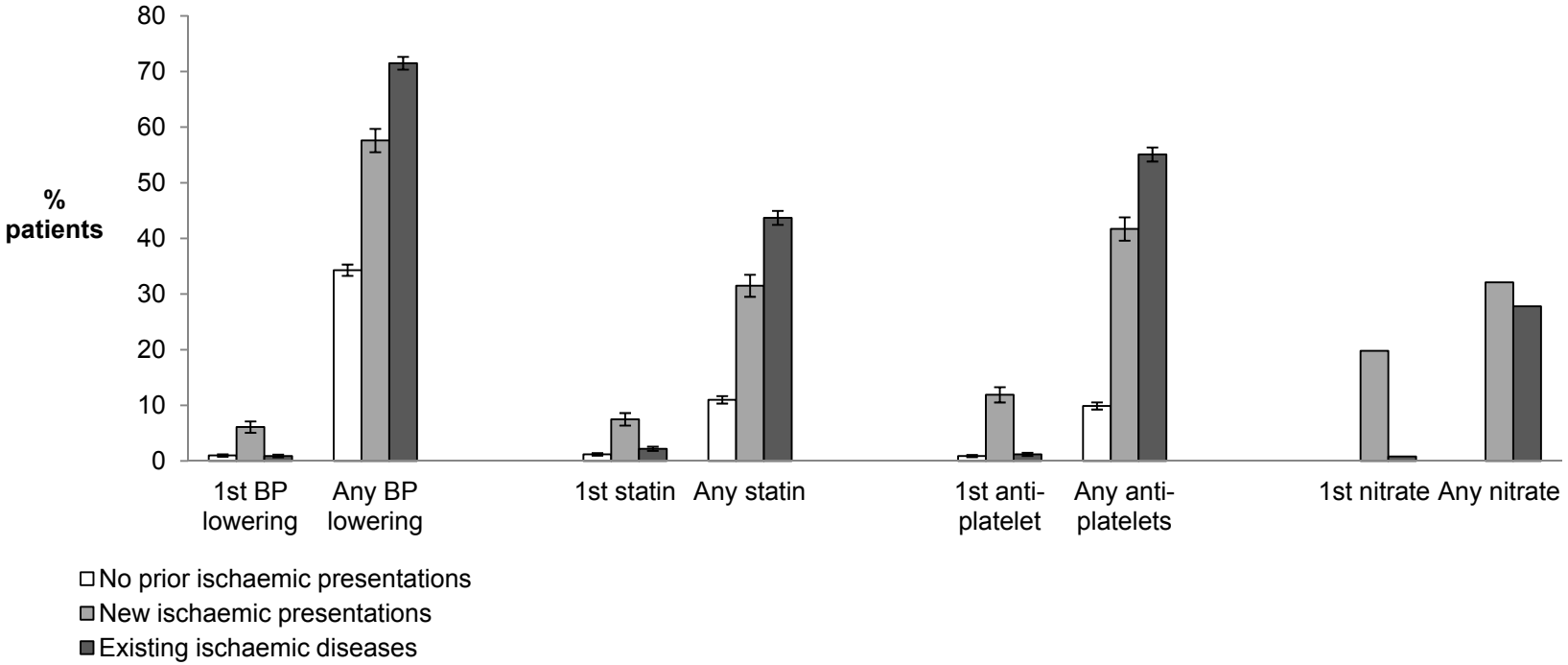


Figure 6.3 Proportion of patients (N=16,439) with first and repeat prescriptions for blood pressure (BP) lowering, lipid lowering and anti-platelet medications in the 90 days before first myocardial infarction, in patients with and without ischaemic presentations, with 95% confidence intervals

6.5.4 MINAP hospital characteristics

In the subset of patients whose MIs were recorded in the MINAP dataset (N=6,693), the clinical characteristics of MI differed across exposure groups (Table 6.10). Those with new ischaemic presentations in the 90 days before MI or with existing ischaemic diseases were more likely to experience a non ST-elevation MI type compared to those without any prior ischaemic presentations (62.3% and 64.6% versus 42.3%, respectively, P<0.001), and as a result, they were less likely to be reperfused.

MI size, measured by peak troponin values, was lower (P<0.001) in those with ischaemic presentations (median 1.3, IQR 0.3-6.9), and in patients with existing ischaemic diseases (1.4, IQR 0.3-7.5) compared to (2.6, IQR 0.6-13.0) those without prior ischaemic presentations. Patients with existing ischaemic diseases had a higher heart rate at admission than those without prior ischaemic presentations (P<0.001), but systolic blood pressure was similar in the three groups.

Table 6.10 Clinical characteristics of 6,693 MINAP patients with and without ischaemic presentations in the 90 days before MI

	No prior ischaemic presentations		New ischaemic presentations		Existing ischaemic diseases	
N MI	3,857		696		2,140	
MI type, n (%)						
STEMI	2,192	(57.7)	257	(37.7)***	786	(35.4)***
NSTEMI	1,604	(42.3)	424	(62.3)	1432	(64.6)
ECG record, n (%)						
ST segment elevation	2,094	(55.2)	237	(34.8)***	719	(32.4)***
Left bundle branch block	91	(2.4)	23	(3.4)	134	(6)
ST segment depression	385	(10.1)	110	(16.2)	414	(18.7)
T wave changes only	437	(11.5)	97	(14.2)	283	(12.8)
other abnormality	288	(7.6)	79	(11.6)	283	(12.8)
Normal ECG	209	(5.5)	45	(6.6)	139	(6.3)
Unknown	292	(7.7)	90	(13.2)	246	(11.1)
Peak troponin in µg/L, median (IQR)	2.6	(0.6-13)	1.3	(0.3-6.9)***	1.4	(0.3-7.5)***
Unknown, n (%)	655	(17.3)	85	(12.5)	261	(11.8)
Raised markers, n (%)	3,408	(89.8)	610	(89.6)	2,006	(90.4)
Unknown, n (%)	388	(10.2)	71	(10.4)	212	(9.6)
Heart rate at admission (bpm), median (IQR)	77	(77.4-525)	77	(65-90)	80	(68-98)***
Unknown, n (%)	857	(22.6)	156	(22.9)	487	(22)
Systolic BP at admission (mmHg), median (IQR)	140	(122-160)	138	(122-157)	140	(120-159)
Unknown, n(%)	861	(22.7)	158	(23.2)	481	(21.7)
Reperfusion, n (%)						
Thrombolysis	1,662	(43.8)	180	(26.4)***	526	(23.7)***
PCI or angioplasty	274	(7.2)	23	(3.4)***	88	(4)***
Reperfusion NOS	10	(0.5)	1	(0.2)	5	(0.3)
Time to admission in minutes, median (IQR)	144.2	(80.8-360.4)	175.9	(89.6-500.3)**	159.5	(85.2-356.1)
Unknown, n(%)	905	(23.8)	235	(34.5)	681	(30.7)
Admission to reperfusion in minutes, median (IQR)	24	(13.1-50.2)	28.4	(17.5-61.2)**	28.4	(15.3-61.2)***
Unknown, n(%)	1,936	(51)	482	(70.8)	1,634	(73.7)
Symptom onset to reperfusion in minutes, median (IQR)	146.4	(96.1-281.8)	172.6	(104.9-345.2)*	170.4	(111.4-290.5)**
Unknown, n(%)	2,166	(57.1)	511	(75)	1704	(76.8)

MI: myocardial infarction; STEMI: ST-elevation MI; NSTEMI; non ST-elevation MI; BP: blood pressure; IQR: inter-quartile range; bpm: beats per minute; ECG: electrocardiogram; PCI: percutaneous coronary intervention; NOS: not otherwise specified.
*P<0.05, **p<0.01, ***p<0.001, compared to patients with no prior ischaemic presentations, from Chi squared test for categorical variables, Kruskal Wallis test for comparing medians, T test for comparing means

6.5.5 Coronary heart disease mortality after MI

Figure 6.4 shows the crude coronary heart disease mortality experience of patients in each of the three main exposure groups. Due to non-proportional hazards (test for proportional hazards in the crude model P<0.001, suggesting strong evidence against the null hypothesis of proportional hazards (Appendix A, Figure 10.7)), follow-up time after MI was split at 7, 30 and 90 days and one and two years. The hazard ratio for the effect of new ischaemic presentations on coronary heart disease death was calculated for each time period (Figure 6.5).

Patients with new ischaemic presentations preceding MI had lower coronary heart disease mortality in the first seven days after MI compared to patients with no prior ischaemic presentations, even after adjustment for age, sex, cardiovascular disease risk factors and cardiovascular medication prescriptions in the six months before MI (HR=0.64 (95% CI 0.57-0.73), P<0.001). In this first week after MI there was weak evidence for an effect of existing ischaemic diseases on coronary heart disease mortality (HR=0.92 (95% CI 0.85-1.00) P=0.051). There was no evidence that the main effect in the first week after MI was modified by age, sex, diabetes, previous hypertension or reperfusion (P>0.05 in each case).

The effects observed in the 7-30 and 30-90 days after MI looked similar and there was no evidence that their effects differed (based on likelihood ratio tests (LRT) comparing nested models P=0.8506), so these periods were combined. During the 7-90 days after MI, the protective effect seen in the first week was lost (HR for new ischaemic presentations 0.88 (0.65-1.20), P=0.421). For patients with existing ischaemic diseases, this period saw an increase in the rate of mortality compared to patients without ischaemic presentations (HR=1.24 (1.01-1.51), P=0.038).

The effects after 90 days until the end of follow-up were also combined based on evidence from LRTs. After 90 days, there was evidence for higher mortality risk in those with new ischaemic presentations prior to MI (HR=1.42 (95% CI 1.13-1.77) P=0.002). There was also a stronger effect of existing ischaemic diseases during this period (HR=2.24 (95% CI 1.91-2.64) P<0.001).

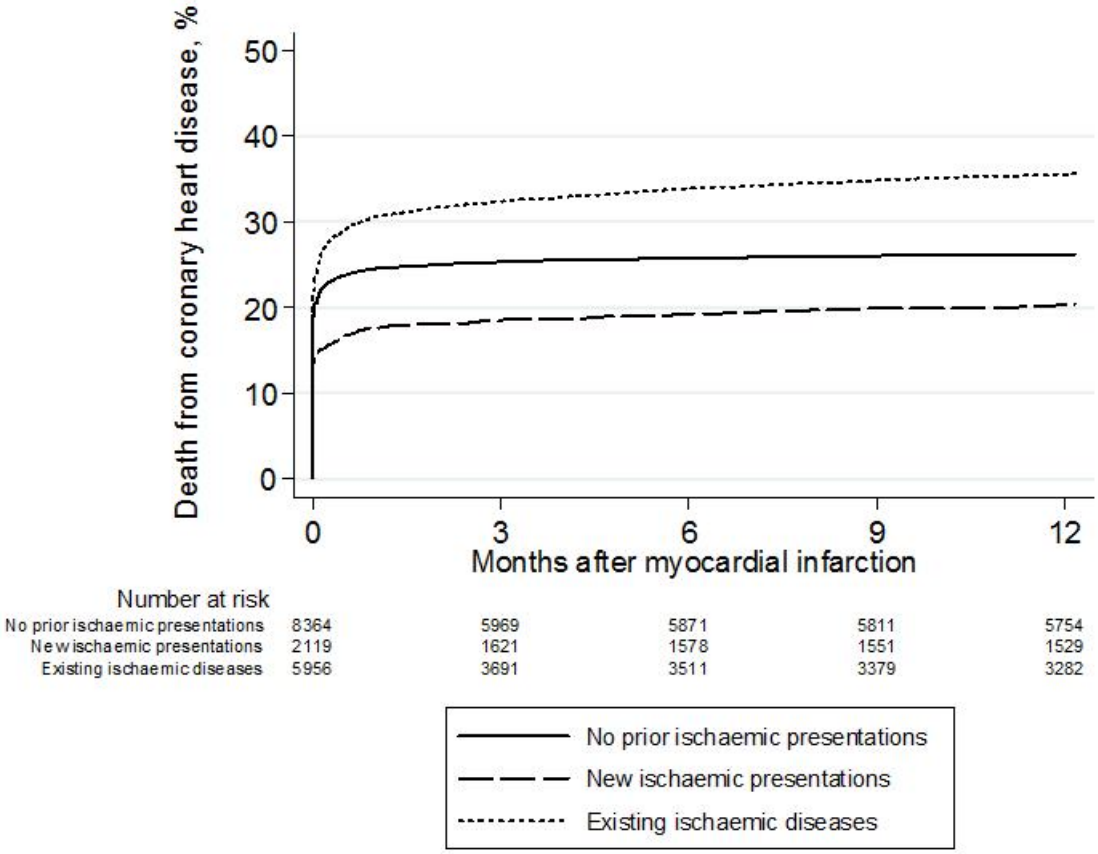
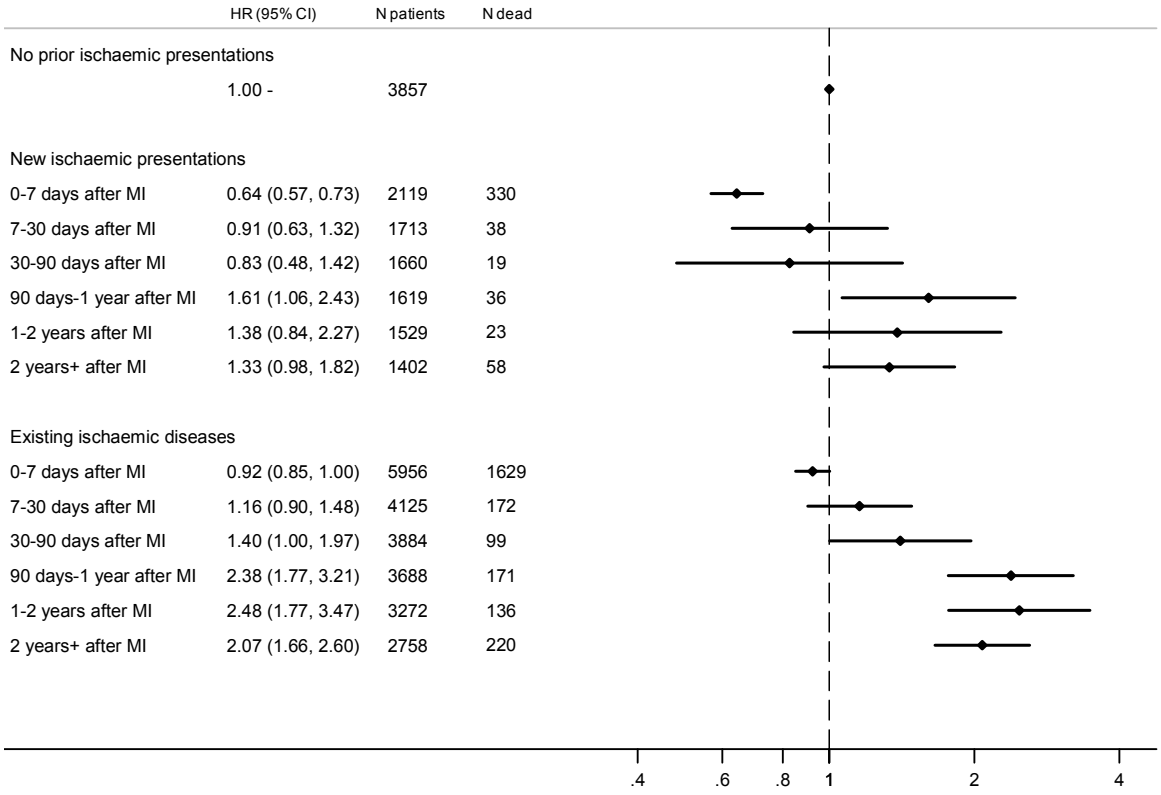
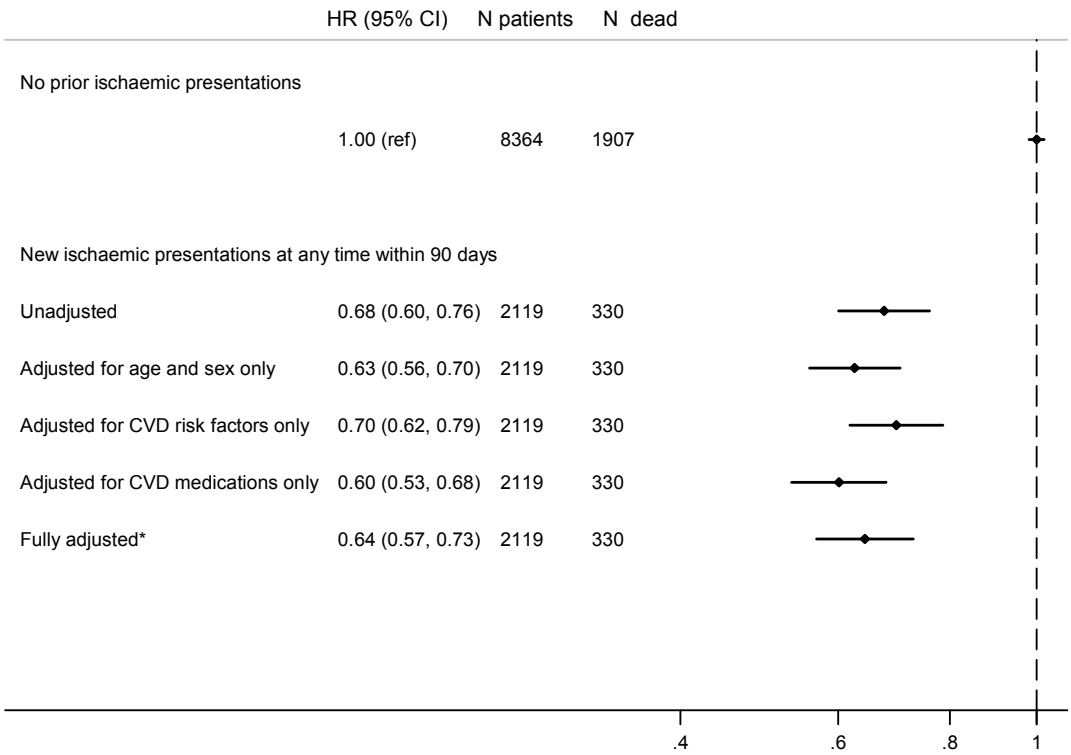


Figure 6.4 Crude Kaplan Meier estimates for coronary heart disease mortality following acute myocardial infarction in patients (N=16,439) with no prior ischaemic presentations, those with new ischaemic presentations and those with existing ischaemic diseases



Notes: MI: myocardial infarction; HR: hazard ratio. The model is adjusted for age, sex, diabetes, total cholesterol, HDL cholesterol, smoking status, hypertension, and use of lipid lowering, blood pressure lowering, antiplatelets and nitrates.

Figure 6.5 Adjusted hazard ratios for the effect of new ischaemic presentations and existing ischaemic diseases on coronary heart disease mortality, split by time after myocardial infarction (N patients=16,439)



Notes: CVD: cardiovascular; HR: hazard ratio. *Fully adjusted model includes age, sex, diabetes, total cholesterol, HDL cholesterol, smoking status, hypertension, and use of lipid lowering, blood pressure lowering, antiplatelets and nitrates.

Figure 6.6 Forest plot describing the hazard ratios for the effect of new ischaemic presentations in the 90 days before myocardial infarction on coronary heart disease mortality, in crude and adjusted models (N=10,483)

6.6 Results: timing of clinical presentation

6.6.1 Number of patients presenting at different times

The time of presentation before MI was split into four groups (1-2 days, 3-7 days, 8-30 days, and 31-90 days). The distribution of disease diagnoses occurring in these time periods is shown in Table 6.11. Patients with existing ischaemic diseases were excluded from this analysis.

6.6.2 Demographic and cardiovascular disease risk factor distribution

The demographic distribution of patients in each group is described in Table 6.12 and the distribution of key cardiovascular disease risk factors is described in Figure 6.7. Median patient age was lowest in the group with no prior ischaemic presentations and increased in patients with presentations. The patients presenting at more distal times to MI tended to be older.

There was some evidence for a trend in the proportion of women in each group. Patients without prior ischaemic presentations had a lower proportion of women and those with presentations in the 31-90 days prior to MI with the highest proportion (P for trend 0.013).

The proportions of patients who were smoking or hypertensive at the time of MI were highest in patients without prior presentations and lowest in those with presentations in the 31-90 days prior to MI (P for trend<0.001 for both) (Figure 6.7). The proportion with diabetes or prescribed cardiovascular drugs in the 90 days prior to MI showed the opposite trend, with the lowest prevalences in patients without prior ischaemic presentations and the highest in those who presented in the 31-90 days prior to MI (P for trend <0.001 for each variable), (Figure 6.7, Figure 6.8).

Patients with no prior ischaemic presentations had the lowest consultation rate in their pre-MI registration, and those who presented in the 31-90 days prior to MI had the highest consultation rate (P for trend<0.001). All patients had a similar duration of registration with their GPRD practice prior to MI (test for trend p=0.380).

Table 6.11 Numbers of patients with each ischaemic presentation including coronary heart disease, peripheral arterial disease, cerebrovascular disease and chest pain, and the timing of these presentations with respect to myocardial infarction (MI)(total N=2,119)

	Timing of ischaemic presentation prior to MI				Total
	1-2 days	3-7 days	8-30 days	31-90 days	
Any atherosclerotic disease	**146**	**186**	**366**	**323**	**1021**
Coronary disease	129	160	292	216	797
Stable angina	*93*	*114*	*232*	*171*	*617*
Unstable angina	*32*	*53*	*98*	*44*	*243*
PCI or CABG	*14*	*17*	*22*	*13*	*91*
CHD not otherwise specified	*31*	*58*	*86*	*73*	*283*
Cerebrovascular disease	17	18	62	75	172
Peripheral arterial disease	1	11	21	44	77
Atherosclerosis recorded but arterial territory not specified	2	3	7	12	24
Chest pain & no atherosclerotic disease	**187**	**109**	**128**	**92**	**516**
Chest pain in established atherosclerotic disease	**114**	**106**	**178**	**164**	**562**
New nitrate prescription	6	6	5	3	20

PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CHD: coronary heart disease

Table 6.12 Demographic distribution of patients with and without clinical presentations in the 90 day period before myocardial infarction (MI), by timing of presentation (N=10,483)

	No prior ischaemic presentations		Timing of ischaemic presentation before MI							
			1-2 days		3-7 days		8-30 days		31-90 days	
N patients	8,364		452		405		676		586	
Age, median (IQR)	68	(57-79)	69	(60-79)	71	(60-80)	72	(62-80)	75	(63-82)
Sex, n female (%)	3,030	(36.2)	152	(33.6)	137	(33.8)	270	(39.9)	244	(41.6)
IMD quintile, n (%)										
1 (least deprived)	1,773	(21.3)	108	(23.9)	120	(29.6)	138	(20.5)	119	(20.4)
2	1,680	(20.1)	79	(17.5)	70	(17.3)	141	(20.9)	128	(22)
3	1,688	(20.2)	90	(20)	78	(19.3)	141	(20.9)	113	(19.4)
4	1,596	(19.1)	98	(21.7)	60	(14.8)	131	(19.4)	100	(17.2)
5 (most deprived	1,603	(19.2)	76	(16.9)	77	(19)	123	(18.2)	123	(21.1)
Ethnicity, n (%)										
White	5,799	(69.3)	326	(72.1)	288	(71.1)	497	(73.5)	451	(77)
South Asian	66	(0.8)	6	(1.3)	3	(0.7)	7	(1)	4	(0.7)
Black or other	184	(2.2)	13	(2.9)	12	(3)	17	(2.5)	9	(1.5)
Unknown	2,315	(27.7)	107	(23.7)	102	(25.2)	155	(22.9)	122	(20.8)
Smoking, n (%)										
Non-smoker	1,225	(14.6)	56	(12.4)	45	(11.1)	100	(14.8)	81	(13.8)
Ex-smoker	4,055	(48.5)	259	(57.3)	243	(60)	392	(58)	368	(62.8)
Current smoker	2,830	(33.8)	133	(29.4)	113	(27.9)	177	(26.2)	131	(22.4)
Unknown	254	(3)	4	(0.9)	4	(1)	7	(1)	6	(1)
Hypertension, n (%)	3,725	(55.5)	240	(46.9)	235	(42)	403	(40.4)	386	(34.1)
Total serum cholesterol in mmol/L, mean (SD)	5.6	(0.8)	5.6	(1)	5.6	(0.9)	5.6	(0.9)	5.5	(1)
HDL cholesterol in mmol/L, mean (SD)	1.3	(0.3)	1.3	(0.3)	1.3	(0.3)	1.4	(0.3)	1.4	(0.3)
Diabetes, n (%)	1,026	(12.3)	52	(11.5)	67	(16.5)	117	(17.3)	141	(24.1)
Consultations per year, n (IQR)	4.7	(2.4-8.3)	6.4	(3.5-10.7)	6.6	(3.7-11.2)	7.5	(4.1-12.7)	9.1	(5.2-14.5)
Years of pre-MI GPRD registration, n (IQR)	8.2	(5.2-12.9)	8.2	(5-14)	8.3	(5.1-12.8)	8.2	(5.1-13.1)	8.5	(5.2-13.5)

IMD: index of multiple deprivation; GPRD: General Practice Research Database; HDL: high density lipoprotein, IQR: inter-quartile range; MI: myocardial infarction

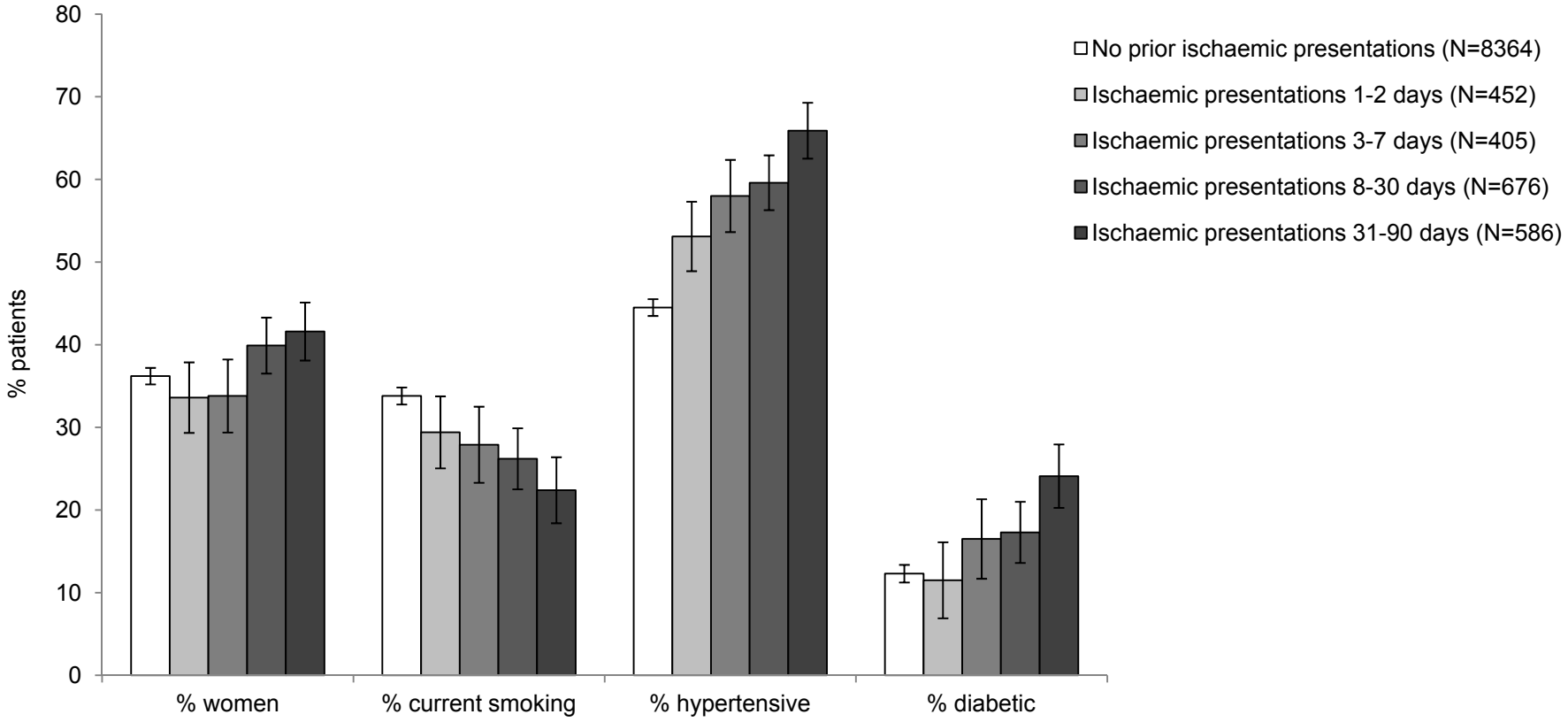


Figure 6.7 Sex and key cardiovascular disease risk factor prevalence, by timing of ischaemic presentation before first myocardial infarction, with 95% confidence intervals (N=10,483)

Table 6.13 Prescription of key cardiovascular medications in the six months and 90 days before myocardial infarction (MI) (N=10,483)

	No prior ischaemic presentations, N=8,364		Timing of ischaemic presentation prior to MI							
			1-2 days, N=452		3-7 days, N=405		8-30 days, N=676		31-90 days, N=586	
Blood pressure lowering, n (%)										
First prescription in 90 days	82	(1)	13	(2.9)	15	(3.7)	39	(5.8)	63	(10.8)
Prescription in 90 days	2,867	(34.3)	221	(48.9)	218	(53.8)	389	(57.5)	392	(66.9)
Prescription in 6 months	3,019	(36.1)	231	(51.1)	222	(54.8)	404	(59.8)	416	(71)
Lipid lowering, n (%)										
First prescription in 90 days	103	(1.2)	11	(2.4)	13	(3.2)	41	(6.1)	93	(15.9)
Prescription in 90 days	918	(11)	81	(17.9)	111	(27.4)	214	(31.7)	262	(44.7)
Prescription in 6 months	994	(11.9)	84	(18.6)	120	(29.6)	224	(33.1)	282	(48.1)
Antiplatelets, n (%)										
First prescription in 90 days	79	(0.9)	40	(8.8)	29	(7.2)	77	(11.4)	107	(18.3)
Prescription in 90 days	825	(9.9)	141	(31.2)	132	(32.6)	282	(41.7)	328	(56)
Prescription in 6 months	914	(10.9)	149	(33)	142	(35.1)	304	(45)	359	(61.3)
Nitrates, n (%)										
First prescription in 90 days	0	(0)	77	(17)	75	(18.5)	132	(19.5)	135	(23)
Prescription in 90 days	0	(0)	114	(25.2)	121	(29.9)	226	(33.4)	219	(37.4)
Prescription in 6 months	5	(0.1)	120	(26.5)	129	(31.9)	232	(34.3)	232	(39.6)

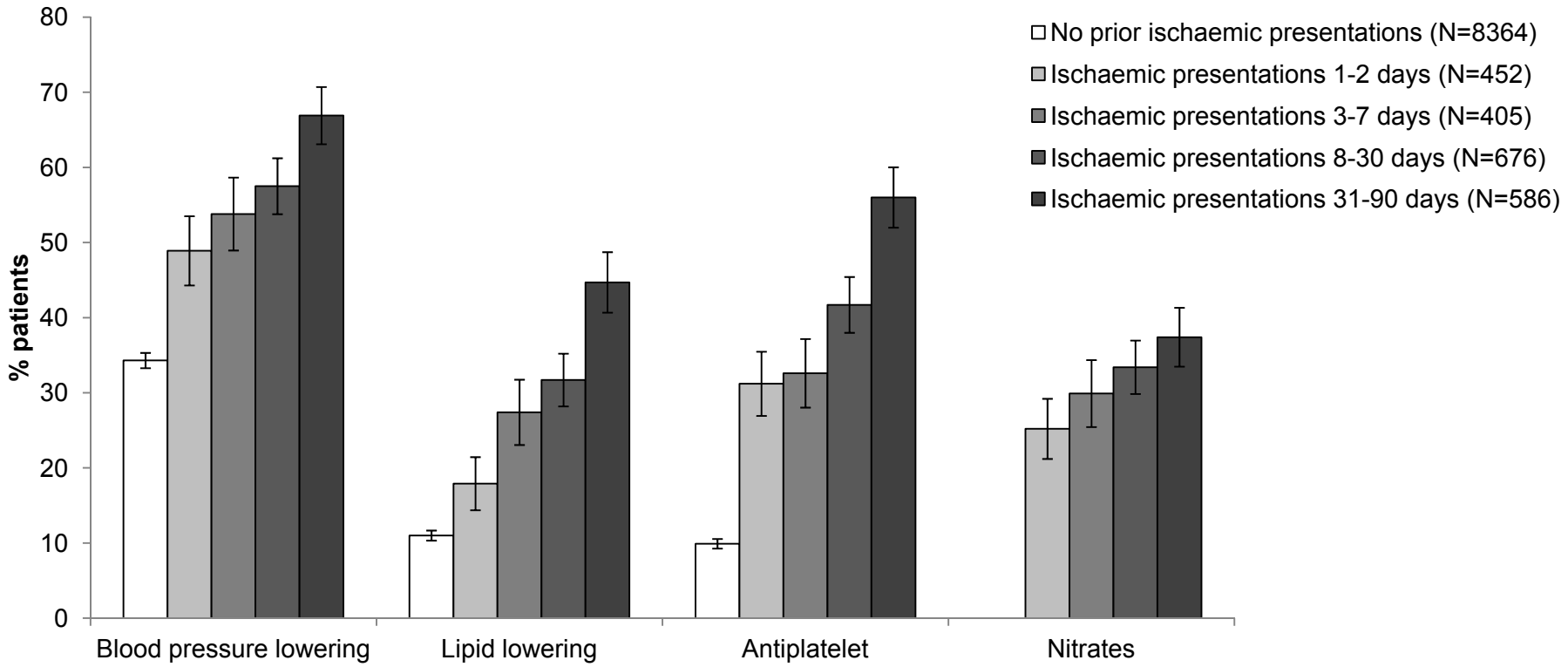


Figure 6.8 Prevalence of patients prescribed cardiovascular medications in the 90 days prior to myocardial infarction, by timing of ischaemic presentation before first myocardial infarction (with 95% confidence intervals) (N=10,483)

6.6.3 Coronary heart disease mortality after MI, by timing of presentation

There was a strong effect of the timing of clinical presentation prior to MI. Patients who presented in the 1-2 days before MI had the lowest rate of coronary heart disease mortality (HR=0.53 (95% CI 0.40-0.714)), with a weaker effect in patients presenting 3-90 days before MI (Figure 6.10). The crude Kaplan Meier survival curves for the first seven days after MI are shown in Figure 6.9, stratified by timing of ischaemic presentation. The hazard ratios are shown in Figure 6.10 (test for trend p=0.07).

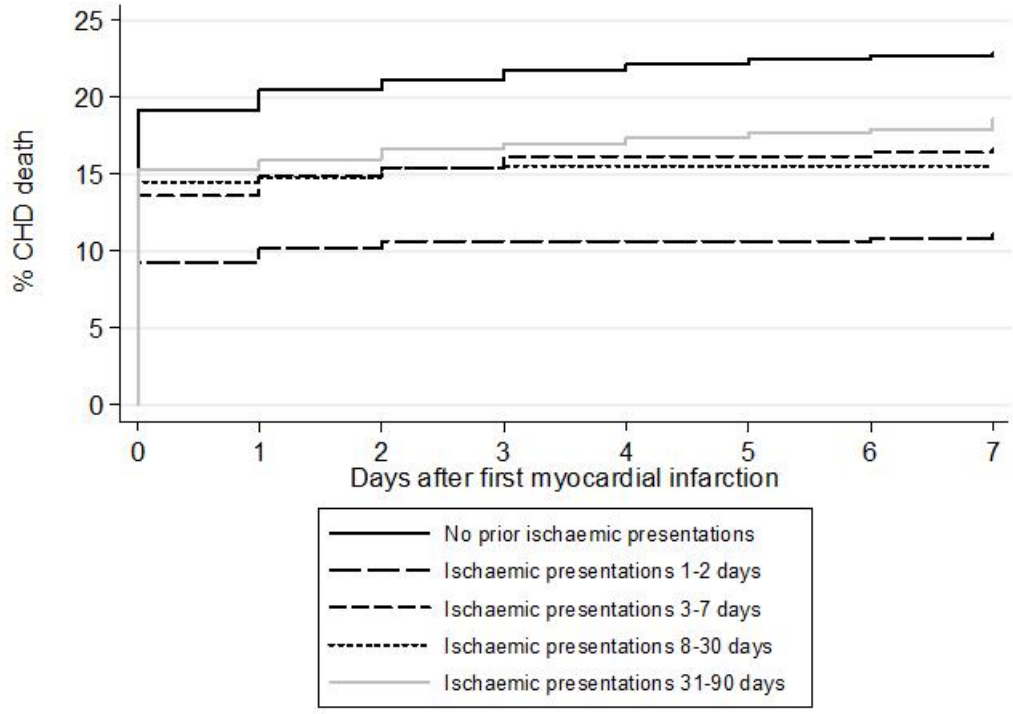
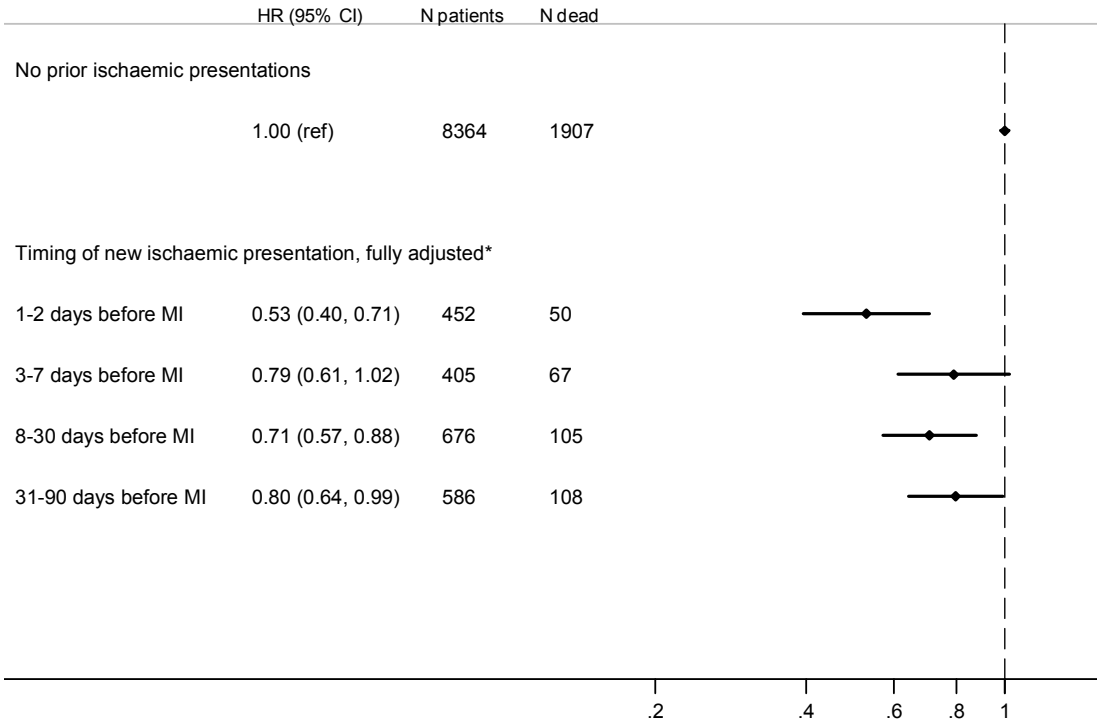


Figure 6.9 Seven day unadjusted Kaplan Meier for coronary heart disease (CHD) death after first acute myocardial infarction, stratified by the timing of ischaemic presentation with relation to the myocardial infarction (N=10,483)



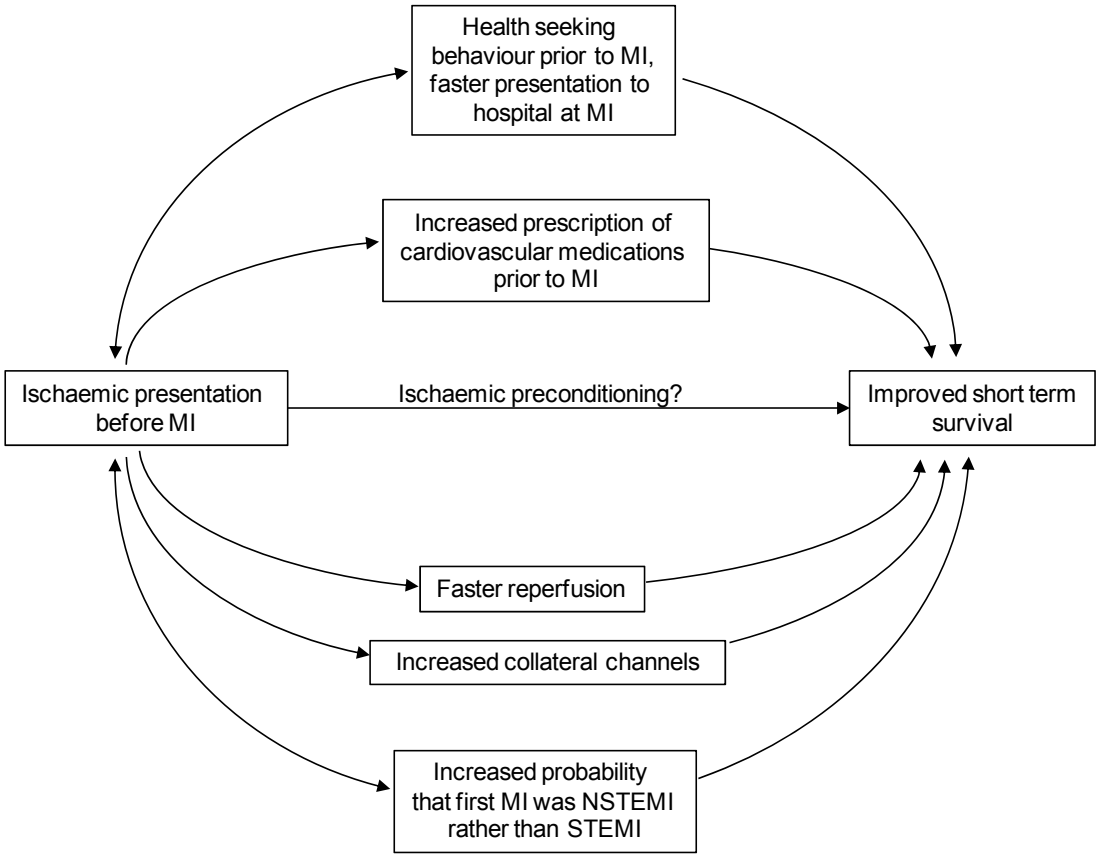
*Multivariable adjusted model includes age, sex, cardiovascular disease risk factors, and cardiovascular medications. HR: hazard ratio.

Figure 6.10 Hazard ratios and 95% confidence intervals describing the association of new ischaemic presentations at different times prior to first myocardial infarction (MI) with coronary heart disease mortality at 7 days after MI (N=10,483)

6.7 Results: possible explanations for the effects

6.7.1 Causal diagram

New ischaemic presentations in the 90 days before MI were strongly associated with improved survival in the first seven days after first MI. Possible mechanisms for this effect are shown in Figure 6.11. Where possible, in a post-hoc analysis, each of these possible pathways were assessed to determine the likelihood of a real ischaemic preconditioning effect.



MI: myocardial infarction; STEMI: ST-elevation MI; NSTEMI: non ST-elevation MI.

Figure 6.11 Causal diagram describing possible mechanisms for improved survival following presentation to the GP with atherosclerotic disease or chest pain before MI

6.7.2 Health seeking behaviour

Patients who consult for ischaemia in the 90 days before MI may be displaying health seeking behaviour, which might be associated with unknown confounders associated with better outcomes. A Cox regression analysis was performed to compare patients who consulted for any reason other than ischaemia in the 90 days before MI to those who did not consult. A consultation for a reason other than ischaemia in the 90 days before MI (n=11,495) was associated with an increased rate of coronary heart disease mortality at 7 days (HR=1.18 (95% CI: 1.09-1.28), P<0.001) (Figure 6.13). This health seeking behaviour could also feasibly affect the time taken for a patient's decision to go to hospital.

6.7.3 Time to hospital presentation and reperfusion treatment

There was insufficient power to adjust for admission and reperfusion treatment times in the subset of patients where this information was recorded. However, a comparison of the times in the two groups (Table 6.10) showed that the times to presentation and reperfusion treatment were longer in patients who consulted their GP for new ischaemic presentations. There was strong evidence for a longer time to presentation (P=0.0057) and longer time to reperfusion treatment (P=0.0062) in the group with clinical presentations before MI. Therefore, a faster time to reperfusion treatment is unlikely to explain the improved short term survival of these patients.

6.7.4 Faster reperfusion and collateral channels

One of the suggested mechanisms by which ischaemia prior to MI improves in-hospital outcomes is through faster reperfusion times. The data to assess this pathway were not available in this analysis and faster reperfusion remains a possible explanation of improved survival. Another mechanism is the development of collateral channels in patients with existing angina. There were no angiographic data in this analysis to assess this mechanism, and collateral channels could be responsible for improved survival, particularly in patients with existing ischaemic diseases.

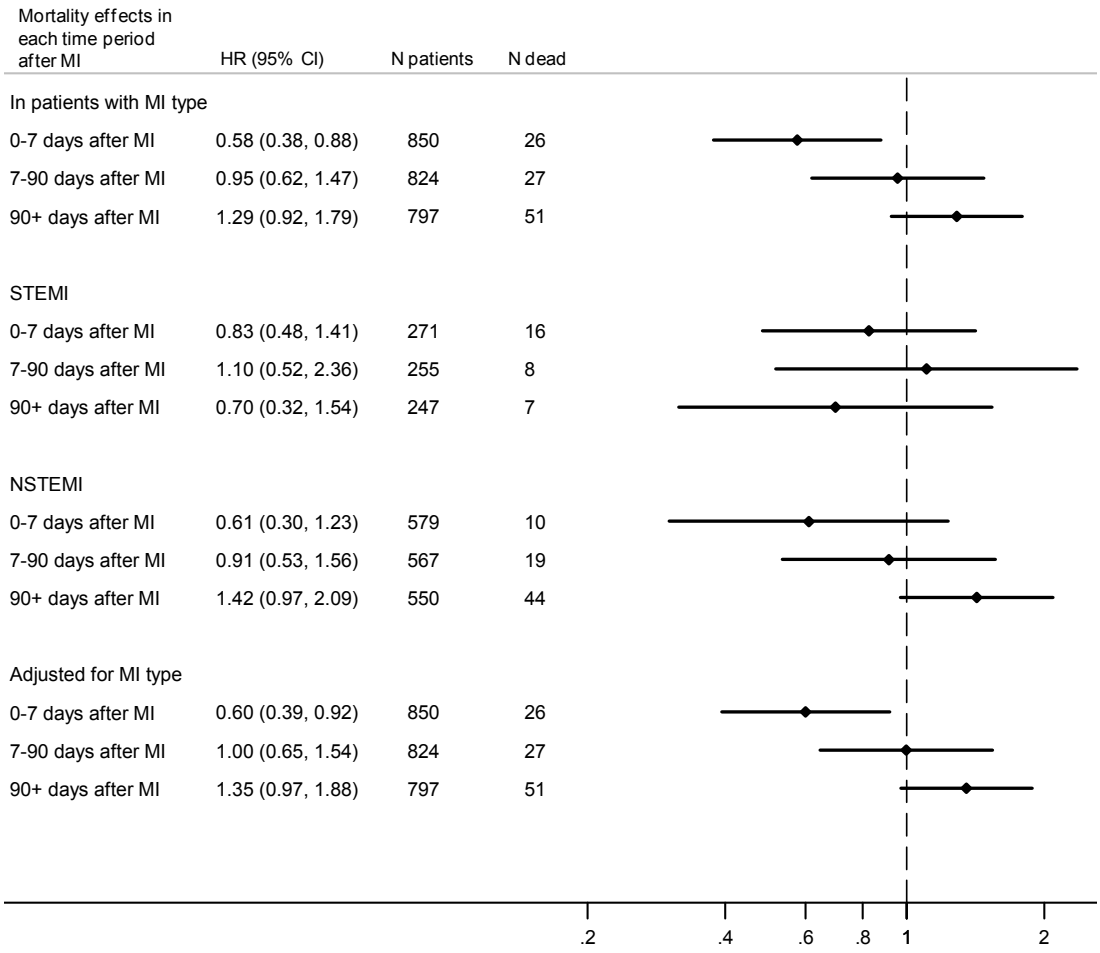
6.7.5 Use of cardiovascular medications

As discussed in section 6.5.3, a higher proportion of patients who had a new ischaemic presentation within 90 days of MI were initiated on blood pressure lowering, lipid lowering and anti-platelet medications compared to patients without prior ischaemic presentations. However, adjusting for prescription of cardiovascular drugs only changed the HR by a small fraction and showed that these drugs were negatively confounding the association (crude HR=0.68 (95% CI 0.60-0.76), cardiovascular medication adjusted HR=0.60 (95% CI 0.53-0.68)).

6.7.6 Adjusting for MI type

MI type was available in 7,666 patients (6,693 from MINAP, 973 from GPRD). Restricting to only these patients, the effect size was similar to the effect seen in the main analysis for the short term effect (HR=0.58 (95% CI 0.38-0.88), P=0.010 compared to 0.64 (95% CI 0.57-0.73) in the main analysis). After adjusting for MI type, the hazard ratio for the first seven days of follow-up in those with new ischaemic presentations was 0.60 (0.39-0.92), P=0.018), suggesting that MI type was not a strong confounder of the main association.

When the results were stratified by MI type, the effect in NSTEMI was similar to the main effect HR=0.61 (95% CI 0.30-1.23), but the effect in STEMI was weaker at 0.83 (95% CI 0.48-1.41), suggesting some of the short term increased survival among people with pre-event ischaemia could be explained by a higher proportion of NSTEMI. However, there was limited power in this smaller subgroup and the observed differences could be due to chance variation (Figure 6.12, Figure 6.13, and Figure 6.14).



Notes: MI: myocardial infarction; HR: hazard ratio; STEMI: ST-elevation MI; NSTEMI: non ST-elevation MI.

Figure 6.12 Hazard ratios comparing coronary heart disease death in patients with new ischaemic presentations in the 90 days prior to myocardial infarction (MI) to those with no prior ischaemic presentations. Hazard ratios are presented for coronary heart disease death in 0-7 days, 7-90 days and 90+ days post MI in patients with MI type recorded, stratified by MI type and adjusted for MI type (N with MI type recorded=7,666)

6.7.7 Coronary risk

Patients with existing ischaemic diseases had the worst Framingham cardiovascular disease risk profile, with 37% of patients in the highest risk category (>20% ten year hard CHD risk), compared to 29% in patients with new ischaemic presentations and 21% in those with no ischaemic presentations. Framingham risk was strongly associated with prior ischaemic presentations (P=0.001). In a crude analysis, Framingham risk was also associated with subsequent mortality.

However, adjusting for coronary risk score did not affect the hazard ratios for patients with new ischaemic presentations or existing ischaemic diseases (risk-adjusted HR=0.64 (95% CI 0.57-0.73) and main analysis 0.64 (95% CI 0.57-0.73) (Figure 6.13, Figure 6.14). This is likely to be because the confounding effect was accounted for by adjustment for the individual cardiovascular disease risk factors; at multivariate analysis Framingham risk score was not associated with mortality.

6.7.8 Further sensitivity analyses

6.7.8.1 30 day mortality

In the 30 days post-MI, the effect on mortality seen for new ischaemic presentations was slightly diluted compared to the effect observed in the first seven days in the main analysis (HR=0.75 (95% CI 0.68-0.83), P<0.001). There was no effect of existing ischaemic diseases compared to patients with no prior presentations (HR=0.97 (95% CI 0.90-1.04), P=0.345). After 30 days, the effect of new ischaemic presentations and existing ischaemic presentations was harmful, similar to the main analysis (Figure 6.13, Figure 6.14).

These results suggest that new ischaemic presentations are strongly associated with mortality benefits very shortly after MI and that after this brief period, mortality worsens. Combining the brief, initial beneficial period with a period of higher subsequent mortality led to a dilution of the beneficial effect. This also shows that the effect of new ischaemic presentations on coronary heart disease mortality changes quickly over follow-up and the analysis incorporating interactions with time in follow-up was appropriate.

6.7.8.2 All-cause mortality

The hazard ratio for the effect of new ischaemic presentations on all-cause mortality was 0.75 (95% CI 0.67-0.84), P<0.001), a slightly weaker effect size than described in the main analysis (Figure 6.13, Figure 6.14). This suggests that there is a reduced effect, or no effect at all, of new ischaemic presentations on non-coronary heart disease mortality, as the inclusion of non-coronary heart disease deaths leads to a diluted effect measure.

6.7.8.3 Definite and possible codes

In the main analysis, diagnostic codes rated by clinicians as 'definite' indicators of disease were used to define ischaemic presentations. When codes rated as 'possible' were included, there was little change in the hazard ratios for the effects on post-MI mortality (7 day HR=0.65 (95% CI 0.57-0.73), P<0.001) (see Figure 6.13, Figure 6.14). This suggests that the lists of codes rated as definite were sensitive enough to capture patients with atherosclerotic disease.

6.7.8.4 Non-ischaemic atherosclerotic disease

In the main analysis, patients with non-ischaemic atherosclerotic disease, including abdominal aortic aneurysm, heart failure and cardiac arrest were excluded. A sensitivity analysis including these additional patients showed a diluted effect. The hazard ratio for coronary heart disease mortality seven days after MI was 0.77 (95% CI 0.69-0.87). This was weaker than for the main analysis (HR=0.64 (9% CI 0.57-0.73)), (Figure 6.13, Figure 6.14). This suggests that the strong association of new ischaemic presentations with mortality seen in the main analysis were the result of ischaemia, rather than a generalised atherosclerotic disease status.

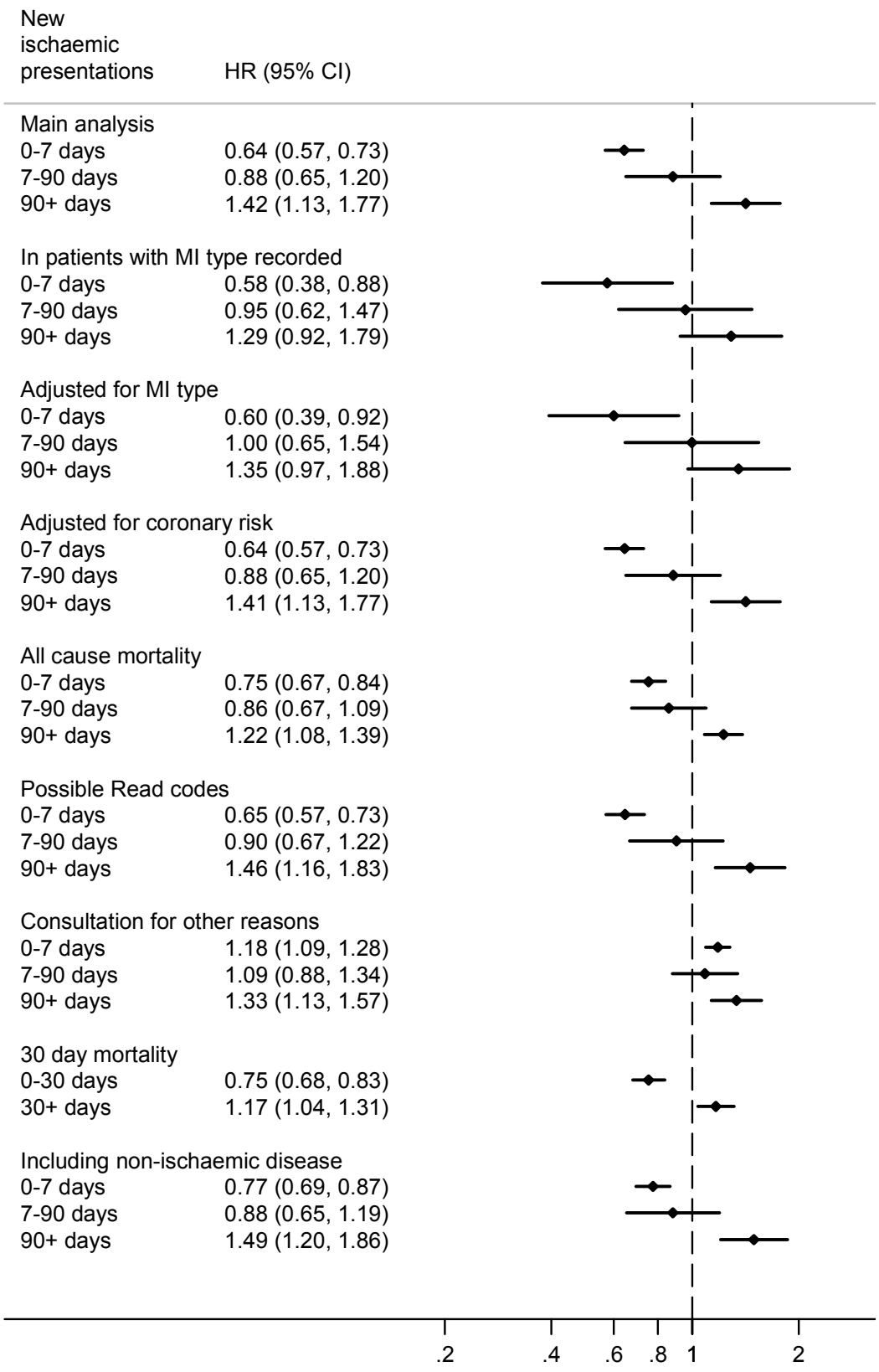


Figure 6.13 Results of sensitivity analyses part 1: hazard ratios (HR) for the 0-7 days, 7-90 days and 90+ days post myocardial infarction (MI), comparing the rate of mortality in patients with new ischaemic presentations (N=2,119) prior to MI to that of patients with no prior ischaemic presentations (N=8,364)

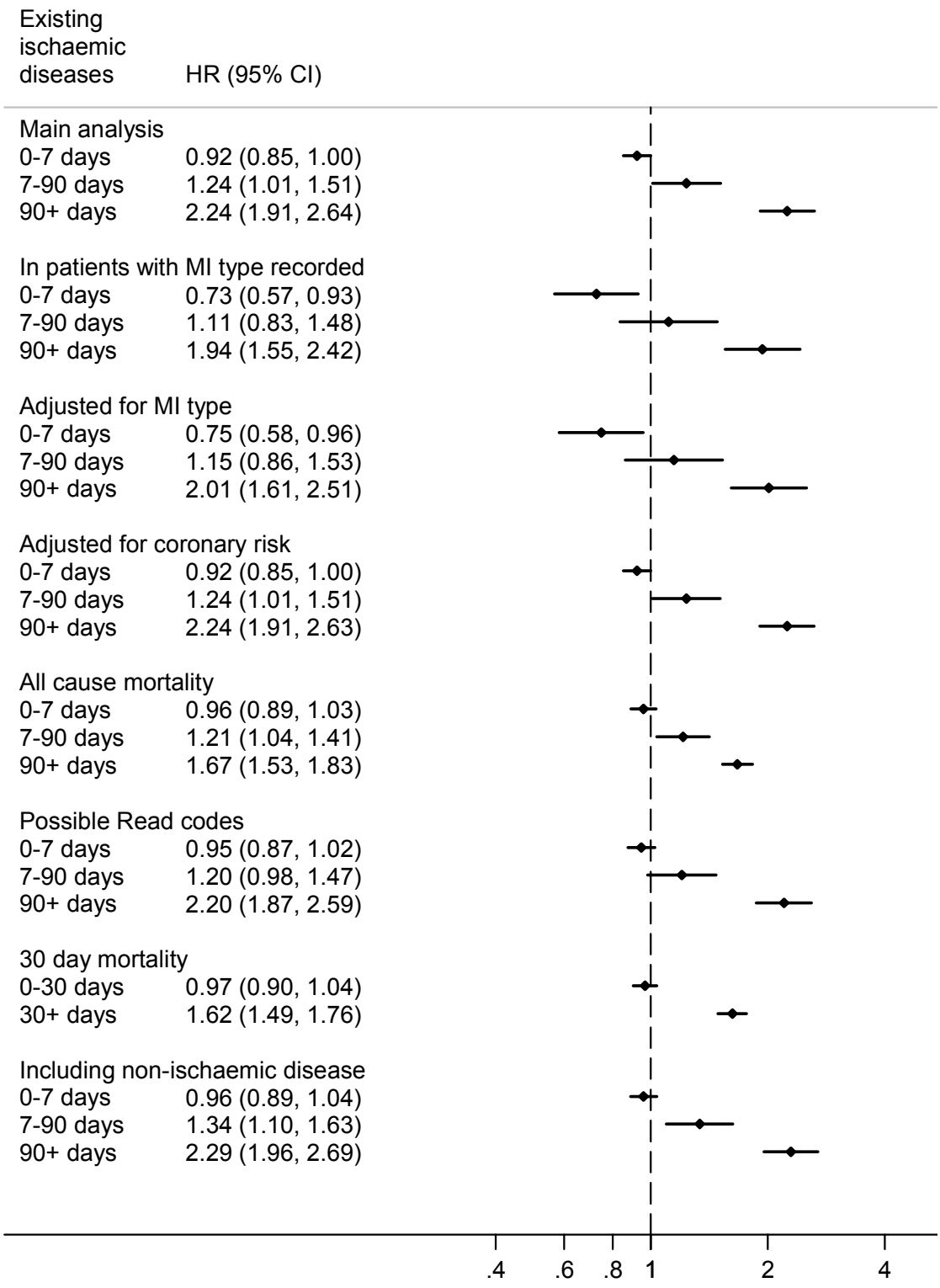


Figure 6.14 Results of sensitivity analyses part 2: hazard ratios (HR) for the 0-7 days, 7-90 days and 90+ days post myocardial infarction (MI), comparing the rate of coronary heart disease mortality in patients with existing ischaemic diseases (N=2,140) prior to MI to that of patients with no prior ischaemic presentations (N=8,364)

6.7.8.5 Chest pain and atherosclerotic disease exposures

In another sensitivity analysis, the exposure was split into new onset ischaemic atherosclerotic disease and chest pain to examine the validity of the combined exposure in the main analysis. The effect was the same (P=0.6445 for LRT) in each group (chest pain 7 day CHD mortality HR=0.67 (95% CI 0.56-0.80), P<0.001, ischaemic atherosclerotic disease HR=0.70 (95% CI 0.58-0.83), P<0.001), so the combined exposure was justified (Figure 6.15).

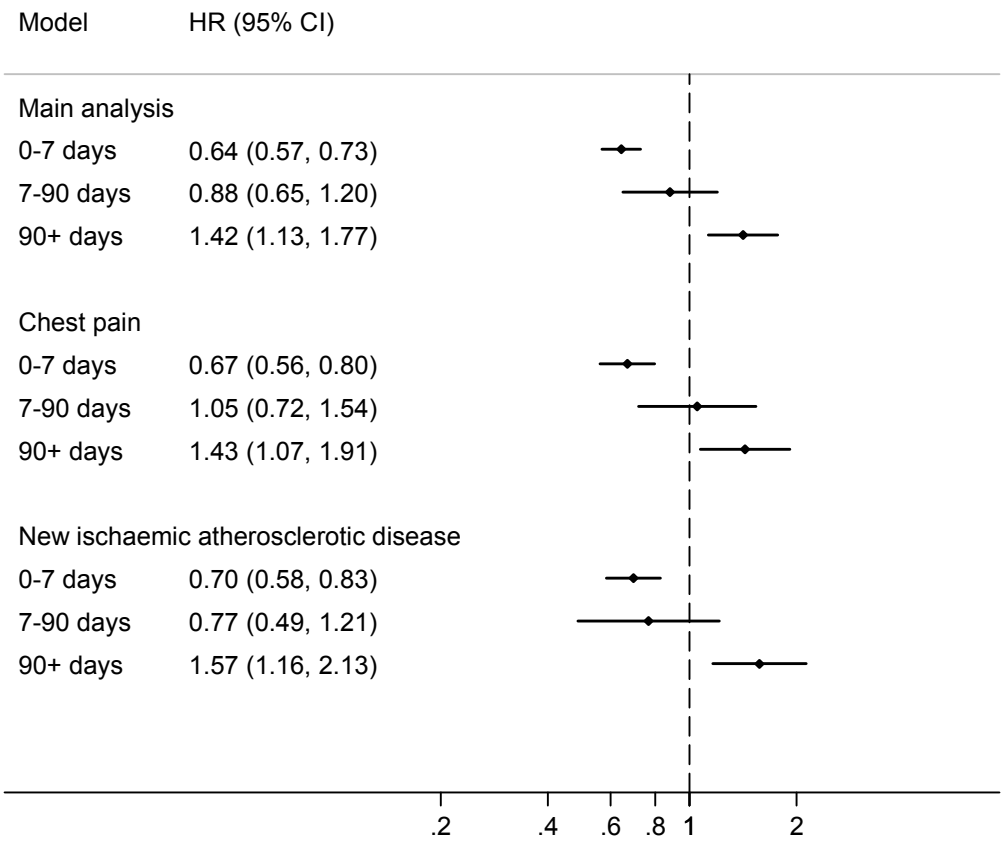


Figure 6.15 Sensitivity analysis describing the seven day coronary heart disease mortality effects in the main analysis, and in those with chest pain in the 90 days prior to myocardial infarction (N=1,078), and in those with new ischaemic atherosclerotic disease (N=1,041), compared to patients without any prior ischaemic presentations (N=8,364)

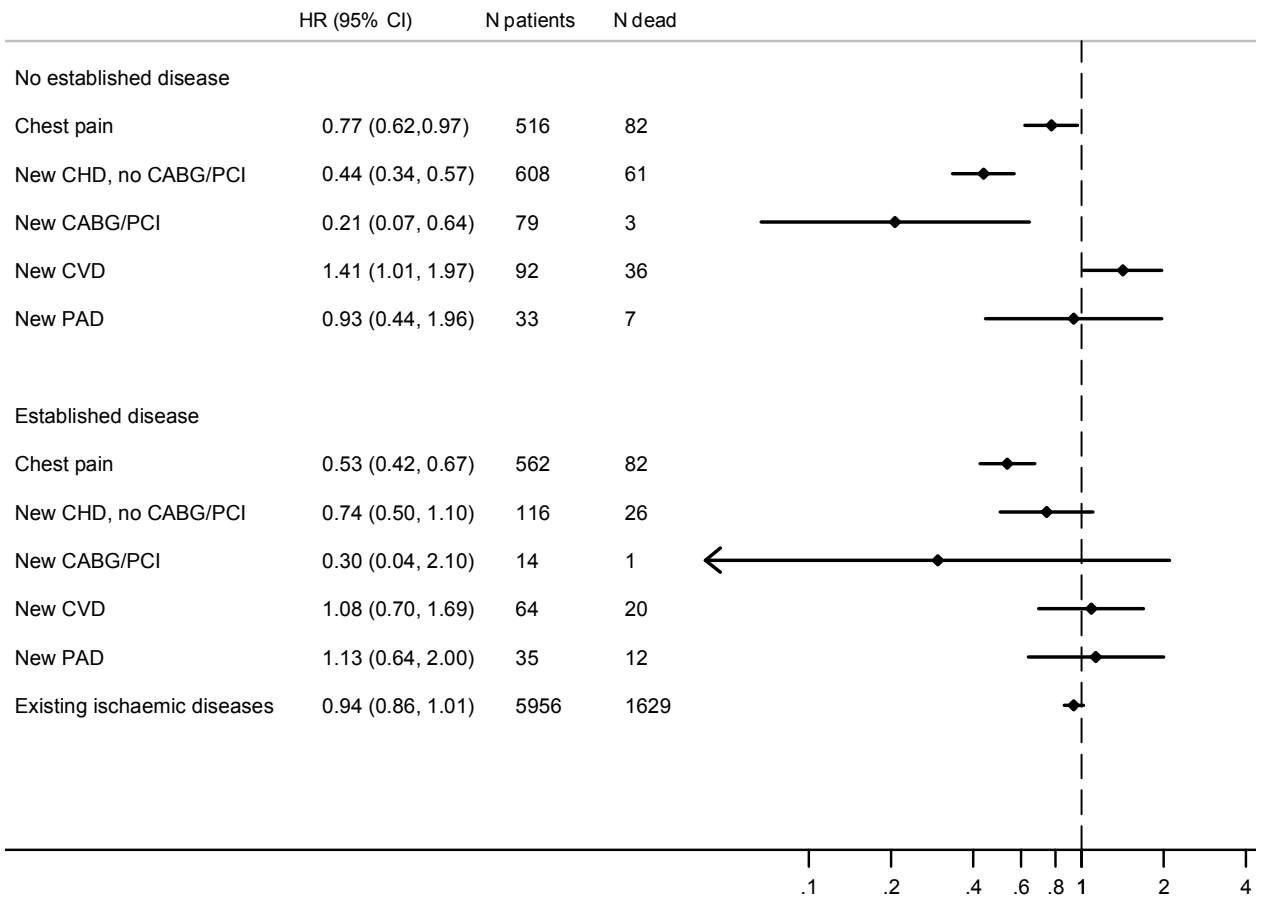
6.7.8.6 Effects of ischaemia in different arterial beds

The main exposure in this analysis was any new ischaemic presentation. This included chest pain, new nitrate prescription, and atherosclerotic disease diagnosis in any arterial bed. To examine this exposure further, the exposure was split into its constituent parts to examine which arterial beds were most strongly associated with mortality. This showed that the effects were restricted to myocardial ischaemia and chest pain. New onset coronary disease, with or without revascularisation, was strongly protective on mortality after MI. Chest pain in established disease and in patients without established disease has a strong protective effect on mortality after MI, compared to patients with no prior ischaemic presentations. Peripheral and cerebrovascular ischaemia were not associated with improved early coronary heart disease mortality. The number of patients with each subtype of exposure is shown in Table 6.14 and results of the Cox regression analyses for the first seven days after MI are shown in Figure 6.16.

Table 6.14 Numbers of patients with each subtype of exposure

		N	(%)
No established atherosclerotic disease >90 days before MI	No prior ischaemic presentations	8,364	(50.9)
	Chest pain	516	(3.1)
	New coronary disease, with CABG or PCI	608	(3.7)
	New coronary disease, no CABG or PCI*	79	(0.5)
	New CVD	92	(0.6)
	New PAD	33	(0.2)
Established atherosclerotic disease >90 days before MI	Chest pain	562	(3.4)
	New CHD, with CABG or PCI	116	(0.7)
	New CHD, no CABG or PCI*	14	(0.1)
	New CVD	64	(0.4)
	New PAD	35	(0.2)
	Existing ischaemic diseases	5,956	(36.2)

*Includes patients with new nitrate prescriptions in the 90 days prior to myocardial infarction (MI).
CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; CVD: cerebrovascular disease; PAD: peripheral arterial disease.



CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; CVD: cerebrovascular disease; PAD: peripheral arterial disease.

Figure 6.16 Hazard ratios for coronary heart disease mortality in the first seven days after myocardial infarction (MI) for patients with new ischaemic presentations (N=2,119) compared to those with no ischaemic presentations (N=8,364), stratified by type of ischaemic presentation prior to MI

6.8 Discussion

6.8.1 Summary

In this prospective analysis of fatal and non-fatal MI patients, those with new ischaemic presentations in the 90 days preceding MI had a lower rate of coronary heart disease mortality in the week following MI compared to those with no prior ischaemic presentations. This effect was largest in patients who consulted shortly before their infarct. Over the following months, the effect transitioned and for patients surviving past 90 days, previous ischaemia was associated with an increased rate of coronary heart disease mortality.

To our knowledge, no other studies have prospectively examined the onset of atherosclerotic disease or chest pain consultations in the period leading to MI. However, several studies have examined the effect of new-onset or chronic 'pre-infarction angina', measured retrospectively after MI. These studies have shown that pre-infarction angina is associated with improved in-hospital outcomes including smaller infarcts and in-hospital coronary heart disease mortality.[28, 30, 32, 147, 195, 206, 209, 216, 223] Our result showing improved mortality at seven days is consistent with this in-hospital effect of previous ischaemia. The effects on longer term coronary heart disease mortality have been less well-studied and have shown contradictory results, perhaps due to variation in the definition and timing of their exposures,[32, 147, 224] or their methods to examine changes in the effect over time. The current analysis showed that after 90 days of follow-up, the rate of coronary heart disease mortality was higher in the group with ischaemic presentations compared to those without any presentations. The effects described in this analysis were not explained by pre-MI coronary risk, MI type or by cardiovascular medications prescribed in response to ischaemic presentations.

Only one study has investigated the timing of angina prior to MI: Kloner showed that patients who reported angina in the 24 hours before infarct had a lower event rate and smaller infarcts, but found no effect of angina occurring more than 24 hours before infarct.[220] The detail of exposure definition, follow-up data and size of the current study provide sufficient power to clarify the effect of exposures at different time points on both short and longer term coronary heart disease mortality.

In this study, ischaemic presentations closest in time to the MI had the strongest effect on mortality, but that there was also an effect of patients with consultations for ischaemic presentations up to 90 days prior to MI.

The overall exposure of ischaemia in any arterial bed prior to MI was associated with improved short term coronary heart disease mortality. However, further analysis showed that the effect was restricted to patients with myocardial ischaemia (chest pain or a new coronary diagnosis). The number of patients with non-myocardial ischaemia in the 90 days prior to MI was low and these effects require further consideration given studies showing evidence for a remote preconditioning effect on post-MI survival.[218, 225, 226]

6.8.2 Possible explanations

Although this study was not designed to investigate mechanisms for differences in survival, various factors were examined to explain the effects that were seen in the main analysis.

6.8.2.1 Time to hospital admission and reperfusion

The differences in rates of coronary heart disease mortality between groups did not appear to be explained by faster time to hospital admission or reperfusion. The times were longer in those who consulted with their primary care physician, perhaps because symptoms built up gradually in these patients. These results are similar to a study of hospitalized MI patients, where patients without angina had the shortest delay time from symptom onset to admission and those with angina (stable or unstable) had longer delays.[222]

6.8.2.2 Prescription of cardiovascular medications

It was hypothesised that patients who presented to their physician with new ischaemia would be prescribed drugs in response to these symptoms to reduce their cardiovascular disease risk (anti-anginal, blood pressure lowering, lipid lowering, or antiplatelets), which could have affected subsequent mortality. The cardiovascular medication prescription data in this study were of high quality: these drugs are mainly prescribed in primary care and cannot be prescribed without being recorded in the database. In this study, patients with new ischaemia were more likely to be prescribed these drugs but adjusting for this did not change the association with coronary heart disease mortality. While other analyses have, to differing degrees, controlled for drug use (ascertained retrospectively),[227, 228] ours is the first to adjust for drugs with data collected prospectively, in all four of these drug classes.

6.8.2.3 The effect of MI type: STEMI and NSTEMI

The majority of studies in natural ischaemic preconditioning were conducted before the relatively new classification of MI into STEMI and NSTEMI, and therefore none have compared the effects between MI types. This study showed that previous ischaemic presentations were associated with increased NSTEMI. This is consistent with our previous study describing a higher atherosclerotic burden in NSTEMI patients overall,[229] and experimental evidence showing reduced ST-elevation on repeated arterial occlusion during CABG.[214] In the Global Registry of Acute Coronary Events, previous nitrate therapy in over 50,000 patients with acute coronary syndrome (ACS) was shown to be associated with increased non ST-elevation ACS. However, in a natural setting, whether ischaemic symptoms are causally related to subsequent MI type, or whether patients with NSTEMI are simply more likely to experience an intermittent, stuttering onset of MI cannot be determined from these data.

In the current study there was a suggestion of differing effects of pre-MI ischaemic presentations on survival among STEMI and NSTEMI patients, though there was insufficient power among those with known MI type to exclude the possibility that the observed differences simply reflected chance variation. The majority of previous research in this field has been in STEMI patients only and has shown evidence for effects on short term outcomes; the results from this study suggest that there may also be an effect in NSTEMI.

It is has been widely shown that in-hospital survival is poorer for STEMI patients than NSTEMI patients, but that NSTEMI patients have a poorer longer term prognosis. Given the finding that patients with first AMI and prior atherosclerotic disease diagnoses are more likely to have NSTEMI,[229] some of the effect seen in the main analysis may have been driven by differences in MI type.

Our subgroup analysis showed that although adjusting for MI type slightly attenuated the hazard ratio for MI overall, some evidence for an effect persisted. This suggests that MI type is not responsible for much of the protective effect of prior ischaemic presentations.

6.8.2.4 Health-seeking behaviours

Patients visiting their physician in the weeks or months before MI may be displaying health seeking behaviour, which is associated with improved outcomes in some studies (e.g. the ‘worried well’). However, in a sensitivity analysis there was no protective effect

associated with consultation for reasons other than ischaemia, suggesting that the observed effect is specific to ischaemic presentations prior to MI and not simply a result of increased health-seeking behaviour.

6.8.2.5 Coronary risk

The initial tabulation of patients showed that patients with existing ischaemic diseases and those with new ischaemic presentations in the 90 days prior to MI had the highest Framingham risk. When the prevalence of each risk factor and medication were examined by timing of ischaemic presentation, the prevalence of risk factors and prescription of cardiovascular medications in those who presented very shortly before MI were at a similar level to the prevalence in patients with no ischaemic presentations. Due to these associations between presentation and risk factors, the multivariate models were adjusted for each risk factor and medication. However, even after taking account of these, an association between presentation and mortality remained.

The main results were also adjusted for pre-MI coronary risk scores (based on Framingham 10 year 'hard' CHD outcomes). This had no effect on the results seen in the main analysis, including for longer term follow-up. This might be for two reasons. First, the analysis was already adjusted for all components of the risk score, so additional adjustment for the composite added little further data to the analysis. Second, the lack of effect may have been due to the unsuitability of Framingham risk scores in this population (some of whom already had diagnosed atherosclerotic disease and diabetes, for whom the score was not designed). It is possible that a risk score designed for UK primary care data, or for patients with and without diagnosed disease, may have had more effect. However, another measure of coronary risk is unlikely to explain away the associations found here.

6.8.2.6 Ischaemic preconditioning

As the effects seen in our analysis were not explained by any of the factors discussed here and are unlikely to be entirely explained by residual confounding, the results may represent a natural ischaemic preconditioning effect in a clinical setting. Classic preconditioning occurs in the few hours prior to MI and is unlikely to explain these observations. However, 'delayed' preconditioning, whereby ischaemia in the 12 hours prior to MI has a beneficial effect on survival,[230] could explain some of the effect that was observed, particularly in the group presenting in the 1-2 days prior to MI. The effects seen

at times further removed from MI are more difficult to explain using classic or delayed preconditioning theory, but it is possible that symptoms of ischaemia persisted after their physician consultation and occurred closer to MI than recorded in these data. An alternative explanation is the possibility of collateral channel formation in patients with ischaemia.[223]

6.8.3 Strengths

This study was in a population based sample, drawn from primary care practices in England. Patients with AMI in this study were drawn from four data sources and inclusion of fatal AMI patients who did not reach hospital is unique, as most other studies drew their samples from hospitals or trial populations.

The quality of the linked data was a major strength of this study. The prospective data from primary care allowed detailed measurement of chest pain and atherosclerotic disease exposures prior to MI without errors in recall. Only codes rated by two clinicians as 'definite' indicators of a diagnosis were used in to define exposure, and a sensitivity analysis confirmed that inclusion of 'possible' codes had no effect on our result, so our exposure definitions were likely to have been adequate. GPRD diagnoses have undergone extensive validation and shown to be of high quality.[53] MINAP hospital data provided detailed information regarding diagnosis of MI, type, size and timing; MINAP data undergo regular checks of validity and completeness to ensure data quality. ONS mortality data are near complete due to mandatory death registration in the UK, and these data allowed us to characterize the exposure effect in fatal MI cases who did not reach hospital, and examine longer term follow-up for all patients in the study.

6.8.4 Weaknesses

Presentations to the GP were referred to as 'ischaemic presentations' but this is an assumption based on patient consultation with their primary care physician and the recording of certain codes for new atherosclerotic disease and chest pain. The ischaemic nature of their symptoms is inferred and not based on ST segment monitoring or myocardial perfusion imaging. This is a weakness of using routinely collected, observational data, which has not been collected for the purpose of research. However, chest pain prior to MI is likely, in retrospect, to have been ischaemic in nature, and a new diagnosis of coronary disease is also likely to be associated with ischaemia. Any misclassification of symptoms is unlikely to

have been differential with respect to coronary heart disease mortality and therefore should not affect the hazard ratios generated in the analysis.

Not all patients with ischaemic symptoms will report these to a primary care physician but any underestimation of exposure is unlikely to account for the observed association. While there is likely to be some residual confounding that our observational analysis could not take account of, this is unlikely to account entirely for the observations in this study. Misclassification in the true timing of symptoms, which may have preceded the date of consultation in general practice, may indicate that our results include a time lag, whereby the effect seen at 1-2 days might actually reflect true symptoms shortly beforehand. Cardiovascular medication data were based on prescriptions issued in primary care. Misclassification of drug exposures could also have arisen from failure to collect or use prescribed medications, from over the counter use of aspirin, or through patients saving medications that were prescribed earlier.

The risk factor measures adjusted for in this analysis may not be an accurate reflection of true cardiovascular disease risk at the time of MI. This is for two reasons. First, the measures of all risk factors may have been collected long before MI; we did not assess the duration between risk factor measurements and the date of MI. Second, our measures of blood pressure and cholesterol were based on means of data collected throughout pre-MI follow-up, so may not have been an accurate reflection of those measures at any one time. Other strategies to deal with such repeated measurements in routinely collected data could have been used (for example taking the closest measure to MI or averaging those taken in the year before MI), but we justify use of averaged measures in this study as a pragmatic attempt to capture past and current information about a patient's cardiovascular disease risk. However, adjustment for cardiovascular disease risk factors did not cause substantial attenuation of the associations described between ischaemic manifestations and coronary heart disease mortality, so any misclassification of these risk factor measures is unlikely to explain the results of this analysis. A final weakness of this analysis was the inability to look at ischaemia occurring in the one to two hours prior to MI, which is suggested as 'classical' preconditioning and associated with large reductions in infarct size. Ischaemic presentations on the date of MI were not included in this analysis as they were likely to represent coding of the infarct itself rather than pre-MI symptoms. This is another disadvantage of using routinely collected data rather than researcher-led studies, but such data are likely to be the only way of ascertaining pre-MI data in a large, population-based sample.

6.8.5 Implications for research

While the overall effect of previous ischaemia was characterised with some certainty, our understanding of the role of MI type was limited by GPRD population coverage and the proportion of practices consenting to data linkage. Future data linkage will involve more primary care practices and may therefore allow characterization of the differential effects of natural preconditioning by MI type and gain improved understanding of the effects in non-coronary arterial beds.

6.8.6 Conclusion

In the first prospective study of symptoms of ischaemia prior to MI, symptoms reported to the general practitioner prior to MI were associated with a lower rate of short term and a higher rate of longer-term coronary heart disease mortality following MI. The strongest effects were observed in patients with exposures closest to MI, but there was still an effect of ischaemia occurring up to 90 days prior to MI. These observations are consistent with a natural ischaemic preconditioning effect, observed for the first time in a clinical setting.

6.9 Chapter summary

- Chest pain, angina and ischaemia occurring shortly before MI have been suggested as clinical correlates to ischaemic preconditioning.

- This study compared patients with and without new or existing ischaemic presentations prior to MI in terms of subsequent infarct characteristics and coronary heart disease mortality.

- Patients with new ischaemic presentations in the 90 days before MI experienced lower CHD mortality in the first seven days after MI compared to those with no prior ischaemic presentations, but subsequent mortality was higher.

- For patients in whom MI type was recorded, those with previous ischaemia were more likely to have non ST-elevation MI type.

- These observations could represent a natural ischaemic preconditioning effect, observed in a clinical setting.

Chapter 7 Aspirin and statins prior to myocardial infarction

7.1 Summary

This chapter describes an investigation into the prescribing of aspirin and statins for primary prevention and their association with outcomes at MI, including presentation with ST-elevation, infarct size and short term mortality. A review of the literature on this topic is followed by an analysis of aspirin and statin prescribing for patients identified with MI in GPRD, HES, MINAP and ONS.

7.2 Literature review

7.2.1 Introduction

Aspirin and statins have been shown to reduce cardiovascular morbidity and mortality in randomised controlled trials, both in primary and secondary prevention.[39-44] Risk prediction scores are often advocated for use in primary care to establish which patients at most risk from cardiovascular disease and to prioritise treatment with aspirin and statins. The first and most well-recognised risk prediction tool is the Framingham risk score, which, for coronary heart disease, takes information on patient age, blood pressure, cholesterol and smoking to generate a predicted risk of 'hard' CHD endpoints (MI and coronary heart disease death) over ten years. UK guidelines for use of aspirin and statins in primary prevention are described in the next sections.

7.2.1.1 Aspirin for primary prevention of cardiovascular disease

Recommendations by British bodies for the use of aspirin in primary prevention of cardiovascular disease are described in Table 7.1. Up until 2009, low dose aspirin was recommended for prophylactic use in patients with a cardiovascular disease risk of 20% or more over ten years by the Joint British Societies' (JBS) guidelines on prevention of cardiovascular disease in clinical practice.[231] It was also recommended by the National Institute for Health and Clinical Excellence (NICE) in nearly all patients with type 2 diabetes mellitus,[232] and by the Scottish Intercollegiate Guidelines Network (SIGN) 2007 guideline on prevention of cardiovascular disease.[233] Framingham risk equations are most frequently used in estimating cardiovascular disease risk, and for the British guidelines described here, recommendations are based on 20% risk of a first cardiovascular disease event (i.e. coronary, cerebrovascular, peripheral arterial) over ten years.

However, in 2009, a meta-analysis of data from randomised trials called into question the use of aspirin in primary prevention, concluding that it was of uncertain value in the reduction of occlusive events.[45] The Medicines and Healthcare Regulatory Agency subsequently issued guidance indicating that use of aspirin in primary prevention of thrombotic vascular disease was unlicensed[234] and more recent guidance issued by SIGN does not recommend aspirin.[235] However, ongoing trials are continuing to establish its effect in primary prevention, and it is likely that many patients initiated on aspirin prior to the 2009 guidance are still using aspirin off label.

Table 7.1 British guidelines for the use of aspirin in primary prevention of cardiovascular disease

Aspirin	
JBS 2, 2005[231]	• Aspirin 75mg daily for: – Individuals with ≥20% cardiovascular disease risk over 10 years once hypertension, if present, is controlled to systolic <150mmHg and diastolic <90mmHg; – All people with diabetes.
NICE, 2008[236]	In patients with diabetes, offer low dose aspirin, 75mg daily to: • A person who is 50 years old or over, if blood pressure is below 145/90mmHg; • A person who is under 50 years old and has significant other cardiovascular disease risk factors (features of metabolic syndrome, strong early family history of cardiovascular disease, smoking, hypertension, extant cardiovascular disease, microalbuminuria).
MHRA, 2009[234]	"Aspirin is not licensed for the primary prevention of vascular events. If aspirin is used in primary prevention, the balance of benefits and risks should be considered for each individual, particularly the presence of risk factors for vascular disease (including conditions such as diabetes) and the risk of gastro-intestinal bleeding."
SIGN, 2007,[233] 2012[235]	**2007 guideline:** • Consider aspirin daily for: – Patients with a calculated cardiovascular disease risk of ≥20% over ten years; – All people with type 2 diabetes who are over 50 years of age, and for selected younger individuals who are considered to be at increased cardiovascular disease risk. **2012 guideline:** • Aspirin is not recommended for the primary prevention of vascular disease when benefits are considered against the increased risk of haemorrhage.

JBS: Joint British Societies; NICE: National Institute for Health and Clinical Excellence; MHRA: Medicines and Healthcare Regulatory Agency; SIGN: Scottish Intercollegiate Network.

7.2.1.2 Statins for primary prevention of cardiovascular disease

Statins have been recommended by NICE, SIGN and the JBS for primary prevention of cardiovascular disease for several years. The guidelines for use of statins are described in Table 7.2. The most recent British guidelines from NICE recommend use of statins in patients who have 20% or greater cardiovascular disease risk over ten years and in people with diabetes. Previous guidelines from JBS and SIGN use the same threshold for statin treatment. Other lipid lowering therapies are not recommended for primary prevention of CHD (including fibrates, nicotinic acid and anion exchange resins, ezetimibe).

Table 7.2 British guidelines for the use of statins in primary prevention of cardiovascular disease

Statins	
JBS, 1998[237]	Prescribe statins preferentially to patients with a 30% ten year risk of CHD. When resources allow, treat patients with ≥15% ten year risk of CHD.
JBS 2, 2005[231]	Prescribe statins in the following groups: • Asymptomatic people at high CVD risk (≥20% over 10 years): in all people to achieve the total and LDL cholesterol targets. (Audit standards: Total cholesterol <5.0mmol/l, LDL cholesterol <3.0mmol/l. Optimal treatment standards: total cholesterol <4.0mmol/l, LDL cholesterol <2.0mmol/l). • All people aged 40 years or more with diabetes. • All people with diabetes aged 18-39 and at least one of the following: retinopathy, nephropathy, poor glycaemic control, elevated blood pressure requiring drug therapy, total cholesterol >6mmol/l, features of metabolic syndrome, family history of premature CVD.
SIGN, 2007[233]	• Adults >40 years of age, with 10 year risk of CVD event ≥20% should be considered for daily treatment
NICE, 2008[232]	• ≥20% risk of cardiovascular disease over 10 years based on an appropriate risk calculator or by clinical assessment in older people, people with diabetes or high risk ethnic groups. Treatment with simvastatin 40mg is recommended.

JBS: Joint British Societies; NICE: National Institute for Health and Clinical Excellence; SIGN: Scottish Intercollegiate Network; CHD: coronary heart disease; CVD: cardiovascular disease.

7.2.1.3 Adherence to guidelines in primary care

There is some evidence to suggest that guidelines regarding use of primary preventative medications are not being met. An analysis of the Health Survey for England in 1998 found that just 3% of people with the highest ten year Framingham CHD risk of over 30% (reflecting the 1998 JBS guidelines[237]) were taking lipid lowering medication.[238] More recently the same authors found that use had increased over time but was still far below the prevalence expected if the guidelines were followed.[239] However, introduction of more guidelines and the Quality Outcomes Framework[183] will also have led to an increase in the prevalence in statin prescribing, particularly to those at high risk.

Lack of guideline adherence is due to multiple factors including concerns of the GP regarding: cost to the patient and health service, increased workload to monitor treatment, dosage and side effects, the unnecessary medicalisation of asymptomatic patients, other treatment priorities, low patient life expectancy, and concerns about lack of change in patient lifestyle and health behaviour.[240] Barriers to guideline adherence on the patient side include refusal to take medication and concerns about side effects.[241]

7.2.1.4 Literature review aim: MI outcomes in users of aspirin and statins

While cardiovascular events are reduced by statin and aspirin use, some patients do have MI while using these drugs. Compared to MI patients who do not use these drugs, these patients may be at higher risk for adverse outcomes at the time of MI for two reasons: first, the GP believed them to be at a high enough vascular disease risk to require medication, and second they have had MI despite this increased level of protection.

Few studies have examined the effects of aspirin and statin use in patients who still go on to have MI. Therefore, the aim of this review was to collate the evidence to date regarding the effect of aspirin and statin prescribed prior to MI on presentation (STEMI and NSTEMI or the appearance of Q waves), infarct size and short term mortality.

7.2.2 Literature review methods

7.2.2.1 Search strategy

Databases and sources

A literature search was completed in May 2012 in the English language medical literature for studies examining the effects of previous antiplatelet or lipid lowering agent use on outcomes at MI.

Search keywords and terms

Searches were conducted in Medline and Embase. Search terms are described in Appendix A, Table 10.21. Three searches were combined: the first to identify studies examining MI, the second to identify studies examining cardiovascular therapies, and the third to restrict the search to studies indicating use prior to infarction.

Inclusion criteria

Studies were included only if they fulfilled the following criteria:

1. Included patients with first MI;
2. Examined a specific objective regarding the effect of prior use of a cardiovascular medication;
3. Examined clinical outcomes at the time of MI including infarct size, or clinical presentation, or post-MI outcomes;
4. Study in humans;
5. Manuscript written in English language.

Procedure

Titles and abstracts of the studies identified in the initial search were screened for relevance. Any studies deemed to be relevant were obtained as full text and were assessed according to the inclusion criteria. To ensure that no relevant studies were missed, the reference lists of all included studies were examined. Cited reference searches were also performed for key studies.

In the first instance, only studies meeting all inclusion criteria were included. However, this was shown to be too restrictive in the evaluation of effects for most drugs. Therefore, the inclusion criteria were relaxed twice: first to include studies in recurrent MI, and second to include studies in all acute coronary syndromes rather than MI only.

7.2.3 Results: aspirin

Three studies met all inclusion criteria and examined the effects of aspirin use prior to first MI.[242-244] These studies investigated effects on infarct size[242] and severity.[242-244] The size of the studies varied from 342 patients in the setting of a randomised trial, to over 100,000 patients in a coronary heart disease register. Aspirin was the most widely studied medication in relation to outcomes at MI and a further eight studies were identified that examined the effects of aspirin use prior to MI as a main research question but did not restrict their study to first MI. The findings from these studies are summarised below and in Table 7.3.

7.2.3.1 Effects on infarct size

Of the three studies that met all inclusion criteria, only one (Ridker, 1991) examined the effects on infarct size.[242] An additional four studies that included recurrent MI also examined infarct size. These are described below.

The US Physicians' Health Study, a randomised, double blind placebo-controlled trial of low-dose aspirin, assessed infarct size in first non-fatal MI.[242] There was no effect of aspirin on infarct size as measured by peak CK-MB levels (145.0 IU/l in aspirin group, 142.8 in placebo group, P=0.93). This result was stratified by age group (40-59, 60-89) and there was no effect modification. No multivariate analysis was performed and although there is no confounding by indication due to randomisation of patients to aspirin or placebo, there may have been important differences in the groups of patients who had MI and these were not accounted for. Additionally this study was restricted to non-fatal MI and the authors acknowledged that there may be a real effect of aspirin on infarct size, but that this may have been unobservable in an analysis restricted to non-fatal MI. Power to detect an effect of aspirin may also have been a limitation of this study. Despite a large study population of over 22,000 physicians, only 342 cases arose over the five year study period.

Abdelnoor (1999),[245] Col (1995)[246] and Mukamal (1999)[247] showed a beneficial effect of aspirin use,[245-247] while one small Israeli study found no effect. The studies showing beneficial effects performed multivariate analyses taking into account demographic variables, previous coronary disease diagnoses, cardiovascular disease risk factor and medication use and still showed an effect of previous aspirin use. After adjustment, there was a smaller infarct size in patients with previous aspirin ($P<0.001$ Abdelnoor,[245] $P=0.03$ Mukamal[247]). Col (1995) dichotomised infarct size into 'large' versus 'small', where large infarcts were defined as those with peak CK levels more than five times normal, and small infarcts were peak CK less than two times normal.[246] Using this categorisation, patients using aspirin prior to MI had 1.40 times the odds (95% CI 1.06-1.84) of having a 'small' infarct after adjusting for demographic variables, risk factors and other cardiovascular medication use prior to MI.

While these studies performed multivariate analyses, there might be some residual confounding by indication if the adjustments were inadequate or confounders were poorly measured.

The randomised trial held information about dose and duration of use. However, this was the same across all exposed patients in the study and therefore no information about potential dose-response effects of aspirin could be examined. Duration of use was not included in the analysis. In each of the other studies described, no information on dose or duration of use was available as exposure information was ascertained retrospectively.

Table 7.3 Studies examining the effect of previous aspirin use on infarct size

Author, year	Country	Patients included	Years of data collection	N patients	N (%) taking aspirin	Exposure measurement	Peak CK or CK-MB (IU/l) in patients +/- aspirin	Was multivariate analysis performed?	Effect measure/ P value, where reported
Ridker, 1991[242]	United States	Hospitalised first MI patients in the Physicians' Health Study	1982-1987	342	129 (38%)	Patients prospectively randomised to aspirin vs. placebo	+ 145.0 -142.8	No	No effect, P=0.93
Col, 1995[246]	United States	Hospitalised MI patients in the Worcester Heart Attack Study	1975-1990	2,114	332 (16%)	Retrospective: categorised as users or non-users	Not stated	Yes, adjusted for age, sex, previous CHD, smoking, beta blocker and calcium channel blocker use, thrombolysis.	Smaller infarct ; adjusted OR=1.40 (95% CI 1.06-1.84)
Abdelnoor, 1999[245]	Norway	Hospitalised MI patients	1993-1995	753	158 (21%)	Retrospective, by patient interview: categorised as users or non-users	In thrombolysed: + 1272 (683-3350) - 2183 (1050-3340) In non-thrombolysed: + 557 (372-928) - 923 (594-1625)	Yes, adjusted for age, previous CHD, smoking, beta blocker and nitrate use.	In thrombolysed: smaller infarct P<0.001 In non-thrombolysed: no effect, P=0.73
Mukamal, 1999[247]	United States	Hospitalised MI patients in the Onset Study	1989-1996	1,043	317 (30%)	Retrospective, by patient interview: categorised as users or non-users	+ 649.8 ± 342.7 - 735.3 ± 41.2*	Yes, adjusted for demographics, risk factors and other cardiovascular medications	Smaller infarct: 12% difference, P=0.03
Beigel, 2011[248]	Israel	Hospitalised MI patients	Not stated	174	56 (32%)	Retrospective, by patient interview: categorised as users or non-users	+ 1428 ± 215 - 1808 ± 339	No	No effect , P=0.35

MI: myocardial infarction; OR: odds ratio; CK: creatine kinase; CHD: coronary heart disease.
*Adjusted for demographics, previous risk factors, previous medication use

7.2.3.2 Effects on clinical presentation

The three studies of first MI investigated the effect of use on clinical presentation. Ridker and Kennon examined the effect on Q wave appearance at ECG and Bjorck examined the effect on ST-elevation at MI (comparing the frequency of STEMI and NSTEMI).[242-244]

In the Physicians' Health Study trial data, Ridker showed no effect of previous aspirin use on clinical presentation with Q waves (aspirin group 56.3% Q wave MI, placebo group 59.0%, P=0.54), but as above with respect to infarct size, may have been underpowered to detect an effect given its relatively small size (n=342).

The more recent studies in first MI showed a beneficial effect, with prior aspirin users experiencing 50% decreased odds of Q wave MI (OR=0.53 (95% CI 0.34-0.84) P=0.007) and 30%-40% decreased odds of ST-elevation (Kennon adjusted OR=0.57 (95% CI 0.35-0.94) p=0.03, Bjorck adjusted OR=0.72 (95% CI 0.69-0.76)), even after taking account of age, gender, previous coronary disease, cardiovascular disease risk factors and use of other cardiovascular medications. Three further studies including recurrent MI also showed decreased odds of Q wave MI in aspirin users. As discussed previously, there is still the possibility of residual confounding in these studies due to poorly measured confounders (ascertained retrospectively in all studies) or insufficient adjustment. However, all of these studies appear to be well-adjusted for cardiovascular disease risk, cardiovascular disease and use of other drugs, so the effect seen in these studies may be real. Additionally these studies were large (there were over 100,000 patients included in the study based on the Swedish registry and in all of the others were over 500 patients) and so their findings were unlikely to be due to chance. Finally the patients included were not highly selected and therefore representative of hospitalised MIs from their respective source populations.

A further four studies were identified that examined the effect of aspirin on clinical presentation in acute coronary syndromes overall. These largely showed the same results regarding the effects on clinical presentation with non-Q wave MI and less ST-elevation in prior aspirin users.[249-252] These studies also showed a tendency for prior aspirin users to manifest with unstable angina rather than MI.[249, 250]

Limitations of all of these studies are that they did not examine the effect of aspirin dose or duration on presentation, and that they are restricted to hospitalised patients who survived for long enough to provide information on previous drug use. The effect in general populations, including patients who die before reaching hospital, is therefore unknown.

Table 7.4 Effect of prior aspirin therapy on clinical presentation at MI

Author, year	Country	Patients included	Years of data collection	N patients	N (%) taking aspirin	Exposure measurement	Effect of aspirin on presentation	Was multivariate analysis performed?	Effect measure/ P value, where reported
Ridker, 1991[242]	United States	Hospitalised first MI patients in the Physicians' Health Study	1982-1987	342	129 (38%)	Patients prospectively randomised to aspirin vs. placebo	Aspirin group: 56.3% Q wave MI placebo group: 59.0% Q wave MI	No	No effect on Q waves, P=0.54
Kennon, 2000[243]	United Kingdom	Hospitalised first MI patients	1988-1998	1,395	121 (9%)	Retrospective: categorised as users or non-users	Aspirin group: 81.8% STEMI 70.0% Q wave MI Non-aspirin group: 89.7% STEMI 80.0% Q wave MI	Yes, adjusted for age sex, ethnicity, cardiovascular disease risk factors and beta blockers use.	Fewer Q wave MI, fewer STEMI; adjusted OR for Q wave development: 0.53 (95% CI 0.34-0.84) P=0.007; adjusted OR for ST-elevation: 0.57 (95% CI 0.35-0.94) P=0.03
Bjorck, 2010[244]	Sweden	Hospitalised first MI patients in the RIKS-HIA Register	1996-2006	103,459	28,583 (28%)	Retrospective: categorised as users or non-users	Aspirin group: 20.2% STEMI Non-aspirin group: 48.0% STEMI	Yes, adjusted for age, sex, previous atherosclerotic disease, cardiovascular disease risk factors and other drugs	Fewer STEMI; adjusted OR for ST-elevation: 0.72 (95% CI 0.69-0.76)
Col, 1995[246]	United States	Hospitalised MI patients in the Worcester Heart Attack Study	1975-1990	2,114	332 (16%)	Retrospective: categorised as users or non-users	Aspirin group: 65% Q wave MI Non-aspirin group: 48% Q wave MI	Yes, adjusted for age, sex, previous CHD, smoking, beta blocker and calcium channel blocker use, thrombolysis.	More non Q wave MI ; adjusted OR for non Q wave MI: 1.38 (95% CI 1.06-1.79)
Abdelnoor, 1999[245]	Norway	Hospitalised MI patients	1993-1995	753	158 (21%)	Retrospective, by patient interview: categorised as users or non-users	Aspirin group: 45% non Q wave Non-aspirin group: 24% non Q wave	Yes, adjusted for age, previous CHD, smoking, beta blocker and nitrate use.	More non Q wave MI; adjusted OR for non Q wave MI: 1.67 (95% CI 1.10-2.54) P=0.018
Mukamal, 1999[247]	United States	Hospitalised MI patients in the Onset Study	1989-1996	1,043	317 (30%)	Retrospective, by patient interview: categorised as users or non-users	Aspirin group: 38.9% Q wave MI Non-aspirin group: 48.7% Q wave MI	Yes, adjusted for demographics, risk factors and other cardiovascular medications	Fewer Q wave MI; adjusted OR for Q wave MI: 0.77 (95% CI 0.61-0.97) P=0.03

MI: myocardial infarction; OR: odds ratio; STEMI: ST-elevation MI
Note: the dashed line separates studies including only first MI and those including recurrent MI

7.2.3.3 Effects on short term mortality

None of the three studies examining the effects of aspirin in first MI described the effects on mortality. However, two studies including recurrent MI and seven studies of ACS investigated the effects of prior aspirin use on short term mortality, with conflicting results (Table 7.5).

Portnay (2005) showed a protective effect of prior aspirin use on 30 day mortality in 118,992 MI patients and 39,531 aspirin users aged over 65 in the US Medicare dataset (RR=0.93 (95% CI 0.90-0.96) P<0.001).[253] The beneficial effect of prior aspirin persisted to six months. The strengths of this study were its large size, the use of prospective data on medications from the medical record, the exclusion of patients who had contraindications to aspirin (bleeding, aspirin allergy) and a well-adjusted multivariate analysis.

This was supported by data from the Global Registry of Coronary Events (GRACE) and from the Myocardial Ischaemia National Audit Project (MINAP). Spencer (2002) showed a beneficial effect of aspirin at 30 days in 4,794 ACS patients with previously diagnosed coronary artery disease (Multivariable adjusted OR=0.69 (95% CI 0.50-0.95)).[254] This was found after multivariate analysis, adjusting for previous disease, risk factors and in-hospital treatment –in an unselected cohort of patients from centres across the world. Based on these and other data from GRACE, prior aspirin use was included in calculation of the GRACE risk score for hospital mortality (aspirin independent association with mortality OR=0.73 (95% CI 0.58-0.91)).[255] A study based on MINAP data also found aspirin to be one of the factors that was independently associated with lower in-hospital mortality in 34,722 STEMI patients.[103]

Conversely, two studies based on patients enrolled in trials showed *higher* mortality in aspirin users at 30 days based on multivariate analysis.[249, 256] These were large studies of over 14,000 patients in total, and since the randomised treatment was aspirin use at the time of MI, the study excluded patients with aspirin contraindications. Multivariate adjusted analyses were also performed here and patients previously using aspirin had 16% increased odds of mortality in one study (OR=1.16 (95% CI 1.00-1.33)) and 42% increased in the other (OR=1.42, no 95% CI reported). Indeed, the TIMI risk score includes aspirin as a predictor of mortality.[257]

In a smaller German study (N=8,224 and 2,022 aspirin users) of STEMI patients, Bauer showed no effect of prior aspirin use on in-hospital mortality at multivariate analysis (OR=0.98 (95% CI 0.80-1.21)), although there was a higher crude mortality in aspirin users

(12.8% in prior aspirin users and 8% in the untreated group).[258] In this analysis, patients with contraindications to aspirin were not excluded.

Four additional large studies found no effect of previous aspirin on mortality. [259-261] Spencer showed that in ACS patients *without* previous coronary artery disease[254] (N=6,414), there was no effect of previous aspirin on mortality. Among this group, 19% were aspirin users. The aspirin users had lower odds of in-hospital death after adjustment for clinical factors, but this was lost after further adjustment for in-hospital medications and cardiac procedures. A study examining predictors of 30 day death and non-fatal re-infarction showed that aspirin was not an independent predictor of these outcomes in 9,461 STEMI patients in the PURSUIT trial.[262]

The overall evidence for short term mortality in previous aspirin users is therefore unclear. Reasons for differences between studies may lie in the differing guidelines for aspirin use across study settings, the types of patients included (all MI or just STEMI), and the quality of adjustment for confounders.

Table 7.5 Effect of prior aspirin therapy on 30 day mortality

Author, year	Country	Patients included	Years of data collection	N patients	N (%) taking aspirin	Exposure measurement	Effect of aspirin on in-hosp/30 day death	Was multivariate analysis performed?	Effect measure/ P value
Portnay, 2005[253]	United States	Hospitalised MI patients in Medicare, the Cooperative Cardiovascular Project (aged ≥65 years) without contraindications to aspirin	1994-1996	118,992	39,531 (33%)	Prospective, in the medical record	Lower mortality in aspirin group.	Yes, adjusted for demographics, cardiovascular disease history, other drugs.	Adjusted RR=0.93 (95% CI 0.90-0.96) P<0.001
Bauer, 2009[258]	Germany	Hospitalised STEMI patients in ACOS registry	2000-2002	8,224	2,022 (25%)	Retrospective, by patient interview: yes/no	Crude higher mortality in aspirin group.	Yes, adjusted for demographics, prior MI and stroke, diabetes.	Adjusted OR=0.98 (95% CI 0.80-1.21)
Borzak, 1998[259]	Multi-centre	Hospitalised unstable angina patients in TIMI 7	Not stated	410	263 (64%)	Retrospective: yes/no	No effect	Yes, adjusted for demographics, cardiovascular disease history, CHD risk factors.	Not given
Alexander, 1999[249]	Multi-centre: N.America, Latin America, Europe	Hospitalised NSTEACS in the Multicentre (PURSUIT trial)	1995-1997	9,461	6,039 (64%)	Retrospective, by case report form: yes/no	Higher mortality	Yes, adjusted for demographics, cardiovascular disease history, CHD risk factors, other drugs.	Adjusted OR=1.16 (95% CI 1.00-1.33)
Lancaster, 2001[256]	Multi-centre: N.America, Latin America, Europe	Hospitalised UA or non-Q wave MI in the ESSENCE or PRISM-PLUS trials	1994-1998	4,690	2,780 (59%)	Retrospective	Higher mortality	Yes, adjusted for demographics, prior coronary disease, CHD risk factors.	Adjusted OR=1.42 (no 95% CI given)
Spencer, 2002[263]	Multi-centre: worldwide	Hospitalised ACS in the Global Registry of Coronary Events	1999-2001	11,388	4,872 (43%)	Retrospective: yes/no	Lower mortality in CAD+. No effect CAD-	Yes, adjusted for demographics, CHD risk factors, history of CHD, PCI and CABG, treatment in-hospital.	Adjusted OR in patients with a history of CAD: 0.69 (0.50-0.95), and without history of CAD: 0.77 (0.55-1.07)
Collet, 2004[264]	France	Hospitalised ACS in a French registry	1999-2002	1,358	355 prior users (26%), 73 recent withdrawers (5%)	Retrospective: non-use, prior use, recent withdrawal	Recent withdrawal predicted death, no effect of prior use	Yes, adjusted for demographics, smoking, diabetes, history of MI, hypercholesterolaemia.	Adjusted OR for withdrawal: 2.05 (95% CI 1.08-3.89), P=0.03
Rich, 2010[260]	Multicentre worldwide	Hospitalised ACS patients enrolled in the TIMI trials	1989-2005	66,443	17,839 (27%)	Retrospective	No effect	Yes, adjusted for demographics, prior coronary disease, CHD risk factors, CABG, PCI.	Adjusted OR=1.01 (95% CI 0.90-1.13)
El-Menyar, 2012[261]	Middle East	Hospitalised ACS in Gulf Registry of Acute Coronary Events	2008-2009	7,827	3,209 aspirin users (41%) (70% aspirin, 1% clopidogrel 29% dual)	Retrospective: yes/no	No effect	Yes, adjusted for demographics, cardiovascular disease history, CHD risk factors, other drugs.	Not given

MI: myocardial infarction; UA: unstable angina; ACS: acute coronary syndrome; NSTEACS: non ST-elevation ACS; STEMI: ST-elevation MI; CAD: coronary artery disease; OR: odds ratio
Note: the dashed line separates studies including recurrent MI and those including all ACS patients.

7.2.4 Results: statins

Three studies were identified that examined the effects of prior statin use at first MI on infarct size, presentation and mortality.[244, 265, 266] One of these was a large study of over 100,000 patients and performed multivariate analysis to examine the presentation of MI (STEMI versus NSTEMI). The two other studies were smaller, in roughly 300 patients and assessed the effects of statins on infarct size, presentation and mortality. One of these smaller studies was restricted to patients without previously diagnosed atherosclerotic disease.[265] Five further studies were identified which examined the effects of statins in patients with recurrent MI. All of these studies were restricted to hospitalised patients, and all but one of these studies measured statin use retrospectively.

7.2.4.1 Effects on infarct size

Two studies in first MI patients measured infarct size,[265, 266] both in STEMI patients (Table 7.6). In a US study of 281 patients drawn from hospitals between 2004 and 2006, prospectively collected electronic health records were used to assess previous statin use. Fifty patients (18%) were statin users and their infarct size was smaller, on average, than non-users (P=0.006). This study reported the type of statin and the mean dose, but did not examine the effects of each statin or dose on the outcome, and did not perform multivariate analysis to assess the independent effects of statin on infarct size, despite large differences between the groups in terms of cardiovascular disease risk.

The second study, including 310 hospitalised patients in Japan, was restricted to those receiving fibrinolytic therapy. Thirty-nine patients were statin users (13%) and at multivariate analysis there was a smaller infarct size in the statin-treated group. The odds of 'large' infarct size (defined as the upper tertile of the Area Under Curve of creatine kinase) in the treated group were a quarter of those in the untreated group (Adjusted OR=0.25 (95% CI 0.07-0.91) P=0.035)[266] after adjusting for demographics, key cardiovascular disease risk factors, Killip class on admission, TIMI flow grade and multivessel disease.

Despite the relatively small size of both of these studies, they both found important differences between statin users and non-users in infarct size. Infarct size was also smaller in statin users in two additional studies that included recurrent MI (Table 7.6), including a large multicentre study of over 10,000 patients with MI.[267, 268]

Table 7.6 Effect of previous statin treatment on infarct size

Author, year	Country	Patients included	Years of data collection	N patients	N (%) taking statin	Exposure measurement	Effect of statin on infarct size	Was multivariate analysis performed?	Effect measure/ P value, where reported
Moran, 2008[265]	United States	Hospitalised STEMI without previous atherosclerotic disease	2004-2006	281	50 (18%)	Used electronic health records	+ statin 87.8ng/ml -statin 134.5ng/ml	No	Smaller infarct in statin users; P=0.006
Kiyokuni, 2009[266]	Japan	Hospitalised first STEMI receiving fibrinolytic therapy	Not stated	310	39 (13%)	Retrospective from patient interview: yes/no	+statin: 2187± 1967 -statin: 3334± 3320 IU/l	Yes, demographics, CHD risk factors, TIMI flow grade, multivessel disease, PCI, MI type	Smaller infarct in statin users; Adjusted OR for large size OR=0.25 (95% CI 0.07-0.91) P=0.035
Ishii, 2006[267]	Japan	Hospitalised first MI with PCI within 24 hours	1998-2003	386	40 (10%)	Retrospective from patient interview: yes/no	Smaller infarct	No	P=0.015
Aronow, 2008[268]	Multi-centre, 13 countries	Hospitalised MI in GUSTO or PURSUIT	1994-1997	10,548	1,028 (10%)	Retrospective : yes/no	Smaller infarct	Yes, adjusted for demographic, clinical and treatment characteristics.	Adjusted OR for large size (>3 times upper limits of normal) OR=0.94 (95% CI 0.88-0.99) P=0.04

MI: myocardial infarction; STEMI: ST-elevation MI; PCI: percutaneous coronary intervention; OR: odds ratio.
Note: the dashed line separates studies including only first MI and those including recurrent MI

7.2.4.2 Effects on clinical presentation

Two studies in first MI patients examined differences in clinical presentation between statin users and non-users.[244, 266] One was a large study of over 100,000 in the Swedish RIKS-HIA register; in an adjusted analysis taking account of differences in demographics, cardiovascular disease risk factors (including smoking, hypertension and diabetes), and other cardiovascular drug use, there was an independent protective effect of statin use on ST-elevation (OR=0.79 (95% CI 0.74-0.84)). This included over 12,000 statin users and so was well-powered to detect a difference between groups. A smaller Japanese study in STEMI patients receiving fibrinolytic therapy found that the sum of ST-elevation was smaller in the statin treated group compared to the untreated group (P=0.004) (Table 7.7).

Table 7.7 Effect of previous statin treatment on presentation at myocardial infarction with ST-elevation

Author, year	Country	Patients included	Years of data collection	N patients	N (%) taking statin	Exposure measurement	Effect of statin on presentation	Was multivariate analysis performed?	Effect measure/ P value, where reported
Bjorck, 2010[244]	Sweden	Hospitalised first MI patients in the RIKS-HIA Register	1996-2006	103,459	12,267 (12%)	Retrospective: yes/no	Fewer STEMI	Yes, adjusted for demographics, CHD risk factors, other drugs, CABG, PCI	Adjusted OR for ST-elevation: 0.79 (95% CI 0.74-0.84)
Kiyokuni, 2009[266]	Japan	Hospitalised first STEMI receiving fibrinolytic therapy	Not stated	310	39 (13%)	Retrospective from patient interview: yes/no	Less ST-elevation	No	P=0.012 for smaller sum of ST-elevation in the statin group on admission, P=0.004 for one hour after admission

MI: myocardial infarction; STEMI: ST-elevation MI; OR: odds ratio

7.2.4.3 Effects on in-hospital mortality

There is disagreement regarding the short term mortality effects of statins prior to MI (Table 7.8). Only one study in first MI patients assessed short term mortality, and this did not perform an adjusted analysis to assess the independent effect of statins, finding no effect of statins on 30 day mortality (P=0.305).[265] Importantly, this was the only study restricting to patients whose first manifestation of atherosclerotic disease was the MI.

However, of the four studies including recurrent MI that examined mortality, three showed a beneficial effect of prior statin use. The largest of these was a US study of 78,224 NSTEMI patients investigating use and recent withdrawal of statins. Patients using statins before and during MI had the lowest mortality, and patients previously using statins who had these withdrawn at MI had higher mortality than never users. This study adjusted for demographics, medical history, cardiovascular disease risk factors and other preadmission medications and suggested that statin use must be continued to the day of MI in order to have a beneficial effect.[254]

Another large study in over 10,000 trial patients showed no effect of previous statin use on mortality (P=0.22), although no multivariate analysis was performed. Two further smaller studies (<1000 patients) in hospitalised STEMI patients undergoing PCI found lower mortality in statin users at multivariate analysis. Additionally, in a study developing the GRACE risk score, prior statin use was independently associated with lower in-hospital mortality (Adjusted OR=0.50 (95% CI 0.34-0.97).[255]

Table 7.8 Effect of previous statin treatment on in-hospital and 30 day mortality

Author, year	Country	Patients included	Years of data collection	N patients	N (%) taking statin	Exposure measurement	Effect of statin on short term mortality	Was multivariate analysis performed?	Effect measure/ P value, where reported
Moran, 2008[265]	United States	Hospitalised STEMI without previous atherosclerotic disease	2004-2006	281	50 (18%)	Used electronic health records	No effect	No	P=0.305
Spencer, 2004[254]	United States	Hospitalised NSTEMI patients in the NRMI*	2000-2002	78,224	13,781 before admission (18%), 4870 of whom withdrawn at MI (35%)	Retrospective : Prior to hospital and in hospital, prior to hospital and continued at hospital, no prior use	Lower mortality in continuing users, no effect in withdrawing compared to never users	Yes, adjusted for demographics, medical history, CHD risk factors and preadmission medications	Withdrawn vs. continuers: HR=1.83 (95% CI 1.58-2.13), Withdrawn vs. never HR=1.03 (95% CI 0.93-1.15)
Aronow, 2008[268]	Multi-centre, 13 countries	Hospitalised MI in GUSTO or PURSUIT	1994-1997	10,548	1,028 (10%)	Retrospective : yes/no	No effect	No	P=0.22
Lev, 2009[269]	Israel	Hospitalised STEMI undergoing PCI	2001-2007	950	327(34%)	Retrospective	Lower mortality	Yes, adjusted for demographics, medical history, CHD risk factors, renal insufficiency, CABG.	Adjusted OR=0.4 (95% CI 0.13-0.96), P=0.045
Garot, 2010[270]	France	Hospitalised STEMI undergoing PCI complicated by cardiogenic shock	Not stated	111	30 (27%)	Retrospective	Lower mortality	Yes	Adjusted OR=0.35 (95% CI 0.15-0.88) P=0.026

MI: myocardial infarction; UA: unstable angina; ACS: acute coronary syndrome; NSTEACS: non ST-elevation ACS; STEMI: ST-elevation MI; NRMI: National Registry of Myocardial Infarction; HR: hazard ratio.
Note: the dashed line separates studies including only first MI and those including recurrent MI

7.2.5 Strengths of previous research

There is some strong evidence for the effects of aspirin and statins prior to MI overall, in terms of their effects on clinical presentation and infarct size. The studies included were often from large samples, from diverse populations in registries and trials, and across different geographic regions. Most of the studies reported large differences in patient baseline characteristics between those treated and not treated with medications. The statistical analyses performed in many of the studies fully adjusted for these differences by adjusting for demographic variables, cardiovascular disease risk factors, other cardiovascular medication use and sometimes hospital treatments.

All of the studies were in hospitalised MI patients and nearly all used a combination of clinical history, raised cardiac markers (troponins, creatine kinase, lactate dehydrogenase) and ECG findings to diagnose MI. While some of the studies into the effects of aspirin were conducted before the redefinition of MI in 2000, many were also conducted after this and effects on ST-elevation and non ST-elevation MI were reported.

7.2.6 Limitations of previous research

While the evidence for use of aspirin and statins in MI overall was often strong, there are several limitations to their findings. These limitations are described in the following sections.

7.2.6.1 First and subsequent atherosclerotic disease presentations

A study of ACS patients in GRACE compared the effect of aspirin on 28 day mortality in patients with and without prior known coronary artery disease (CAD).[263] This suggested that aspirin was protective in patients with prior CAD but not in patients without. No other studies examined differences between those with and without disease, but one study restricting to patients *without* prior atherosclerotic disease found no effect on mortality. These findings are particularly relevant to the focus of this thesis: MI as the first manifestation of atherosclerotic disease, and the provision of aspirin and statins for primary prevention.

Since the pattern of prescribing of aspirin and statins in patients with and without prior disease is likely to be different, and there is a suggestion that their effects on outcomes may be different, further research differentiating between patients with and without disease

would be of interest. If aspirin and statins can improve outcomes of patients who have MI, in addition to their effects in preventing MI altogether, then the evidence for use of these medications in primary prevention will be strengthened.

7.2.6.2 Differing levels of cardiovascular disease risk

The effect modification by previous disease shown in the GRACE study may also suggest that there are differing effects by level of cardiovascular disease risk. The majority of studies included in this review performed multivariate adjusted analyses taking account of cardiovascular disease risk factors and previous disease but none stratified results according to level of risk. Patients at more risk may be afforded more protection in the same way that patients with previously diagnosed atherosclerotic disease were more protected in the aforementioned study.[254] Given that prescribing guidelines recommend use of statins in the high risk group only, and that patients at high risk have previously been recommended aspirin, then examining their effects by level of risk would be pertinent.

7.2.6.3 Generalisability of patients

Many studies included in this review reported outcomes for patients in trial populations: TIMI,[260] PURSUIT,[268] ESSENCE/PRISM-PLUS.[271] These patients are often specially selected and are unrepresentative of all patients with MI, although no systematic differences were noted between results from trial populations and results from registries.

In studies recruiting hospital patients (i.e. non-trial settings), strict inclusion criteria were often applied to reach the final study population such as inclusion of specific MI types,[254, 258] age ranges,[253] patients surviving to discharge,[268] undergoing specific procedures such as angiography or PCI,[267, 269] or not undergoing thrombolysis.[247] Few studies used an unselected patient population. Therefore, the representativeness of these studies is questionable. Additionally, a third of MI patients do not reach hospital, so there may be considerable error in the estimates of these studies if patterns of drug use in patients who reach hospital are different to those who do not.

7.2.6.4 Study design

With a few exceptions, all of the studies included in this review identified patients at the time of MI and enquired retrospectively about history of cardiovascular medication use. (exceptions: Ridker, where aspirin use was randomised, Moran, where electronic health records were used, and Portnay, where Medicare records regarding prescriptions were extracted). These studies will also have used retrospective data on cardiovascular disease risk and previous cardiovascular disease. All of this information is subject to error in recall, which could have led to residual confounding and incorrect effect estimates.

Additionally, since these drugs are usually prescribed for increased global cardiovascular disease risk, there may be important confounding by indication. It is therefore important to adjust carefully for cardiovascular disease risk and previous cardiovascular disease to avoid this bias.

A final issue in study design was the failure of most studies to exclude patients with contraindications for aspirin and statins (aspirin allergy, gastrointestinal bleeding, pregnancy or breast-feeding, and liver injury (acute or chronic)).

7.2.6.5 Differing exposure definitions: dose, duration and withdrawal

In most studies, previous drug use was defined simply as use or not prior to MI. Other studies used more complex definitions such as use within four days of admission, use for more than a week before admission, use 'on a regular basis' before admission, use for one month or more before admission, or use at the time of hospital admission. These different exposure definitions are likely to affect the study outcome, making the studies less comparable. The timing of exposure is potentially of importance if the drug itself triggers responses at the time of MI, or if the effects are cumulative.

Due to the retrospective nature of the majority of exposure data, detailed information on dose and duration had not been collected. One early study of aspirin use did investigate the effect of dose and duration on clinical presentation of ACS, based on retrospective data.[250] This showed that there was no effect of low doses aspirin (<500mg per week) on clinical presentation, but that there was a dose-response effect with higher doses. The effects on subsequent mortality were not described. The effects of dose and duration of statins have not yet been investigated.

There has also been some interest in the effect of withdrawing from aspirin and statins shortly before ACS and the effect that this has on outcomes. Collet (2004) showed that recent withdrawal of aspirin, within three weeks of ACS, was a predictor of mortality.[264] Similarly, withdrawing statin treatment shortly before MI was associated with similar mortality to patients who never used statins, while patients who continued use had the best mortality experience. This suggests that statin use must be continued to the day of MI in order to have an effect.[254]

7.2.7 Limitations of this literature review

There is a possibility that some published studies will have been missed as the grey literature was not searched and the search terms may not have been sensitive enough to capture all relevant studies. However, the search strategy was relatively broad and the reference lists of all studies were searched. In addition, cited reference searches were performed for the largest studies. Therefore, the key studies of cardiovascular medication use prior to MI were likely to have been identified. Finally, there may have been publication bias where studies failing to show an association have not been published.

7.2.8 Conclusion

A summary of the findings of this review are described in Table 7.9. There is good evidence that prior aspirin and statin therapy benefit both clinical presentation and infarct size in MI overall, but their effects on subsequent short term mortality are unclear. However, the effects of prescribing for primary prevention in patients without prior diagnosed atherosclerotic disease and at different levels of cardiovascular disease risk have not been well studied. Given guidelines to prescribe these medications in those at high risk, an understanding of their effects on MI outcomes is important. Additionally, more complex facets of exposure have not been well studied, including the effects of withdrawal prior to MI, and the effects of dose and duration of use. Finally, all studies to date have been in hospitalised patients and therefore effects in general populations are unclear. The following study aims to address these limitations.

Table 7.9 Summary of the associations described in the literature review between aspirin use, statin use and infarct size, clinical presentation and mortality

	Aspirin	Statins
Infarct size	↓	↓
Clinical presentation severity (% ST-elevation)	↓	↓
Mortality	?	?

7.3 Objectives

Among people who have first MI without previously diagnosed atherosclerotic disease:

1. To describe initiation and duration of use of aspirin and statins prior to MI.

2. To compare receipt of aspirin or statin prescriptions by level of cardiovascular disease risk.

3. To compare infarct type and size in users and non-users of aspirin or statins, and examine effect modification by cardiovascular disease risk.

4. To compare 30 day mortality in users and non-users of aspirin or statins, and examine effect modification by cardiovascular disease risk.

7.4 Methods

The prospectively collected medical records of a cohort of MI patients without previously diagnosed atherosclerotic disease were reviewed to assess prescriptions of cardiovascular medications prior to MI, and outcomes at the time of MI and post-MI.

7.4.1 Definition of acute myocardial infarction

Patients with MI were identified based on a record in any one of the four data sources. MI definitions are described in detail in Chapter 3 (Methods) and briefly in Table 7.10.

Table 7.10 Definition of acute myocardial infarction in each of the four data sources: GPRD, HES, MINAP and ONS

Data source	MI definition
GPRD	Read code for MI, raised markers of myocardial necrosis, or ECG result indicative of MI.
HES	ICD-10 code I21, I22 or I23 as the primary diagnosis in the first hospital episode.
MINAP	ST-elevation MI or non ST-elevation MI following the joint American Heart Association / European Society of Cardiology definition.[6]
ONS	ICD-10 code I21, I22 or I23 as the underlying cause of death.

7.4.2 Diagnosed atherosclerotic disease prior to MI

Patients with previous atherosclerotic disease, identified as described in Chapter 3 (General Methods) were excluded from this analysis. Only patients with Read codes rated as 'definite' indicators of atherosclerotic disease were included in this analysis; a sensitivity analysis including patients with 'possible' codes was performed to assess how this may have affected the results.

7.4.3 Measuring cardiovascular disease risk scores prior to MI

Using only data collected *prior to MI*, age, sex, smoking, blood pressure, antihypertensive use, total cholesterol and HDL cholesterol were used to calculate the Framingham risk score for 'hard' CHD endpoints (MI and coronary heart disease

death),[129, 272] which assigns points to different levels of cardiovascular disease risk factors and sums them to generate an overall ten year risk of hard CHD endpoints. These risk factors were identified as described in Chapter 3 (General Methods). The Framingham risk point scores (ranging from -4 to 26 in this cohort), based on combinations of these risk factors, are usually categorised to give an estimate of the percentage risk for hard CHD endpoints over the subsequent ten years, where a higher point total indicates higher CHD risk. In this analysis, the scores were categorised as high risk (>20% risk of CHD over ten years), intermediate risk (10-20% risk) and low risk (<10% risk over ten years). In men, high (>20%) risk is defined as a point score of 16 and above, intermediate risk (10-20%) as 12-15 points and low risk (<10%) as 11 points or lower. In women, high risk is defined as a score of 23 or above, intermediate risk as 20-22 points and low risk as 19 points or fewer. However, the point scores were also used in their raw form to give a more refined picture of coronary risk and to examine the comparability of current aspirin users compared to non-users. The Framingham scores were also used to assess prescribing in accordance with guidelines. A 15% CHD risk is equivalent to a 20% cardiovascular disease risk,[231] which is the guideline recommended point at which statins (and previously aspirin) should be considered for intervention. Therefore, prescribing above and below this cut-off was examined.

7.4.4 Other cardiovascular disease risk factors prior to MI

Other cardiovascular disease risk factors included in this analysis were hypertension and diabetes. Only patients with definite diagnoses of type 1 or type 2 diabetes and hypertension were included in this analysis.

7.4.5 Aspirin and statin prescriptions prior to MI

Information regarding aspirin and statin use was extracted from the GPRD records. For aspirin, drugs of interest were defined as any aspirin-containing product. Statins included were atorvastatin, fluvastatin, lovastatin, pravastatin rosuvastatin, simvastatin, and cerivastatin (withdrawn from the market in 2001 due to safety concerns, but historical records of cerivastatin were available).

7.4.5.1 Use of aspirin and statins at MI

To calculate use at the time of MI, the date of the last prescriptions issued prior to MI was recorded. Patients were allocated to one of the following categories:

- *Current use*, defined as use at the time of MI. This was based on the number of days before MI that the prescription was issued and the duration that the prescription was intended to last. A buffer of 14 days was added to account for time lags in the patient filling the prescription and beginning to use the tablets (sensitivity analyses were conducted to assess whether the results were altered by shorter and longer buffers or by different definitions of 'current' use);

- *Previous use*, defined as patients who had one or more prescriptions in their medical record, but the final prescription issued prior to MI was not indicated to last until the date of MI;

- *Never use*, defined as no record of prescription in the database.

7.4.5.2 Duration of use and dose prior to MI

Duration of use was calculated for patients who were current users at the time of MI. It was calculated as the duration in years between the date of first prescription and the date of MI. For the last prescription, the dose was recorded in order to assess the effects of the dose taken at the time of MI. As the relative effects of each statin are different, dosages were standardised to the equivalent dose of simvastatin as presented in the Statin Drug Class Review (Table 7.11).[273]

Table 7.11 Equivalent doses of statins (Source[273])

Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
-	40	20	20	-	10
10	80	40 or 80	40	5	20
20	-	80	-	10	40
40	-	-	-	-	80
80	-	-	-	-	-

7.4.6 Exclusion criteria

Patients were excluded if they had a recorded history of MI (n=6,337), were under the age of 18 at MI (n=2), had not been registered with the primary care practice for at least one year before MI (n=8,516), whose MIs occurred outside the period where all databases were collecting data (outside 1st January 2003 to 31st December 2008, n=23,804), and patients without any primary care consultations in their record prior to MI (n=12). Patients who had a clear contraindication to aspirin or statins were also excluded. Exclusions were: history of stomach ulcer or gastrointestinal bleeding (n=1,454), aspirin intolerance (n=481), pregnancy or breastfeeding within a year of MI (n=9) and acute or chronic liver disease (n=634).

7.4.7 Infarct size, presentation and subsequent mortality

Infarct size was determined using peak troponin values recorded in the MINAP data source. Only patients with a MINAP record had this information recorded (N=2,964). MI presentation with ST-elevation or non ST-elevation was recorded in all patients included in the MINAP dataset and in a subset of those in the GPRD (N=4,010). HES and ONS data do not record MI type. All-cause mortality was recorded in ONS mortality data within 30 days of MI with a date of death.

7.4.8 Statistical analysis

The demographic characteristics and missingness of key cardiovascular disease risk factors were tabulated. The initiation and duration of prescribing of aspirin and statins prior to MI were described. For men and women separately, age and other components of Framingham risk were then compared for current, previous and never users of aspirin and statins.

The numbers of patients who were never, current or previous users of aspirin and statins were then compared at each Framingham risk point score. This comparison was performed to assess whether patients taking these medications were comparable to those who did not. Substantial overlap in the distribution of Framingham risk would suggest some degree of haphazardness in the prescription of aspirin and statins to people with similar cardiovascular disease risk, suggesting that valid comparisons could be made in terms of MI type, size and mortality outcome.

A DAG in Appendix A, Section 10.6.2 describes the relationships between the variables included in the following analyses.

7.4.8.1 Presentation with STEMI or NSTEMI

In the subset of patients for whom MI type (STEMI or NSTEMI) was recorded, this was compared in never, current and previous users of each medication using logistic regression. Complete case analyses were performed. Three models were fitted: (i) a crude model to examine the unadjusted association between aspirin or statin and presentation, (ii) a model adjusted for age at MI, sex, diabetes (based on a diagnosis or abnormal test results), smoking status (categorised as non, current, ex at the time of MI), hypertension (based on a diagnosis or measured blood pressure over 140/90mm Hg) and use of antihypertensive drugs including ACEI, ARBs and beta blockers, and (iii) a final model adjusting for the same parameters as model (ii) but with the inclusion of total cholesterol. Total cholesterol was not included in the second model because this was a complete case analysis; the high missingness in total cholesterol (roughly 50%, see section 7.5.2.1) would resulted in loss of power in the final, multivariable adjusted model. Therefore, results from both models (ii) and (iii) were examined to interpret the association between medication use and the outcome.

7.4.8.2 Infarct size

In patients with a record of infarct size, this was compared in never, current and previous users of aspirin and statins using multiple linear regression. After examining the distribution of peak troponin values, there was a substantial skew and therefore the outcome was log transformed (Appendix A, section 10.6.1). Results presented are the exponentiated coefficients from the log-linear regression model, which can be interpreted as the estimated relative effects of the exposure on infarct size. Three models were fitted to the data as above ((i) crude, (ii) adjusted, (iii) adjusted including total cholesterol). For the final adjusted models, the assumptions of multiple linear regression were checked by plotting the residuals on a histogram to assess their normality: these are shown in Appendix A, section 10.6.6.

7.4.8.3 30 day mortality

Cox regression analysis was used to compare 30 day mortality after MI in never, current and previous aspirin and statin users. Crude and adjusted models were fitted, as above. Tests for proportional hazards were performed on all models and interactions with time were fitted where there was non-proportionality. Interactions with time were fitted based on follow-up time categories of 0-7 days and 8-30 days, which were considered to be the time points at which the mortality effects may change (i.e. reflecting in-hospital mortality and a short post-hospital period).

7.4.8.4 Model specification

For each of the three outcomes, effect modification by Framingham risk category (low, intermediate, high, missing) was examined using likelihood ratio tests comparing the final adjusted model with and without interaction terms. Age and total cholesterol were initially fitted in all models as linear variables; the assumption of linearity was tested with likelihood ratios tests comparing these models to models where these variables were fitted as quadratic and cubic terms. If there was evidence that these terms contributed to a better model, the quadratic or cubic terms were used in the main analysis.

7.4.8.5 Dose and duration of use

The effect of aspirin duration and statin dose and duration were separately assessed in each of the models described above. These effects were assessed only in patients who were defined as current users, as the effects in previous users were expected to be more complex and potentially associated with the reasons for drug withdrawal rather than use of the drug itself.

7.4.8.6 Sensitivity analyses

Several sensitivity analyses were performed. The main cardiovascular disease risk factors were accounted for in the main analysis. In additional analyses, the final models were also adjusted for BMI, family history of CHD and social deprivation (IMD quintile).

Exclusion of patients with atherosclerotic disease, and recording of patients with diabetes and hypertension were based on definite diagnoses recorded in the GPRD data.

Therefore, an analysis was performed excluding patients with 'possible' atherosclerotic disease diagnoses, and using possible hypertension and diabetes diagnoses in addition to definite diagnoses.

The prescription data in this analysis were based solely on GPRD prescribing data. In the subset of patients with MINAP data, there were also data available regarding use of antiplatelets and statins at admission. The MINAP data were not used in the main analysis as the time of administration of these drugs (i.e. for chronic, daily use, or whether administered at admission) was unclear. However, the prevalence of use in the GPRD and MINAP data were compared.

Presentation with ST-elevation or not at MI is related to comorbidity; patients with more comorbidity tend to have NSTEMI rather than STEMI.[10] To assess whether the associations between the medications and ST-elevation were driven by greater morbidity in users of these medications, the results were adjusted for GPRD consultation rate, which is a marker of general morbidity.

Sensitivity analyses were performed to assess the robustness of the definition of 'current' aspirin and statin use. In addition to changing the buffer of time allowed for a prescription to be collected and used (14 days in the main analysis, zero and 28 days in the sensitivity analyses), the definition of current use was changed to 'two or more prescriptions in the six months prior to MI.'

Due to concerns regarding the use of peak troponin to accurately measure infarct size, and problems with its recording in MINAP, a sensitivity analysis was conducted using peak creatine kinase as the measure of infarct size, rather than peak troponin.

All analyses were performed in Stata version 11. The study details are registered online at clinicaltrials.gov (NCT01692795, September 2012) and a time-stamped detailed analytic protocol is shown in Appendix B.

7.5 Results

7.5.1 Study population

Of the 14,807 patients identified with first MI who did not have contraindications to aspirin or statins, 6,703 had previously diagnosed atherosclerotic disease. There were 8,104 patients remaining who experienced first MI across the four data sources and met all inclusion criteria. The median age was 68 (IQR 57-79) and 2,951 (36.4%) were women (Table 7.12). Of these patients 1,324 (16.3%) had been prescribed aspirin prior to their MI, and 1,160 (14.3%) had been prescribed statins.

Table 7.12 Demographic and risk factors characteristics of 8,104 patients with first MI

Age, median (IQR)	68 (57-79)
Women, n (%)	2,951 (36.4)
Smoking, n (%)	
Non-smoker	1,201 (14.8)
Ex-smoker	3,924 (48.4)
Current smoker	2,724 (33.6)
Unknown	255 (3.1)
Diabetes, n (%)	938 (11.6)
Systolic blood pressure in mmHg, mean (SD)	145 (16.4)
Missing blood pressure, n (%)	444 (5.5)
Blood pressure lowering, n (%)	3,461 (42.7)
Total serum cholesterol in mmol/L, mean (SD)	5.8 (1.1)
Missing total cholesterol, n (%)	3,989 (49.2)
HDL cholesterol in mmol/L, mean (SD)	1.4 (0.4)
Missing HDL cholesterol, n (%)	5,053 (62.4)
Framingham risk, n (%)	
<10%	572 (7.1)
10-20%	1,604 (19.8)
>20%	857 (10.6)
Missing	5,071 (62.6)

IQR: inter-quartile range; SD: standard deviation; HDL: high density lipoprotein

7.5.2 Framingham risk scores

Framingham risk scores were calculated only using data collected prior to MI in patients without previously diagnosed atherosclerotic disease. For the patients whose risk scores could be calculated, 572 patients (7.1%) were in the lowest risk group (<10%), 1,604 (19.8%) were in the intermediate risk group (10-20%) and 857 (10.6%) were in the highest risk group (>20%).

7.5.2.1 Missingness in Framingham risk

For 5,071 (62.6%) patients, a Framingham risk could not be calculated due to missingness in total cholesterol, HDL cholesterol, smoking or blood pressure values (49.2% of MI patients in this study had missing total cholesterol, 62.4% had missing HDL values, 3.2% missing smoking and 5.5% missing blood pressure values). The main analysis was based on patients with non-missing data only, reducing the power (particularly when adjusting for total cholesterol). To assess the potential for any bias in the complete case analysis, patients with missing Framingham risk were compared to those with complete values in terms of risk factors that were recorded (Table 7.13). Logistic regression analyses were also performed to assess predictors of missingness.

The primary care consultation rate in patients with missing Framingham risk was lower than that of patients with complete scores. Patients with missing risk scores were comparable to the overall group of patients with complete risk scores in terms of age and sex; their levels of current smoking were between the prevalence for intermediate and high risk groups. Their mean systolic blood pressure was between the low and intermediate risk groups but fewer patients were in receipt of blood pressure lowering medications than in any of the groups with calculable risk.

In a logistic regression analysis, missingness in smoking was strongly associated with older ages ($P<0.001$), being a woman ($P=0.001$), consulting less frequently ($P=0.02$) and being normotensive ($P<0.001$). Missingness in blood pressure was strongly associated with lower age ($P=0.006$), lower consultation rate ($P<0.001$) and being an ex-smoker ($P=0.003$). Missingness in total cholesterol and HDL cholesterol were associated with older age ($P<0.001$), being a woman and having a lower consultation rate. It was also associated with being normotensive, non-diabetic and being categorised as an ex-smoker ($P<0.001$ for all).

Overall, patients who consulted less frequently were more likely to have missing values. The true Framingham risk of these patients is likely to be a mixture of those at high and lower risk, based on the recorded risk factors in these patients. The implications of this missingness are considered in the Discussion.

Table 7.13 Risk factor distribution in patients at each level of Framingham risk compared to those whose Framingham risk could not be calculated due to missingness in one or more variables (N=8,104)

	<10%		10-20%		>20%		Missing	
N patients	572		1,604		857		5,071	
Age, median (IQR)	59	(49-66)	67	(59-75)	75	(63-81)	69	(56-80)
Women, n (%)	384	(67.1)	452	(28.2)	234	(27.3)	1,881	(37.1)
Smoking, n (%)								
Non-smoker	117	(20.5)	228	(14.2)	83	(9.7)	773	(15.2)
Ex-smoker	332	(58)	963	(60)	405	(47.3)	2,224	(43.9)
Current smoker	122	(21.3)	409	(25.5)	365	(42.6)	1,828	(36)
Unknown	0	(0)	0	(0)	0	(0)	246	(4.9)
Systolic blood pressure in mm Hg, mean (SD)	139	(13.6)	146	(13.5)	154	(13.4)	144	(17.4)
Missing blood pressure, n (%)	0	(0)	0	(0)	0	(0)	444	(8.8)
Blood pressure lowering, n (%)	227	(39.7)	959	(59.8)	704	(82.1)	1,571	(31)
Total serum cholesterol in mmol/L, mean (SD)	6	(1.2)	6	(1)	6	(1.2)	6	(1.1)
Missing total cholesterol, n (%)	0	(0)	0	(0)	0	(0)	3,989	(78.7)
HDL cholesterol in mmol/L, mean (SD)	2	(0.5)	1	(0.4)	1	(0.3)	1	(0.3)
Missing HDL cholesterol, n (%)	0	(0)	0	(0)	0	(0)	5,053	(99.6)
Rate of primary care consultation, median (IQR)	6.4	(3.8-10.9)	5.6	(3.4-9.2)	5.9	(3.8-9.7)	3.7	(1.7-7.0)

IQR: inter-quartile range; SD: standard deviation; HDL: high density lipoprotein

The rest of the results section is separated into two parts, first describing aspirin use and its associations with each outcome, and then statins.

7.6 Results: aspirin

7.6.1 Description of aspirin use prior to MI

Of the 1,324 patients who had ever been prescribed aspirin, 761 were defined as *current* users at the time of MI, and 563 were *previous* users.

7.6.1.1 Initiation on aspirin therapy

The rate of initiation on aspirin therapy in the ten years prior to MI is described Figure 7.1, increasing from six per thousand patients ten years before MI to 35 per 1000 patients in the year prior to MI.

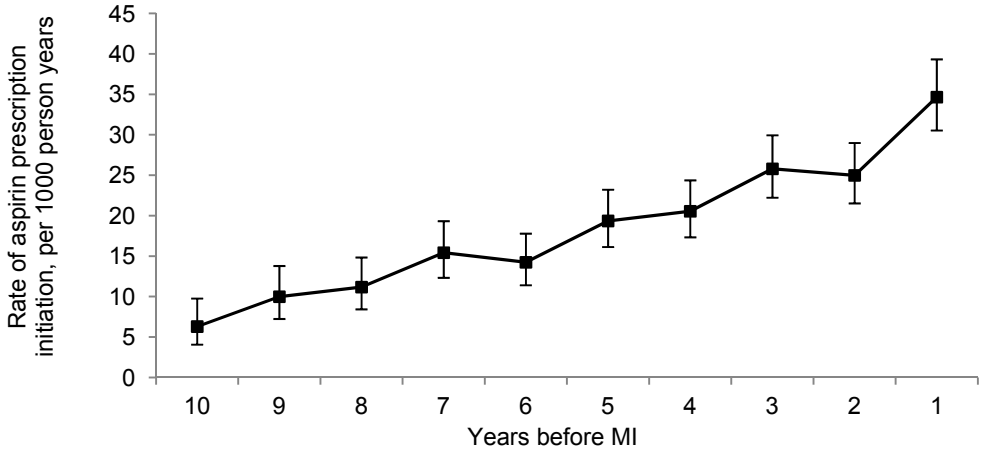


Figure 7.1 Rate of initiation on aspirin in the ten years prior to first myocardial infarction (MI), for 8,104 patients

7.6.1.2 Duration of aspirin use

In 761 current users, the duration of use ranged from just one day to seventeen years (median 3.0 years (IQR 1.14-5.56 years)). In the 563 previous users, the duration of use also ranged from two weeks to seventeen years but the distribution was more highly skewed, with half of patients using aspirin for a year or less (median 0.91 years (IQR 0.19-3.12 years)) (see Appendix A, section 10.6.4 for more detail). In previous users, the median time between last aspirin use and MI was 1.7 years (IQR 0.3-4.7 years).

7.6.2 Aspirin use and Framingham risk

7.6.2.1 Risk factor distribution in never, current and previous aspirin users

The cardiovascular disease risk factors included in the Framingham risk score were tabulated for never, current and previous aspirin users (Table 7.14). These were all recorded prior to MI. Current and previous users of aspirin were older than never users, they were less likely to be current smokers and had lower levels of total cholesterol, but had higher blood pressure and a greater prevalence of blood pressure lowering drugs. Levels of missingness in total and HDL cholesterol were lower in current and previous aspirin users. Of the patients whose overall Framingham risk could be calculated, current and previous aspirin users were more likely to fall in the highest risk category than never users. However, in never users, missingness in blood pressure and cholesterol (HDL or total) meant that calculation of a Framingham score was possible in fewer patients.

Table 7.14 Demographic distribution and components of the Framingham risk score in never aspirin users and current users (N=8,104)

	No aspirin		Current aspirin		Previous aspirin	
N patients	6,780		761		563	
Age, median (IQR)	66	(56-77)	77	(69-84)	76	(66-84)
Women, n (%)	2,336	(34.5)	354	(46.5)	261	(46.4)
Smoking, n (%)						
Non-smoker	984	(14.5)	137	(18)	80	(14.2)
Ex-smoker	3,142	(46.3)	459	(60.3)	323	(57.4)
Current smoker	2,437	(35.9)	142	(18.7)	145	(25.8)
Unknown	217	(3.2)	23	(3)	15	(2.7)
Systolic blood pressure in mm Hg, mean (SD)	144	(16.6)	150	(13.5)	149	(15.3)
Missing blood pressure, n (%)	433	(6.4)	8	(1.1)	3	(0.5)
Blood pressure lowering, n (%)	2,463	(36.3)	603	(79.2)	395	(70.2)
Total serum cholesterol in mmol/L, mean (SD)	5.9	(1.1)	5.4	(1)	5.6	(1)
Missing total cholesterol, n (%)	3,562	(52.5)	225	(29.6)	202	(35.9)
HDL cholesterol in mmol/L, mean (SD)	1.4	(0.4)	1.4	(0.4)	1.4	(0.4)
Missing HDL cholesterol, n (%)	4,432	(65.4)	352	(46.3)	269	(47.8)
Framingham risk, n (%)						
<10%	481	(7.1)	49	(6.4)	42	(7.5)
10-20%	1,246	(18.4)	207	(27.2)	151	(26.8)
>20%	606	(8.9)	153	(20.1)	98	(17.4)
Missing	4,447	(65.6)	352	(46.3)	272	(48.3)

IQR: inter-quartile range; SD: standard deviation; HDL: high density lipoprotein

7.6.2.2 Use of aspirin at different levels of Framingham risk

Framingham risk scores are calculated differently in men and women. Therefore, in a comparison of use of aspirin at different risk scores, the results were stratified by sex. There were 1,963 men and 1,070 women with a calculable Framingham risk score based on information recorded in their GPRD record prior to MI.

Men

For each Framingham risk score, the numbers of patients never, previously and currently prescribed aspirin is shown in Figure 7.2, Figure 7.2 and Table 7.15. Of the 623 men categorised with CHD risk of >20%, 103 (16.5%) were current aspirin users. Prescribing of aspirin was proportionally higher in those at highest risk, but there was considerable prescribing in those categorised as medium risk (10-20% CHD risk), 123 of

1152 patients, (10.7%)), and some prescribing in those categorised at low (<10%) risk (14 of 188 patients, 7.5%). Large numbers of patients at high cardiovascular disease risk did not receive aspirin.

Women

In women, prescribing of aspirin in the high risk group was greater than for men (Figure 7.3, Table 7.16). Fifty of 234 (21.4%) women categorised as >20% CHD risk were currently receiving aspirin. There was also a relatively high frequency of aspirin prescription in women at intermediate CHD risk, of whom 84 of 452 patients were currently using aspirin (18.6%). Just 35 of 384 (9.1%) patients categorised at low risk were receiving aspirin. The overlap in Framingham risk scores between current users and non-users at the time of MI indicates that a valid comparison can be made between these groups in both men and women.

7.6.2.3 Use of aspirin and prescribing guidelines

Until 2009, aspirin was recommended at ≥20% *cardiovascular disease risk*. This is equivalent to *≥15% CHD risk* using this Framingham risk score, and a point total of 14 in men and 22 in women. Of the 1,393 men who were categorised as ≥20% cardiovascular disease risk, 202 (14.5%) were receiving aspirin at the time of MI. Of the 400 women categorised with >20% cardiovascular disease risk, 81 (20.3%) were receiving aspirin.

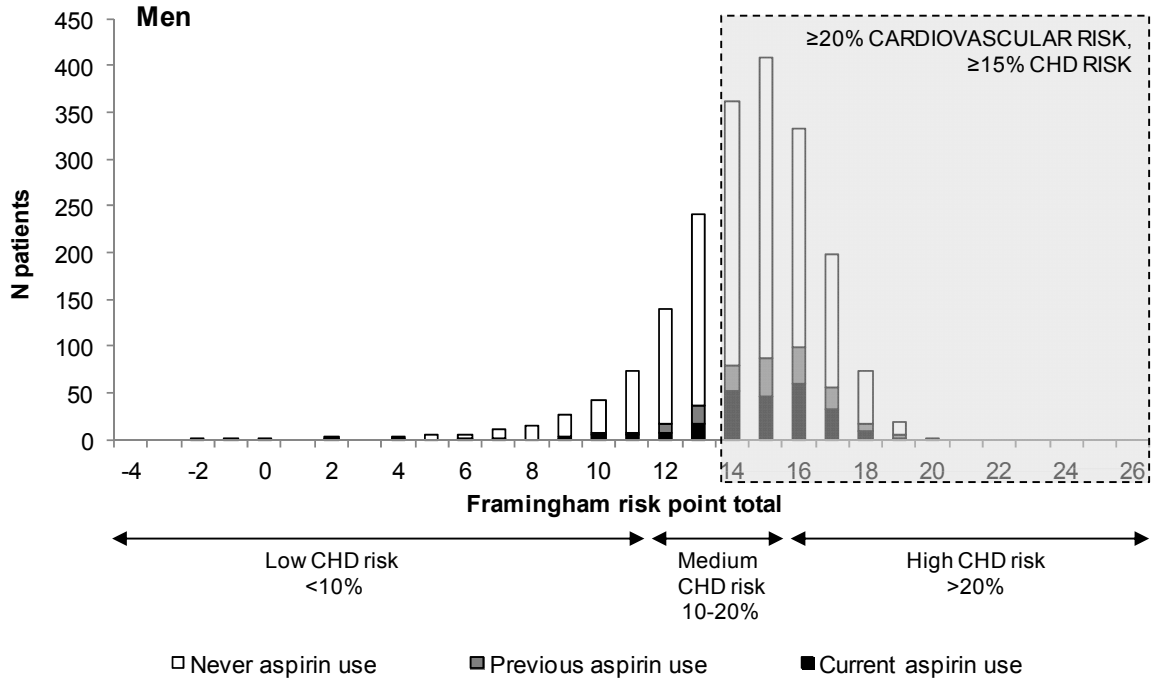


Figure 7.2 Number of current and never aspirin users by Framingham risk point total, in 1,963 men

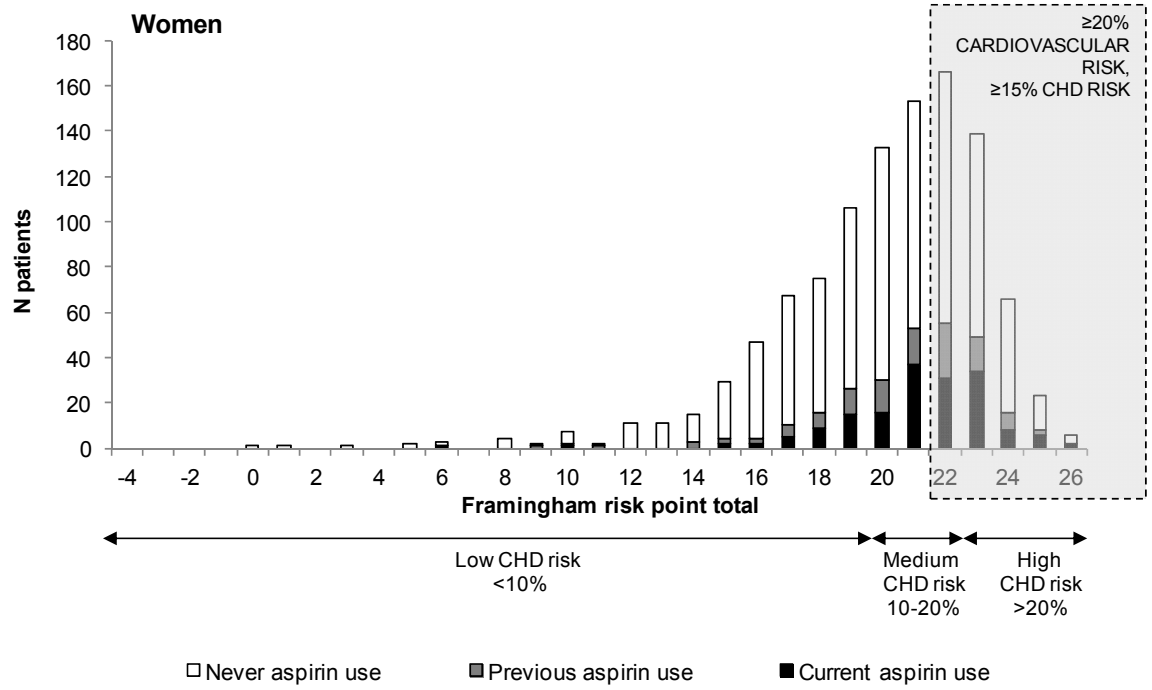


Figure 7.3 Number of current and never aspirin users by Framingham risk point total, in 1,070 women

Table 7.15 Number and percentage of men who were current, previous or never aspirin users at each level of risk (N=1,963)

Men Framingham point total	CHD risk	Current n	(%)	Previous n	(%)	Never n	(%)	Total n	(%)	
≤6		1	(0.4)	2	(1.1)	15	(1)	18	(0.9)	
7		1	(0.4)	0	(0)	11	(0.7)	12	(0.6)	
8	Low	0	(0)	0	(0)	15	(1)	15	(0.8)	
9	<10%	2	(0.8)	1	(0.6)	23	(1.5)	26	(1.3)	
10		5	(2.1)	3	(1.7)	35	(2.3)	43	(2.2)	
11		5	(2.1)	3	(1.7)	66	(4.3)	74	(3.8)	
12		8	(3.3)	9	(5)	123	(8)	140	(7.1)	
13	Medium	16	(6.7)	20	(11.2)	206	(13.3)	242	(12.3)	
14	10-20%	52	(21.7)	27	(15.1)	282	(18.3)	361	(18.4)	
15		47	(19.6)	41	(22.9)	321	(20.8)	409	(20.8)	
16		59	(24.6)	39	(21.8)	234	(15.2)	332	(16.9)	High CVD risk: ≥20% PRESCRIBE ASPIRIN
17	High	33	(13.8)	23	(12.8)	142	(9.2)	198	(10.1)	
18	>20%	9	(3.8)	8	(4.5)	57	(3.7)	74	(3.8)	
19		2	(0.8)	3	(1.7)	13	(0.8)	18	(0.9)	
≥20		0	(0)	0	(0)	1	(0)	1	(0)	
Total		240	(100)	179	(100)	1544	(100)	1963	(100)	

Point score totals in men ≤11 indicate low risk of *CHD*, 12-15 indicate intermediate risk of *CHD*, and ≥16 indicate high risk of *CHD*. A point score of ≥15 indicates high *cardiovascular* disease risk (used by current guidelines), including the risk of coronary, cerebrovascular and peripheral events as outcomes.

Table 7.16 Number and percentage of women who were current, previous or never aspirin users at each level of risk (N=1,070)

Women Framingham point total	CHD risk	Current n	(%)	Previous n	(%)	Never n	(%)	Total n	(%)	
≤6		1	(0.6)	0	(0)	7	(0.9)	8	(0.7)	
7		0	(0)	0	(0)	0	(0)	0	(0)	
8		0	(0)	0	(0)	4	(0.5)	4	(0.4)	
9		0	(0)	1	(0.9)	1	(0.1)	2	(0.2)	
10		1	(0.6)	1	(0.9)	5	(0.6)	7	(0.7)	
11		0	(0)	1	(0.9)	1	(0.1)	2	(0.2)	
12	Low	0	(0)	0	(0)	11	(1.4)	11	(1)	
13	<10%	0	(0)	0	(0)	11	(1.4)	11	(1)	
14		0	(0)	3	(2.7)	12	(1.5)	15	(1.4)	
15		2	(1.2)	2	(1.8)	25	(3.2)	29	(2.7)	
16		2	(1.2)	2	(1.8)	43	(5.4)	47	(4.4)	
17		5	(3)	5	(4.5)	57	(7.2)	67	(6.3)	
18		9	(5.3)	7	(6.3)	59	(7.5)	75	(7)	
19		15	(8.9)	11	(9.8)	80	(10.1)	106	(9.9)	
20		16	(9.5)	14	(12.5)	103	(13.1)	133	(12.4)	
21	Medium	37	(21.9)	16	(14.3)	100	(12.7)	153	(14.3)	
22	10-20%	31	(18.3)	24	(21.4)	111	(14.1)	166	(15.5)	
23		34	(20.1)	15	(13.4)	90	(11.4)	139	(13)	High CVD risk: ≥20% PRESCRIBE ASPIRIN
24	High	8	(4.7)	8	(7.1)	50	(6.3)	66	(6.2)	
25	>20%	6	(3.6)	2	(1.8)	15	(1.9)	23	(2.1)	
26		2	(1.2)	0	(0)	4	(0.5)	6	(0.6)	
Total		**169**	**(100)**	**112**	**(100)**	**789**	**(100)**	**1070**	**(100)**	

Point score totals in women ≤19 indicate low risk of *CHD*, 20-22 indicate intermediate risk of *CHD*, and ≥20 indicate high risk of *CHD*. A point score of ≥22 indicates high *cardiovascular* disease risk (used by current guidelines), including the risk of coronary, cerebrovascular and peripheral events as outcomes.

7.6.3 Aspirin and ST-elevation at MI presentation

In the subset of patients whose MIs were recorded with MI type (N=4,010), 2,122 (52.9%) were STEMI and 1,888 (47.1%) were NSTEMI. Compared to never users, current aspirin users were less likely to have ST-elevation (54.6% STEMI in never users, 37.7% in current users). The proportion presenting with STEMI in previous users was also lower than that of never users (48.4%) (Figure 7.4).

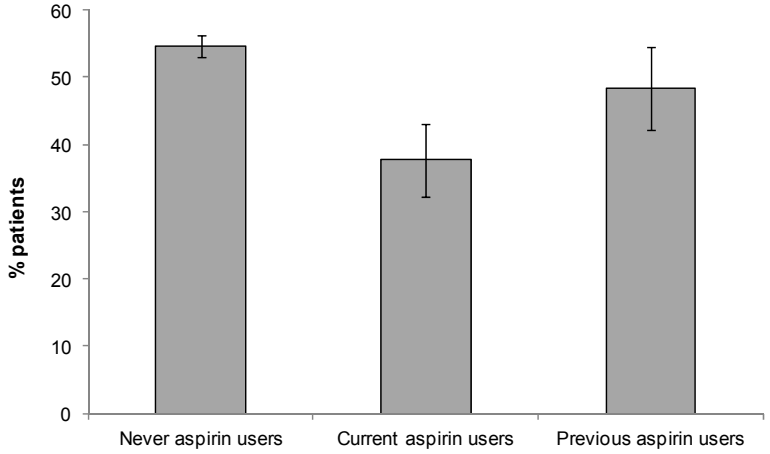


Figure 7.4 Proportion of patients with ST-elevation at myocardial infarction in never, current and previous aspirin users, with 95% confidence intervals (N=4,010)

At logistic regression analysis (Table 7.17), the crude odds of ST-elevation in *current* aspirin users were half of those of never users (OR=0.50 (0.40-0.64)). There was also some evidence for an association between *previous* aspirin use and ST-elevation (OR=0.78 (0.60-1.01)). The association between current use and ST-elevation was slightly attenuated on adjustment for age and sex, but further attenuated at a multivariable adjusted analysis taking account of all cardiovascular disease risk factors included in the Framingham risk score and diabetes. At multivariate analysis *current* aspirin users had lower odds of ST-elevation at MI (multivariable adjusted OR=0.66 (0.49-0.89), P=0.006), but there was no association between *previous* use and ST-elevation (OR=1.02 (0.74-1.42), P=0.894). When stratified by Framingham risk category (Appendix A, Figure 10.13), there was no evidence for a difference in the proportion of patients with ST-elevation by risk group (P value for interaction=0.3015).

Table 7.17 Crude and adjusted odds ratios to describe the association between aspirin use and ST-elevation at MI (N=4,010)

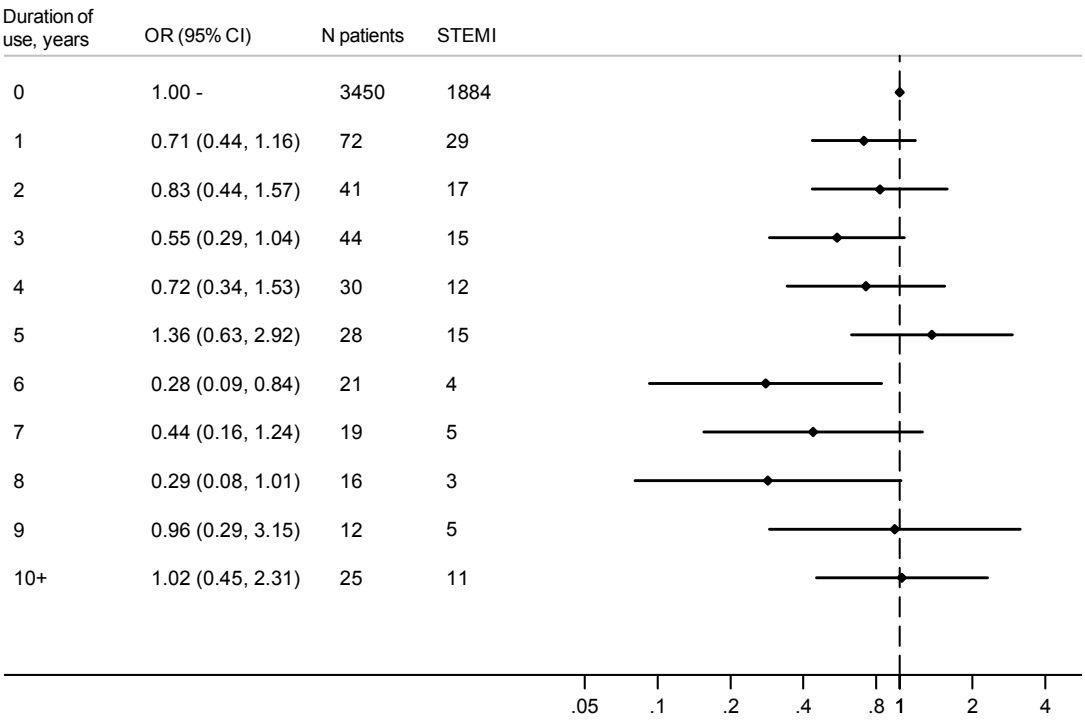
Aspirin use prior to MI	n	STEMI	(%)	Crude OR (95% CI) N=4,010	Age and sex adjusted OR (95% CI) N=4,010	Multivariable adjusted OR (95% CI)± N=4,001	Multivariable adjusted OR (95% CI)± including cholesterol† N=2,153
Never aspirin users	3,450	1,884	(54.6)	1 -	1 -	1 -	1 -
Current	308	116	(37.7)	0.50 (0.40-0.64) ***	0.59 (0.46-0.76) ***	0.64 (0.50-0.83) **	0.66 (0.49-0.89) **
Previous	252	122	(48.4)	0.78 (0.60-1.01)	0.88 (0.68-1.15)	0.93 (0.71-1.22)	1.02 (0.74-1.42)

± Adjusted for statin and antihypertensive use, age (as a linear term in this model), sex, hypertension, diabetes, smoking
† Total cholesterol fitted as a quadratic term in this model (likelihood ratio test compared to a linear term P=0.0512)
OR: odds ratio; STEMI: ST-elevation myocardial infarction.

*** P<0.001, ** P<0.01, * P<0.05

7.6.3.1 Duration of aspirin and ST-elevation at MI presentation

In a crude logistic regression analysis, the duration of aspirin use was associated with presentation. For each one year increase in duration of use, the odds of ST-elevation reduced by 11% (crude OR=0.89 (95% CI 0.85-0.94)). After adjusting for age, all cardiovascular disease risk factors and cardiovascular drug use except total cholesterol, there was some attenuation of the association, but still some evidence for 6% lower odds of ST-elevation for each additional year of aspirin use (multivariable adjusted OR=0.94 (95% CI 0.90-0.99), P=0.024). However, after taking account of total cholesterol, the association was no longer statistically significant OR=0.96 (0.91-1.02), P=0.207. There was no evidence of an interaction by Framingham risk score and both age and total cholesterol were fitted as quadratic terms. Categories of duration of aspirin use were also created and the association in each one year categories is described in Figure 7.5.



OR: odds ratio; STEMI: ST-elevation myocardial infarction.

Figure 7.5 Forest plot describing the multivariable adjusted odds ratios (OR) for ST-elevation myocardial infarction, comparing patients with different durations of aspirin use to patients never using aspirin (N=4,010)

7.6.4 Aspirin and infarct size

Overall the median observed peak troponin values were higher in never users compared to current and previous users (Figure 7.6). In crude multiple linear regression analysis using log-transformed peak troponin as an outcome, *current* aspirin use was associated with a 30% reduction in infarct size (relative infarct size 0.71 (95% CI: 0.54-0.93)). *Previous* aspirin use was not associated with a crude reduction in infarct size (estimated relative infarct size 0.85 (95% CI 0.63-1.15)).

When adjusted for all cardiovascular disease risk factors (age fitted as a linear term) except total cholesterol, the association was no longer statistically significant and was attenuated further still on adjustment for total cholesterol (fitted as a linear term) (adjusted relative infarct size in current users compared to never users 0.99 (95% CI 0.72-1.38), P=0.973, and in previous users 1.01 (95% CI 0.69-1.46), P=0.976). When the final model was stratified by risk category, there was no evidence for different effects of aspirin in different categories of Framingham risk (P for interaction 0.278, Appendix A, Figure 10.15).

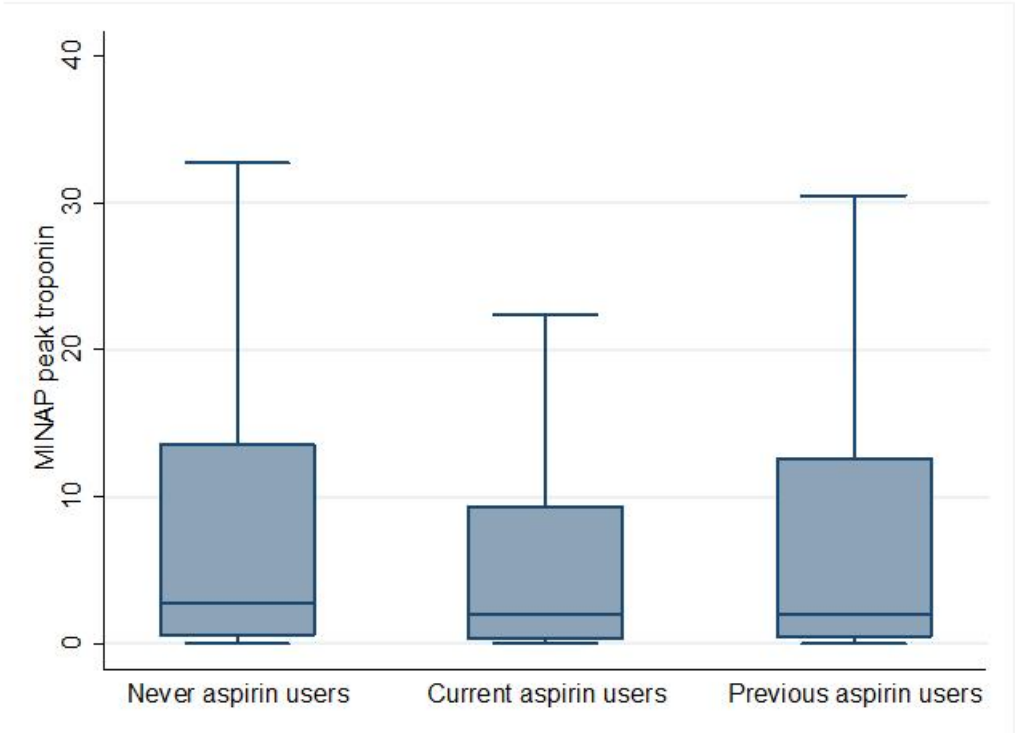


Figure 7.6 Box plots describing the median and inter-quartile range of infarct size (based on peak troponin in µg/L) in never, current and previous aspirin users (N=2,964)

7.6.5 Aspirin and 30 day mortality

In a crude analysis, there was strong evidence for higher 30 day mortality in current and previous aspirin users than never users (HR for current use=1.52 (95% CI: 1.34-1.72), previous use HR=1.39 (95% CI 1.20-1.61)). These associations were attenuated and no longer significant on adjustment for age and sex, and there was little further attenuation on adjusting for statin use, hypertension, diabetes and smoking, (adjusted HR for current use HR=1.10 (95% CI 0.95-1.26), P=0.20, and for previous use HR=1.02 (95% CI 0.87-1.20), P=0.783). The association was further attenuated on adjustment for total cholesterol (Table 7.18). There was no evidence for effect modification by level of Framingham risk (P=0.90), although stratification of the crude model showed a strong association between aspirin use and mortality in those with missing Framingham risk (Figure 7.8).

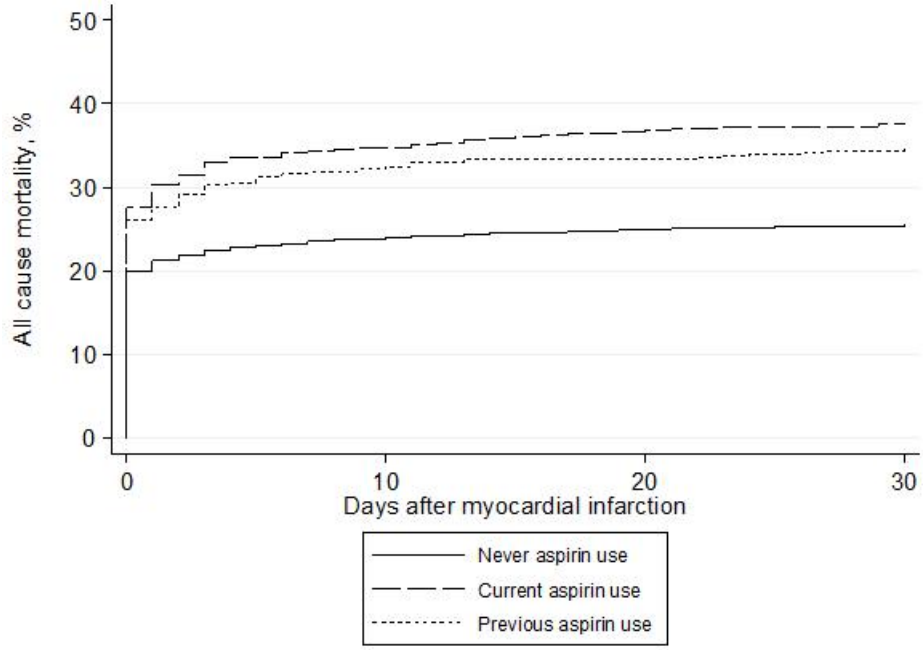


Figure 7.7 Crude all-cause mortality in the 30 days after myocardial infarction in current, previous and never aspirin users (N=8,104)

7.6.6 Aspirin dose and MI outcomes

In the main study population, 739 (97.1%) aspirin users at the time of MI were prescribed 75mg. Just 22 patients (2.9%) were prescribed a dose of 300mg, but there was insufficient power to examine the effect of this higher dose on MI presentation, infarct size or mortality.

Table 7.18 Crude and adjusted hazard ratios (HR) describing the association between current and previous aspirin use and 30 day mortality(N=8,104)

Aspirin use prior to MI	n	Dead at 30 days (%)	Crude HR (95% CI) N=8,104	Age and sex adjusted HR (95% CI) N=8,104	Multivariable adjusted HR (95% CI)± N=7,849	Multivariable adjusted HR (95% CI)± and total cholesterol† N=4,088
Never	6,780	1,733 (25.6)	1 -	1 -	1 -	1 -
Current	761	286 (37.6)	1.52 (1.34-1.72) ***	1.09 (0.96-1.24)	1.10 (0.95-1.26)	1.05 (0.87-1.25)
Previous	563	195 (34.6)	1.39 (1.20-1.61) ***	1.02 (0.88-1.19)	1.02 (0.87-1.20)	1.00 (0.81-1.24)

± Adjusted for statin and antihypertensive use, age (as a cubic term in this model, likelihood ratio test P=0.0032 for age as a cubic term compared to a quadratic term), sex, hypertension, diabetes, and smoking.

† Adjustment for total cholesterol as a cubic term in this model (likelihood ratio test P=0.0718 for total cholesterol as a cubic term compared to a quadratic term)

*** P<0.001, ** P<0.01, * P<0.05

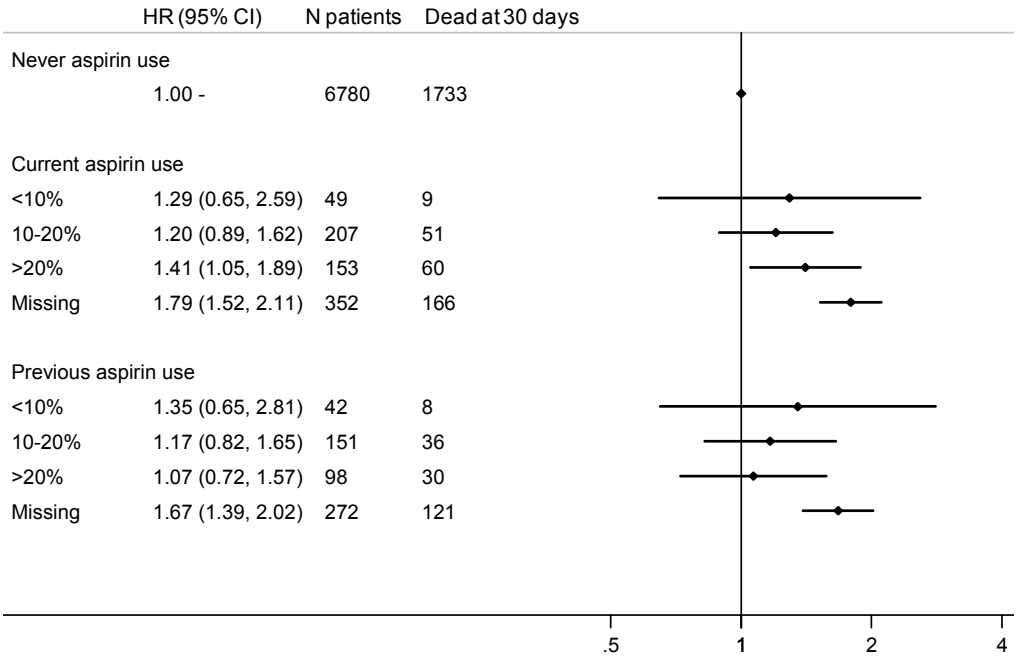


Figure 7.8 Crude hazard ratios (HR) describing 30 day mortality in never, current and previous aspirin users, at different levels of Framingham risk (N=8,104)

7.7 Results: statins

7.7.1 Description of statin use prior to MI

Amongst the 8,104 patients in this study, 804 were currently using statins at the time of MI and 356 had previously used statins but their prescription record indicated that they were no longer taking statins at the time of MI.

7.7.1.1 Initiation on statin therapy

The rate of initiation is shown in Figure 7.9. The rate increased from three per thousand patients ten years before MI to forty-seven per thousand patients in the year before MI.

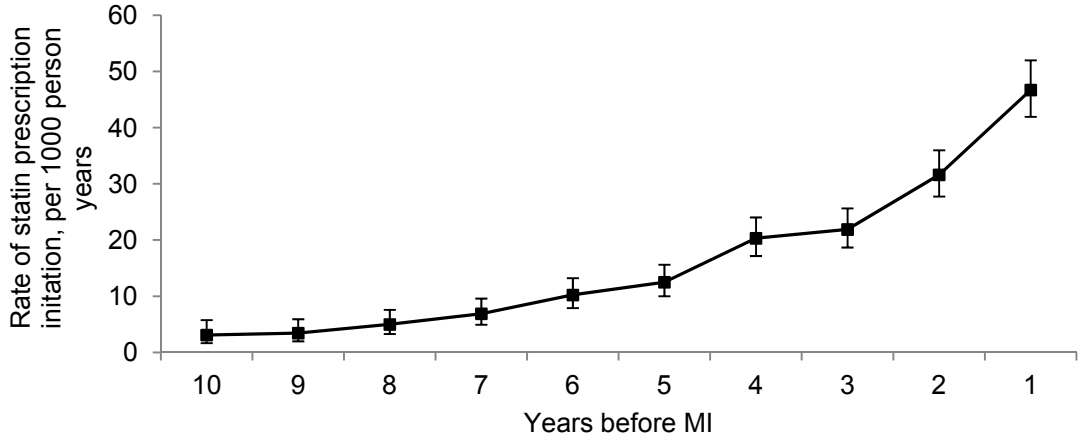


Figure 7.9 Rate of initiation on statins in the ten years prior to first myocardial infarction in 8,104 patients

7.7.1.2 Duration of statin use

In 804 current users, the duration of use ranged from just one day to nearly eighteen years (median 2.0 years (IQR 0.78-4.0 years)). The distribution of durations is described in Appendix A, section 10.6.5. In the 356 previous users, the duration of use ranged from forty days to fourteen years but the distribution was more highly skewed, with half of patients using statins for a year or less (median 0.87 (IQR 0.20-2.4 years)). In previous users, the time between last statin use and MI was estimated at a median of 0.74 years (IQR 0.1-2.3 years).

7.7.2 Statin use and Framingham risk

7.7.2.1 Risk factor distribution in never, current and previous statin users

The demographic and risk factor characteristics, stratified by statin use, are described in Table 7.19. Current and previous users of statins were the same age as never-users, were more likely to be female and more likely to have a calculable Framingham risk score. The proportion of current smokers was higher in never users.

Of the 857 patients identified by this study in the highest Framingham risk category (>20% CHD risk over ten years), only 298 (34.8%) of them had ever been prescribed a statin. High missingness in recording of total and HDL cholesterol in never statin users meant that risk scores could not be calculated in 70.3% of this group.

Table 7.19 Demographic and risk factor characteristics, stratified by previous statin use, in 8,104 first MI patients

	Never statin users		Current statin users		Previous statin users	
N patients	6,944		804		356	
Age, median (IQR)	68	(57-79)	68	(59-75)	67	(57.5-76)
Women, n (%)	2,488	(35.8)	318	(39.6)	145	(40.7)
Smoking, n (%)						
Non-smoker	1,032	(14.9)	117	(14.6)	52	(14.6)
Ex-smoker	3,269	(47.1)	471	(58.6)	184	(51.7)
Current smoker	2,396	(34.5)	214	(26.6)	114	(32)
Unknown	247	(3.6)	2	(0.2)	6	(1.7)
Systolic blood pressure in mm Hg, mean (SD)	145	(16.8)	148	(13.3)	147	(14.6)
Missing blood pressure, n (%)	443	(6.4)	0	(0)	1	(0.3)
Blood pressure lowering, n (%)	2,606	(37.5)	627	(78)	228	(64)
Total serum cholesterol in mmol/L, mean (SD)	5.8	(1.1)	5.7	(1)	6.2	(1.1)
Missing total cholesterol, n (%)	3,947	(56.8)	23	(2.9)	19	(5.3)
HDL cholesterol in mmol/L, mean (SD)	1.4	(0.4)	1.3	(0.4)	1.4	(0.4)
Missing HDL cholesterol, n (%)	4,862	(70)	131	(16.3)	60	(16.9)
Framingham risk, n (%)						
<10%	396	(5.7)	126	(15.7)	50	(14)
10-20%	1,109	(16)	342	(42.5)	153	(43)
>20%	559	(8.1)	205	(25.5)	93	(26.1)
Missing	4,880	(70.3)	131	(16.3)	60	(16.9)

IQR: inter-quartile range; SD: standard deviation; HDL: high density lipoprotein

7.7.2.2 Statin use at different levels of Framingham risk

Men

The numbers of patients currently, previously and never prescribed statins are described in Figure 7.10 and Table 7.20 by Framingham CHD risk score. There were 623 men defined as being at high risk of CHD (>20%), of whom 149 (23.9%) were current statin users. Of the 1,152 men at intermediate risk, 228 (19.8%) were current statin users. Of 188 patients categorised at low risk, 32 (17.0%) were statin users. In 3,190 patients with missing Framingham risk scores, the prevalence of statin prescribing was 2.4% (77 patients).

Women

Figure 7.11 and Table 7.21 describe current, previous and never statin use in the 1,070 patients for whom Framingham risk could be calculated. Of these, 234 women were categorised at high risk and 23.9% of them were current statin users. However, of the 452 patients categorised as at intermediate risk, 25.2% were current statin users and of those at low risk, 24.5% were statin users. However, there were 1,881 women whose Framingham risk score could not be calculated and just 2.9% of them were statin users. The substantial overlap in scores between users and non-users, for both men and women, indicates that a valid comparison can be made in the subsequent analyses.

7.7.2.3 Use of statins and prescribing guidelines

Statins are recommended for patients at ≥20% *cardiovascular* disease risk (same threshold as for aspirin). This is equivalent to >15% *CHD* risk using this Framingham risk score, and a point total of 14 in men and 22 in women (Figure 7.2 and Figure 7.2). Of the 1,393 men who were categorised as ≥20% cardiovascular disease risk, 315 (22.6%) were receiving statins at the time of MI. Of the 400 women categorised with ≥20% cardiovascular disease risk, 94 (23.5%) were receiving aspirin. However, 25.4% of patients who did not have high cardiovascular disease risk were in receipt of statins prior to MI.

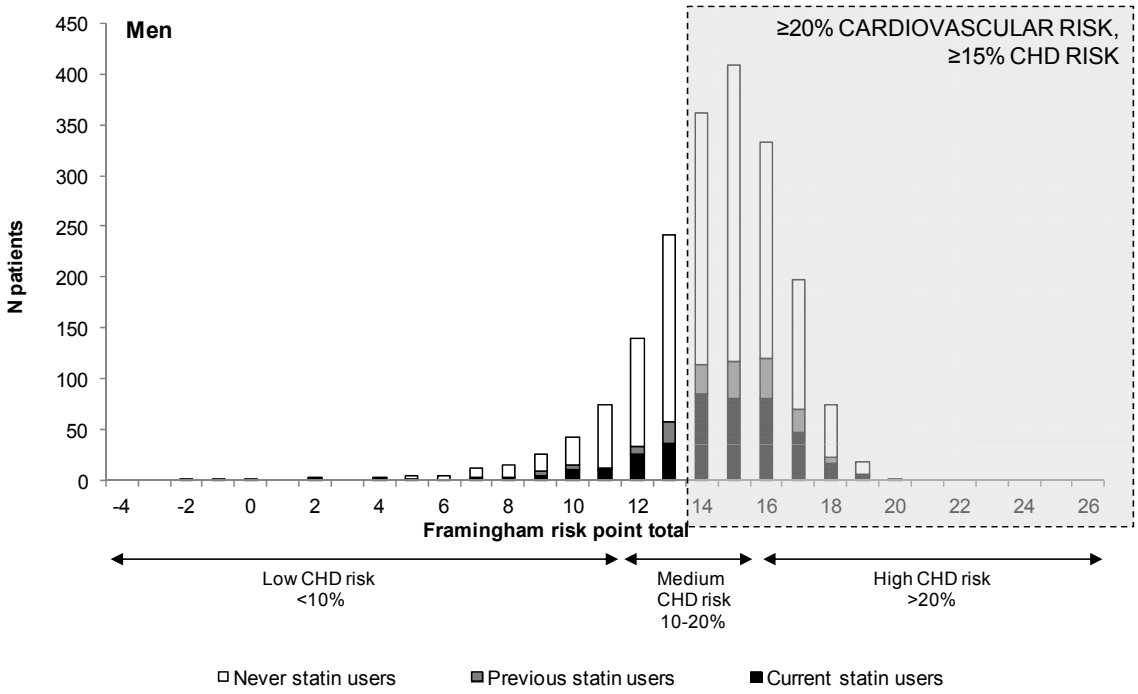


Figure 7.10 Number of current, previous and never statin users by Framingham risk point total, in 1,963 men

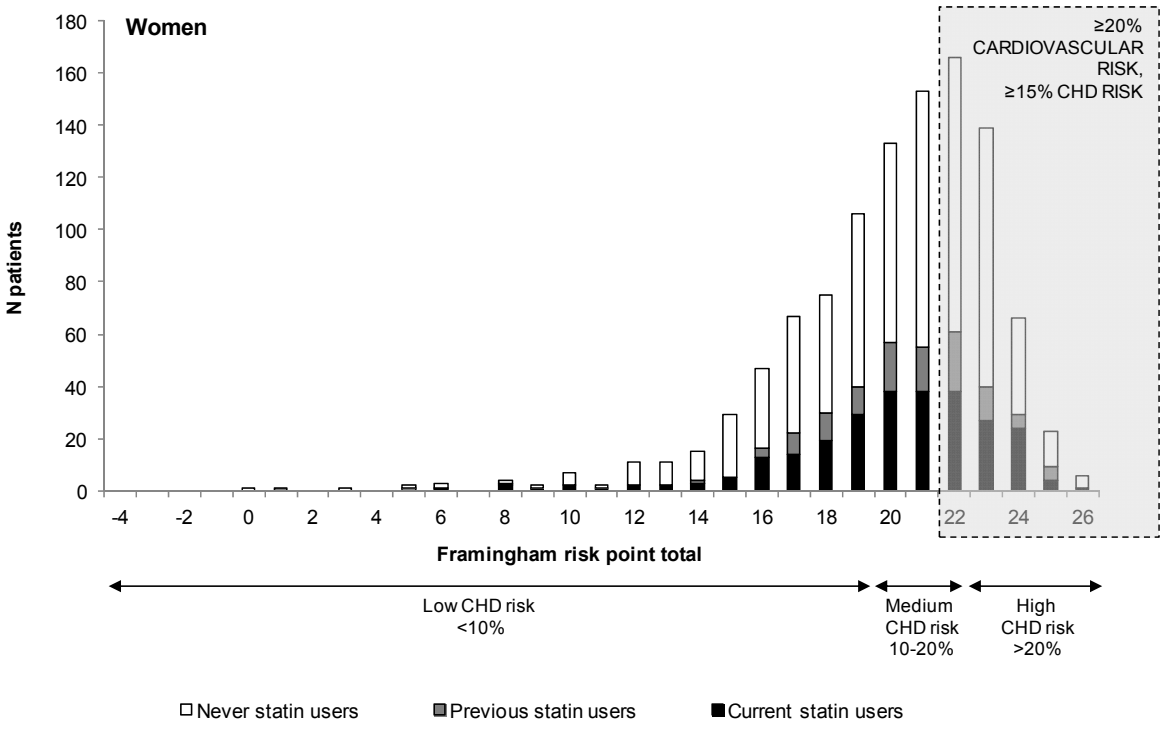


Figure 7.11 Number of current, previous and never statin users by Framingham risk point total, in 1,070 women

Table 7.20 Number and percentage of men who were current, previous or never statin users at each level of risk (N=1,963)

Men Framingham point total	CHD risk	Current n	Current (%)	Previous n	Previous (%)	Never n	Never (%)	Total n	Total (%)	
≤6		1	(0.2)	2	(1.1)	15	(1.1)	18	(0.9)	
7		1	(0.2)	2	(1.1)	9	(0.7)	12	(0.6)	
8	Low	3	(0.7)	0	(0)	12	(0.9)	15	(0.8)	
9	<10%	5	(1.2)	4	(2.3)	17	(1.2)	26	(1.3)	
10		11	(2.7)	4	(2.3)	28	(2)	43	(2.2)	
11		11	(2.7)	1	(0.6)	62	(4.5)	74	(3.8)	
12		26	(6.4)	7	(4)	107	(7.8)	140	(7.1)	
13	Medium	36	(8.8)	22	(12.4)	184	(13.4)	242	(12.3)	
14	10-20%	85	(20.8)	29	(16.4)	247	(17.9)	361	(18.4)	
15		81	(19.8)	36	(20.3)	292	(21.2)	409	(20.8)	High CVD risk: ≥20% PRESCRIBE STATIN
16		81	(19.8)	39	(22)	212	(15.4)	332	(16.9)	
17	High	47	(11.5)	23	(13)	128	(9.3)	198	(10.1)	
18	>20%	16	(3.9)	7	(4)	51	(3.7)	74	(3.8)	
19		5	(1.2)	1	(0.6)	12	(0.9)	18	(0.9)	
≥20		0	(0)	0	(0)	1	(0.1)	1	(0.1)	
Total		409	(100)	177	(100)	1377	(100)	1963	(100)	

Point score totals in men ≤11 indicate low risk of *CHD*, 12-15 indicate intermediate risk of *CHD*, and ≥16 indicate high risk of *CHD*. A point score of ≥15 indicates high *cardiovascular* disease risk (used by current guidelines), including the risk of coronary, cerebrovascular and peripheral events as outcomes.

Table 7.21 Number and percentage of women who were current, previous or never statin users at each level of risk (N=1,070)

Women Framingham point total	CHD risk	Current n	Current (%)	Previous n	Previous (%)	Never n	Never (%)	Total n	Total (%)	
≤6		1	(0.4)	2	(1.7)	5	(0.7)	8	(0.7)	
7		0	(0)	0	(0)	0	(0)	0	(0)	
8		2	(0.8)	1	(0.8)	1	(0.1)	4	(0.4)	
9		1	(0.4)	0	(0)	1	(0.1)	2	(0.2)	
10		2	(0.8)	0	(0)	5	(0.7)	7	(0.7)	
11		1	(0.4)	0	(0)	1	(0.1)	2	(0.2)	
12	Low	2	(0.8)	0	(0)	9	(1.3)	11	(1)	
13	<10%	2	(0.8)	0	(0)	9	(1.3)	11	(1)	
14		3	(1.1)	1	(0.8)	11	(1.6)	15	(1.4)	
15		5	(1.9)	0	(0)	24	(3.5)	29	(2.7)	
16		13	(4.9)	3	(2.5)	31	(4.5)	47	(4.4)	
17		14	(5.3)	8	(6.7)	45	(6.6)	67	(6.3)	
18		19	(7.2)	11	(9.2)	45	(6.6)	75	(7)	
19		29	(11)	11	(9.2)	66	(9.6)	106	(9.9)	
20	Medium	38	(14.4)	19	(16)	76	(11.1)	133	(12.4)	
21	10-20%	38	(14.4)	17	(14.3)	98	(14.3)	153	(14.3)	
22		38	(14.4)	23	(19.3)	105	(15.3)	166	(15.5)	High CVD risk: ≥20% PRESCRIBE STATINS
23		27	(10.2)	13	(10.9)	99	(14.4)	139	(13)	
24	High	24	(9.1)	5	(4.2)	37	(5.4)	66	(6.2)	
25	>20%	4	(1.5)	5	(4.2)	14	(2)	23	(2.1)	
26		1	(0.4)	0	(0)	5	(0.7)	6	(0.6)	
Total		**264**	**(100)**	**119**	**(100)**	**687**	**(100)**	**1070**	**(100)**	

Point score totals in women ≤19 indicate low risk of *CHD*, 20-22 indicate intermediate risk of *CHD*, and ≥20 indicate high risk of *CHD*. A point score of ≥22 indicates high *cardiovascular* disease risk (used by current guidelines), including the risk of coronary, cerebrovascular and peripheral events as outcomes.

7.7.3 Statin and ST-elevation at MI presentation

There were some crude differences in the presentation of MI in statin users and non-users. As described Figure 7.12, never users were more likely to have a STEMI compared to current and previous users. Current users had 24% lower odds of ST-elevation compared to never users (OR=0.76 (95% CI 0.62-0.94)). There was no evidence for an association between previous statin use and MI type (P=0.979). Adjusting for age and sex attenuated the association between current use and ST-elevation only slightly, but when the association between statin use and ST-elevation at MI was adjusted for all known cardiovascular disease risk factors, the association of current use and ST-elevation was no longer statistically significant (Multivariable adjusted OR=0.95 (95% CI 0.75-1.21), P=0.697) (Table 7.22). There was no evidence for effect modification by level of Framingham risk (Appendix A, Figure 10.19).

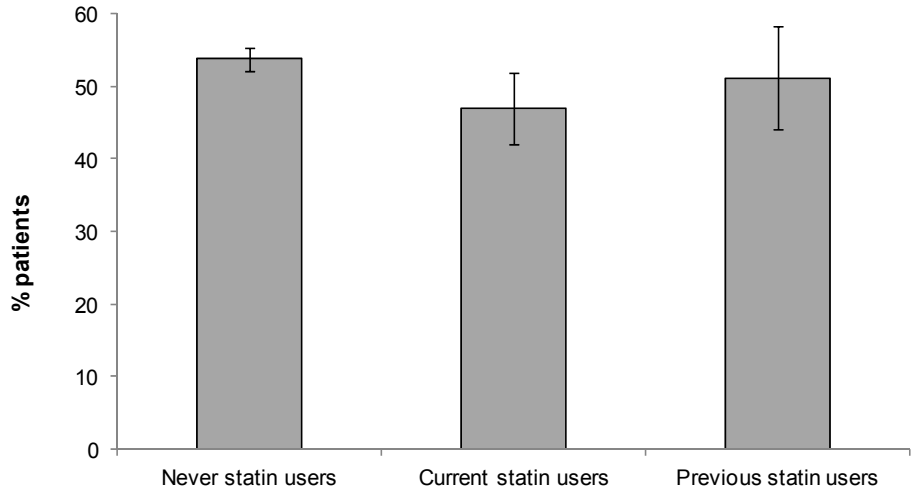


Figure 7.12 Proportion of patients with ST-elevation at MI in never, current and previous statin users (N=4,010)

Table 7.22 Odds ratios for ST-elevation among patients with myocardial infarction (MI), comparing never, current and previous users of statins (N=4,010)

Statin use prior to MI	n	STEMI	(%)	Crude OR (95% CI) N=4,010	Age and sex adjusted OR (95% CI) N=4,010	Multivariable adjusted OR (95% CI)± N=4,001	Multivariable adjusted OR (95% CI)± including total cholesterol† N=2,153
Never	3,415	1,835	(53.7)	1 -	1-	1-	1 -
Current	405	190	(46.9)	0.76 (0.62-0.94) **	0.78 (0.63-0.96) *	0.93 (0.74-1.17)	0.95 (0.75-1.21)
Previous	190	97	(51.1)	0.90 (0.67-1.20)	0.90 (0.67-1.21)	1.00 (0.73-1.35)	0.96 (0.70-1.33)

± Adjusted for aspirin and antihypertensive use, age (as a linear term in this model), sex, hypertension, diabetes and smoking.
† Total cholesterol adjusted for as a quadratic term in this model (likelihood ratio test P=0.0512 compared to cholesterol as a linear term).
OR: odds ratio.
*** P<0.001, ** P<0.01, * P<0.05

7.7.4 Statins and infarct size

Median infarct size was smaller in current and previous statin users than never users (peak troponin 2.7µg/L in never users, 2.27µg/L in current users, 2.07µg/L in previous users, Figure 7.13), (estimated relative infarct size in current users: 0.81 (95% CI 0.63-1.03), previous use 0.73 (95% CI 0.51-1.03)). Adjusting the regression model for age and sex did not change the effect measures, but further adjustment for, cardiovascular disease risk factors including hypertension, diabetes, smoking, aspirin and antihypertensive use attenuated the associations and showed no independent association between statin use and infarct size (Table 7.23). On stratification by Framingham risk, there was no evidence of an interaction between statin use and Framingham risk on infarct size (P=0.546, Appendix A, Figure 10.20).

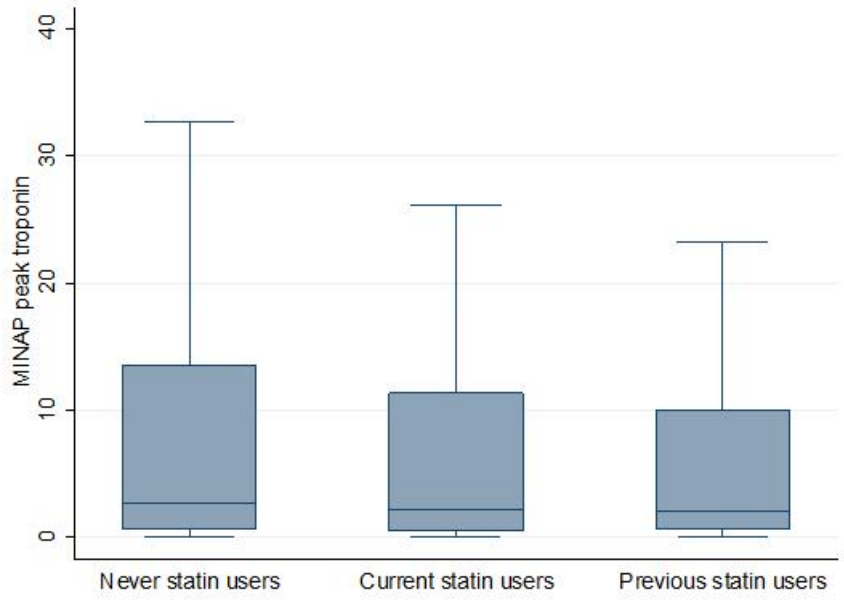


Figure 7.13 Box plots describing the median and inter-quartile range of peak troponin (in µg/L) in never, current and previous statin users (N=2,964)

Table 7.23 Multiple linear regression analysis to describe the effect of statin use prior to MI on infarct size in 2,964 patients

Statin use prior to MI	n	Median size (IQR)	Crude regression coefficient (95% CI) N=2,964	Age and sex adjusted regression coefficient (95% CI) N=2,964	Multivariable adjusted regression coefficient (95% CI)± N=2,912	Multivariable adjusted regression coefficient (95% CI)± including total cholesterol† N=1,583
Never	2,530	2.7 (0.6-13.5)	1 -	1 -	1-	1 -
Current	298	2.2 (0.5-11.3)	0.81 (0.63-1.03)	0.82 (0.65-1.05)	0.94 (0.72-1.23)	0.98 (0.74-1.30)
Previous	136	2 (0.6-10.1)	0.73 (0.51-1.03)	0.73 (0.52-1.03)	0.79 (0.55-1.13)	0.82 (0.56-1.19)

Note: estimated relative infarct size was calculated by exponentiating the coefficients from the multiple linear regression model.
± Adjusted for aspirin, antihypertensive use, age (as a linear term in this model), sex, hypertension, diabetes and smoking
† Total cholesterol fitted as a linear term in this model.
IQR: inter-quartile range.

*** P<0.001, ** P<0.01, * P<0.05

7.7.5 Statins and 30 day all-cause mortality after MI

There was a crude association between current statin use and 30 day mortality; *current* statin use was associated with lower mortality (HR=0.84 (95% CI 0.73-0.98)). There was no crude association between *previous* statin use and mortality. This is also described in the Kaplan Meier mortality curves in Figure 7.14. After adjusting for age and sex, there was no longer a significant association between current statin use and mortality (Table 7.24). Further multivariable analysis did not attenuate the association any further. Model diagnostics are described in Appendix A, section 10.6.6. There was no evidence for an interaction between statin use and Framingham risk category (P value for interaction 0.657).

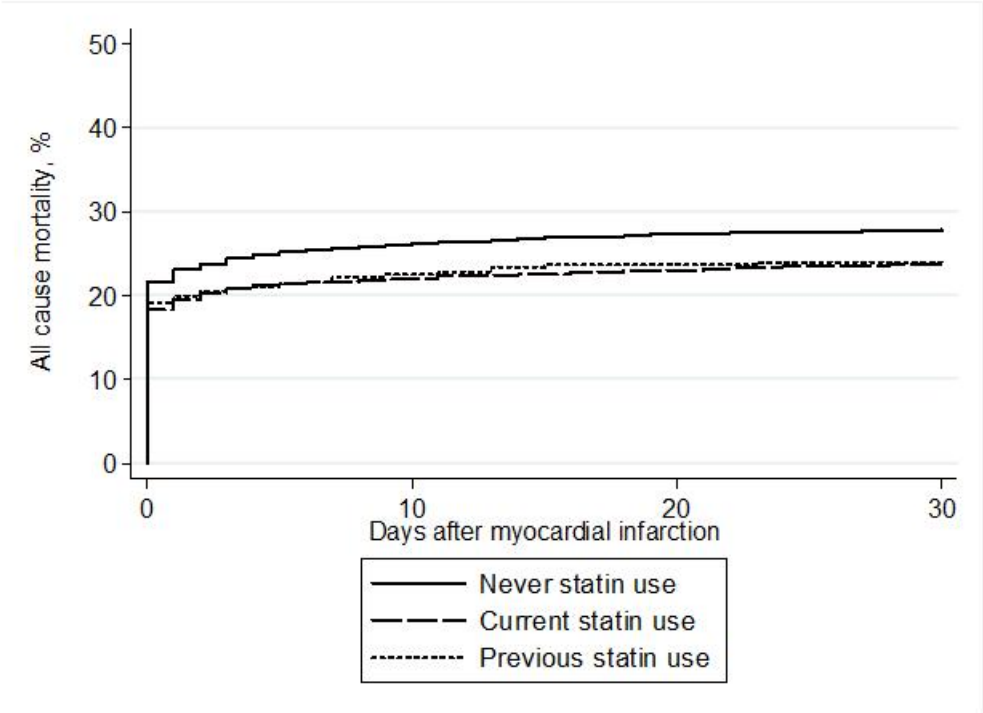


Figure 7.14 Crude all-cause mortality in the 30 days after myocardial infarction (MI), stratified by statin use prior to MI in 8,104 patients

Table 7.24 Hazard ratios (HR) for death at 30 day all-cause mortality following myocardial infarction (N=8,104)

Statin use prior to MI	n	Dead at 30 days (%)		Crude HR (95% CI) N=8,104	Age and sex adjusted HR (95% CI) N=8,104	Multivariable adjusted HR (95% CI)± N=7,849	Multivariable adjusted HR (95% CI)± including total cholesterol† N=4,088
Never	6,944	1,937	(27.9)	1 -	1 -	1-	1 -
Current	804	191	(23.8)	0.84 (0.73-0.98) *	0.93 (0.80-1.09)	0.91 (0.77-1.08)	0.97 (0.81-1.16)
Previous	356	86	(24.2)	0.86 (0.69-1.06)	0.93 (0.95-1.15)	0.91 (0.73-1.15)	0.98 (0.77-1.24)

± Adjusted for aspirin use, antihypertensive use, age (fitted as a cubic term, likelihood ratio test P=0.0032), sex, hypertension, diabetes, smoking
† Additional adjustment for total cholesterol included as a cubic term (likelihood ratio test P=0.0718 compared to cholesterol as a quadratic term).

*** P<0.001, ** P<0.01, * P<0.05

7.7.6 Statin dose

There was variation in the dose of statins prescribed (between 5mg per day and 80mg per day, as shown in Table 7.25). The patients taking 5mg doses per day were combined with those taking 10mg for their inclusion at analysis. In a comparison of the demographic and risk factor characteristics of patients prescribed these different doses, stronger doses were not associated with increased coronary risk, but were associated with higher total cholesterol (Appendix A, Table 10.22).

The dose variation allowed an analysis of the effect of statin dose on MI presentation, infarct size and 30 day mortality. There was no effect of increasing dose on any of the outcomes (Multivariable adjusted OR for ST-elevation at MI=1.00 (0.99-1.00)), multivariable adjusted estimated relative infarct size 1.00 (0.99-1.00), multivariable adjusted hazard ratio for 30 day mortality 1.00 (0.99-1.00) (Table 7.26).

Table 7.25 Statin dose and number of patients prescribed that dose prior to MI

Dose, mg*	Current statin users	Previous statin users	Total
5	6	11	17
10	90	72	162
20	353	143	496
40	293	111	404
80	62	15	77
Missing dose	0	4	4

*standardised to simvastatin equivalent dose.

Table 7.26 Number and proportion of patients with ST-elevation at myocardial infarction (MI), median infarct size, and number and proportion of patients dead at 30 days, according to various doses of statins prescribed prior to MI in 8,104 patients

Statin dose prior to MI	N with MI type recorded	STEMI (%)		N with infarct size recorded	Median size (IQR)		N with mortality record	Dead at 30 days (%)	
No statins	3,418	1,835	(53.7)	2,533	2.7	(0.6-13.5)	6,944	1,937	(27.9)
10mg	79	42	(53.2)	61	2.1	(0.5-13.8)	96	24	(25)
20mg	249	111	(44.6)	183	2.0	(0.5-13.6)	353	90	(25.5)
40mg	231	119	(51.5)	162	2.4	(0.5-11)	293	63	(21.5)
80mg	33	15	(45.5)	25	2.8	(0.7-10)	62	14	(22.6)

IQR: inter-quartile range; STEMI: ST-elevation myocardial infarction.

7.7.7 Sensitivity analysis

7.7.7.1 Additional cardiovascular disease risk factors

The models described in these analyses were repeated in an adjusted analysis taking account of BMI, family history of CHD and social deprivation, as measured by IMD quintile. Adjusting for these additional factors made no difference to the conclusions in the main analysis. The multivariable adjusted OR in the sensitivity analysis was 0.65 (95% CI 0.48-0.88)), P=0.005, compared to 0.66 (95% CI 0.49-0.89) p=0.006 in the main analysis. Full results of these additional analyses are shown in Appendix A, section 10.6.7.

7.7.7.2 Inclusion of possible diagnoses

The main analysis included only patients with definite atherosclerotic disease diagnoses prior to MI. In an analysis including patients with possible diagnoses of atherosclerotic disease, 7,666 patients without atherosclerotic disease were identified. Of these patients, 668 (8.7%) were current aspirin users, 515 (6.7%) were previous aspirin users. There were 722 current statin users (9.4%) and 324 (4.2%) previous statin users. When the main analyses of the three outcomes were repeated, there were no differences in the conclusions. The results are shown in Appendix A, section 10.6.7.

7.7.7.3 GPRD prescription data versus MINAP admission drug use

Of the subset of patients included in this analysis who had a MINAP record (N=3576), 92% had a record of antiplatelet use, and 52% had a valid record of statin use prior to MI. For patients who had a record of drug use, concordance between GPRD prescription data and MINAP data are described in tables Table 7.27 and Table 7.28. For never users, concordance between GPRD and MINAP was high (>90% agreement). However, for current and previous users, agreement was poorer. In particular, for aspirin use, there was only 51% agreement. For MINAP patients, it is unclear whether the aspirin was taken by the patient for primary prevention (therefore representing the exposure of interest), or whether it was administered in the ambulance or the emergency room (and therefore not the exposure of interest). Since admission drug use was only available in a small subset of patients, and due to the high missingness in statin use and the unclear timing of antiplatelet use, MINAP data were not used as part of the main exposure in this analysis.

7.7.7.4 Adjustment for consultation rate

Patients experiencing NSTEMI tend to be those with more comorbidity. Therefore, aspirin use may be simply a marker of poorer health rather than being independently associated with NSTEMI. Therefore, the main analysis describing presentation in users and non-users of aspirin was adjusted for consultation rate, a marker of general morbidity in the GPRD. After adjusting for consultation rate, the odds ratio comparing current and never users in terms of ST-elevation MI was unchanged. (OR in main analysis=0.66 (95% CI 0.49-0.89) p=0.006, and in an analysis adjusted for consultation rate OR=0.67 (95% CI 0.52-0.87), P=0.004). Results are shown in Appendix A, section 10.6.7.

7.7.7.5 Differing definitions of 'current use'

The buffer of 14 days between a last prescription and MI was changed in two sensitivity analyses to zero or 28 days. Using either of these definitions did not affect the conclusions of the main analysis. An alternative definition of current use was also tested in a sensitivity analysis, where current use was defined as two or more prescriptions in the six months prior to MI. Using this definition, there were no changes in the conclusions of the main analysis. Results of these analyses are in Appendix A, section 10.6.7.

7.7.7.6 Peak creatine kinase as a measure of infarct size

Due to limitations of the recording of peak troponin in terms of the grouping of data around round numbers and the lack of information on assay type in this analysis, the analyses describing the associations between aspirin and statin use and infarct size were repeated using peak creatine kinase as the measure of infarct size. This showed the same result as the main analysis, with no associations between either drug and infarct size at multivariable adjustment (current aspirin use exponentiated multiple linear regression coefficient 0.83 (95% CI 0.63-1.11), P=0.207, and for current statin use 1.02 (95% CI 0.82-1.27), P=0.865).

Table 7.27 Comparison of GPRD prescription and MINAP aspirin use at admission in 3,437 patients

Aspirin at admission: MINAP response	GPRD prescription: Never n	(%)	Current n	(%)	Previous n	(%)	Total n	(%)
No	2,841	(96.0)	130	(48.7)	181	(85.8)	3,152	(91.7)
Yes	118	(4.0)	137	(51.3)	30	(14.2)	285	(8.3)
Total	2,959	(100)	267	(100)	211	(100)	3,437	(100)

GPRD: General Practice Research Database; MINAP: Myocardial Ischaemia National Audit Project

Table 7.28 Comparison of GPRD prescription and MINAP statin use at admission in 1,928 patients

Statin at admission: MINAP response	GPRD prescription: Never n	(%)	Current n	(%)	Previous n	(%)	Total n	(%)
No	1,464	(91.5)	49	(22.4)	73	(67)	1,586	(82.3)
Yes	136	(8.5)	170	(77.6)	36	(33)	342	(17.7)
Total	1,600	(100)	219	(100)	109	(100)	1,928	(100)

GPRD: General Practice Research Database; MINAP: Myocardial Ischaemia National Audit Project

7.8 Discussion

7.8.1 Summary

This study was the first to our knowledge to prospectively assess the prescription of statins and aspirin for *primary prevention* and their associations with outcomes at MI, and to assess these associations at different levels of coronary risk. It was also the first to assess the associations between these medications and mortality in general populations. Our results show that prescribing of aspirin was most frequent in the groups with highest Framingham risk, but there was also considerable prescribing in patients with intermediate risk, and some prescribing in patients with low risk. Prescribing of statins was of a similar prevalence across all risk groups. The variation in Framingham risk across patients for whom this was measured also indicates the failure of this risk score to accurately identify patients at high risk.

There was evidence to suggest that current aspirin use at the time of MI was a marker for attenuated infarct severity, even after adjusting for age, sex, cardiovascular disease risk factors, statin and antihypertensive use. This association was robust to further adjustment for family history, BMI, social deprivation and for GPRD consultation rate, an indicator of general morbidity. Longer duration of aspirin use was also associated with lower odds of ST-elevation. However, there was no association between aspirin use and infarct size or mortality. Patients defined as previous aspirin users, i.e. withdrawers, had the same MI outcomes as patients who had never used aspirin. Statin use, dose and duration were not associated with any of the outcomes examined in this study. Explanations for these associations are described below in the context of other literature.

7.8.2 Possible explanations: aspirin

7.8.2.1 Prescription of aspirin by Framingham risk category

Reflecting previous guidelines (Table 7.29, reproduced from the literature review), prescribing was highest in those categorised as high risk. Prescribing in patients at intermediate and low risk is likely to reflect guidance to prescribe aspirin in patients with type 2 diabetes, which is not included in the Framingham score. However, 80% of women and 85% of men defined as at high cardiovascular disease risk were not being treated. This may be an underestimate of true aspirin use due to over the counter use. It may also reflect both patient and GP preference in not prescribing aspirin, concerns of polypharmacy in the elderly,[274] or a lack of recognition of high risk by GPs, as this study did not measure GP

recognition of raised risk. There is evidence that many GPs do not use risk calculators, at least in other parts of Europe, which may also have contributed to the under-use observed here.[275]

Table 7.29 British guidelines for the use of aspirin in primary prevention of cardiovascular disease

Aspirin	
JBS 2, 2005[231]	• Aspirin 75mg daily for: – Individuals with ≥20% cardiovascular disease risk over 10 years once hypertension, if present, is controlled to systolic <150mmHg and diastolic <90mmHg; – All people with diabetes.
NICE, 2008[236]	In patients with diabetes, offer low dose aspirin, 75mg daily to: • A person who is 50 years old or over, if blood pressure is below 145/90mmHg; • A person who is under 50 years old and has significant other cardiovascular disease risk factors (features of metabolic syndrome, strong early family history of cardiovascular disease, smoking, hypertension, extant cardiovascular disease, microalbuminuria).
MHRA, 2009[234]	"Aspirin is not licensed for the primary prevention of vascular events. If aspirin is used in primary prevention, the balance of benefits and risks should be considered for each individual, particularly the presence of risk factors for vascular disease (including conditions such as diabetes) and the risk of gastro-intestinal bleeding."
SIGN, 2007,[233] 2012[235]	**2007 guideline:** • Consider aspirin daily for: – Patients with a calculated cardiovascular disease risk of ≥20% over ten years; – All people with type 2 diabetes who are over 50 years of age, and for selected younger individuals who are considered to be at increased cardiovascular disease risk. **2012 guideline:** • Aspirin is not recommended for the primary prevention of vascular disease when benefits are considered against the increased risk of haemorrhage.

JBS: Joint British Societies; NICE: National Institute for Health and Clinical Excellence; MHRA: Medicines and Healthcare Regulatory Agency; SIGN: Scottish Intercollegiate Network.

7.8.2.2 Presentation with ST-elevation

The studies included in the literature review support the results found in this analysis, with less ST-elevation at MI in aspirin users.[243-246] Attenuated severity of coronary presentations in aspirin users has also been reported in other contexts; Garcia-Dorado[250] and Alexander[249] examined the association between aspirin and the severity of manifestation in acute coronary syndromes overall, finding that previous aspirin use was associated with less MI and more unstable angina. Garcia-Dorado also showed that longer duration of use was also associated with severity of ACS, which is similar to our results describing less ST-elevation in patients who had been using aspirin for longer periods.[250]

It is plausible that aspirin does have a true effect on presentation with ST-elevation; its antiplatelet properties may reduce the likelihood of sudden thrombotic events that often characterise STEMI patients. The association in the current study was the same at all levels of cardiovascular disease risk, indicating that aspirin may reduce the occurrence of thrombotic events irrespective of baseline risk. This result is further strengthened by the absence of an association in previous users, who had similar distribution of Framingham risk, indicating that the results are less likely to be due to confounding by indication. However, all of the studies examining the effects of aspirin, including the current study, are observational and therefore none can describe the causal nature of the relationship. For example, even within the highest risk group, patients with a poorer risk factor profile (e.g. with very high blood pressure, uncontrolled diabetes, smokers) may have more severe atherosclerosis and may be more likely to receive aspirin than their high risk peers, therefore confounding the association observed between aspirin and ST-elevation.

While the causal relationships remain unclear, this study has described and reported the association between aspirin use and ST-elevation for the first time in patients taking aspirin for primary prevention.

7.8.2.3 Infarct size

Larger infarcts, measured by increased troponin or CK release, are usually associated with ST-elevation, a marker of greater myocardial damage. However, while aspirin use was a marker for decreased ST-elevation in this study, it did not drive an association between aspirin use and infarct size.

The literature review described consistently smaller infarcts in aspirin users, even in studies which were adjusted for cardiovascular disease, cardiovascular disease risk factors,

and other drug use. While there was a crude association with infarct size in our study, this was lost after adjustment for all cardiovascular disease risk factors and other drug use. The studies reviewed may not have measured or adjusted sufficiently for confounding factors, due to their respective design. Alternatively, the lack of association with infarct size in our study may be due to several limitations in its measurement in this study.

First, peak troponin is not the optimal measure of infarct size; imaging techniques including MRI scanning are likely to be the gold standard in measuring damage to the myocardium. While there is a correlation between peak troponin and infarct size ([276]), this is imperfect. Second, recording of troponin in MINAP is grouped around round numbers, for example at 50 and 100 (see Appendix A, Section 10.6.2). Peak troponin data in MINAP are not collected for the type of research in this study and therefore the recorded data may not be an accurate reflection of the true value. Third, for patients who are reperfused early, there may not be a characteristic rise and fall in troponin, meaning that no peak troponin value is collected. Fourth, the meaning of the peak troponin values are dependent on the assay used (T or I) and these data were not used in this analysis. However, a sensitivity analysis using peak creatine kinase (which does not show this grouping) instead of peak troponin as a measure of infarct size showed the same result. Finally, there may be selection bias in the patients included. Peak troponin was recorded in 83% of patients with a MINAP record, but only 37% of the whole sample. As discussed in Chapter 4 (Data quality), patients recorded in MINAP tend to be younger and more likely to survive than other hospitalised patients who do not have a MINAP record. If there is also a bias in the patients who have their peak troponin values recorded, then the effect measure produced in this study is unlikely to reflect any true association between prior aspirin use and infarct size.

7.8.2.4 Mortality

There was no overall association between aspirin use and mortality. However, in a crude analysis, stratification by Framingham risk showed that the association between aspirin and mortality was strongest in patients with missing Framingham risk. This was explained entirely by the confounding effects of cardiovascular disease risk factors in this group and the mixture of patients in this group at very high risk (who were in receipt of aspirin) and very low risk patients who were not.

The associations of aspirin use with short term mortality were inconsistent in the literature, with results in different directions (see Table 7.5). Interestingly, a MINAP study

examining predictors of mortality in STEMI patients in the MINAP dataset showed an independent protective effect of aspirin use prior to hospitalisation (OR=0.55 (95% CI 0.46-0.67), P<0.001).[103] In a crude analysis our results for hospitalised and non-hospitalised MIs showed the opposite trend. In the literature review, the largest study of over 118,000 elderly US patients described a protective association between aspirin and mortality.[253] It is possible that aspirin use in this large US study reflected a healthy user effect, or that the effects were different in the older population covered by the study. Another plausible explanation is effect modification by previous coronary disease diagnosis, as reported by Spencer (2002).[263] In patients with previous disease, aspirin was protective, while there was no association in those without disease. If coronary disease prevalence was high in the elderly patients of the US study, this could partially explain the reported decreased risk. In the current analysis, higher mortality was found in users with the highest coronary risk, reflecting UK guidelines which previously indicated use of aspirin in patients at the highest coronary risk.

Other large studies of ACS patients have also shown higher mortality in aspirin users, or no association at all.[249, 260, 271] Given the effect measures produced by the studies in Table 7.5, it is plausible that there is no true association between mortality and aspirin use for primary prevention, and studies showing higher mortality in aspirin users are confounded due to poorly measured confounders or insufficient adjustment.

7.8.3 Possible explanations: statins

7.8.3.1 Prescription of statins by Framingham risk category

Despite guidance to prescribe statins to patients at high cardiovascular disease risk, only 23% of MI patients with cardiovascular disease risk above the 20% threshold (i.e. above 15% CHD risk) were in receipt of statins and the level of statin prescribing was the same across levels of Framingham risk. This is likely to reflect prescribing in patients with high total cholesterol, irrespective of other cardiovascular disease risk factors. In patients whose Framingham scores could not be calculated (mostly due to lack of cholesterol measurement), levels of statin prescribing were below 3%. These results indicate that for the majority of patients, statin prescribing is dependent on a measurement of cholesterol rather than a raised global cardiovascular disease risk score. This also means that there the results described regarding statin use and outcomes are less likely to be confounded by high cardiovascular disease risk.

7.8.3.2 Presentation with ST-elevation

Of the two studies reporting associations with MI presentation, both described lower ST-elevation in users of statins. Further evidence for the association of statins with reduced severity of coronary disease presentation is from the ADVANCE study in the United States,[277] which reported a favourable influence of statins on initial presentation with CHD, being associated with stable angina rather than MI. A study of GRACE registry patients with ACS also described lower odds of ST-elevation in statin users. In a crude analysis, the current study showed an attenuated severity of MI presentation in statin users, which was lost on adjustment. Since information on MI type was only available from a sub-sample of patients in the main study and the majority of these from MINAP patients, it is possible that selection bias affected the results in this study, or that there was not enough power to identify a real effect of statins. However, it is also possible that our study was better adjusted that those described above because information on confounders was measured prospectively.

7.8.3.3 Infarct size

Two small studies of previous statin use prior to first MI described smaller infarct in statin users. One studied only patients without previous atherosclerotic disease, and although statin users had smaller infarcts, no adjusted analysis was performed.[265] The other study was well-adjusted for demographics, cardiovascular disease risk factors and multivessel disease, still showing an association with infarct size.[266] As described above, a true association between statins and infarct size may have been obscured by selection bias of patients in whom peak troponin was recorded.

7.8.3.4 Mortality

In the UK, statins, like aspirin, are recommended for patients at high cardiovascular disease risk. While statins were not associated with any of the outcomes at multivariate analysis, they were crudely associated with lower mortality, which is opposite to the crude association seen in aspirin users due to the prescribing of statins across all risk groups.

A null association of previous statin use on mortality was also reported in another study of patients without prior atherosclerotic disease.[265] While other studies have shown evidence for lower mortality in the statin treated group, these were all retrospective in design

so confounders may have been measured poorly. The current study is the first to describe the association between statins and mortality in general populations and despite a strong beneficial effect in preventing MI, [39, 41] statins appear to have no effect on outcomes in patients who still have MI.

7.8.4 Strengths

Data quality is a major strength of this study. The MI outcomes were validated in Chapter 4, and were shown to have a high positive predictive value and accurate data on timing. MI records were taken from all four data sources (GPRD, HES, MINAP and ONS) to gather the most representative sample. A unique strength of this study was inclusion of patients who died before hospital admission. All other previous studies have been unable to investigate fatal MI events. If patients who made it to hospital were systematically different to those who did not in terms of their previous aspirin use, the associations produced by previous studies may have been biased. This is therefore the first study to present findings in a general population.

Patient records from the GPRD are prospectively collected, with repeated measures of smoking, blood pressure, and detailed records of cardiovascular disease risk factors and atherosclerotic disease diagnoses. Prescribing data from the GPRD are of excellent quality because all drugs prescribed in primary care are automatically recorded in the dataset, including the product prescribed, the date and the dosage. For statins and other drugs unavailable over the counter, the data on patients receiving these agents are complete. This detailed prospective data allowed analysis of duration and dose, which had not previously been examined in patients with MI.

In the main analysis, atherosclerotic disease diagnoses and cardiovascular disease risk factors were present if a patient had a 'definite' Read or ICD code for that diagnosis based on clinician rating. A sensitivity analysis indicated that addition of 'possible' terms did not materially change the results.

7.8.5 Weaknesses

While the data on prescribing in the GPRD are of high quality, over the counter use of drugs is not recorded. Therefore, aspirin data are likely to be incomplete if the GP has recommended use of aspirin without a record of prescriptions. Over the counter use of

aspirin is cheaper than a prescription; general practitioners may not prescribe aspirin through their computer system, and instead recommend that the patient purchase and use aspirin. In some cases, patients may not visit their GP at all and purchase the drugs. There are currently no information available regarding over the counter use of aspirin for the patients in this study. Misclassification of aspirin exposure would have attenuated the associations described here, so it is possible that an association between aspirin use, infarct size or mortality was missed.

Additionally, there is currently no information available regarding collection of prescriptions or compliance, which is a drawback of using routinely collected data for research. However, in this analysis receiving repeat prescriptions was used an indicator of drug use, and the majority of current users had received more than one prescription.

As discussed in the limitations of Chapter 6, the risk factor measures adjusted for in this analysis may not accurately reflect true cardiovascular disease risk at the time of MI because they were based on averages of repeated measures collected during follow-up. Other strategies to deal with repeated measurements of blood pressure and cholesterol over time may have been more useful (last measurement prior to MI, mean of measurements in the year prior to MI), although these were not explored in this analysis. The potential misclassification of risk factors means that there may be some residual confounding in the estimate of the association between current aspirin use and ST-elevation at MI.

Missingness in measurement of total and HDL cholesterol, smoking and blood pressure is a further disadvantage of routinely collected data and had two consequences in this analysis. First it limited the power to determine the independent association of aspirin and statin with each outcome at multivariate analysis. Second it may have introduced selection bias at multivariate analysis. The majority of missingness was in the measurement of cholesterol and patients who have had cholesterol measurements may not have been representative of those who did not. Some may have been healthy patients who had cholesterol measured in a well-patient check, while others may have had measurements due to being overweight or because the GP considered them to be at high risk.

Because the mechanisms of missingness cannot be determined and the assumption of missing at random may not be valid, the option of multiple imputation was not pursued. However, a further exploration of the missingness mechanism with more data may aid our interpretation of these results.

This level of missingness is unsurprising given that the patients in this study did not have diagnosed atherosclerotic disease and many of them were likely to be at low global cardiovascular disease risk. Importantly, levels of cholesterol measurement were high in users of statins, reflecting its use as a lipid lowering medication.

As discussed above, MI type and infarct size were only available for subsample of the whole dataset, which may have been biased in terms of the patients included. It is unclear what effect this had on the results.

The Framingham risk score is not necessarily a good predictor in a UK population. In this analysis, all patients had MI and their predicted risk should therefore have been high, but risk scores did not reflect this. The Framingham risk score was derived from patients in the United States, and a systematic review has shown that in some populations it over-predicts and in other populations it under-predicts CHD.[278] The Framingham risk score has been criticised because it does not take into account potentially important factors including BMI, family history and social deprivation, which studies have repeatedly shown are important predictors of coronary disease. However, in a sensitivity analysis, adjusting for socioeconomic status, BMI and family history of CHD, there was no effect on the estimates produced in the main analyses.

Finally, a comparison of statin and aspirin use at admission in MINAP to the GPRD data used in this analysis revealed substantial discrepancies, particularly for aspirin use. This is likely to reflect MINAP recording aspirin administration in the ambulance or emergency room, in addition to use for primary prevention that was captured in GPRD. Comparison of statin use revealed nearly 80% agreement in current use, and 90% agreement in never use, which indicates that the exposure measurement in this study, although likely imperfect, was adequate.

7.8.6 Implications for research

There is uncertainty regarding the benefits of aspirin for primary prevention. Trials are ongoing to assess its relative benefits and harms. In these trials it would be useful to examine whether MI outcomes, including infarct severity, infarct size and mortality, are improved in aspirin users. In the context of a trial setting, it would be possible to collect further data on the extent of atherosclerosis in patients who do have MI, along with detailed information of their medical history at baseline and during follow-up. This would allow extensive adjustment for confounders and may give an indication of the true effect of aspirin

use, and duration of use, on outcomes at MI. It would also be pertinent to collect data on non-fatal outcomes following MI, which some studies have suggested are improved in aspirin and statin users, and may affect patient quality of life and longer term mortality after MI.

7.8.7 Implications for policy

In this analysis, statins had no beneficial or detrimental associations with infarct presentation, size or subsequent short term mortality. Given the beneficial effects of statins shown by randomised trials for the primary prevention of MI, current recommendations for statin use in primary prevention are unaffected by these results.

Aspirin is not currently recommended for the primary prevention of cardiovascular disease. The evidence from this study alone is insufficient to make any firm conclusions regarding the beneficial effects of prior aspirin in users who still have MI.

7.8.8 Conclusion

In this UK primary care population of MI patients, prior aspirin use and longer duration of use were markers for attenuated MI severity. No associations were observed between prior statin use and infarct severity, size, or subsequent mortality. Decreased infarct severity in aspirin users has been described by other authors but due to the observational nature of these studies, there is a strong possibility of residual confounding by the underlying differences between users and non-users of primary prevention medications. Therefore, the evidence is insufficient to make any conclusion regarding the beneficial effects of prior aspirin use at MI.

7.9 Chapter summary

- Aspirin and statin use is recommended to patients at high cardiovascular disease risk, yet studies have shown that their use prior to MI is associated with improved outcomes.

- A review of the literature showed some evidence for attenuated infarct severity, smaller infarct size, and some differences in short term mortality in aspirin and statin users. However, no studies focused on use of these drugs for primary prevention of MI.

- In this study, 8,104 patients without previously diagnosed atherosclerotic disease were categorised as current, previous or never users of aspirin and statins. Dose and duration of use were also examined. MI severity (measured by ST-elevation at MI), infarct size and 30 day mortality outcomes were compared between groups.

- There was strong evidence that current aspirin use was a marker of decreased likelihood of ST-elevation at MI, and that longer term aspirin use was associated with decreased likelihood of ST-elevation at MI. However, aspirin use was not associated with infarct size or mortality. There were no associations between statin use and MI severity, infarct size or mortality.

- Given the known benefits of statins in primary prevention, the lack of associations shown here between statin use and outcomes at MI do not provide evidence against the recommendations to prescribe statins in patients at high risk.

- The evidence described here suggests that aspirin use is associated with attenuated MI severity, and may represent a causal effect given the association was present at each level of Framingham risk. However, data limitations regarding over the counter aspirin use and selection bias introduced by missingness of key cardiovascular disease risk factors must be considered when interpreting these results.

Chapter 8 Discussion

8.1 Summary

This chapter draws together the main findings and key discussion points of the four major analyses presented in this thesis. A summary of the research undertaken is first presented, followed by a description of the key findings of each study and its place in the context of other research. The main strengths and limitations of the work are then discussed, followed by the implications for policy and future research.

8.2 Summary of research undertaken

Four analyses were undertaken:

I. A prospective study to compare capture, risk factors, mortality and diagnostic validity of MI in primary care, hospital discharge, disease registry and mortality statistics.

II. A prospective study to examine the evolution of atherosclerotic disease and cardiovascular disease risk prior to first MI.

III. A prospective study of the occurrence, timing and effect of ischaemic presentations, including new atherosclerotic disease in different arterial beds and chest pain before non-fatal and fatal MI.

IV. A prospective study to examine the use of aspirin and statins prescribed prior to first MI for primary prevention and the effects on infarct presentation, size and short term mortality.

8.3 Capture, risk factors, mortality and diagnostic validity of MI in primary care, hospital discharge, hospital registry and mortality statistics

8.3.1 Key findings

- In a comparison of the recording of non-fatal MI across three data sources (GPRD, HES, MINAP), around a third were captured by three sources, and two thirds by at least two sources.

- Capture of fatal MI was over 80% in ONS mortality records, but only half of patients who died within seven days of a MI record were recorded with MI in GPRD, suggesting that researchers should use both sources when capturing fatal MI events.

- Cardiovascular disease risk factor prevalences and other co-existing conditions were similar across patients identified in GPRD, HES and MINAP. While early mortality was higher in GPRD, which (unlike HES and MINAP) includes out of hospital MI, one year mortality rates in cohorts from each of the sources were similar. This shows that the cohorts of MI patients captured by each source were similar and there are unlikely to be important selection biases between sources.

- The timing of MI tended to be concordant where more than one source captured a patient's MI.

- These results indicate that although their sensitivity is suboptimal, the cohorts of MIs identified in each source are of sufficient quality to be used in this thesis and for wider research studies.

8.3.2 Findings in the context of other research

- The quality of MI records in GPRD and HES has been previously internally validated and both showed high positive predictive value compared to case note review. The incidence of MI in the GPRD has also been shown to be broadly comparable to other UK sources (see Chapter 2, Data Sources). However, few data are available regarding the external validity of these sources at the patient level, including the completeness of capture for each source. To our knowledge, the

external validity of MI records in MINAP and ONS has not previously been reported.

- Our results were in accordance with the majority of single-source comparisons for GPRD and HES, but our study was the first to compare records of MI across sources in primary care, hospitalisation, MI registry and cause-specific mortality data and the first to look at the validity of the timing of MI. It was also the first to report on the validity of ONS and MINAP MIs.

- Capture of MI in hospitals may be expected to be lower given that patients may have MI secondary to the cause of their admission, or in non-cardiac wards. Lack of recording in the GPRD (particularly non-fatal MI) may be the most difficult to explain because patients would require lifelong secondary prevention and CHD monitoring. Work is currently underway to decode the non-coded section of the GPRD data, which could hold valuable information regarding patient morbidity, and could explain some of the non-capture in GPRD.

8.4 The evolution of atherosclerotic disease and risk factors prior to MI

8.4.1 Key findings

- Of hospitalised patients identified with their first MI, the majority with previously diagnosed atherosclerotic disease had been diagnosed for several years before MI (median 6.7 years), allowing an extended period of time for the use of secondary prevention. However, a premonitory period was identified in the 90 days prior to MI, where the rates of both incident coronary disease and the frequency of chest pain consultations were increased.

- 56.5% of first MI patients did not have previously diagnosed atherosclerotic disease. In the majority of these patients there was at least one elevated traditional cardiovascular disease risk factor, and therefore targets for primary prevention.

- 7.2% of patients with first MI had no previously diagnosed atherosclerotic disease, and no previously recorded elevated cardiovascular disease risk factors. These patients had their MI without warning.

8.4.2 Findings in the context of other research

- The prevalences of coronary, peripheral and cerebrovascular disease were in line with estimates from international registry data and UK data sources. Additionally, our findings regarding the prevalence of MI patients without elevated cardiovascular disease risk factors were similar to published data.

- Our study showed a similar duration of atherosclerotic disease compared to one other study that estimated the duration of coronary disease prior to MI.

- However, this study was the first to have estimated the proportion of MIs that were unheralded by both atherosclerotic disease and elevated cardiovascular disease risk factors. Therefore, ours is the first study to identify the proportion of patients who have MI 'without warning'. Similarly, no studies have described the evolution of different atherosclerotic disease manifestations prior to MI.

8.5 Timing and effect of ischaemic presentations prior to MI

8.5.1 Key findings

- Patients with recorded chest pain, new onset atherosclerotic disease, or new manifestations of atherosclerotic disease in the 90 days prior to MI had lower mortality in the week after infarct compared to patients who were unheralded by these manifestations. However, patients with MI unheralded by ischaemic manifestations had better longer term survival after MI.

- Patients with ischaemic manifestations closest to the time of MI had the lowest mortality, but there was an effect of ischaemic presentations occurring up to 90 days prior to MI.

- In patients where MI type was recorded, those with ischaemic presentations prior to MI were more likely to experience non ST-elevation MI.

8.5.2 Findings in the context of other research

- There has been extensive research into the effects of preinfarction angina on mortality and non-fatal outcomes at MI. Ischaemic preconditioning is the suggested mechanism by which patients with angina shortly before MI have improved outcomes and better survival.

- Whilst similar results have been described in hospital settings and in highly selected groups of patients, this is the first study to describe the phenomenon (a) in a primary care setting, (b) with prospectively collected exposure data, including detail on timing of exposure, (c) for ischaemia in coronary *and* non-coronary arterial beds, (d) in a general population setting including patients who die before reaching hospital, and (e) in both patients with ST-elevation and non ST-elevation MI.

- Ischaemic preconditioning has been proven experimentally to prevent myocardial cell death, but the effects of preinfarction angina shown in this and other studies have not been proven to be causally related to improved outcomes.

- Possible mechanisms include:
  i. the formation of collateral channels. This is unlikely to explain the strong effects on survival in patients manifesting with ischaemia very closely before MI;
  ii. an increased atherosclerotic burden in patients manifesting with ischaemia prior to their MI, which is associated with NSTEMI, which is known to have better short term survival than STEMI. In our study there was insufficient power to adequately assess the effects by MI type and this would be a priority for future research;
  iii. a mechanism involving ischaemic preconditioning.

8.6 Aspirin and statins for primary prevention and MI outcomes

8.6.1 Key findings

- In accordance with UK guidelines, patients without diagnosed atherosclerotic disease and higher cardiovascular disease risk tended to receive prescriptions of

aspirin and statins prior to MI. However, many patients categorised at high risk prior to MI were not in receipt of these medications.

- Patients prescribed aspirin prior to MI had less severe infarcts, as indicated by fewer ST-elevation MIs. Longer duration of aspirin use was also associated with less severe infarcts. There was no association between prior aspirin use and infarct size or mortality.

- Statins were not associated with MI type, size or subsequent mortality.

8.6.2 Findings in the context of other research

- The studies identified in the literature showed similar results in the association between aspirin use and ST-elevation at MI. However, all studies, including the analysis in this thesis, were observational and therefore subject to residual confounding by poorly measured or unmeasured variables. Therefore, although aspirin appears to be a marker for attenuated infarct severity, the causal mechanism driving this association is unknown.

- Several previous studies have reported an association between aspirin use and infarct size, which was not repeated in the current study. Whether the associations described in the literature are artefacts of poorly conducted analyses or unmeasured confounders, or whether the sample of patients in our study with infarct size recorded was biased, is unclear. The same is true for the lack of associations shown for the effects of statin use.

- The reported effects of aspirin on short term mortality were variable, with studies showing no effect, beneficial effects and harmful effects at multivariate analysis. These effects may be so widely different between studies due to differing degrees of measurement and adjustment for confounding variables at multivariate analysis, or differing prescribing guidelines across study populations. The data in the current study suggested that patients using aspirin in the UK were at higher cardiovascular disease risk and of a more advanced age, and therefore had higher crude mortality, but that aspirin had no independent association with mortality.

8.7 Strengths

- Traditionally in studies of MI, patients are identified at hospitalization and therefore detailed, prospectively collected data prior to MI are not available. In this study hospital MI data from MINAP and HES were combined with primary care records from the GPRD, and mortality data from ONS. This created a rich longitudinal dataset, which allowed us to reconstruct the patient journey from a healthy state, through MI and to death. Due to the detailed nature of data held by the GPRD, a wealth of atherosclerotic disease and cardiovascular disease risk factor data were gathered for each patient, without the errors in recall associated with ascertaining this information at the time of hospitalisation.

- The second major strength of these analyses was the statistical power. Each analysis included over 8,000 patients, each with prospective data regarding pre and post-hospital exposures.

- Linkage of the four sources provided the unique opportunity to validate MI by comparing patient records between sources, and to research MI as the first manifestation of disease, which would not have been possible using one source alone.

- Importantly, the patients included in GPRD are representative of the UK population, and so the patients included in this study are likely to be representative of all MI patients in the UK. The data have also been extensively validated and shown to be of high quality for research.

- Pre-MI follow-up for all patients was sufficient. In the GPRD, all patients were registered in their practice for at least one year prior to MI (and in fact, most patients had several years of follow-up before MI), so there was sufficient time for any disease or risk factors to be detected by the GP and recorded electronically. Patients without any pre-MI consultations with the GP were excluded, but did not introduce a minimum consultation rate as this could have biased patient selection towards sicker patients.

- For three of the analyses, patients were included who did not reach hospital. Inclusion of both fatal and non-fatal MI in our analyses allowed the effect in the general population to be established, which has not been feasible in many other large studies of MI.

8.8 Limitations

- The main limitations of each data source were described in Chapter 2 and major limitations of each analysis were discussed in their respective chapters. The overall limitations of the thesis are discussed here.

- The GPRD holds a wealth of data on each patient but is limited by the fact that it only holds symptoms and diagnoses reported by patients during consultations and is routinely collected data rather a than researcher-led study. Therefore, if patients do not report symptomatic disease or poor health to their GP, it will not be captured by the dataset, resulting in misclassification. For most GPRD data, if a patient does not have any codes relating to a condition, then they are regarded as being negative for that condition and there is no 'missing' data. For measurement of risk factors such as blood pressure or lipid levels, there is sometimes missingness, which is a problem for analyses focussing on these variables as main exposures and outcomes, but less so for analyses such as those presented here.

- While the linked data provided unique opportunities and great strengths in terms of data quality, there were some drawbacks to the wealth of data. Since GPRD, HES and MINAP often held the same kind of information on a patient, their concordance with respect to cardiovascular disease risk factors and atherosclerotic disease, for example, could be compared. Throughout this thesis, the most sensitive approach in categorising patients with morbidity was followed, i.e. patients were categorised as positive if identified as such in any data source. This could have led to some misclassification of risk factors and disease. However, the misclassification would unlikely to have been differential with respect to the outcomes in this analysis, and so would have attenuated the associations described.

- These analyses were observational. For the analysis of ischaemic presentations prior to MI, observational clinical data are likely to be the gold standard as patients cannot be randomised to have ischaemia prior to MI. However, in the analysis of primary prevention medications, despite extensive adjustment at multivariate analysis, there is a possibility of residual confounding by indication. While a trial for statins in primary prevention in patients at high risk would be not ethically acceptable due to the known benefits of statins, trials of aspirin in primary prevention are ongoing. By randomising patients to receive aspirin or not, confounding by indication is eliminated.

8.9 Implications for public health and policy

- Suboptimal capture of MI across data sources indicates that use of one or even two sources is likely to be insufficient in estimating the true incidence of MI in the UK. Instead, healthcare commissioners and policy-makers should use multiple linked sources in estimating incidence and costs for healthcare provision.

- Roughly half of first MIs were heralded by diagnosed atherosclerotic disease. While current policy recommends use of aspirin, statins and blood pressure lowering drugs in these patients, our data suggested that there is room for improvement in the provision of these medications. A drive to promote the importance of the use of secondary prevention medications in patients with coronary, cerebrovascular and peripheral arterial disease could substantially reduce the incidence of MI.

- Given the most recent statistics published by the British Heart Foundation indicating an estimated 124,000 MIs in the UK per year, and assuming that 70% of these are first MIs (as described in the MONICA and GRACE MI registers), our results suggest that approximately 49,000 MIs occur as the first manifestation of atherosclerotic disease every year and 6,000 of these occur without warning. These are large numbers and indicate that current policy for primary prevention recommending the measurement of cardiovascular disease risk, and management of that risk should continue to be followed with care. An understanding of whether MIs occur in these patients due to missed opportunities for care is a priority for further research.

- The current UK guidelines for primary prevention recommend the use of statins but not the use of aspirin. The results described here uphold these guidelines, as they do not indicate a positive or negative impact of these drugs on patient mortality.

8.10 Future research

- For researchers working with one of these four sources, it would be useful to improve the search strategies used to identify MI patients, so that incidence is estimated more accurately.

- Importantly, this was a case-only analysis. A comparison to atherosclerotic disease-free controls would be pertinent to aid our understanding of MIs that occur as the

first manifestation of disease, and in particular those that occur without warning. This may reveal missed opportunities for care in the assessment or management of cardiovascular disease risk, or could elucidate novel risk factors for MI.

- To enhance our understanding of the effects of ischaemic presentations shortly before MI on MI outcomes, our analysis should be repeated in a larger population of hospitalised MIs in whom MI type has been recorded. If the short term mortality benefits described in patients who experience ischaemia are shown exclusively in STEMI patients, then this would support the idea of preconditioning in these patients, rather than simply confounding by underlying atherosclerotic disease.

- Since the four data sources were linked for the first time in 2010, more GPRD practices have consented to the linkage and therefore more data are being made available from all data sources. The new Clinical Practice Research Datalink has plans to incorporate every NHS patient into the dataset. Utilising data for the whole of the UK would bring power to detect effects that current analyses were underpowered to detect.

- The possibility of confounding by indication in patients receiving aspirin and statin for primary prevention cannot be unravelled using observational data. Patients randomised in trials to receive aspirin and statins for primary prevention should measure both fatal and non-fatal outcomes at the time of MI to gauge their effects on these outcomes, in addition to their primary preventative benefits or harms and without confounding by indication.

8.11 Conclusions

The work presented in this thesis utilised linked data from four UK data sources, providing the unique opportunity to study patients with MI as the first manifestation of their atherosclerotic disease. Although our study showed that the capture of MI in each source was suboptimal, there was evidence that all four sources contributed cohorts of MI of sufficient quality to be used in this thesis.

In describing the evolution of atherosclerotic disease prior to MI, this analysis showed that over half of first MI patients were experiencing their first manifestation of disease. This has two implications: firstly it highlights the importance of measuring and managing cardiovascular disease risk for primary prevention, and secondly it underlines the need for further research into these events which, if not fatal, instantly transform a person without known atherosclerotic disease into a coronary heart disease patient requiring intensive, lifelong secondary prevention treatment.

In examining the survival of patients experiencing MI as the first manifestation of disease, those who presented to their general practitioner with ischaemia shortly before MI had a lower rate of mortality in the seven days after MI than patients who first manifested with MI, but that their subsequent mortality was poorer. This finding may represent an ischaemic preconditioning effect in patients with pre-infarct ischaemia. While the concept of ischaemic preconditioning has been proven in experimental studies, its relevance to the clinical setting is unproven and further research, including the possibility of harnessing its effects, is required.

In the final analysis aspirin and statins for primary prevention were not independently associated with a survival benefit following MI, although there was some indication that aspirin use was a marker of reduced severity of MI. Statin use has proven effectiveness in the primary prevention of MI in patients at high cardiovascular disease risk, and the results here indicate no harm or benefit of statin use on outcomes at MI. Conversely, the effects of aspirin as a primary preventative medication and its effects on outcomes at the time of MI require further study, as no clear benefits or harms were discernible in this study and the beneficial effects of aspirin for primary prevention have recently been called into question.

Together, these results provide a unique insight into the pre-MI experience of patients with a first MI, which is difficult area of research due to their sudden nature. These findings represent a step forward in our understanding of these unexpected events.

8.12 Chapter summary

	What previous studies have shown	What this study found	Key unanswered questions
I. Capture and validity of MI in GPRD, HES, MINAP and ONS	Previous studies have reported high positive predictive value of GPRD and HES MI, but poor completeness of HES MI.	Capture of MI in each of the four sources was suboptimal, but MIs that were recorded tended to be accurate and timely.	Can we alter our search strategies in finding patients with MI in each source?
II. Heralding of first MI by atherosclerotic disease and cardiovascular disease risk factors	No previous studies assessed heralding of first MI by both atherosclerotic disease and cardiovascular disease risk factors.	56.5% had no previously diagnosed atherosclerotic disease, and 7.2% of patients experienced MI without warning.	In patients who appear to have MI without warning, were coronary risk factors measured and treated appropriately in line with current guidelines?
III. Manifestations of ischaemia prior to MI and effects on MI outcomes	There is an apparent protective effect of preinfarction angina on outcomes at MI.	Patients with manifestations of ischaemia prior to MI had a lower rate of mortality in the seven days after MI, but this beneficial effect was lost after seven days.	What role does MI type have in the effect of previous manifestations of ischaemia and outcomes at MI?
IV. Use of aspirin and statin for primary prevention and effects on MI outcomes	Aspirin and statins have a protective effect on MI severity and infarct size. The effects on mortality are unclear.	Aspirin use and longer duration of use were associated with some attenuation of MI severity in hospitalised patients. There were no other associations between use of aspirin or statins and infarct size, presentation and mortality.	Is aspirin or statin use associated with a beneficial effect on non-fatal outcomes? Are there differences in MI outcomes in patients randomised to receive aspirin compared to those randomised to not receive aspirin?

Chapter 9 References

1. *Hypertension and coronary artery disease: classification and criteria for epidemiological studies.*, in *World Health Organization Technical Report Series*1959.
2. Char, D.M., E. Israel, and J. Ladenson, *Early laboratory indicators of acute myocardial infarction.* Emergency Medicine Clinics of North America, 1998. **16**(3): p. 519-39, vii.
3. Trevelyan, J., et al., *Impact of the recommendations for the redefinition of myocardial infarction on diagnosis and prognosis in an unselected United Kingdom cohort with suspected cardiac chest pain.* Am J Cardiol, 2004. **93**(7): p. 817-21.
4. Alpert, J.S., et al., *Myocardial infarction redefined - A consensus Document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction.* Journal of the American College of Cardiology, 2000. **36**(3): p. 959-969.
5. Pell, J.P., et al., *Impact of changing diagnostic criteria on incidence, management, and outcome of acute myocardial infarction: retrospective cohort study.* BMJ, 2003. **326**(7381): p. 134-5.
6. Thygesen, K., et al., *Universal definition of myocardial infarction.* Circulation, 2007. **116**(22): p. 2634-2653.
7. Thygesen, K., et al., *Third Universal Definition of Myocardial Infarction.* Circulation, 2012. **126**(16): p. 2020-2035.
8. Bode, C. and A. Zirlik, *STEMI and NSTEMI: the dangerous brothers.* Eur Heart J, 2007. **28**(12): p. 1403-4.
9. Goldberg, R.J., et al., *Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (the Global Registry of Acute Coronary Events [GRACE]).* Am J Cardiol, 2004. **93**(3): p. 288-93.
10. Terkelsen, C.J., et al., *Mortality rates in patients with ST-elevation vs. non-ST-elevation acute myocardial infarction: observations from an unselected cohort.* Eur Heart J, 2005. **26**(1): p. 18-26.
11. *ST elevation at ECG*. Available from: http://www.stemcellmx.com/treatable-conditions/stem-cell-treatment-for-heart-conditions/st-elevation-treatment-with-stem-cell-therapy/.
12. White, H.D. and D.P. Chew, *Acute myocardial infarction.* Lancet, 2008. **372**(9638): p. 570-584.
13. Lampe, F.C., et al., *Is the prevalence of coronary heart disease falling in British men?* Heart, 2001. **86**(5): p. 499-505.
14. Scarborough, P., et al., *Coronary heart disease statistics, 2010 edition*. Department of Public Health, University of Oxford.
15. Tunstall-Pedoe, H., et al., *Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991. Presentation, diagnosis, treatment, and 28-day case fatality of 3991 events in men and 1551 events in women.* Circulation, 1996. **93**(11): p. 1981-92.
16. Schmidt, M., et al., *25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study.* BMJ, 2012. **344**: p. e356.
17. *Health care costs of CHD by country, 2006, EU.* [cited 2009; Available from: www.heartstats.org.
18. Hammar, N., et al., *A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden.* International Journal of Epidemiology, 2001. **30 Suppl 1**: p. S30-4.

19. Lampe, F.C., et al., *Trends in rates of different forms of diagnosed coronary heart disease, 1978 to 2000: prospective, population based study of British men.* British Medical Journal, 2005. **330**(7499): p. 1046-1049.
20. Tunstall-Pedoe, H., et al., *Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease.* Lancet, 1999. **353**(9164): p. 1547-57.
21. Unal, B., J.A. Critchley, and S. Capewell, *Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000.* Circulation, 2004. **109**(9): p. 1101-7.
22. *Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction.* Eur Heart J, 2000. **21**(18): p. 1502-13.
23. Deitelzweig, S.B., et al., *Prevalence of stroke/transient ischemic attack among patients with acute coronary syndromes in a real-world setting.* Hospital practice (1995) Hospital practice, 2010. **38**(4): p. 7-17.
24. Bogaty, P., et al., *Comparison of coronary angiographic findings in acute and chronic first presentation of ischemic heart disease.* Circulation, 1993. **87**(6): p. 1938-46.
25. Murry, C.E., *Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium.* Circulation, 1986. **74**: p. 1124-1136.
26. Kloner, R.A. and D. Yellon, *DOES ISCHEMIC PRECONDITIONING OCCUR IN PATIENTS.* Journal of the American College of Cardiology, 1994. **24**(4): p. 1133-1142.
27. Yellon, D.M. and J.M. Downey, *Preconditioning the myocardium: From cellular physiology to clinical cardiology.* Physiological Reviews, 2003. **83**(4): p. 1113-1151.
28. Kloner, R.A., et al., *PREVIOUS ANGINA ALTERS IN-HOSPITAL OUTCOME IN TIMI-4 - A CLINICAL CORRELATE TO PRECONDITIONING.* Circulation, 1995. **91**(1): p. 37-45.
29. Murry, C.E., R.B. Jennings, and K.A. Reimer, *Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium.* Circulation, 1986. **74**(5): p. 1124-36.
30. Ottani, F., et al., *PRODROMAL ANGINA LIMITS INFARCT SIZE - A ROLE FOR ISCHEMIC PRECONDITIONING.* Circulation, 1995. **91**(2): p. 291-297.
31. Anzai, T., et al., *EFFECT ON SHORT-TERM PROGNOSIS AND LEFT-VENTRICULAR FUNCTION OF ANGINA-PECTORIS PRIOR TO FIRST Q-WAVE ANTERIOR WALL ACUTE MYOCARDIAL-INFARCTION.* American Journal of Cardiology, 1994. **74**(8): p. 755-759.
32. Anzai, T., et al., *Preinfarction angina as a major predictor of left ventricular function and long-term prognosis after a first Q wave myocardial infarction.* Journal of the American College of Cardiology, 1995. **26**(2): p. 319-27.
33. Ottani, F., et al., *Clinical relevance of prodromal angina before acute myocardial infarction.* International Journal of Cardiology, 1999. **68 Suppl 1**: p. S103-8.
34. Fujita, M., *Determinants of collateral development in patients with acute myocardial infarction.* Clin Cardiol, 1999. **22**: p. 595-599.
35. Nakae, I., et al., *Age-dependent impairment of coronary collateral development in humans.* Heart & Vessels, 2000. **15**(4): p. 176-80.
36. Habib, G.B., et al., *Influence of coronary collateral vessels on myocardial infarct size in humans. Results of phase I thrombolysis in myocardial infarction (TIMI) trial. The TIMI Investigators.* Circulation, 1991. **83**(3): p. 739-46.
37. Ottani, F., *Prodromal angina limits infarct size. A role for ischemic preconditioning.* Circulation, 1995. **91**: p. 291-297.

38. Yamagishi, H., *Effects of preinfarction angina on myocardial injury in patients with acute myocardial infarction: a study with resting 123I-BMIPP and 201Tl myocardial SPECT.* J Nucl Med, 2000. **41**: p. 830-836.
39. Schwartz, G.G., et al., *Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial.* JAMA, 2001. **285**(13): p. 1711-8.
40. *Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group.* N Engl J Med, 1998. **339**(19): p. 1349-57.
41. Downs, J.R., et al., *Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study.* JAMA, 1998. **279**(20): p. 1615-22.
42. Juul-Moller, S., et al., *Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group.* Lancet, 1992. **340**(8833): p. 1421-5.
43. Peto, R., et al., *Randomised trial of prophylactic daily aspirin in British male doctors.* Br Med J (Clin Res Ed), 1988. **296**(6618): p. 313-6.
44. *Secondary prevention of vascular disease by prolonged antiplatelet treatment. Antiplatelet Trialists' Collaboration.* Br Med J (Clin Res Ed), 1988. **296**(6618): p. 320-31.
45. Baigent, C., et al., *Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials.* Lancet, 2009. **373**(9678): p. 1849-60.
46. National Institute for Health and Clinical Excellence (NICE), *MI: secondary prevention. NICE clinical guideline 48*, 2007: London.
47. Clinical Practice Research Datalink. *Clinical Practice Research Datalink (CPRD)*. [cited 2012 3rd October]; Available from: http://www.cprd.com.
48. Bhaskaran, K., et al., *Angiotensin receptor blockers and risk of cancer: cohort study among people receiving antihypertensive drugs in UK General Practice Research Database.* BMJ, 2012. **344**: p. e2697.
49. Khan, N.F., S.E. Harrison, and P.W. Rose, *Validity of diagnostic coding within the General Practice Research Database: a systematic review.* British Journal of General Practice, 2010. **60**(572): p. e128-36.
50. General Practice Research Database, *[Internet] [cited 2009 July 28] Available http://www.gprd.com.*
51. Soedamah-Muthu, S.S., et al., *All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992-1999.* Diabetologia, 2006. **49**(4): p. 660-6.
52. Chisholm, J., *The Read clinical classification.* BMJ, 1990. **300**(6732): p. 1092.
53. Herrett, E., et al., *Validation and validity of diagnoses in the General Practice Research Database: a systematic review.* British Journal of Clinical Pharmacology, 2010. **69**(1): p. 4-14.
54. Nazareth, I., et al., *Accuracy of diagnosis of psychosis on general practice computer system.* BMJ, 1993. **307**(6895): p. 32-4.
55. Soriano, J.B., et al., *Validation of general practitioner-diagnosed COPD in the UK General Practice Research Database.* Eur J Epidemiol, 2001. **17**(12): p. 1075-80.
56. Jick, H., S.S. Jick, and L.E. Derby, *Validation of information recorded on general practitioner based computerised data resource in the United Kingdom.* BMJ, 1991. **302**(6779): p. 766-8.
57. Jick, H., et al., *Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom.* Pharmacoepidemiol Drug Saf, 1992. **1**: p. 347-349.

58. Jick, S.S., et al., *Validity of the general practice research database.* Pharmacotherapy, 2003. **23**(5): p. 686-9.
59. van Staa, T. and L. Abenheim, *The quality of information recorded on a UK database of primary care records: A study of hospitalisations due to hypoglycemia and other conditions.* Pharmacoepidemiol Drug Saf, 1994. **3**: p. 15-21.
60. Wurst, K.E., et al., *The utility of the general practice research database to examine selected congenital heart defects: A validation study.* Pharmacoepidemiology and Drug Safety, 2007. **16**(8): p. 867-877.
61. Garcia Rodriguez, L.A., et al., *Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population.* Circulation, 2004. **109**(24): p. 3000-6.
62. Meier, C.R., et al., *Acute respiratory-tract infections and risk of first-time acute myocardial infarction.* Lancet, 1998. **351**(9114): p. 1467-71.
63. Jick, H., et al., *Risk of acute myocardial infarction and low-dose combined oral contraceptives.* Lancet, 1996. **347**(9001): p. 627-8.
64. Hall, G.C., et al., *Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice.* Neurology, 2004. **62**(4): p. 563-8.
65. Johansson, S., et al., *Is there any association between myocardial infarction, gastro-oesophageal reflux disease and acid-suppressing drugs?* Aliment Pharmacol Ther, 2003. **18**(10): p. 973-8.
66. Hammad, T.A., et al., *Onset of acute myocardial infarction after use of non-steroidal anti-inflammatory drugs.* Pharmacoepidemiol Drug Saf, 2008. **17**(4): p. 315-21.
67. Andersohn, F., S. Suissa, and E. Garbe, *Use of first- and second-generation cyclooxygenase-2 selective nonsteroidal antiinflammatory drugs and risk of acute myocardial infarction.* Circulation, 2006. **113**(16): p. 1950-1957.
68. Moser, K. and A. Majeed, *Prevalence of treated chronic diseases in general practice in England and Wales - trends over time and variations by the ONS area classification.* Health Statist Quart, 1999. **2**: p. 25-32.
69. Colhoun, H.M. and P. Prescott-Clarke, *Health Survey for England 1994*, 1996: London.
70. Arana, A., et al., *Hormone therapy and cerebrovascular events: a population-based nested case-control study.* Menopause, 2006. **13**(5): p. 730-6.
71. Carter, M., K. Moser, and S. Kelly, *Health of older people: disease prevalence, prescription and referral rates, England and Wales 1996.* Health Stat Q, 1999. **4**: p. 9-15.
72. MacDonald, T.M., S.V. Morant, and D. Pettitt, *Prevalence of clinically recognized hypertension (HT) and Dyslipidaemia (DL) in the UK.* Pharmacoepidemiol Drug Saf, 2003. **12 Suppl 1**: p. S25-6.
73. Ryan, R. and A. Majeed, *Prevalence of treated hypertension in general practice in England and Wales, 1994 and 1998.* Health Stat Q, 2002. **16**: p. 14-18.
74. Hollowell, J., *The General Practice Research Database: quality of morbidity data.* Popul Trends, 1997(87): p. 36-40.
75. Newnham, A., et al., *Prevalence of diagnosed diabetes mellitus in general practice in England and Wales.* Health Stat Q, 2002. **14**: p. 5-13.
76. Cardwell, C.R., D.J. Carson, and C.C. Patterson, *No association between routinely recorded infections in early life and subsequent risk of childhood-onset Type 1 diabetes: a matched case-control study using the UK General Practice Research Database.* Diabetic Medicine, 2008. **25**(3): p. 261-267.
77. Mulnier, H.E., et al., *Mortality in people with type 2 diabetes in the UK.* Diabet Med, 2006. **23**(5): p. 516-21.
78. Ryan, R., et al., *New cases of diabetes mellitus in England and Wales, 1994-1998: database study.* Public Health, 2005. **119**(10): p. 892-9.

79. Lewis, J.D. and C. Brensinger, *Agreement between GPRD smoking data: a survey of general practitioners and a population-based survey.* Pharmacoepidemiol Drug Saf, 2004. **13**(7): p. 437-41.
80. Campbell, S.M., et al., *Effects of Pay for Performance on the Quality of Primary Care in England.* New England Journal of Medicine, 2009. **361**(4): p. 368-378.
81. Gillam S., S.A., *The Quality and Outcomes Framework. QOF-transforming general practice*. 2011: Oxford-New York: Radcliffe Publisher.
82. Jick, H., et al., *Statins and the risk of dementia.* Lancet, 2000. **356**(9242): p. 1627-31.
83. Van Staa, T.P., et al., *Use of oral corticosteroids and risk of fractures.* J Bone Miner Res, 2000. **15**(6): p. 993-1000.
84. Gelfand, J.M., et al., *Risk of myocardial infarction in patients with psoriasis.* JAMA, 2006. **296**(14): p. 1735-41.
85. Smeeth, L., et al., *MMR vaccination and pervasive developmental disorders: a case-control study.* Lancet, 2004. **364**(9438): p. 963-9.
86. GPRD. *General Practice Research Database (GPRD)*. [cited 20011 21st October]; Available from: http://www.gprd.com
87. Delaney, J.A., E.E. Moodie, and S. Suissa, *Validating the effects of drug treatment on blood pressure in the General Practice Research Database.* Pharmacoepidemiol Drug Saf, 2008.
88. Marston, L., et al., *Issues in multiple imputation of missing data for large general practice clinical databases.* Pharmacoepidemiology and Drug Safety, 2010. **19**(6): p. 618-626.
89. Lewis, J.D., et al., *The relationship between time since registration and measured incidence rates in the General Practice Research Database.* Pharmacoepidemiol Drug Saf, 2005. **14**(7): p. 443-51.
90. Herrett, E., et al., *The Myocardial Ischaemia National Audit Project (MINAP).* Heart, 2010. **96**(16): p. 1264-7.
91. Department of Health, *National Service Framework for Coronary Heart Disease - Modern Standards and Service Models*, 2000, Department of Health: London.
92. Central Cardiac Audit Database (CCAD). [cited 2009 22nd September]; Available from: http://www.ic.nhs.uk/services/national-clinical-audit-support-programme-ncasp/heart-disease.
93. The Healthcare Quality Improvement Partnership. [cited 2009 30th September]; Available from: http://www.hqip.org.uk/
94. Royal College of Physicians. *MINAP core dataset version 8.1*. [cited 2012 7th February]; Available from: http://www.ucl.ac.uk/nicor/audits/minap/datacollection.
95. Royal College of Physicians, *National Data Quality Assessment 2008: Validation and Data Quality Exercise.* 2008.
96. Walker, L., et al., *How the NHS Manages Heart Attacks*, 2009, Royal College of Physicians: London.
97. British Cardiovascular Intervention Society. *Percutaneous Coronary Intervention Database*. [cited 2009 30th September]; Available from: http://www.bcis.org.uk/resources/current_database.
98. Society for Cardiothoracic Surgery in Great Britain and Ireland. *National Adult Cardiac Surgical Database*. [cited 2009 30th September]; Available from: http://www.scts.org/sections/audit/Cardiac/index.html
99. Birkhead, J., *Where are we today? Early results from MINAP, the National Audit of Myocardial Infarction Project.* Heart, 2003. **89 Suppl 2**: p. ii13-5; discussion ii35-7.
100. Birkhead, J.S., C. Weston, and D. Lowe, *Impact of specialty of admitting physician and type of hospital on care and outcome for myocardial infarction in England and Wales during 2004-5: observational study.* BMJ, 2006. **332**(7553): p. 1306-11.
101. Weston, C., L. Walker, and J. Birkhead, *Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome.* Heart, 2007. **93**(12): p. 1542-6.

102. Ben-Shlomo, Y., H. Naqvi, and I. Baker, *Ethnic differences in healthcare-seeking behaviour and management for acute chest pain: secondary analysis of the MINAP dataset 2002-2003.* Heart, 2008. **94**(3): p. 354-9.
103. Gale, C.P., et al., *Predictors of in-hospital mortality for patients admitted with ST-elevation myocardial infarction: a real-world study using the Myocardial Infarction National Audit Project (MINAP) database.* Heart, 2008. **94**(11): p. 1407-12.
104. Birkhead, J.S., C.F. Weston, and R. Chen, *Determinants and outcomes of coronary angiography after non-ST-segment elevation myocardial infarction. A cohort study of the Myocardial Ischaemia National Audit Project (MINAP).* Heart, 2009.
105. Cattle, B.A., et al., *Ups and downs of balloon times.* BMJ, 2009. **338**: p. b2424.
106. Hospital Episode Statistics. *HES Website*. [cited 2012 8th May]; Available from: http://www.hesonline.nhs.uk.
107. Goldacre, M. and L. Gill, *Linkage of Hospital Episode Statistics in England: Opportunities for Public Health.* Faculty of Public Health Newsletter, 2005. **December**: p. 12.
108. Health and Social Care Information Centre, *HES User Guide*, 2010, www.hesonline.nhs.uk.
109. Audit Commission, *Data remember: improving the quality of patient-based information in the the NHS*, 2002, Belmont Press, Northants: UK.
110. Audit Commission, *Improving coding, costing and commissioning: annual report on the Payment by Results data assurance programme 2010/11*, 2011, Audit Commission.
111. Dixon, J., et al., *Assessment of the reproducibility of clinical coding in routinely collected hospital activity data: a study in two hospitals.* J Public Health Med, 1998. **20**(1): p. 63-9.
112. Williams, J.G. and R.Y. Mann, *Hospital episode statistics: time for clinicians to get involved?* Clinical Medicine, 2002. **2**(1): p. 34-7.
113. Department of Health. *Payment by Results*. [cited 2012 8th May]; Available from: http://www.dh.gov.uk/health/category/policy-areas/nhs/resources-for-managers/payment-by-results/.
114. Hodgson, S., et al., *Creating a national register of childhood type 1 diabetes using routinely collected hospital data.* Pediatr Diabetes, 2011.
115. Brophy, S., et al., *Population based absolute and relative survival to 1 year of people with diabetes following a myocardial infarction: a cohort study using hospital admissions data.* BMC Public Health, 2010. **10**: p. 338.
116. Silver, L.E., et al., *SUBSTANTIAL UNDERESTIMATION OF INCIDENCE OF ACUTE MYOCARDIAL INFARCTION BY HOSPITAL DISCHARGE DIAGNOSTIC CODING DATA: A PROSPECTIVE POPULATION-BASED STUDY.* Heart, 2009. **95**: p. A5-A5.
117. Carroll, D., et al., *Admissions for myocardial infarction and World Cup football: database survey.* BMJ, 2002. **325**(7378): p. 1439-42.
118. Sims, M., et al., *Short term impact of smoke-free legislation in England: retrospective analysis of hospital admissions for myocardial infarction.* BMJ, 2010. **340**: p. c2161.
119. Holt, P.J.E., et al., *Epidemiological study of the relationship between volume and outcome after abdominal aortic aneurysm surgery in the UK from 2000 to 2005.* British Journal of Surgery, 2007. **94**(4): p. 441-8.
120. Halliday, A.W., et al., *Waiting times for carotid endarterectomy in UK: observational study.* BMJ, 2009. **338**: p. b1847.
121. Raine, R., et al., *Social variations in access to hospital care for patients with colorectal, breast, and lung cancer between 1999 and 2006: retrospective analysis of hospital episode statistics.* BMJ, 2010. **340**: p. b5479.
122. Love, E.R., et al., *Effect of interpregnancy interval on outcomes of pregnancy after miscarriage: retrospective analysis of hospital episode statistics in Scotland.* BMJ, 2010. **341**: p. c3967.

123. Keown, P., G. Mercer, and J. Scott, *Retrospective analysis of hospital episode statistics, involuntary admissions under the Mental Health Act 1983, and number of psychiatric beds in England 1996-2006.* BMJ, 2008. **337**: p. a1837.
124. Rooney, C.I.F. and S.K. Smith, *Implementation of ICD-10 for mortality data in England and Wales from January 2001.* Health Stat Q, 2000: p. 41-51.
125. World Health Organization, *International Statistical Classification of Diseases and related health Problems, Tenth Revision. Volume 2: Instruction Manual.*, 1993: Geneva.
126. Office for National Statistics, *Mortality statistics: Metadata*, 2012: Cardiff.
127. Denaxas, S., et al., *Data Resource Profile: Cardiovascular disease research using Linked Bespoke studies and Electronic health Records (CALIBER). In press.* International Journal of Epidemiology, 2012.
128. Noble, M., et al., *The English Indices of Deprivation 2007*, Office of the Deputy Prime Minister, Editor 2008: London.
129. *Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III).* JAMA, 2001. **285**(19): p. 2486-97.
130. Lewsey, J.D., et al., *Using routine data to complement and enhance the results of randomised controlled trials.* Health Technology Assessment, 2000. **4**(22): p. 1-55.
131. Nieminen, P., et al., *A randomised public-health trial on automation-assisted screening for cervical cancer in Finland: performance with 470,000 invitations.* Int J Cancer, 2005. **115**(2): p. 307-11.
132. Gulliford, M.C., et al., *Cluster randomised trial in the General Practice Research Database: 1. Electronic decision support to reduce antibiotic prescribing in primary care (eCRT study).* Trials, 2011. **12**: p. 115.
133. *Computerised record linkage: compared with traditional patient follow-up methods in clinical trials and illustrated in a prospective epidemiological study. The West of Scotland Coronary Prevention Study Group.* J Clin Epidemiol, 1995. **48**(12): p. 1441-52.
134. Ford, I., et al., *Long-term follow-up of the West of Scotland Coronary Prevention Study.* N Engl J Med, 2007. **357**(15): p. 1477-86.
135. UK Biobank. *Long-term follow-up of health.* [cited 2012 14th May]; Available from: http://www.ukbiobank.ac.uk.
136. Rapola, J.M., et al., *Validity of diagnoses of major coronary events in national registers of hospital diagnoses and deaths in Finland.* Eur J Epidemiol, 1997. **13**(2): p. 133-8.
137. Madsen, M., et al., *The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry.* J Clin Epidemiol, 2003. **56**(2): p. 124-30.
138. Goldacre, M.J., S.E. Roberts, and M. Griffith, *Place, time and certified cause of death in people who die after hospital admission for myocardial infarction or stroke.* Eur J Public Health, 2004. **14**(4): p. 338-42.
139. Payne, R.A., G.A. Abel, and C.R. Simpson, *A retrospective cohort study assessing patient characteristics and the incidence of cardiovascular disease using linked routine primary and secondary care data.* BMJ Open, 2012. **2**(2): p. e000723.
140. Boyle, C.A. and A.J. Dobson, *The accuracy of hospital records and death certificates for acute myocardial infarction.* Aust N Z J Med, 1995. **25**(4): p. 316-23.
141. Merry, A.H., et al., *Validity of coronary heart diseases and heart failure based on hospital discharge and mortality data in the Netherlands using the cardiovascular registry Maastricht cohort study.* Eur J Epidemiol, 2009. **24**(5): p. 237-47.
142. Boggon, R., et al., *Cancer recording and mortality in the General Practice Research Database and linked cancer registries.* Pharmacoepidemiology and Drug Safety, in press, 2012.

143. Gallagher, A.M., S. Puri, and T. Van Staa, *Linkage of the General Practice Research Database (GPRD) with other data sources.* Pharmacoepidemiol Drug Saf, 2011. **20**: p. S1-S364.
144. Cupples, L.A., et al., *Preexisting cardiovascular conditions and long-term prognosis after initial myocardial infarction: the Framingham Study.* American Heart Journal, 1993. **125**(3): p. 863-72.
145. Bhatt, D.L., et al., *Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes.* Eur Heart J, 2009. **30**(10): p. 1195-202.
146. Yawn, B.P., et al., *The gender specific frequency of risk factor and CHD diagnoses prior to incident MI: a community study.* BMC Fam Pract, 2007. **8**: p. 18.
147. Kobayashi, Y., et al., *Previous angina reduces in-hospital death in patients with acute myocardial infarction.* American Journal of Cardiology, 1998. **81**(2): p. 117-122.
148. Yawn, B.P., et al., *Identification of women's coronary heart disease and risk factors prior to first myocardial infarction.* Journal of Women's Health, 2004. **13**(10): p. 1087-100.
149. Anzai, T., *Preinfarction angina as a major predictor of left ventricular function and long-term prognosis after a first Q wave myocardial infarction.* J Am Coll Cardiol, 1995. **26**: p. 319-327.
150. Behar, S., et al., *The prognostic significance of angina pectoris preceding the occurrence of a first acute myocardial infarction in 4166 consecutive hospitalized patients.* American Heart Journal, 1992. **123**(6): p. 1481-6.
151. Pierard, L.A., et al., *Prognostic significance of angina pectoris before first acute myocardial infarction.* American Journal of Cardiology, 1988. **61**(13): p. 984-7.
152. Steg, P.G., et al., *Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE).* Am J Cardiol, 2002. **90**(4): p. 358-63.
153. Wiviott, S.D., et al., *Application of the Thrombolysis in Myocardial Infarction risk index in non-ST-segment elevation myocardial infarction: evaluation of patients in the National Registry of Myocardial Infarction.* J Am Coll Cardiol, 2006. **47**(8): p. 1553-8.
154. Hasdai, D., et al., *A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS).* Eur Heart J, 2002. **23**(15): p. 1190-201.
155. Lawesson, S.S., et al., *Time trends in STEMI--improved treatment and outcome but still a gender gap: a prospective observational cohort study from the SWEDEHEART register.* BMJ Open, 2012. **2**(2): p. e000726.
156. Sala, C., et al., *Trends in Q-wave acute myocardial infarction case fatality from 1978 to 2007 and analysis of the effectiveness of different treatments.* Am Heart J, 2011. **162**(3): p. 444-50.
157. Yusuf, S., et al., *Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study.* Lancet, 2004. **364**(9438): p. 937-52.
158. Shaper, A.G., et al., *Risk factors for ischaemic heart disease: the prospective phase of the British Regional Heart Study.* J Epidemiol Community Health, 1985. **39**(3): p. 197-209.
159. Khot, U.N., et al., *Prevalence of conventional risk factors in patients with coronary heart disease.* JAMA, 2003. **290**(7): p. 898-904.
160. Roe, M.T., et al., *Documented traditional cardiovascular risk factors and mortality in non-ST-segment elevation myocardial infarction.* American Heart Journal, 2007. **153**(4): p. 507-514.
161. Greenland, P., et al., *Major risk factors as antecedents of fatal and nonfatal coronary heart disease events.* JAMA, 2003. **290**(7): p. 891-7.

162. Simpson, C.R., et al., *Five-year prognosis in an incident cohort of people presenting with acute myocardial infarction.* PLoS ONE, 2011. **6**(10): p. e26573.
163. Bhatt, D.L., et al., *Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes.* European Heart Journal, 2009. **30**(10): p. 1195-202.
164. Harper, R.W., et al., *INCIDENCE AND PATTERN OF ANGINA PRIOR TO ACUTE MYOCARDIAL-INFARCTION - STUDY OF 577 CASES.* American Heart Journal, 1979. **97**(2): p. 178-183.
165. Stowers, M. and D. Short, *WARNING SYMPTOMS BEFORE MAJOR MYOCARDIAL INFARCTION.* British Heart Journal, 1970. **32**(6): p. 833-&.
166. Ruigomez, A., et al., *Chest pain without established ischaemic heart disease in primary care patients: associated comorbidities and mortality.* Br J Gen Pract, 2009. **59**(560): p. e78-86.
167. Psychari, S.N., et al., *Preinfarction angina does not alter infarct size and in hospital outcome after acute myocardial infarction with ST elevation.* International Journal of Cardiology, 2004. **94**(2-3): p. 187-191.
168. Rezkalla, S.H. and R.A. Kloner, *Preconditioning in humans.* Heart Failure Reviews, 2007. **12**(3-4): p. 201-6.
169. Mensah, G.A., et al., *Major coronary risk factors and death from coronary heart disease - Baseline and follow-up mortality health and nutrition examination data from the second national survey (NHANES II).* American Journal of Preventive Medicine, 2005. **29**(5): p. 68-74.
170. Canto, J.G. and A.E. Iskandrian, *Major risk factors for cardiovascular disease - Debunking the "only 50%" myth.* Jama-Journal of the American Medical Association, 2003. **290**(7): p. 947-949.
171. Alpert, J.S., *Fascination with myocardial infarction and normal coronary arteries.* Eur Heart J, 2001. **22**(16): p. 1364-6.
172. Chandrasekaran, B. and A.S. Kurbaan, *Myocardial infarction with angiographically normal coronary arteries.* J R Soc Med, 2002. **95**(8): p. 398-400.
173. Da Costa, A., et al., *Clinical characteristics, aetiological factors and long-term prognosis of myocardial infarction with an absolutely normal coronary angiogram; a 3-year follow-up study of 91 patients.* Eur Heart J, 2001. **22**(16): p. 1459-65.
174. Ammann, P., et al., *Characteristics and prognosis of myocardial infarction in patients with normal coronary arteries.* Chest, 2000. **117**(2): p. 333-8.
175. Royal College of Physicians. *MINAP Data Quality*. [cited 2012 7th February]; Available from: http://www.ucl.ac.uk/nicor/audits/minap/datacollection.
176. Hospital Episode Statistics. *HES Data Quality*. . [cited 2012 7th February]; Available from: http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=97.
177. Hammad, T.A., et al., *Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database.* Pharmacoepidemiol Drug Saf, 2008. **17**(12): p. 1197-201.
178. Ryan, R. and A. Majeed, *Prevalence of ischaemic heart disease and its management with statins and aspirin in general practice in England and Wales, 1994 and 1998.* Health Stat Q, 2001. **12**: p. 34-39.
179. Mulnier, H.E., et al., *Risk of stroke in people with type 2 diabetes in the UK: a study using the General Practice Research Database.* Diabetologia, 2006. **49**(12): p. 2859-65.
180. Maru, S., et al., *Antidiabetic drugs and heart failure risk in patients with type 2 diabetes in the U.K. primary care setting.* Diabetes Care, 2005. **28**(1): p. 20-26.
181. Johansson, S., et al., *Incidence of newly diagnosed heart failure in UK general practice.* Eur J Heart Fail, 2001. **3**(2): p. 225-31.

182. Gibbs, R.G., et al., *Diagnosis and initial management of stroke and transient ischemic attack across UK health regions from 1992 to 1996: experience of a national primary care database.* Stroke, 2001. **32**(5): p. 1085-90.
183. National Health Service. *The Quality and Outcomes Framework (QOF)*. [cited 2012 9th February]; Available from: http://www.ic.nhs.uk/statistics-and-data-collections/audits-and-performance/the-quality-and-outcomes-framework.
184. Lowel, H., et al., *Coronary heart disease case fatality in four countries. A community study. The Acute Myocardial Infarction Register Teams of Auckland, Augsburg, Bremen, FINMONICA, Newcastle, and Perth.* Circulation, 1993. **88**(6): p. 2524-31.
185. Eisen, A., et al., *Ischemic preconditioning: nearly two decades of research. A comprehensive review.* Atherosclerosis, 2004. **172**(2): p. 201-10.
186. Rezkalla, S.H. and R.A. Kloner, *Ischemic preconditioning and preinfarction angina in the clinical arena.* Nature Clinical Practice Cardiovascular Medicine, 2004. **1**(2): p. 96-102.
187. Romero-Farina, G., et al., *Influence of chronic angina prior to infarction in the diagnosis of viability and left ventricular remodelling in myocardial perfusion gated-spect.* Revista Espanola De Medicina Nuclear, 2008. **27**(4): p. 245-252.
188. Abe, Y., A. Tamura, and M. Nasu, *Effect of preinfarction angina on heart rate variability in the early phase of the first anterior wall acute myocardial infarction.* Circulation Journal, 2002. **66**(5): p. 431-4.
189. Yellon, D.M. and A. Dana, *The preconditioning phenomenon: A tool for the scientist or a clinical reality?* Circ Res, 2000. **87**(7): p. 543-50.
190. Ottani, F., et al., *Prodromal angina limits infarct size in the setting of acute anterior myocardial infarction treated with primary percutaneous intervention.* Journal of the American College of Cardiology, 2005. **45**(9): p. 1545-7.
191. Noda, T., *Evidence for the delayed effect in human ischemic preconditioning: prospective multicenter study for preconditioning in acute myocardial infarction.* J Am Coll Cardiol, 1999. **34**: p. 1966-1974.
192. Iglesias-Garriz, I., et al., *In-hospital mortality and early preinfarction angina: a meta-analysis of published studies.* Revista Espanola de Cardiologia, 2005. **58**(5): p. 484-490.
193. Napoli, C., *New-onset angina preceding acute myocardial infarction is associated with improved contractile recovery after thrombolysis.* Eur Heart J, 1998. **19**: p. 411-419.
194. Inoue, K., et al., *Antecedent angina pectoris as a predictor of better functional and clinical outcomes in patients with an inferior wall acute myocardial infarction.* Am J Cardiol, 1999. **83**(2): p. 159-63.
195. De Felice, F., et al., *Potential influence of pre-infarction angina on myocardial viability and residual ischemia.* Italian Heart Journal: Official Journal of the Italian Federation of Cardiology, 2001. **2**(5): p. 356-62.
196. Colonna, P., *Reduced microvascular and myocardial damage in patients with acute myocardial infarction and preinfarction angina.* Am Heart J, 2002. **144**: p. 796-803.
197. Papadopoulos, C.E., et al., *Evidence of ischemic preconditioning in patients experiencing first non-ST-segment elevation myocardial infarction (NSTEMI).* International Journal of Cardiology, 2003. **92**(2-3): p. 209-17.
198. Tomoda, H. and N. Aoki, *Coronary blood flow in evolving myocardial infarction preceded by preinfarction angina: a critical reevaluation of preconditioning effects in clinical cases.* Angiology, 2004. **55**(1): p. 9-15.
199. Iglesias-Garriz, I., et al., *Preinfarction angina limits myocardial infarction size in nondiabetic patients treated with primary coronary angioplasty.* Chest, 2005. **127**(4): p. 1116-21.
200. Tamura, A., et al., *Effect of preinfarction angina pectoris on myocardial blush grade after reperfusion in first anterior wall acute myocardial infarction.* Circulation Journal, 2006. **70**(6): p. 698-702.

201. Mladenovic, Z.T., et al., *The cardioprotective role of preinfarction angina as shown in outcomes of patients after first myocardial infarction.* Texas Heart Institute Journal, 2008. **35**(4): p. 413-8.
202. Takeuchi, T., et al., *Ischemic preconditioning effect of prodromal angina is attenuated in acute myocardial infarction patients with hypertensive left ventricular hypertrophy.* Circulation Journal, 2011. **75**(5): p. 1192-9.
203. Ishihara, M., et al., *Impact of prodromal angina pectoris and white blood cell count on outcome of patients with acute myocardial infarction.* International Journal of Cardiology, 2005. **103**(2): p. 150-5.
204. Papadopoulos, C.E., et al., *Preconditioning reduces QTc value in patients with first non-ST-segment elevation myocardial infarction (NSTEMI).* Annals of Noninvasive Electrocardiology, 2003. **8**(4): p. 275-83.
205. Jacquemin, L., et al., *Prognostic significance of angina pectoris >=30 days before acute myocardial infarction in patients >=75 years of age.* American Journal of Cardiology, 1997. **80**(2): p. 198-200.
206. Kobayashi, Y., et al., *Effect on survival of previous angina pectoris after acute myocardial infarction.* American Journal of Cardiology, 1997. **79**(11): p. 1534-&.
207. Ishihara, M., et al., *Beneficial effect of prodromal angina pectoris is lost in elderly patients with acute myocardial infarction.* Am Heart J, 2000. **139**(5): p. 881-8.
208. Kosuge, M., et al., *Beneficial effect of preinfarction angina on in-hospital outcome is preserved in elderly patients undergoing coronary intervention for anterior acute myocardial infarction.* Circulation Journal, 2005. **69**(6): p. 630-5.
209. Abete, P., et al., *Angina-induced protection against myocardial infarction in adult and elderly patients: a loss of preconditioning mechanism in the aging heart?* J Am Coll Cardiol, 1997. **30**(4): p. 947-54.
210. Tomoda, H. and N. Aoki, *Comparison of protective effects of preinfarction angina pectoris in acute myocardial infarction treated by thrombolysis versus by primary coronary angioplasty with stenting.* American Journal of Cardiology, 1999. **84**(6): p. 621-5.
211. Ober, M.C., et al., *Prodromal angina reduces infarcted mass less in interventionally reperfused than in thrombolysed myocardial infarction.* Romanian Journal of Internal Medicine, 2004. **42**(3): p. 533-43.
212. Hosokawa, S., et al., *The impact of gender difference on the effects of preinfarction angina on microvascular damage with reperfused myocardial infarction.* Clinical Cardiology, 2010. **33**(7): p. 412-7.
213. Ishihara, M., et al., *Effect of acute hyperglycemia on the ischemic preconditioning effect of prodromal angina pectoris in patients with a first anterior wall acute myocardial infarction.* American Journal of Cardiology, 2003. **92**(3): p. 288-91.
214. Kloner, R.A. and R.B. Jennings, *Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 2.* Circulation, 2001. **104**(25): p. 3158-67.
215. Andreotti, F., *Preinfarction angina as a predictor of more rapid coronary thrombolysis in patients with acute myocardial infarction.* N Engl J Med, 1996. **334**: p. 7-12.
216. Andreotti, F., et al., *Preinfarction angina as a predictor of more rapid coronary thrombolysis in patients with acute myocardial infarction.* New England Journal of Medicine, 1996. **334**(1): p. 7-12.
217. Evrengul, H., et al., *The effect of preinfarction angina on clinical reperfusion time in patients with acute myocardial infarction receiving successful thrombolytic therapy.* Canadian Journal of Cardiology, 2005. **21**(11): p. 915-20.
218. Botker, H.E., et al., *Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial.* Lancet, 2010. **375**(9716): p. 727-34.

219. Przyklenk, K., et al., *REGIONAL ISCHEMIC PRECONDITIONING PROTECTS REMOTE VIRGIN MYOCARDIUM FROM SUBSEQUENT SUSTAINED CORONARY-OCCLUSION.* Circulation, 1993. **87**(3): p. 893-899.
220. Kloner, R.A., et al., *Prospective temporal analysis of the onset of preinfarction angina versus outcome: an ancillary study in TIMI-9B.* Circulation, 1998. **97**(11): p. 1042-5.
221. Hirai, T., et al., *Significance of preinfarction angina for preservation of left ventricular function in acute myocardial infarction.* American Heart Journal, 1992. **124**(1): p. 19-24.
222. Herlitz, J., et al., *Occurrence of angina pectoris prior to acute myocardial infarction and its relation to prognosis.* Eur Heart J, 1993. **14**(4): p. 484-91.
223. Ishihara, M., et al., *Comparison of the cardioprotective effect of prodromal angina pectoris and collateral circulation in patients with a first anterior wall acute myocardial infarction.* Am J Cardiol, 2005. **95**(5): p. 622-5.
224. Barbash, G.I., et al., *Antecedent angina pectoris predicts worse outcome after myocardial infarction in patients receiving thrombolytic therapy: experience gleaned from the International Tissue Plasminogen Activator/Streptokinase Mortality Trial.* Journal of the American College of Cardiology, 1992. **20**(1): p. 36-41.
225. Gho, B.C.G., et al., *Myocardial protection by brief ischemia in noncardiac tissue.* Circulation, 1996. **94**(9): p. 2193-2200.
226. Kharbanda, R.K., et al., *Transient limb ischemia induces remote ischemic preconditioning in vivo.* Circulation, 2002. **106**(23): p. 2881-2883.
227. Bahr, R.D., E.V. Leino, and R.H. Christenson, *Prodromal unstable angina in acute myocardial infarction: prognostic value of short- and long-term outcome and predictor of infarct size.* Am Heart J, 2000. **140**(1): p. 126-33.
228. Kloner, R.A., *Prospective temporal analysis of the onset of preinfarction angina versus outcome: an ancillary study in TIMI-9B.* Circulation, 1998. **97**: p. 1042-1045.
229. Herrett, E., et al., *Type and timing of heralding in ST-elevation and non ST-elevation myocardial infarction: an analysis of prospectively collected electronic healthcare records linked to the national registry of acute coronary syndromes.* European Heart Journal: Acute Cardiac Care, 2012. **Under review.**
230. Yellon, D.M. and G.F. Baxter, *A "second window of protection" or delayed preconditioning phenomenon: future horizons for myocardial protection?* J Mol Cell Cardiol, 1995. **27**(4): p. 1023-34.
231. *JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice.* Heart, 2005. **91 Suppl 5**: p. v1-52.
232. National Institute for Health and Clinical Excellence (NICE), *Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). NICE clinical guideline 66*, 2008: London.
233. Scottish Intercollegiate Guidelines Network (SIGN), *Risk estimation and the prevention of cardiovascular disease: A national clinical guideline. (SIGN publication no. 97)*, 2007: Edinburgh.
234. Medicines and Healthcare products Regulatory Authority (MHRA), *Drug safety update.* 2009. **3**(3).
235. Scottish Intercollegiate Guidelines Network (SIGN), *Antithrombotics: indications and management. (SIGN publication no. 129)*, 2012: Edinburgh.
236. National Institute for Health and Clinical Excellence (NICE), *Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 67*, 2008: London.
237. *Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association.* Heart, 1998. **80 Suppl 2**: p. S1-29.

238. Primatesta, P. and N.R. Poulter, *Lipid concentrations and the use of lipid lowering drugs: evidence from a national cross sectional survey.* BMJ, 2000. **321**(7272): p. 1322-5.
239. Primatesta, P. and N.R. Poulter, *Levels of dyslipidaemia and improvement in its management in England: results from the Health Survey for England 2003.* Clin Endocrinol (Oxf), 2006. **64**(3): p. 292-8.
240. Kedward, J. and L. Dakin, *A qualitative study of barriers to the use of statins and the implementation of coronary heart disease prevention in primary care.* British Journal of General Practice, 2003. **53**(494): p. 684-689.
241. Ab, E., et al., *Reasons of general practitioners for not prescribing lipid-lowering medication to patients with diabetes: a qualitative study.* BMC Family Practice, 2009. **10**.
242. Ridker, P.M., et al., *Clinical characteristics of nonfatal myocardial infarction among individuals on prophylactic low-dose aspirin therapy.* Circulation, 1991. **84**(2): p. 708-11.
243. Kennon, S., et al., *Influence of previous aspirin treatment and smoking on the electrocardiographic manifestations of injury in acute myocardial infarction.* Heart, 2000. **84**(1): p. 41-5.
244. Bjorck, L., et al., *Medication in relation to ST-segment elevation myocardial infarction in patients with a first myocardial infarction: Swedish Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA).* Archives of Internal Medicine, 2010. **170**(15): p. 1375-81.
245. Abdelnoor, M. and K. Landmark, *Infarct size is reduced and the frequency of non-Q-wave myocardial infarctions is increased in patients using aspirin at the onset of symptoms.* Cardiology, 1999. **91**(2): p. 119-26.
246. Col, N.F., et al., *DOES ASPIRIN CONSUMPTION AFFECT THE PRESENTATION OR SEVERITY OF ACUTE MYOCARDIAL-INFARCTION.* Archives of Internal Medicine, 1995. **155**(13): p. 1386-1389.
247. Mukamal, K.J., et al., *Recent aspirin use is associated with smaller myocardial infarct size and lower likelihood of Q-wave infarction.* American Heart Journal, 1999. **137**(6): p. 1120-1128.
248. Beigel, R., et al., *Relation of aspirin failure to clinical outcome and to platelet response to aspirin in patients with acute myocardial infarction.* Am J Cardiol, 2011. **107**(3): p. 339-42.
249. Alexander, J.H., et al., *Prior aspirin use predicts worse outcomes in patients with non-ST-elevation acute coronary syndromes.* American Journal of Cardiology, 1999. **83**(8): p. 1147-1151.
250. Garcia-Dorado, D., et al., *Previous aspirin use may attenuate the severity of the manifestation of acute ischemic syndromes.* Circulation, 1995. **92**(7): p. 1743-8.
251. Santopinto, J., et al., *Prior aspirin users with acute non-ST-elevation coronary syndromes are at increased risk of cardiac events and benefit from enoxaparin.* American Heart Journal, 2001. **141**(4): p. 566-72.
252. Hoshida, S., et al., *Differences in the mode of presentation for acute coronary syndrome by pre-hospitalization medication, in relation to coronary risk factors, East-Osaka acute coronary syndrome (EACS) registry.* Atherosclerosis, 2011. **219**(1): p. 355-60.
253. Portnay, E.L., et al., *Prior aspirin use and outcomes in elderly patients hospitalized with acute myocardial infarction.* Journal of the American College of Cardiology, 2005. **46**(6): p. 967-74.
254. Spencer, F.A., et al., *Early withdrawal of statin therapy in patients with non-ST-segment elevation myocardial infarction: national registry of myocardial infarction.* Archives of Internal Medicine, 2004. **164**(19): p. 2162-8.
255. Granger, C.B., et al., *Predictors of hospital mortality in the global registry of acute coronary events.* Archives of Internal Medicine, 2003. **163**(19): p. 2345-53.

256. Lancaster, G.I., et al., *Prior aspirin use in unstable angina predisposes to higher risk: the aspirin paradox.* International Journal of Cardiology, 2001. **80**(2-3): p. 201-7.
257. Antman, E.M., et al., *The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making.* JAMA, 2000. **284**(7): p. 835-42.
258. Bauer, T., et al., *Impact of Chronic Antithrombotic Therapy on Hospital Course of Patients with Acute Myocardial Infarction.* Clinical Cardiology, 2009. **32**(12): p. 718-723.
259. Borzak, S., et al., *Effects of prior aspirin and anti-ischemic therapy on outcome of patients with unstable angina. TIMI 7 Investigators. Thrombin Inhibition in Myocardial Ischemia.* Am J Cardiol, 1998. **81**(6): p. 678-81.
260. Rich, J.D., et al., *Prior aspirin use and outcomes in acute coronary syndromes.* Journal of the American College of Cardiology, 2010. **56**(17): p. 1376-85.
261. El-Menyar, A., et al., *Prior Antiplatelet Use and Cardiovascular Outcomes in Patients Presenting with Acute Coronary Syndromes.* American Journal of Cardiovascular Drugs, 2012. **12**(2): p. 127-135.
262. Boersma, E., et al., *Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators.* Circulation, 2000. **101**(22): p. 2557-67.
263. Spencer, F.A., et al., *Impact of Aspirin on presentation and hospital outcomes in patients with acute coronary syndromes (The global registry of acute coronary events GRACE).* American Journal of Cardiology, 2002. **90**(10): p. 1056-1061.
264. Collet, J.P., et al., *Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes.* Circulation, 2004. **110**(16): p. 2361-7.
265. Moran, L., et al., *Statin pretreatment is protective despite an association with greater coronary artery disease burden in patients presenting with a first ST-elevation myocardial infarction.* Preventive Cardiology, 2008. **11**(1): p. 21-5.
266. Kiyokuni, M., et al., *Effects of pretreatment with statins on infarct size in patients with acute myocardial infarction who receive fibrinolytic therapy.* Circ J, 2009. **73**(2): p. 330-5.
267. Ishii, H., et al., *Effects of receipt of chronic statin therapy before the onset of acute myocardial infarction: a retrospective study in patients undergoing primary percutaneous coronary intervention.* Clin Ther, 2006. **28**(11): p. 1812-9.
268. Aronow, H.D., et al., *Relation between previous lipid-lowering therapy and infarct size (creatine kinase-MB level) in patients presenting with acute myocardial infarction.* Am J Cardiol, 2008. **102**(9): p. 1119-24.
269. Lev, E.I., et al., *Effect of previous treatment with statins on outcome of patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention.* American Journal of Cardiology, 2009. **103**(2): p. 165-9.
270. Garot, P., et al., *Favourable effect of statin therapy on early survival benefit at the time of percutaneous coronary intervention for ST-elevation myocardial infarction and shock.* Eurointervention, 2010. **6**(3): p. 350-5.
271. Lancaster, G.I., A.V. Srivastava, and S.W. Zarich, *Previous aspirin use in acute coronary syndromes: more than a marker?* Journal of the American College of Cardiology, 2011. **57**(16): p. 1715; author reply 1715-6.
272. Wilson, P.W., et al., *Prediction of coronary heart disease using risk factor categories.* Circulation, 1998. **97**(18): p. 1837-47.
273. Kelley, C., et al., *Hydroxymethylglutaryl-coenzyme A Reductase Inhibitors (statins) VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel.* 2002.
274. Fulton, M.M. and E.R. Allen, *Polypharmacy in the elderly: a literature review.* J Am Acad Nurse Pract, 2005. **17**(4): p. 123-32.

275. Eichler, K., et al., *Barriers to apply cardiovascular prediction rules in primary care: a postal survey.* BMC Family Practice, 2007. **8**: p. 1.
276. Licka, M., et al., *Troponin T concentrations 72 hours after myocardial infarction as a serological estimate of infarct size.* Heart, 2002. **87**(6): p. 520-4.
277. Go, A.S., et al., *Statin and beta-blocker therapy and the initial presentation of coronary heart disease.[see comment][summary for patients in Ann Intern Med. 2006 Feb 21;144(4):I22; PMID: 16490905].* Annals of Internal Medicine, 2006. **144**(4): p. 229-38.
278. Brindle, P., et al., *Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review.* Heart, 2006. **92**(12): p. 1752-1759.

Chapter 10 Appendix A

10.1 Appendices for Chapter 2

10.1.1 GPRD patient acceptability criteria

GPRD patient acceptability criteria (determining whether a patient's file can be used for research purposes):

- An empty or invalid first registration date;
- Absence of a record for a year of birth;
- A first registration date prior to their birth year;
- A transferred out reason with no transferred out date;
- A transferred out date with no transferred out reason;
- A transferred out date prior to their first registration date;
- A transferred out date prior to their current registration date;
- A current registration date prior to their first registration date;
- A current registration date prior to their birth year;
- A gender other than Female/Male/Indeterminate;
- An age of greater than 115 at end of follow up;
- Recorded health care episodes in years prior to birth year; and
- Registration status of temporary patients.

If any of these conditions are true then the patient is labelled unacceptable, and is not recommended for use in research.

10.1.2 Linkage of GPRD, HES, MINAP and ONS

Purpose of the linkage

Linkage of these GPRD, HES, MINAP and ONS mortality statistics goes some way in addressing the weaknesses and using the strengths of each individual data source. The linkage was instigated by the Cardiovascular disease research using Linked Bespoke studies and Electronic Records (CALIBER) programme, established in 2009. CALIBER aims to improve the aetiology and prognosis of specific coronary phenotypes through linkage of data sources. Linkage of the four data sources described here creates a unique opportunity to examine the detailed medical history of patients who present with MI and to follow the patient journey in the pre- and post-MI periods, through to death.

How was the linkage done?

The linkage was performed by a Trusted Third Party (TTP) to maintain the confidentiality of the patients involved in the linkage. Of the 600 practices who contribute data to the GPRD, 244 consented for their data to be linked to further data sources. This includes linkage to HES, ONS and MINAP data. In November 2010, the patient identifiers from these 244 practices were sent to the TTP. At the same time, patient identifiers from HES, ONS and MINAP were also sent to the TTP. The TTP used deterministic linkage based on NHS number, date of birth, postcode and gender. Of the 5.8 million patients sent for linkage, 4.4 million had a valid NHS number in GPRD and HES, and 4.2 million (94%) of these were eligible for the MINAP linkage, based on the following criteria:

- Active registration with a consenting practice at some point during the data coverage period of ONS, HES or MINAP (Table 10.1);
- Marked as an acceptable patient in the November 2010 version of GPRD; and
- EITHER the patient is matched 1:1 between GPRD and HES by their NHS number, date of birth and gender OR the patient had a valid NHS number, but was not matched to any patient in the HES data (i.e. they had not been hospitalised).

The data used in this thesis consists of only those patients who were matched by the linkage, or who had a valid NHS number (i.e. who should have appeared in HES or MINAP if they were hospitalised with an acute coronary syndrome). Therefore, visitors to the UK, and patients who registered with primary care temporarily would not have been linked.

Linkage success statistics

Since the linkage was carried out by a Trusted Third Party, no details regarding the success rates of the linkage were available in this study.

Coverage periods of the linked data

Each of the data sources has been recording data from a different point in time. The GPRD began collecting data in 1987, HES in 1997, MINAP in 2003, and ONS recording is available from 1995. Table 10.1 describes the time periods covered by each source. Analysis of MI in this thesis is restricted to the time when all sources were providing data so that in the absence of error, each hospitalised MI patient would be recorded in GPRD, HES and MINAP, and each fatal MI would be recorded in GPRD and ONS.

Table 10.1 Coverage periods of each data source

Data source	Coverage period	Unique patient identifiers
GPRD	1987 – 11/2010	NHS number, date of birth, gender, postcode
HES	01/04/1997 – 31/10/2010	NHS number, date of birth, gender, postcode
MINAP	01/01/2003 – 31/03/2009	NHS number, date of birth, gender,
ONS	02/10/1995 – 19/10/2010	NHS number, date of birth, gender,

Linkage of ONS

The ONS linkage was performed in only those patients who had been admitted to HES at any point in their lives. Analyses showed that this may have led to roughly 2% underestimation of mortality in patients who had never been admitted to HES.

Validation of the linkage

The trusted third party performed the linkage and therefore few details are available about the success rate of patient linkage. Additional work concerning the validity of the linkage is currently underway by the CALIBER group.

Ethical approvals and funding

CALIBER is funded by the Wellcome Trust and the National Institute of Health research. CALIBER has received both Ethics approval (ref 09/H0810/16) and ECC approval (ref ECC 2-06(b)/2009 CALIBER dataset).

10.2 Appendices for Chapter 3

10.2.1 MI code lists

GPRD MI code lists

Table 10.2 GPRD Read codes used to define MI in this thesis

GPRD medical code	Read code	Read term	Code classification
35674	14A3.00	H/O: myocardial infarct <60	History of MI
40399	14A4.00	H/O: myocardial infarct >60	History of MI
50372	14AH.00	H/O: Myocardial infarction in last year	History of MI
23579	G310.00	Postmyocardial infarction syndrome	History of MI
4017	G32..00	Old myocardial infarction	History of MI
16408	G32..11	Healed myocardial infarction	History of MI
17464	G32..12	Personal history of myocardial infarction	History of MI
9555	G33z500	Post infarct angina	History of MI
61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct	Definite MI
241	G30..00	Acute myocardial infarction	Definite MI
13566	G30..11	Attack - heart	Definite MI
2491	G30..12	Coronary thrombosis	Definite MI
30421	G30..13	Cardiac rupture following myocardial infarction (MI)	Definite MI
1204	G30..14	Heart attack	Definite MI
1677	G30..15	MI - acute myocardial infarction	Definite MI
13571	G30..16	Thrombosis - coronary	Definite MI
17689	G30..17	Silent myocardial infarction	Definite MI
12139	G300.00	Acute anterolateral infarction	Definite MI
5387	G301.00	Other specified anterior myocardial infarction	Definite MI
40429	G301000	Acute anteroapical infarction	Definite MI
17872	G301100	Acute anteroseptal infarction	Definite MI
14897	G301z00	Anterior myocardial infarction NOS	Definite MI
8935	G302.00	Acute inferolateral infarction	Definite MI
29643	G303.00	Acute inferoposterior infarction	Definite MI
23892	G304.00	Posterior myocardial infarction NOS	Definite MI
14898	G305.00	Lateral myocardial infarction NOS	Definite MI
63467	G306.00	True posterior myocardial infarction	Definite MI
3704	G307.00	Acute subendocardial infarction	Definite MI
9507	G307000	Acute non-Q wave infarction	Definite MI
1678	G308.00	Inferior myocardial infarction NOS	Definite MI
30330	G309.00	Acute Q-wave infarct	Definite MI
17133	G30A.00	Mural thrombosis	Definite MI
32854	G30B.00	Acute posterolateral myocardial infarction	Definite MI
29758	G30X.00	Acute transmural myocardial infarction of unspecif site	Definite MI
34803	G30y.00	Other acute myocardial infarction	Definite MI
28736	G30y000	Acute atrial infarction	Definite MI
62626	G30y100	Acute papillary muscle infarction	Definite MI
41221	G30y200	Acute septal infarction	Definite MI

Continued...

GPRD MI code list continued...

GPRD medical code	Read code	Read term	Code classification
46017	G30yz00	Other acute myocardial infarction NOS	Definite MI
14658	G30z.00	Acute myocardial infarction NOS	Definite MI
15661	G310.11	Dressler's syndrome	Definite MI
68357	G31y100	Microinfarction of heart	Definite MI
18842	G35..00	Subsequent myocardial infarction	Definite MI
45809	G350.00	Subsequent myocardial infarction of anterior wall	Definite MI
38609	G351.00	Subsequent myocardial infarction of inferior wall	Definite MI
72562	G353.00	Subsequent myocardial infarction of other sites	Definite MI
46166	G35X.00	Subsequent myocardial infarction of unspecified site	Definite MI
36423	G36..00	Certain current complication follow acute myocardial infarct	Definite MI
24126	G360.00	Haemopericardium/current comp folow acut myocard infarct	Definite MI
23708	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct	Definite MI
37657	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn	Definite MI
59189	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI	Definite MI
59940	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct	Definite MI
69474	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct	Definite MI
29553	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI	Definite MI
32272	G38..00	Postoperative myocardial infarction	Definite MI
46112	G380.00	Postoperative transmural myocardial infarction anterior wall	Definite MI
46276	G381.00	Postoperative transmural myocardial infarction inferior wall	Definite MI
41835	G384.00	Postoperative subendocardial myocardial infarction	Definite MI
68748	G38z.00	Postoperative myocardial infarction, unspecified	Definite MI
96838	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site	Definite MI
10562	G307100	Acute non ST segment elevation myocardial infarction	Definite MI
12229	G30X000	Acute ST segment elevation myocardial infarction	Definite MI

Table 10.3 GPRD Read codes used to define Creatine kinase codes

GPRD medical code	Read code	Read term	Code classification
14350	44H8.00	Serum creatinine phosphokinase MB isoenzyme level	Result not recorded
49201	44HJ.00	Plasma creatinine phosphokinase MB isoenzyme level	Result not recorded
43046	44I5.00	MB/total creatine kinase ratio	Result not recorded

Table 10.4 GPRD Read codes used to define troponin codes

GPRD medical code	Read code	Read term	Code classification
97137	44p3.00	Cardiac troponin negative	Normal/negative
97001	44p2.00	Cardiac troponin positive	Abnormal/positive
13803	44MC.00	Serum troponin T level	Result not recorded
13806	44ME.00	Plasma troponin I level	Result not recorded
13800	44MG.00	Serum troponin I level	Result not recorded
43984	44MH.00	Plasma troponin T level	Result not recorded

Table 10.5 GPRD Read codes used to define cardiac marker codes of unspecified type

GPRD medical code	Read code	Read term	Code classification
19634	44H2.00	Cardiac enzymes normal	Normal/negative
5221	44H3.00	Cardiac enzymes abnormal	Abnormal/positive
60664	44H3000	Cardiac enzymes abnormal - first set	Abnormal/positive
2403	44H..00	Cardiac enzymes	Result not recorded
61960	44H1.00	Blood sent: cardiac enzymes	Result not recorded
27207	44HI.00	Cardiac markers	Result not recorded
19849	44HZ.00	Cardiac enzymes NOS	Result not recorded

HES and ONS MI code list

Table 10.6 ICD-10 codes to define MI in this thesis

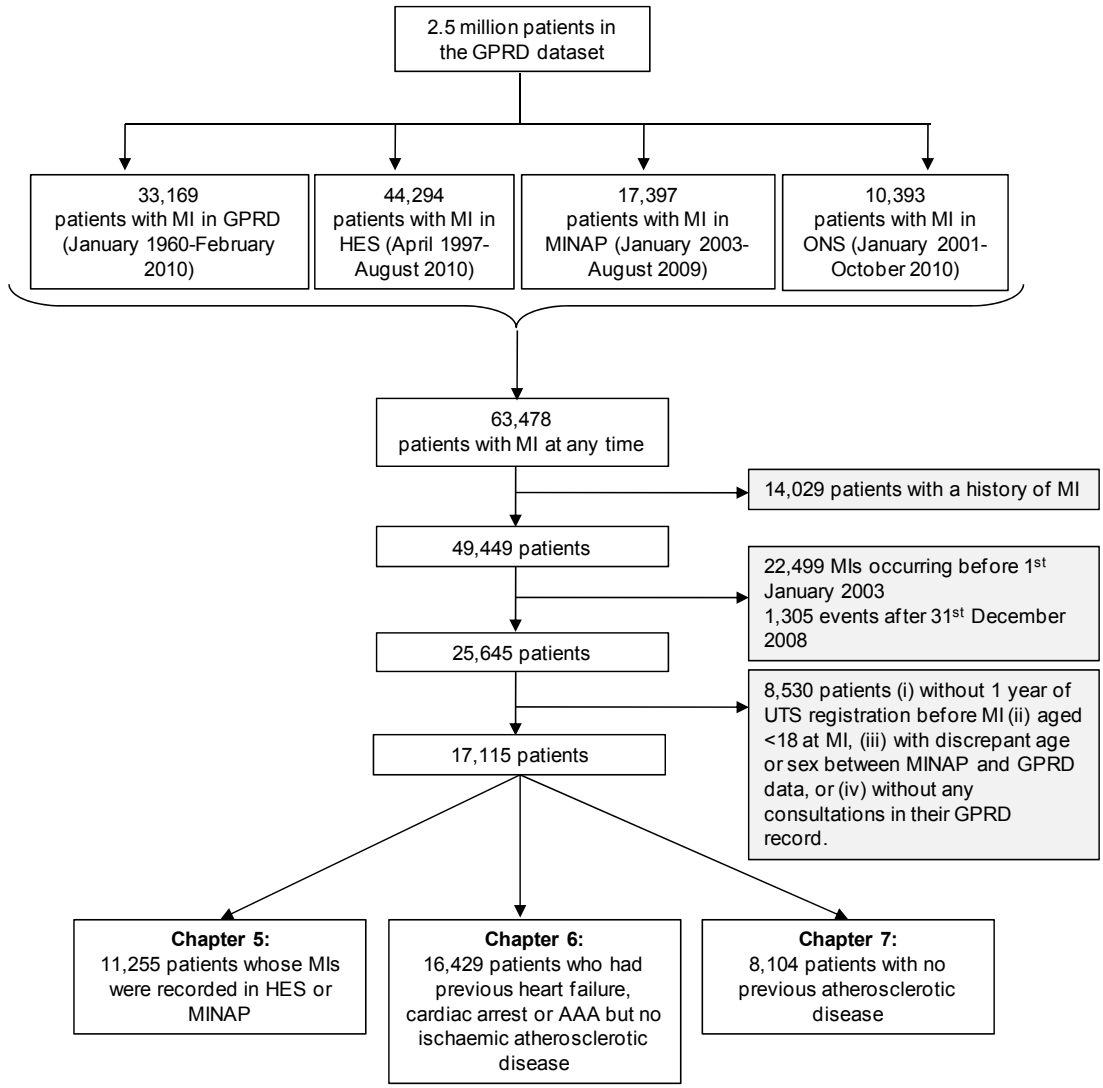
ICD-10 code	ICD-10 term
I21	Acute myocardial infarction
I210	Acute transmural myocardial infarction of anterior wall
I211	Acute transmural myocardial infarction of inferior wall
I212	Acute transmural myocardial infarction of other sites
I213	Acute transmural myocardial infarction of unspecified site
I214	Acute subendocardial myocardial infarction
I219	Acute myocardial infarction, unspecified
I22	Subsequent myocardial infarction
I220	Subsequent myocardial infarction of anterior wall
I221	Subsequent myocardial infarction of inferior wall
I228	Subsequent myocardial infarction of other sites
I229	Subsequent myocardial infarction of unspecified site
I23	Certain current complication follow acute myocardial infarct
I230	Haemopericardium as current comp following acute myocardial infarction
I231	Atrial sept defect as current comp following acute myocardial infarction
I232	Ventric sep defect as current comp following acute myocardial infarction
I233	Rup cardiac wall without haemopericardium as current complication following acute MI
I234	Rup chordae tendinae as current comp following acute myocardial infarction
I235	Rup papillary muscle as current complication following acute myocardial infarction
I236	Thromb atrium/auric append/vent as current complication following acute MI
I238	Other current complication following acute myocardial infarction

10.2.2 Consultation types included in the calculation of consultation rate

- Clinic
- Night visit, Deputising service
- Follow-up/routine visit
- Night visit, Local rota
- Night visit, practice
- Out of hours, Practice
- Out of hours, Non Practice
- Surgery consultation
- Acute visit
- Emergency Consultation
- Telephone call to a patient
- Home Visit
- Hotel Visit
- Nursing Home Visit
- Residential Home Visit
- Twilight Visit
- Triage
- Walk-in Centre
- Co-op Telephone advice
- Co-op Surgery Consultation
- Co-op Home Visit
- Night Visit
- Telephone Consultation

Figure 10.1. Consultation types included in the calculation of consultation rate

10.2.3 Flow chart of data losses for Chapters 5, 6 and 7



MI: myocardial infarction; AAA: abdominal aortic aneurysm; MINAP: Myocardial Ischaemia National Audit Project; GPRD: General Practice Research Database; HES: Hospital Episode Statistics; ONS: Office for National Statistics mortality data.

Figure 10.2 Flow chart of data losses from 2.5 million GPRD patients to the 11,255 pateints described in Chapter 5, 16,429 patients described in Chapter 6 and 8,104 patients described in Chapter 7.

10.3 Appendices for Chapter 4

10.3.1 GPRD Read code list used for validation chapter

Table 10.7 GPRD Read codes used to define myocardial infarction in the validation chapter

GPRD medical code	Read code	Read term	Code classification
241	G30..00	Acute myocardial infarction	MI unknown type
1204	G30..14	Heart attack	MI unknown type
1677	G30..15	MI - acute myocardial infarction	MI unknown type
1678	G308.00	Inferior myocardial infarction NOS	MI unknown type
2491	G30..12	Coronary thrombosis	MI unknown type
3704	G307.00	Acute subendocardial infarction	MI unknown type
5387	G301.00	Other specified anterior myocardial infarction	MI unknown type
7783	323..00	ECG: myocardial infarction	MI unknown type
8935	G302.00	Acute inferolateral infarction	MI unknown type
9507	G307000	Acute non-Q wave infarction	MI unknown type
10562	G307100	Acute non ST segment elevation myocardial infarction	NSTEMI
12139	G300.00	Acute anterolateral infarction	MI unknown type
12229	G30X000	Acute ST segment elevation myocardial infarction	STEMI
13566	G30..11	Attack - heart	MI unknown type
13571	G30..16	Thrombosis - coronary	MI unknown type
14658	G30z.00	Acute myocardial infarction NOS	MI unknown type
14897	G301z00	Anterior myocardial infarction NOS	MI unknown type
14898	G305.00	Lateral myocardial infarction NOS	MI unknown type
15661	G310.11	Dressler's syndrome	MI unknown type
17133	G30A.00	Mural thrombosis	MI unknown type
17689	G30..17	Silent myocardial infarction	MI unknown type
17872	G301100	Acute anteroseptal infarction	MI unknown type
18842	G35..00	Subsequent myocardial infarction	MI unknown type
23708	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct	MI unknown type
23892	G304.00	Posterior myocardial infarction NOS	MI unknown type
24126	G360.00	Haemopericardium/current comp folow acut myocard infarct	MI unknown type
26972	3234.00	ECG:posterior/inferior infarct	MI unknown type
26975	3233.00	ECG: antero-septal infarct.	MI unknown type
28736	G30y000	Acute atrial infarction	MI unknown type
29553	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI	MI unknown type
29643	G303.00	Acute inferoposterior infarction	MI unknown type
29758	G30X.00	Acute transmural myocardial infarction of unspecif site	MI unknown type
30330	G309.00	Acute Q-wave infarct	MI unknown type
30421	G30..13	Cardiac rupture following myocardial infarction (MI)	MI unknown type
32272	G38..00	Postoperative myocardial infarction	MI unknown type
32854	G30B.00	Acute posterolateral myocardial infarction	MI unknown type
34803	G30y.00	Other acute myocardial infarction	MI unknown type
35119	G501.00	Post infarction pericarditis	MI unknown type
36423	G36..00	Certain current complication follow acute myocardial infarct	MI unknown type
37657	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn	MI unknown type
38609	G351.00	Subsequent myocardial infarction of inferior wall	MI unknown type
40429	G301000	Acute anteroapical infarction	MI unknown type
41221	G30y200	Acute septal infarction	MI unknown type
41835	G384.00	Postoperative subendocardial myocardial infarction	MI unknown type

Continued...

Continued...

GPRD medical code	Read code	Read term	Code classification
45809	G350.00	Subsequent myocardial infarction of anterior wall	MI unknown type
46017	G30yz00	Other acute myocardial infarction NOS	MI unknown type
46112	G380.00	Postoperative transmural myocardial infarction anterior wall	MI unknown type
46166	G35X.00	Subsequent myocardial infarction of unspecified site	MI unknown type
46276	G381.00	Postoperative transmural myocardial infarction inferior wall	MI unknown type
52705	3236.00	ECG: lateral infarction	MI unknown type
55401	3235.00	ECG: subendocardial infarct	MI unknown type
59032	323Z.00	ECG: myocardial infarct NOS	MI unknown type
59189	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI	MI unknown type
59940	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct	MI unknown type
61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct	MI unknown type
62626	G30y100	Acute papillary muscle infarction	MI unknown type
63467	G306.00	True posterior myocardial infarction	MI unknown type
68357	G31y100	Microinfarction of heart	MI unknown type
68748	G38z.00	Postoperative myocardial infarction, unspecified	MI unknown type
69474	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct	MI unknown type
72562	G353.00	Subsequent myocardial infarction of other sites	MI unknown type
96838	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site	MI unknown type

Table 10.8 Recording in primary care, hospital data, ACS registry and death registry of MI patients and records in other data sources within 30 days

		Non-fatal MI						MI and death of any cause within seven days							
		Primary care (GPRD, N=13,282)		**Hospital admission (HES, N=12,096)**		**ACS registry (MINAP, N=9,464)**		**Primary care (GPRD, N=2,009)**		**Hospital admission (HES, N=1,248)**		**ACS registry (MINAP, N=623)**		**Cause specific mortality (ONS N=2,882)**	
		n (cum %)		**n (cum %)**		**n (cum %)**		**n (cum %)**		**n (cum %)**		**n (cum %)**		**n (cum %)**	
What was recorded in GPRD?	STEMI	**705**	**(5.3)**	664	(5.5)	557	(5.9)	**11**	**(0.6)**	7	(0.6)	6	(1)	7	(0.2)
	NSTEMI	**2,624**	**(19.8)**	1,948	(21.6)	1,347	(20.1)	**9**	**(0.5)**	6	(1)	3	(1.4)	7	(0.5)
	MI NOS	**9,953**	**(74.9)**	6,437	(74.8)	4,782	(70.6)	**1,989**	**(99.0)**	469	(38.6)	224	(37.4)	1,607	(56.2)
	Unstable angina or ACS			304	(77.3)	408	(75)			7	(39.2)	4	(38)	11	(56.6)
	Other cardiac			1,104	(86.5)	959	(85.1)			112	(48.2)	58	(47.4)	191	(63.3)
	Chest pain			331	(89.2)	282	(88.1)			59	(52.9)	38	(53.5)	71	(65.7)
	Evidence for contact with secondary care[±]			647	(94.5)	595	(94.4)			303	(77.2)	152	(77.8)	428	(80.6)
	Transfer out of GPRD practice			102	(95.4)	65	(95)			266	(98.5)	128	(98.4)	526	(98.8)
	None of the above*			559	(100)	469	(100)			19	(100)	10	(100)	34	(100)
What was recorded in HES?	Primary diagnosis of MI (I21-I23), 1st hospital episode	9,049	(68.1)	**12,096**	**(100)**	6,865	(72.5)	482	(24)	**1,248**	**(100)**	423	(67.9)	1,065	(37)
	Primary diagnosis of MI (I21-I23) after 1st episode	619	(72.8)			516	(78)	81	(28)			30	(72.7)	97	(40.3)
	Unstable angina	643	(77.6)			655	(84.9)	25	(29.3)			10	(74.3)	36	(41.6)
	Other cardiac	976	(85)			786	(93.2)	150	(36.7)			51	(82.5)	199	(48.5)
	Chest pain	125	(85.9)			76	(94)	11	(37.3)			3	(83)	16	(49)
	None of the above†	1,870	(100)			566	(100)	1,260	(100)			106	(100)	1,469	(100)

*For both HES and MINAP MI patients, the most common GPRD codes if none of the listed codes were recorded included 'telephone encounter', 'home visit' and codes indicating blood pressure readings and blood tests (which are some of the most commonly codes used in the GPRD data source).

†For both GPRD and MINAP MI patients, the most common ICD codes if none of the listed codes were recorded included end-stage renal disease, hypertensive renal disease, and unknown/unspecified causes of morbidity.

[±]Evidence for contact with secondary care included codes for hospital discharge, attendance at accident and emergency, consultation with a cardiologist, etc.

Continued...

Table 10.8 continued... Recording in primary care, hospital data, ACS registry and death registry of MI patients and records in other data sources within 30 days

		Non-fatal MI						MI and death of any cause within seven days							
		Primary care (GPRD, N=13,282)		Hospital admission (HES, N=12,096)		ACS registry (MINAP, N=9,464)		Primary care (GPRD, N=2,009)		Hospital admission (HES, N=1,248)		ACS registry (MINAP, N=623)		Cause specific mortality (ONS N=2,882)	
		n (cum %)		n (cum %)		n (cum %)		n (cum %)		n (cum %)		n (cum %)		n (cum %)	
What was recorded in MINAP?	STEMI	3,392	(25.5)	3,440	(28.4)	**3,917**	**(41.4)**	152	(7.6)	276	(22.1)	**348**	**(55.9)**	303	(10.5)
	NSTEMI	3,294	(50.3)	3,425	(56.8)	**5,547**	**(58.6)**	81	(11.6)	147	(33.9)	**275**	**(44.1)**	193	(17.2)
	Discharge diagnosis of unstable angina	375	(53.2)	421	(60.2)			14	(12.3)	28	(36.1)			38	(18.5)
	Admission diagnosis of ACS (including MI)	121	(54.1)	138	(61.4)			17	(13.1)	26	(38.2)			37	(19.8)
	No record in MINAP	6,100	(100)	4,672	(100)			1,745	(100)	771	(100)			2,311	(100)
What was recorded in ONS?	MI (I21-I23) underlying							1,621	(80.7)	1,066	(85.4)	496	(79.6)	**2,882**	**(100)**
	MI (I21- I23) any other cause							176	(89.4)	71	(91.1)	50	(87.6)		
	Other coronary disease (I20-I25) underlying							109	(94.9)	51	(95.2)	32	(92.8)		
	Other coronary disease (I20-I25) any other cause							24	(96.1)	18	(96.6)	13	(94.9)		
	None of the above							79	(100)	42	(100)	32	(100)		

*For both HES and MINAP MI patients, the most common GPRD codes if none of the listed codes were recorded included 'telephone encounter', 'home visit' and codes indicating blood pressure readings and blood tests (which are some of the most commonly codes used in the GPRD data source).
†For both GPRD and MINAP MI patients, the most common ICD codes if none of the listed codes were recorded included end-stage renal disease, hypertensive renal disease, and unknown/unspecified causes of morbidity.
‡Evidence for contact with secondary care included codes for hospital discharge, attendance at accident and emergency, consultation with a cardiologist, etc.

Table 10.9 Recording of non-fatal GPRD MI in HES and MINAP within 30 days by type of GPRD record (number and %)

Code or category	N patients with code	HES primary MI, first episode		HES primary MI, not first episode		HES other CHD		MINAP STEMI		MINAP NSTEMI		MINAP unstable angina	
Table													
Clinical	15,252	9,040	(68.2)	618	(4.7)	1,615	(12.2)	3,390	(25.6)	3,290	(24.8)	373	(2.8)
Referral	114	45	(40.9)	3	(2.7)	19	(17.3)	28	(25.5)	8	(7.3)	4	(3.6)
Test	22	13	(61.9)	2	(9.5)	0	(0)	6	(28.6)	3	(14.3)	0	(0)
Entity code													
Medical history	13,789	8,853	(68.7)	606	(4.7)	1,573	(12.2)	3,333	(25.9)	3,214	(24.9)	366	(2.8)
CHD register	6,637	4,679	(71.1)	283	(4.3)	699	(10.6)	2,002	(30.4)	1,501	(22.8)	180	(2.7)
CV/BP consultation	4	1	(25)	0	(0)	2	(50)	1	(25)	1	(25)	0	(0)
Well person concerns	1	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Cause of death	1,265	75	(70.8)	2	(1.9)	8	(7.5)	10	(9.4)	29	(27.4)	2	(1.9)
Serum cholesterol	2	2	(100)	0	(0)	0	(0)	1	(50)	1	(50)	0	(0)
ECG	20	11	(57.9)	2	(10.5)	0	(0)	5	(26.3)	2	(10.5)	0	(0)
Read term													
Acute myocardial infarction	5,189	3,450	(66.5)	239	(4.6)	665	(12.8)	1,420	(27.4)	1,115	(21.5)	167	(3.2)
MI - acute myocardial infarction	3,294	2,159	(65.5)	124	(3.8)	419	(12.7)	916	(27.8)	725	(22)	98	(3)
Acute non ST segment elevation myocardial infarction	2,624	1,886	(71.9)	168	(6.4)	320	(12.2)	102	(3.9)	1,200	(45.7)	64	(2.4)
Acute myocardial infarction NOS	749	496	(66.2)	49	(6.5)	86	(11.5)	161	(21.5)	181	(24.2)	26	(3.5)
Acute ST segment elevation myocardial infarction	708	614	(86.7)	16	(2.3)	55	(7.8)	460	(65)	62	(8.8)	6	(0.8)
Inferior myocardial infarction NOS	446	373	(83.6)	7	(1.6)	20	(4.5)	255	(57.2)	29	(6.5)	14	(3.1)
Anterior myocardial infarction NOS	114	92	(80.7)	2	(1.8)	8	(7)	66	(57.9)	11	(9.6)	3	(2.6)
Other specified anterior myocardial infarction	78	50	(64.1)	4	(5.1)	9	(11.5)	28	(35.9)	6	(7.7)	1	(1.3)
Heart attack	73	31	(42.5)	8	(11)	13	(17.8)	12	(16.4)	14	(19.2)	0	(0)

Continued...

Code or category	N patients with code	HES primary MI, first episode		HES primary MI, not first episode		HES other CHD		MINAP STEMI		MINAP NSTEMI		MINAP unstable angina	
Acute anterolateral infarction	58	48	(82.8)	2	(3.4)	3	(5.2)	29	(50)	4	(6.9)	1	(1.7)
Acute inferolateral infarction	57	45	(78.9)	2	(3.5)	2	(3.5)	31	(54.4)	2	(3.5)	2	(3.5)
Acute non-Q wave infarction	38	24	(63.2)	2	(5.3)	5	(13.2)	3	(7.9)	11	(28.9)	1	(2.6)
Acute anteroseptal infarction	34	28	(82.4)	1	(2.9)	1	(2.9)	16	(47.1)	6	(17.6)	1	(2.9)
Acute subendocardial infarction	30	22	(73.3)	1	(3.3)	1	(3.3)	1	(3.3)	11	(36.7)	1	(3.3)
ECG: myocardial infarction	28	12	(42.9)	2	(7.1)	2	(7.1)	6	(21.4)	2	(7.1)	0	(0)
Posterior myocardial infarction NOS	23	14	(60.9)	2	(8.7)	2	(8.7)	8	(34.8)	4	(17.4)	0	(0)
Silent myocardial infarction	22	2	(9.1)	0	(0)	3	(13.6)	0	(0)	1	(4.5)	0	(0)
Postoperative myocardial infarction	18	1	(5.6)	1	(5.6)	4	(22.2)	1	(5.6)	3	(16.7)	0	(0)
Mural thrombosis	16	3	(18.8)	0	(0)	3	(18.8)	0	(0)	0	(0)	0	(0)
Acute inferoposterior infarction	16	13	(81.3)	0	(0)	1	(6.3)	8	(50)	3	(18.8)	1	(6.3)
Lateral myocardial infarction NOS	14	8	(57.1)	0	(0)	3	(21.4)	6	(42.9)	1	(7.1)	0	(0)
Dressler's syndrome	12	0	(0)	0	(0)	6	(50)	0	(0)	0	(0)	0	(0)
Other acute myocardial infarction	8	6	(75)	0	(0)	2	(25)	1	(12.5)	2	(25)	0	(0)
Acute septal infarction	8	2	(25)	1	(12.5)	1	(12.5)	3	(37.5)	0	(0)	0	(0)
Attack - heart	7	2	(28.6)	0	(0)	1	(14.3)	2	(28.6)	0	(0)	0	(0)
Subsequent myocardial infarction	7	2	(28.6)	0	(0)	2	(28.6)	1	(14.3)	2	(28.6)	0	(0)
Other acute myocardial infarction NOS	7	2	(28.6)	0	(0)	1	(14.3)	0	(0)	1	(14.3)	0	(0)
ECG: antero-septal infarct.	6	1	(16.7)	0	(0)	0	(0)	0	(0)	1	(16.7)	0	(0)
Coronary thrombosis	5	2	(40)	0	(0)	2	(40)	1	(20)	2	(40)	0	(0)
Thrombosis - coronary	5	3	(60)	0	(0)	1	(20)	0	(0)	3	(60)	0	(0)
Subsequent myocardial infarction of inferior wall	4	3	(75)	0	(0)	0	(0)	3	(75)	0	(0)	0	(0)
ECG:posterior/inferior infarct	3	2	(66.7)	0	(0)	1	(33.3)	1	(33.3)	0	(0)	0	(0)
Acute posterolateral myocardial infarction	3	2	(66.7)	0	(0)	0	(0)	2	(66.7)	0	(0)	0	(0)
True posterior myocardial infarction	3	3	(100)	0	(0)	0	(0)	1	(33.3)	1	(33.3)	0	(0)

Continued...

Code or category	N patients with code	HES primary MI, first episode	HES primary MI, not first episode	HES other CHD	MINAP STEMI	MINAP NSTEMI	MINAP unstable angina
Acute atrial infarction	2	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)
Acute transmural myocardial infarction of unspecif site	2	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)
Acute Q-wave infarct	2	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)
Post infarction pericarditis	2	1 (50)	0 (0)	1 (50)	1 (50)	0 (0)	0 (0)
Postoperative myocardial infarction, unspecified	2	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)
Atrial septal defect/curr comp folow acut myocardal infarct	1	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Thrombosis atrium,auric append&vent/curr comp foll acute MI	1	0 (0)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)
Certain current complication follow acute myocardial infarct	1	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
Acute anteroapical infarction	1	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Postoperative subendocardial myocardial infarction	1	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
ECG: myocardial infarct NOS	1	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subsequent myocardial infarction of other sites	1	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)

Note: Agreement varied between specific Read terms used to identify MI in GPRD. Read terms stating MI with an anatomical location (e.g. 'Acute anterolateral infarction') were associated with a HES primary record of MI within 30 days in about 80% of cases, whereas for less specific terms stating 'acute myocardial infarction' the proportion was slightly lower, at 67%. Even fewer patients with Read terms stating 'heart attack' or 'coronary thrombosis' had a HES primary record of MI (43% and 40%, respectively) (supplementary table 3). There was a similar pattern in the Read codes associated with MI in the ACS registry.

Table 10.10 Recording of fatal and non-fatal HES MI in GPRD and MINAP within 30 days by type of HES record (number and %)
Non-fatal MI

MI record in HES	N patients	Any GPRD MI		GPRD STEMI		GPRD NSTEMI		GPRD MI NOS		GPRD other CHD		MINAP STEMI		MINAP NSTEMI		MINAP unstable angina	
ICD I21	10,870	8,221	(75.6)	610	(5.6)	1,731	(15.9)	5,880	(54.1)	1,227	(11.3)	3,213	(29.6)	3,009	(27.7)	368	(3.4)
ICD I22	1,213	823	(67.8)	53	(4.4)	216	(17.8)	554	(45.7)	178	(14.7)	225	(18.5)	415	(34.2)	53	(4.4)
ICD I23	13	5	(38.5)	1	(7.7)	1	(7.7)	3	(23.1)	3	(23.1)	2	(15.4)	1	(7.7)	0	(0)

Fatal MI

MI record in HES	N patients	Any GPRD MI		GPRD STEMI		GPRD NSTEMI		GPRD MI NOS		GPRD ACS or other cardiac		MINAP STEMI		MINAP NSTEMI		MINAP unstable angina	
ICD I21	1,098	415	(37.8)	7	(0.6)	5	(0.5)	403	(36.7)	100	(9.1)	254	(23.1)	128	(11.7)	21	(1.9)
ICD I22	146	67	(45.9)	0	(0)	1	(0.7)	66	(45.2)	19	(13)	22	(15.1)	18	(12.3)	7	(4.8)
ICD I23	4	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	1	(25)	0	(0)

Table 10.11 Recording of fatal and non-fatal MINAP MI in GPRD and HES within 30 days by type of MINAP record (number and %)

Non-fatal MI

MI record in MINAP	N patients	GPRD any MI		GPRD STEMI		GPRD NSTEMI		GPRD MI NOS		GPRD ACS or other cardiac		HES primary first episode MI		HES primary MI, not first episode		HES other CHD	
STEMI	3,917	3,381	(86.3)	489	(12.5)	105	(2.7)	2,787	(71.2)	241	(6.2)	3,430	(87.6)	91	(2.3)	276	(7)
NSTEMI	5,547	3,305	(59.6)	68	(1.2)	1,242	(22.4)	1,995	(36)	1,126	(20.3)	3,435	(61.9)	425	(7.7)	1,165	(21)

Fatal MI

MI record in MINAP	N patients	GPRD any MI		GPRD STEMI		GPRD NSTEMI		GPRD MI NOS		GPRD ACS or other cardiac		HES primary first episode MI		HES primary MI, not first episode		HES other CHD	
STEMI	348	152	(43.7)	5	(1.4)	0	(0)	147	(42.2)	23	(75.9)	276	(79.3)	5	(1.4)	23	(6.6)
NSTEMI	275	81	(29.5)	1	(0.4)	3	(1.1)	77	(28)	39	(14.2)	147	(53.5)	25	(9.1)	38	(13.8)

10.3.2 Prevalence and concordance of atherosclerotic disease and risk factors in each data source

Prevalence and concordance in MINAP and GPRD

The prevalences of angina, PAD, CVD and heart failure were higher in GPRD for all disease types, but was similar for PCI and CABG. Despite small differences in prevalences, concordance was above 90% for all diagnoses. Concordance for risk factors and medication use was also relatively high, although there were some differences in prevalence. The prevalences were lower in MINAP, particularly for medication use. This is due to high amounts of missingness in these MINAP variables (missing was defined as concordant in this analysis).

Table 10.12 Prevalence and concordance of key atherosclerotic disease diagnoses, cardiovascular disease risk factors and medications used in the six months before MI in 8,059 patients

For 8059 MINAP cases	Prevalence in MINAP N=8,059	Prevalence in GPRD N=8,059	% concordance MINAP vs GPRD*
Atherosclerotic disease			
Angina	15.6	20.3	90.2
PAD	3.2	8.7	93.5
CVD	5.8	7.6	94.9
Heart failure	3.0	5.9	95.0
PCI	1.9	1.6	98.1
CABG	1.6	1.8	99.3
Risk factors			
Hypertension	39.3	39.3	82.5
Diabetes	13.4	13.4	97.1
Overweight or obese	12.5	12.4	99.6
Dyslipidaemia	21.1	13.6	80.3
Family history	16.7	21.6	84.6
Medications before AMI			
Statins	16.2	26.0	92.0
Antiplatelets	16.6	28.2	82.1
Beta blockers	11.9	19.0	93.5
ACEI	14.4	27.4	92.3

*Assuming missingness in MINAP is concordant with GPRD

Sensitivity and specificity of GPRD and MINAP

If GPRD is taken as the gold standard diagnosis, the sensitivity of a MINAP record of previous diagnoses or medication use is low (ranging from 24% for heart failure to 78% for diabetes). Specificity of MINAP is better, ranging from 46% for statin use to 85% for diabetes).

If MINAP is taken as the gold standard diagnosis, the sensitivity of a GPRD record of previous diagnosis or medication use is variable (ranging from 30% in dyslipidaemia to 89% in diabetes). The specificity of GPRD is even higher, ranging from 78% in hypertension to nearly 100% for the recording of CABG.

Table 10.13 Sensitivity and specificity of MINAP with respect to GPRD, and GPRD with respect to MINAP for key atherosclerotic disease, risk factors and medication use before MI in 8,059 patients

For 8,059 MINAP cases	Sensitivity of MINAP	Specificity of MINAP	Sensitivity of GPRD	Specificity of GPRD
Atherosclerotic disease				
Angina	57.4	78.0	74.8	91.4
PAD	22.6	78.2	62.4	93.1
CVD	44.4	77.7	58.6	96.3
Heart failure	24.4	78.9	48.0	95.7
PCI	47.3	80.6	40.3	99.1
CABG	71.2	81.5	80.0	99.6
Risk factors				
Hypertension	65.7	68.9	80.8	78.2
Diabetes	77.9	84.8	89.3	98.0
Dyslipidaemia	46.8	62.9	30.0	91.7
Family history	29.1	34.1	37.6	84.4
Medications before MI				
Statins	45.9	46.4	73.5	90.2
Antiplatelets	43.9	84.7	74.4	81.7
Beta blockers	42.4	48.5	67.3	93.9
ACEI	40.9	47.5	78.1	88.4

PAD: peripheral arterial disease; CVD: cerebrovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; ACEI: angiotensin converting enzyme inhibitors.

Concordance in HES and GPRD

Concordance of atherosclerotic disease, PCI and CABG was high between HES and GPRD. Recording of hypertension, dyslipidaemia and family history were lower in HES.

Table 10.14 Prevalence and concordance of key atherosclerotic disease diagnoses, cardiovascular disease risk factors and medications in the six months before MI in 12,005 patients

For 12,005 HES cases	HES prevalence N=12,005	GPRD prevalence N=12,005	% concordance HES vs GPRD*
Atherosclerotic disease			
Angina	10.0	22.0	84.8
PCI	1.3	1.7	98.6
CABG	1.3	1.9	98.2
PAD	3.8	9.3	92.4
CVD	4.8	9.1	93.0
TIA	1.2	5.9	94.6
Heart failure	5.0	7.2	93.6
Cardiac arrest	0.9	0.2	99.0
Risk factors			
Hypertension	21.6	49.2	65.6
Diabetes	8.9	15.9	92.5
Dyslipidaemia	5.4	13.8	85.4
Family history	17.9	21.2	74.4

*Assuming absence of codes in both HES and GPRD indicate a negative result.
Note: cardiovascular medications are not recorded in HES.
PAD: peripheral arterial disease; CVD: cerebrovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; TIA: transient ischaemic attack.

Sensitivity and specificity of GPRD and HES

The specificity of records in GPRD and HES were both high and all measures were above 80%. The sensitivity of diagnoses was less high.

Table 10.15 Sensitivity and specificity of HES with respect to GPRD, and GPRD with respect to HES for key atherosclerotic disease, risk factors and medication use before MI in 12,005 patients

For 12,005 HES cases	Sensitivity of HES	Specificity of HES	Sensitivity of GPRD	Specificity of GPRD
Atherosclerotic disease				
Angina	38.1	97.9	83.7	84.9
PCI	46.7	99.5	64.5	99.1
CABG	36.8	99.4	56.6	98.8
PAD	29.5	98.9	73.4	93.2
CVD	38.1	98.5	71.8	94.1
TIA	15.1	99.6	72.3	94.9
Heart failure	39.9	97.7	57.9	95.4
Cardiac arrest	20.0	99.2	4.8	99.8
Risk factors				
Hypertension	37.0	93.4	84.4	60.4
Diabetes	54.5	99.6	96.6	92.1
Dyslipidaemia	16.9	96.4	43.0	87.8
Family history	31.9	85.9	37.8	82.4

Note: cardiovascular medications are not recorded in HES.
PAD: peripheral arterial disease; CVD: cerebrovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; TIA: transient ischaemic attack.

10.4 Appendices for Chapter 5

10.4.1 Literature review search strategy

Table 10.16 Medline search strategies.

Search number	Terms included
1. Myocardial infarction	The following MI synonyms in the title: myocardial infarct* OR stemi OR heart attack OR cardiac infarct* OR acute infarct* OR STEAMI OR coronary attack OR myocardial thrombosis OR coronary thrombosis OR coronary infarct* OR heart infarct* OR Q wave infarct* OR acute coronary OR pre-infarct* OR preinfarct*
2. Heralding synonyms	The following terms in the title: before OR preced* OR herald* OR previous* OR prior OR earlier OR advance OR former OR ahead OR sooner OR pre-exist* OR exist* OR precur* OR prodrom* OR anteced* OR presence OR history OR prevalen* OR recogni* OR document OR record* OR preinfarct* OR pre-infarct*
3. Inclusion criteria	1 & 2, restricted to studies in humans and in the English language

10.4.2 Heralding by atherosclerotic disease, by calendar year

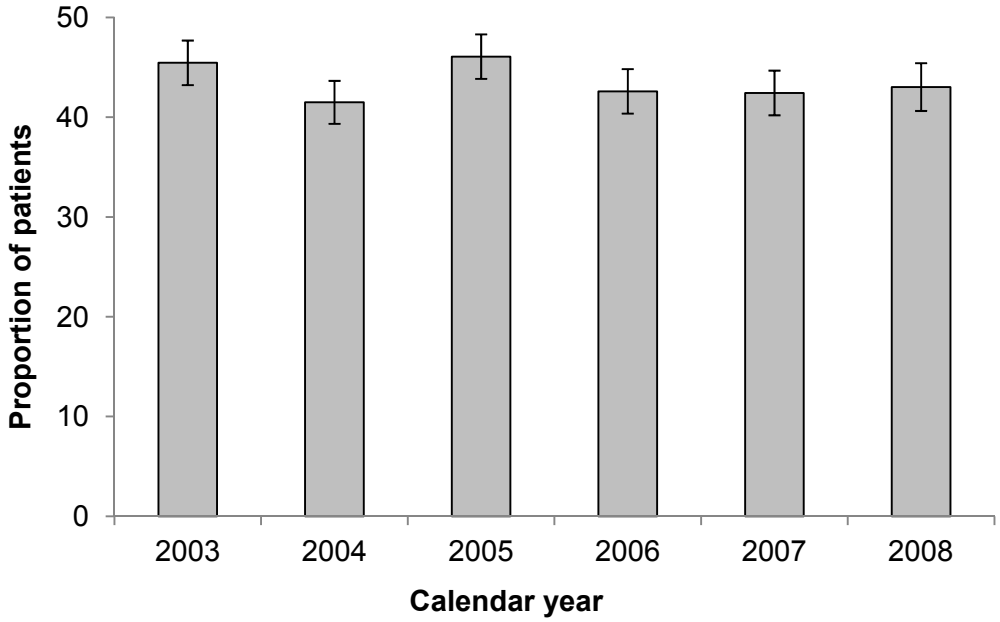


Figure 10.3 Proportion of patients with previously diagnosed atherosclerotic disease, by calendar year of myocardial infarction, with 95% confidence intervals (N=11,255)

10.4.3 Initial manifestation of atherosclerotic disease in patients heralded by atherosclerotic disease

Table 10.17 Initial previous disease manifestation in cases, and duration of disease before MI in 11,255 patients

	n	(%)	Median duration before MI, years (IQR)	
Any atherosclerotic disease	**4,897**	**(43.5)**	**6.7**	**(2.5-11.9)**
Coronary disease	**3,170**	**(29.7)**	**3.7**	**(0.8-8.4)**
Stable angina	1,686	(15)	8.1	(3.1-13.3)
Unstable angina	163	(1.4)	0.9	(0-4.9)
PCI or CABG	104	(0.9)	11.4	(0.8-18.3)
Heart failure	516	(4.6)	4.4	(1.5-8.3)
Cardiac arrest	13	(0.1)	4.9	(0.1-7.7)
CHD not otherwise specified	688	(6.1)	7.9	(3-12.2)
Other atherosclerotic disease	**1,678**	**(16.1)**	**5.6**	**(2.3-9.9)**
Cerebrovascular disease	943	(8.4)	6.9	(2.9-12.5)
Peripheral arterial disease	735	(6.5)	5.9	(2.6-9.8)
Unknown atherosclerotic disease	**49**	**(0.4)**	**7.7**	**(2.5-11.9)**

MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CHD: coronary heart disease; IQR: inter-quartile range.

10.4.4 Heralding by atherosclerotic disease, by myocardial infarction type

Table 10.18 The prevalence of atherosclerotic disease at any time, by MI type (N=6,871)

	STEMI (N=3,304)		NSTEMI (N=3,567)	
	n	(%)	n	(%)
Any atherosclerotic disease	**973**	**(29.4)**	**1,799**	**(50.4)**
Coronary disease	**695**	**(21)**	**1,472**	**(41.3)**
Stable angina	509	(15.4)	1,177	(33)
Unstable angina	58	(1.8)	215	(6.0)
PCI or CABG	87	(2.6)	215	(6.0)
Heart failure	133	(4)	422	(11.8)
Cardiac arrest	15	(0.5)	37	(1.0)
CHD not otherwise specified	371	(11.2)	864	(24.2)
Other atherosclerotic disease	**460**	**(13.9)**	**839**	**(23.5)**
Cerebrovascular disease	237	(7.2)	444	(12.4)
Peripheral arterial disease	231	(7.0)	466	(13.1)
Unknown atherosclerotic disease	**18**	**(0.5)**	**52**	**(1.5)**

STEMI: ST-elevation myocardial infarction; NSTEMI: non ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CHD: coronary heart disease; IQR: inter-quartile range.

10.4.5 Demographics in patients with and without elevated vascular disease risk factors

Table 10.19 Demographic distribution of patients without previously diagnosed atherosclerotic disease and with or without elevated cardiovascular disease risk (N=6,358)

	No disease with risk factors* N=5,548		Without warning N=810		Total	
Median age, years (IQR)	65	(56-76)	73	(62-82)	66	(56-77)
Female, n (%)	1,896	(34.2)	270	(33.3)	2,166	(34.1)
Ethnicity, n (%)						
White	4,443	(80.1)	644	(79.5)	5,087	(80)
South Asian	45	(0.8)	4	(0.5)	49	(0.8)
Other	109	(2)	15	(1.9)	124	(2)
Unknown	951	(17.1)	147	(18.1)	1,098	(17.3)
IMD quintile, n (%)						
1 (Least deprived)	1,117	(26)	205	(32.6)	1,322	(26.8)
2	951	(22.1)	141	(22.5)	1,092	(22.2)
3	906	(21.1)	123	(19.6)	1,029	(20.9)
4	764	(17.8)	111	(17.7)	875	(17.8)
5 (Most deprived)	559	(13)	48	(7.6)	607	(12.3)
Consultations per year, n (IQR)	5.0	(2.6-8.5)	3.5	(1.7-6.6)	4.7	(2.4-8.3)
Years of pre-MI GPRD registration, n (IQR)	8.5	(5.4-13.2)	8.3	(5.2-13.3)	8.4	(5.3-13.2)

IMD: index of multiple deprivation; IQR: inter-quartile range; GPRD: General Practice Research Database
*Patients without previously diagnosed atherosclerotic disease, but with elevated cardiovascular disease risk factors or using one or more cardiovascular medications.

10.4.6 Sensitivity analyses figures

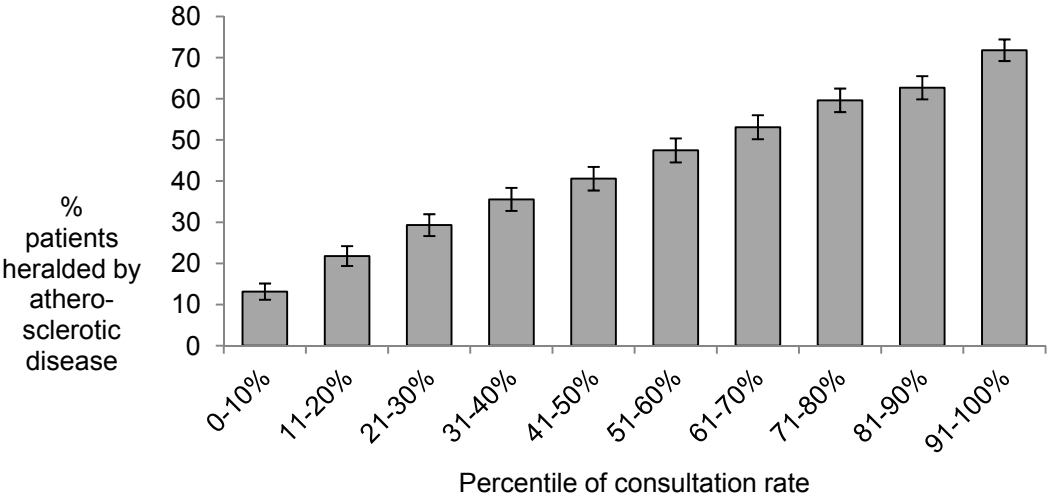


Figure 10.4 Proportion of patients heralded, by percentile of consultation rate (95% CIs) (N=11,255)

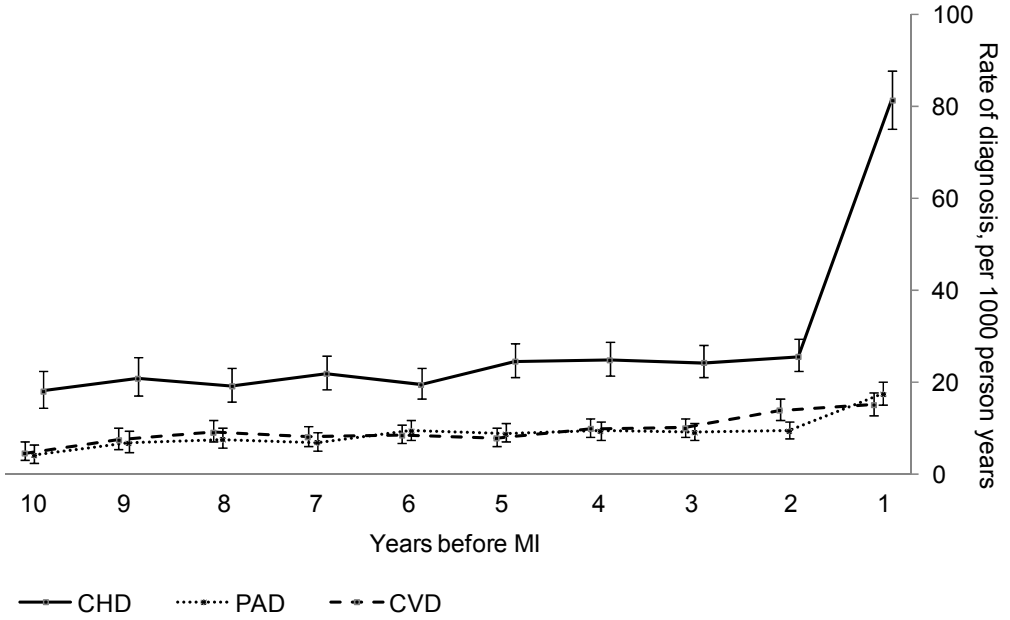


Figure 10.5 Rate of onset of atherosclerotic disease before MI in patients whose first date of atherosclerotic disease was inside UTS, with 95% confidence intervals. Note that patients whose first date of atherosclerotic disease diagnosis was before the start of their UTS follow-up were dropped from analysis (N=11,255)

10.4.7 Submitted paper

Type and timing of heralding in ST-elevation and non ST-elevation myocardial infarction: an analysis of prospectively collected electronic healthcare records linked to the national registry of acute coronary syndromes

Emily Herrett, Research Degree Student[1], Julie George, Doctoral Fellow[2], Spiros Denaxas, Research Fellow[2], Krishnan Bhaskaran, Lecturer[1], Adam Timmis, Professor[3], Harry Hemingway, Professor[2], Liam Smeeth, Professor[1]

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom

[2]University College London, London, United Kingdom

[3]Barts and the London School of Medicine and Dentistry, London, United Kingdom

Address for correspondence:

Emily Herrett

Faculty of Epidemiology and Population Health

London School of Hygiene and Tropical Medicine

Keppel Street

London WC1E 7HT

UK

T: 0207 927 2495

E: emily.herrett@lshtm.ac.uk

F: 020 7636 8636

Word count: 4999

Abstract

Aims: It is widely thought that ST-elevation myocardial infarction (STEMI) is more likely to occur without warning (i.e. an unanticipated event in a previously healthy person) than non ST-elevation myocardial infarction (NSTEMI), but no large study has evaluated this using prospectively collected data.

Methods and results: We identified patients experiencing STEMI and NSTEMI in the national registry of myocardial infarction for England and Wales (Myocardial Ischaemia National Audit Project), for whom linked primary care records were available in the General Practice Research Database (as part of the CALIBER collaboration). We compared the prevalence and timing of atherosclerotic disease and major cardiovascular risk factors including smoking, hypertension, diabetes, and dyslipidaemia, between patients later experiencing STEMI to those experiencing NSTEMI.

8174 myocardial infarction patients were included (3780 STEMI, 4394 NSTEMI). The proportion occurring unheralded by previously diagnosed atherosclerotic disease, risk factors or chest pain was 14% (95% CI: 13-16%) in STEMI and 9% (95% CI: 9-10%) in NSTEMI, but there was a greater prior atherosclerotic burden in NSTEMI than STEMI patients. The rate of heralding coronary diagnoses was particularly high in the 12 months before infarct; 4.1 times higher (95% CI: 3.3-5.0) in STEMI and 3.6 times higher (95% CI: 3.1-4.2) in NSTEMI compared to the rate in earlier years.

Conclusion: Acute myocardial infarction occurring without prior coronary, cerebrovascular or peripheral arterial disease, risk factors or symptoms is uncommon for both STEMI and NSTEMI. Better understanding of the antecedents in the year before myocardial infarction is required.

Key words: epidemiology, myocardial infarction, cardiovascular diseases, risk factors

Background

The extent to which first acute myocardial infarction (AMI) with or without ST-elevation is heralded by previous symptomatic atherosclerotic disease, major risk factors or symptoms has important implications for understanding the etiology of each phenotype, as well as the provision of optimal services. Studies which retrospectively evaluate medical history suggest that prior atherosclerotic disease is common in people with AMI,(1-5) and patterns differ according to ST-elevation myocardial infarction (STEMI) and non ST-elevation myocardial infarction (NSTEMI). Patients with NSTEMI tend to have higher levels of angina,(6, 7) heart failure symptoms,(8) CABG and PCI,(6, 9, 10) and peripheral vascular disease(7) compared to patients with STEMI.

However many of these studies take a single, retrospective snapshot of medical history and have important limitations. They may underestimate the burden of prior disease (i.e. falsely inflating the estimate of unheralded AMI) and may poorly reflect the timing of initial and subsequent manifestations of disease. To our knowledge, no large scale study to date has evaluated the extent and nature of STEMI and NSTEMI heralding using prospectively collected information on the onset of atherosclerotic disease (in coronary, cerebral and peripheral circulations) and other risk factors.

Therefore this paper aims to compare the evolution of atherosclerotic disease and cardiovascular risk between people going on to experience STEMI and NSTEMI. Using prospectively collected longitudinal primary care data linked to detailed hospital data on acute coronary syndromes, we describe the initial manifestation, distribution and timing of different atherosclerotic presentations before first STEMI and NSTEMI, and the proportion of MIs that occur without any previously diagnosed atherosclerotic disease, cardiovascular risk factors or chest pain.

Methods

Study design

As part of the CALIBER research programme (Cardiovascular disease research using Linked Bespoke studies and Electronic Records, www.caliberresearch.org),(11) the records of patients presenting with STEMI and NSTEMI in the Myocardial Ischaemia National Audit Project (MINAP) were linked to longitudinal electronic health records from primary care from the General Practice Research Database (GPRD).

MINAP

MINAP is the national registry of patients admitted to hospitals in England and Wales with ACS.(12) The MINAP dataset records timing of symptom onset and admission, clinical features and investigations (including ECG results and cardiac biomarkers), past medical history, hospital treatment and discharge diagnosis.(12)

GPRD

The GPRD is a primary care database containing anonymised patient records from general practices for approximately eight percent of the UK population (5.2 million patients).(13) General practitioners (GPs) play a key role in the UK healthcare system as they are responsible for primary health care and specialist referrals. Patients are affiliated to a practice, which centralizes the medical information from the GP (diagnoses, symptoms, prescriptions, treatments and health behaviors), specialist referrals, and hospitalizations, so that GP data provide a comprehensive longitudinal health record. Around 40% of the general practices in GPRD permit linkage of individual patient records with other data sources.(14) Data from these practices, all in England, are used in the current study.

Linkage

Linkage of MINAP with GPRD permits researchers to establish a longitudinal patient journey before and after ACS, while providing greater clinical detail on ACS events than is reliably available within GPRD. The pseudoanonymised dataset was created using a

Trusted Third Party to perform the linkage, based on patient NHS number, date of birth, gender and postcode.(11)

Definition of acute myocardial infarction

STEMI or NSTEMI was defined by details recorded in MINAP, following the joint American Heart Association / European Society of Cardiology definition.(15) In order to confine the analysis to first acute myocardial infarction (AMI), we excluded patients with a history of AMI noted in their MINAP record, or with evidence of AMI in their GPRD record prior to the first AMI recorded in MINAP. We included patients fulfilling the following criteria: at least eighteen years of age at AMI, first AMI occurring between 1st January 2003 and 31st December 2008; registered with the GPRD practice at the time of AMI; with at least one year of observation before AMI and at least one consultation during pre-AMI follow-up to allow prevalent diagnoses to be recorded once a patient joins a practice (Supplementary Figure 1).

Identifying atherosclerotic cardiovascular disease and risk factors in the linked data

MINAP and GPRD data were used to identify atherosclerotic disease and cardiovascular risk factors among study patients. Atherosclerotic disease included cardiac disease, (AMI, stable angina, unstable angina, cardiac arrest, heart failure, coronary heart disease (CHD) not otherwise specified, receipt of percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG)); ischemic cerebrovascular disease, including stroke, non stroke cerebrovascular disease and transient ischemic attack; peripheral arterial disease (PAD), including abdominal aortic aneurysm.

Risk factors investigated were smoking (categorized as non, ex, current or unknown at the time of AMI), hypertension (either diagnosed hypertension or three consecutive raised (>140/90mm Hg) measurements), dyslipidaemia (abnormal lipid measurements or

management of high lipids) and diabetes (diagnosed diabetes or insulin prescription) and were defined by codes in the primary care or MINAP hospital record. We also determined whether patients had been prescribed blood pressure lowering, lipid-lowering or antiplatelet medications in the six months before AMI. Missing data from MINAP variables and absence of any diagnostic codes in the GPRD were taken to indicate absence of the risk factor or morbidity.

Determining onset and duration of diagnosed atherosclerotic disease before AMI

For patients whose AMI was heralded by a diagnosis of atherosclerotic disease, we took the earliest record of any atherosclerotic disease before AMI in the GPRD to be the date of onset (data on timing of prior disease is not recorded in MINAP). Where this code was for a prevalent diagnosis (e.g. 'history of stroke') or the morbidity was recorded only in MINAP, the date of onset was recorded as missing. The earliest date of each subtype of atherosclerotic disease (coronary, cerebrovascular, peripheral arterial) was ascertained using the same method. This allowed calculation of the duration of diagnosed disease before AMI and the rate of diagnosis before STEMI and NSTEMI.

Consultation or admission for chest pain in the linked data

In patients without diagnosed atherosclerotic disease, we assessed the frequency of primary care consultations for chest pain.

Statistical analysis

The proportions with diagnosed atherosclerotic disease and risk factors were calculated for STEMI and NSTEMI patients. Since the age and sex profiles of STEMI and NSTEMI patients differed, we included each atherosclerotic disease/risk factor in turn in an age- and sex-adjusted logistic regression model to determine whether the odds of prior disease/risk factor differed between STEMI and NSTEMI patients, after accounting for age and sex differences. We used the models to assess interaction between age and sex. We

also calculated the age and sex standardized prevalences of each atherosclerotic disease subtype and risk factor for STEMI and NSTEMI patients, using the age and sex distribution of the study population as the standard.

To investigate the timing of disease prior to AMI, we calculated rates of new coronary, cerebrovascular, and peripheral arterial disease in one-year timebands in the period before AMI, and rates of new coronary diagnoses and chest pain consultations in one-month timebands in the period before AMI. We used Poisson regression to calculate rate ratios and 95% confidence intervals, comparing the rate of coronary diagnosis in the year before AMI to the rate in the previous nine years, and also to test for linear trend in the rate of diagnosis in the years leading to AMI. All analyses were performed in STATA. The study details are registered online at clinicaltrials.gov (NCT01379131) and a time-stamped detailed analytic protocol is available on request. CALIBER has received ethics approval (ref 09/H0810/16) for creation of linked pseudoanonymised data encompassing GPRD and MINAP.

Results

We identified 8174 first AMI patients who met the eligibility criteria. Their median age was 71 (IQR 59-80), 2946 (36%) were women and 3780 (46%) had STEMI. The median duration of follow-up before AMI was 8.7 years (overall 77,228 person years of follow-up). Table 1 shows the demographic and hospital admission characteristics of patients by AMI type.

[Table 1] [Figure 1]

Acute myocardial infarction occurring with and without heralding

Among patients with STEMI, 29% had prior atherosclerotic disease, 56% had no prior atherosclerotic disease diagnosis but at least one cardiovascular risk factor and 0.6% experienced only chest pain, leaving 14% (95% CI: 13-16%) unheralded. In NSTEMI patients 50% had previous disease, 40% had no previous disease but at least one cardiovascular risk factor, 0.7% reported only chest pain and 9% (9-10%) experienced unheralded AMI (Figure 1). Thus NSTEMIs were more often heralded by prior atherosclerotic disease rather than other risk factors only. STEMIs were more likely to be unheralded than NSTEMIs, but the absolute proportions of unheralded MIs were low for both types.

Diagnosed atherosclerotic disease before first AMI

Overall 3326 (41%) of patients had previously diagnosed atherosclerotic disease. Patients with NSTEMI experienced more disease (STEMI 29%, NSTEMI 50%, age and sex standardized values 32% and 47%, respectively, $P<0.001$) and this pattern was consistent across age groups, for men and women and for different atherosclerotic disease manifestations, even after standardizing for age and sex (Table 2). There was no age-sex interaction. Coronary disease was the most common presentation before AMI, diagnosed in 21% of STEMI patients and 41% of NSTEMI; most of these patients had stable angina (16% in STEMI and 33% in NSTEMI). Although most patients with previous disease had a

coronary diagnosis, 9% of STEMIs and 10% of NSTEMIs were heralded only by PAD and/or atherosclerotic cerebrovascular disease.

Thirty percent of patients were diagnosed with disease in only one arterial bed, 9% in two and 2% in three. The extent of disease differed by AMI type (age and sex adjusted logistic regression P<0.001); overall 15% of patients with NSTEMI had disease at more than one site, compared to 6% in STEMI, Figure 2).

[Figure 2] [Table 2]

Of the 3326 patients with atherosclerotic disease diagnoses, we were able to estimate a date of disease onset for 2891 (87%; 84% STEMI, 89% NSTEMI). Throughout the ten years preceding infarction, the rates of diagnosis of coronary, cerebrovascular and peripheral disease were higher in NSTEMI than STEMI (Figure 3). The rates of cerebrovascular disease and PAD remained stable throughout follow-up, with an upward trend towards AMI over time (average increase in rate per one year timeband: 1.06 (95% CI 1.03-1.10), P<0.001). Rates of coronary disease were higher than rates of peripheral or cerebrovascular disease throughout follow-up, consistent with the higher prevalence of coronary disease at the time of AMI.

In contrast to the patterns observed in cerebrovascular and peripheral diseases, the rate of coronary disease diagnosis rose rapidly in the year before AMI (Figures 3 & 4A). Compared to the rate in the previous nine years, the rate of coronary diagnosis was 4.1 times higher (95% CI: 3.3-5.0) in the year before STEMI and 3.6 (3.1-4.2) times higher in the year before NSTEMI. Figure 4A shows that these increases were largely restricted to the three months before infarct, during which 159 (2%) patients were first diagnosed with coronary disease or received a coronary intervention (stable angina (n=102), unstable angina (n=17), CHD of unspecified type (n=26), PCI/CABG (n=14)). A similar pattern was observed in the rate of chest pain consultations in patients without diagnosed atherosclerotic disease (Figure 4B).

Among patients with prior atherosclerotic disease, the median duration between first diagnosis and STEMI was 6.2 years (IQR 2.2-11.7) and in NSTEMI 7.6 years (3.2-13.4) (Table 2). The median duration of all atherosclerotic diseases combined was longer in NSTEMI at all age groups and for men and women (Supplementary Table 1). Importantly, the duration of diagnosed disease tended to be long: 26% of atherosclerotic disease heralding in STEMI and 35% in NSTEMI was ten or more years' duration (48% and 57% five or more years, respectively).

Use of cardiovascular medications in patients with atherosclerotic disease

Of those with previously diagnosed atherosclerotic disease, 87% were being prescribed one or more of aspirin, statins and blood-pressure lowering treatment in the six months before AMI, but only 34% were receiving all three.

Cardiovascular risk factors and medications in patients without previous atherosclerotic disease

Fifty nine percent of AMIs were unheralded by previously diagnosed atherosclerotic disease (71% STEMI, 50% NSTEMI). Overall 79% of these patients had at least one elevated or treated risk factor (ever had a record of diabetes, hypertension, dyslipidaemia, current smoking, or a prescription for statins, blood pressure lowering or antiplatelets in the six months before MI). This was the same in STEMI (79%) and NSTEMI (80%) (Table 3). The most common risk factors were diagnosed hypertension or recent use of blood pressure lowering drugs (42% of STEMI patients and 53% of NSTEMI), and current smoking (39.8% STEMI, 28.3% NSTEMI); one or both of these risk factors was present in 70% of STEMI and 80% of NSTEMI patients. STEMI patients tended to have a slightly lower burden of cardiovascular risk factors than NSTEMI (median two risk factors in STEMI patients, three in NSTEMI).

Discussion

We found that heart attack without clinically ascertained and recorded warning is uncommon. In the first large-scale evaluation of coronary, cerebral and peripheral atherosclerotic disease manifestations, risk factors and symptoms prior to STEMI and NSTEMI using prospectively collected data, we found large differences in the pattern of diagnosed atherosclerotic disease by AMI type in the period leading up to AMI. While the proportion of AMI that occurs without disease, cardiovascular risk factors, medications or chest pain (i.e. 'out of the blue') was slightly higher in STEMI, an important proportion of unheralded AMIs are NSTEMI (14% versus 9%, respectively). We also found that there was a premonitory period for both MI types during which the rates of both coronary disease diagnosis and chest pain consultation were raised, but there was no equivalent increase in the rate of peripheral artery or cerebrovascular disease diagnoses.

Previous atherosclerotic disease and risk factors

Uniquely, our study provided prospective data on the rate of onset of different subtypes of atherosclerotic disease in the years leading to AMI. Patients with NSTEMI had a consistently higher rate of coronary, cerebrovascular and peripheral disease diagnosis throughout follow-up compared to STEMI. This is in line with other studies showing that patients with NSTEMI are more likely to have prior atherosclerotic disease than STEMI patients.(6-10, 16, 17)

Our results describing the extent of disease across vascular territories are also similar to published findings for NSTEMI, (5) and we have shown that in STEMI patients, disease in two or more sites is less common. This is consistent with the idea that NSTEMI patients tend to be a sicker group overall. The widely different pattern in the prevalence and rate of onset of atherosclerotic disease between AMI types lends support to the hypothesis that STEMI and NSTEMI are two different patho-physiological entities (NSTEMI is more often caused by a non-occlusive thrombus and STEMI is more often caused by a complete occlusion(18)).

If AMI occurs without prior symptomatic atherosclerotic disease, to what extent can it be considered to occur "out of the blue"? Although a substantial proportion of infarcts were unheralded by diagnosed atherosclerotic disease, the majority of these had at least one cardiovascular risk factor (smoking, hypertension, dyslipidaemia, diabetes) or were being treated with a cardiovascular medication. The relatively high prescription of antiplatelets before both STEMI and NSTEMI indicates that general practitioners (GP) suspected a high risk of atherosclerotic disease in many of these patients. Our findings are consistent with other prospective studies showing high risk factor burdens in AMI patients overall.(19, 20)

To our knowledge, there are no other estimates for the proportion of STEMI and NSTEMI occurring without heralding. We have shown that unheralded AMI is uncommon, occurring in roughly one in ten patients in our study. The true prevalence of unheralded AMI is likely to be lower than our data suggest because our data were from general practice where risk factors are recorded opportunistically during patient consultations.

Premonitory period

Clinical experience and retrospective studies have long suggested that AMI might be preceded by premonitory symptoms of chest pain presenting to a family physician or ambulatory care.(21, 22) Our study extends knowledge in several respects. First we confirmed this association with prospective data. Second we found that there were increases in coronary disease diagnoses and chest pain consultations in both STEMI and NSTEMI. This is in contrast to the widely-held view that STEMI is usually of sudden onset. Third we showed that the increases were specific to coronary diagnoses and chest pain, rather than disease in cerebral or peripheral circulations, suggesting a local rather than systemic pro-thrombotic state.

Clinical implications and missed opportunities for care?

In patients with previously diagnosed atherosclerotic disease or risk factors, AMI represents the unmet potential of secondary prevention, and primary prevention respectively. Despite a clear premonitory period where many patients were diagnosed with coronary

disease shortly before AMI, the majority of disease was diagnosed long in advance of both AMI types. Therefore there is an extended period during which secondary prevention could be implemented. Our data describing the use of secondary prevention measures in the six months before AMI showed that most patients with diagnosed atherosclerotic disease were receiving one of either statins, aspirin or blood pressure-lowering drugs, but only a third were in receipt of all three, indicating that there are likely to be missed opportunities for secondary prevention in this group.

Interestingly, while coronary disease was the most common pre-AMI presentation, ten percent of both STEMIs and NSTEMIs were heralded by peripheral artery disease and/or cerebrovascular disease alone. This emphasises the importance of further efforts to improve the secondary prevention following diagnoses in the cerebral and peripheral arteries in order to prevent an important proportion of AMI. The high prevalence of risk factors in both STEMI and NSTEMI suggests the importance of tackling the widely reported missed opportunities for implementation of existing interventions known to be effective.(23-26) Additionally, lowering blood pressure and lipids in those not diagnosed as hypertensive or dyslipidemic may also prevent AMI as the risk associated with blood pressure and lipids is not binary.

Strengths

The main strength of this study is the quality of data from the linked MINAP and GPRD records. MINAP collects data from all hospitals in England and undergoes annual assessments to ensure the data are of research quality.(27) ECG and cardiac marker results are recorded and our STEMI and NSTEMI case definitions were based on the international definition of AMI.(15) The recording of admission date in MINAP allowed us to interpret the timing of previous atherosclerotic disease diagnoses in relation to AMI. The GPRD is representative of the UK population(13) and roughly half of GPRD practices consented to

linkage with MINAP; patients in practices that participated in the linkage were representative of the GPRD as a whole.(14)

The primary care GPRD data are collected prospectively as part of usual clinical care and therefore are not subject to recall bias or differential error related to outcome. Data regarding new diagnoses and treatment of disease were available for a median of 8.7 years before AMI, allowing sufficient time for incident diagnoses to arise and be recorded. The GPRD closely monitors data quality and the recording of a wide range of atherosclerotic disease outcomes have undergone validation in GPRD studies, which, for example, have compared the electronic data to paper-based medical records or compared the rate of a condition in the GPRD to an external source. These have shown most diagnoses to be of high quality.(28-31)

Our analysis was based on patients with 'definite' atherosclerotic disease diagnoses, using diagnostic codes which had been rated by two clinicians as being indicative of disease. If 'possible' diagnoses were included, the proportion with previous disease rose from 41% to 44%; this small change indicates that our 'definite' atherosclerotic disease definition had high sensitivity.

Weaknesses

Inclusion of only hospitalised cases from MINAP will have introduced a selection bias towards patients who survived for long enough to reach hospital. Therefore, our results cannot necessarily be generalised to patients who die outside hospital, and we cannot rule out that the prevalence of heralding factors may differ among those dying of AMI before hospital admission.

Because our analyses of heralding are based largely on general practice data, symptomatic atherosclerotic disease may be undiagnosed if patients do not consult their GP. We excluded only fourteen patients without any consultations as these patients never had an

opportunity for measurement of risk factors or morbidity. However, introducing a minimum consultation rate could introduce a bias towards sicker patients. The data available for this analysis did not allow us to differentiate between patients with a low consultation rate because of good health and those that did not consult despite symptomatic disease.

Implications for research

A small but important proportion of STEMI and NSTEMI do appear to occur with no recognised heralding signs and further research is warranted to better characterise these phenotypes, their causes and their prognosis. For patients with different forms of heralding the challenge remains to better characterise short term risk of coronary events in order to identify for which patients this represents a (potentially remediable) premonitory period.

Conclusion

The majority of STEMIs and NSTEMI were heralded by prior disease or at least one other risk factor, suggesting that opportunities for prevention may be being missed.

Acknowledgements

A Timmis acknowledges the support of Barts and the London Cardiovascular Biomedical Research Unit. which is funded by the National Institute for Health Research.

Sources of funding

This work is supported by grants from the UK National Institute for Health Research (grant number RP-PG-0407-10314), the Wellcome Trust (086091/Z/08/Z), and the Medical Research Council. LS is supported by a senior clinical fellowship from the Wellcome Trust. KB is supported by a post-doctoral fellowship from the National Institute for Health Research. JG is supported by a doctoral fellowship from the National Institute for Health Research.

Disclosures

None.

References

1. Yawn BP, Wollan PC, Jacobsen SJ, Fryer GE, Roger VL. Identification of women's coronary heart disease and risk factors prior to first myocardial infarction. Journal of Women's Health. 2004;13(10):1087-100.

2. Pierard LA, Dubois C, Smeets JP, Boland J, Carlier J, Kulbertus HE. Prognostic significance of angina pectoris before first acute myocardial infarction. Am J Cardiol. 1988;61(13):984-7.

3. Cupples LA, Gagnon DR, Wong ND, Ostfeld AM, Kannel WB. PREEXISTING CARDIOVASCULAR CONDITIONS AND LONG-TERM PROGNOSIS AFTER INITIAL MYOCARDIAL-INFARCTION - THE FRAMINGHAM-STUDY. American Heart Journal. 1993;125(3):863-72.

4. Kobayashi Y, Miyazaki S, Itoh A, Daikoku S, Morii I, Matsumoto T, et al. Previous angina reduces in-hospital death in patients with acute myocardial infarction. Am J Cardiol. 1998;81(2):117-22.

5. Bhatt DL, Peterson ED, Harrington RA, Ou FS, Cannon CP, Gibson CM, et al. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. Eur Heart J. 2009;30(10):1195-202. Epub 2009/04/03.

6. Terkelsen CJ, Lassen JF, Norgaard BL, Gerdes JC, Jensen T, Gotzsche LB, et al. Mortality rates in patients with ST-elevation vs. non ST-elevation acute myocardial infarction: observations from an unselected cohort. Eur Heart J. 2005;26(1):18-26. Epub 2004/12/24.

7. Abbott JD, Ahmed HN, Vlachos HA, Selzer F, Williams DO. Comparison of outcome in patients with ST-elevation versus non-ST-elevation acute myocardial infarction treated with percutaneous coronary intervention (from the National Heart, Lung, and Blood Institute Dynamic Registry). Am J Cardiol. 2007;100(2):190-5. Epub 2007/07/17.

8. Dziewierz A, Siudak Z, Dykla D, Rakowski T, Mielecki W, Dubiel JS, et al. Management and mortality in patients with non-ST-segment elevation vs. ST-segment elevation myocardial infarction. Data from the Malopolska Registry of Acute Coronary Syndromes. Kardiol Pol. 2009;67(2):115-20; discussion 21-2. Epub 2009/03/17.

9. Bin Song Y, Hahn JY, Kim JH, Lee SY, Choi SH, Choi JH, et al. Comparison of Angiographic and Other Findings and Mortality in Non ST-Segment Elevation versus ST-Segment Elevation Myocardial Infarction in Patients Undergoing Early Invasive Intervention. Am J Cardiol. 2010;106(10):1397-403.

10. Abbas AE, Boura JA, Brewington SD, Dixon SR, O'Neill WW, Grines CL. Acute angiographic analysis of non-ST-segment elevation acute myocardial infarction. Am J Cardiol. 2004;94(7):907-9. Epub 2004/10/07.

11. CALIBER Group. CArdiovascular disease research using Linked Bespoke studies and Electronic Records (CALIBER), http://www.caliberresearch.org (accessed 14th October 2010).

12. Herrett E, Smeeth L, Walker L, Weston C. The Myocardial Ischaemia National Audit Project (MINAP). Heart. 2010;96(16):1264-7. Epub 2010/07/28.

13. GPRD. General Practice Research Database (GPRD) http://www.gprd.com (accessed 21/10/2011). [cited 2009].

14. Gallagher AM, Puri S, Van Staa T. Linkage of the General Practice Research Database (GPRD) with other data sources. Pharmacoepidemiol Drug Saf. 2011;20:S1-S364.

15. Thygesen K, Alpert JS, White HD, Force EAAWT. Universal definition of myocardial infarction. Circulation. 2007;116(22):2634-53.

16. Simpson CR, Buckley BS, McLernon DJ, Sheikh A, Murphy A, Hannaford PC. Five-year prognosis in an incident cohort of people presenting with acute myocardial infarction. PLoS ONE. 2011;6(10):e26573. Epub 2011/10/27.

17. Steg PG, Goldberg RJ, Gore JM, Fox KA, Eagle KA, Flather MD, et al. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). Am J Cardiol. 2002;90(4):358-63. Epub 2002/08/06.

18. Rott D, Leibowitz D. STEMI and NSTEMI are two distinct pathophysiological entities. European Heart Journal. 2007;28(21):2685-.

19. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA. 2003;290(7):891-7. Epub 2003/08/21.

20. Mensah GA, Brown DW, Croft JB, Greenlund KJ. Major coronary risk factors and death from coronary heart disease - Baseline and follow-up mortality health and nutrition examination data from the second national survey (NHANES II). American Journal of Preventive Medicine. 2005;29(5):68-74.

21. Harper RW, Kennedy G, Desanctis RW, Hutter AM. INCIDENCE AND PATTERN OF ANGINA PRIOR TO ACUTE MYOCARDIAL-INFARCTION - STUDY OF 577 CASES. American Heart Journal. 1979;97(2):178-83.

22. Stowers M, Short D. WARNING SYMPTOMS BEFORE MAJOR MYOCARDIAL INFARCTION. British Heart Journal. 1970;32(6):833-&.

23. Primatesta P, Poulter NR. Lipid concentrations and the use of lipid lowering drugs: evidence from a national cross sectional survey. BMJ. 2000;321(7272):1322-5. Epub 2000/11/25.

24. Primatesta P, Poulter NR. Levels of dyslipidaemia and improvement in its management in England: results from the Health Survey for England 2003. Clin Endocrinol (Oxf). 2006;64(3):292-8. Epub 2006/02/21.

25. Foss FA, Dickinson E, Hills M, Thomson A, Wilson V, Ebrahim S. Missed opportunities for the prevention of cardiovascular disease among British hypertensives in primary care. British Journal of General Practice. 1996;46(411):571-5.

26. Teeling M, Bennett K, Feely J. The influence of guidelines on the use of statins: analysis of prescribing trends 1998-2002. Br J Clin Pharmacol. 2005;59(2):227-32. Epub 2005/01/29.

27. Royal College of Physicians. MINAP Data Quality. http://www.ucl.ac.uk/nicor/audits/minap/datacollection (accessed 7th February 2012).

28. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010;69(1):4-14. Epub 2010/01/19.

29. Maru S, Koch GG, Stender M, Clark D, Gibowski L, Petri H, et al. Antidiabetic drugs and heart failure risk in patients with type 2 diabetes in the U.K. primary care setting. Diabetes Care. 2005;28(1):20-6.

30. Hammad TA, McAdams MA, Feight A, Iyasu S, Dal Pan GJ. Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database. Pharmacoepidemiol Drug Saf. 2008;17(12):1197-201. Epub 2008/11/06.

31. Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA, et al. Risk of stroke in people with type 2 diabetes in the UK: a study using the General Practice Research Database. Diabetologia. 2006;49(12):2859-65. Epub 2006/10/31.

Figure legends

Figure 1. Previous atherosclerotic disease and risk factors in patients with first ST-elevation myocardial infarction (STEMI, N=3780) and non ST-elevation myocardial infarction (NSTEMI, N=4394).

Figure 2. Proportion of patients with ST-elevation myocardial infarction (STEMI, N=3780), (above) and non ST-elevation myocardial infarction (NSTEMI, N=4394) (below), with different combinations of disease in one, two or three arterial beds (CHD: coronary heart disease; PAD: peripheral arterial disease; CVD: cerebrovascular disease). 71% of STEMI patients and 50% of NSTEMI patients were unheralded by atherosclerotic disease at any site.

Figure 3. Rate of coronary heart disease (CHD), peripheral arterial disease (PAD) and cerebrovascular disease (CVD) in the ten years before diagnosis of ST-elevation myocardial infarction (STEMI) and non ST-elevation myocardial infarction (NSTEMI) (with 95% confidence intervals). Note: each time point covers a one year timeband (1=0-1 years before AMI, 2=1-2 years before AMI, etc).

Figure 4. Rate of coronary diagnosis (A) and chest pain consultations (B) in the months leading to ST-elevation myocardial infarction (STEMI) and non ST-elevation myocardial infarction (NSTEMI), with 95% confidence intervals. Consultations for chest pain are only in those without diagnosed atherosclerotic disease. Note: each time point covers a one month timeband (0-1 months, 1-2 months, etc).

Table 1. Demographics and hospital admission characteristics of STEMI and NSTEMI patients.

	STEMI (N=3780)		NSTEMI (N=4394)	
Age, y*	67.0	(57.0-77.0)	74.0	(63.0-82.0)
Female, n (%)	1172	(31.0)	1774	(40.4)
Ethnicity, n (%)				
White	3146	(83.2)	3739	(85.1)
South Asian	13	(0.3)	18	(0.4)
Other	59	(1.6)	63	(1.4)
Unknown	562	(14.9)	574	(13.1)
ECG at admission, n (%)				
ST segment elevation	3552	(94.0)	0	(0)
Left bundle branch block	87	(2.3)	246	(5.6)
ST segment depression	0	(0.0)	1144	(26.0)
T wave changes only	0	(0.0)	1024	(23.3)
other abnormality	0	(0.0)	836	(19.0)
Normal ECG	0	(0.0)	473	(10.8)
Unknown	141	(3.7)	671	(15.3)
Peak troponin at admission, μg/L*†	5.2	(1.2-25.0)	1.0	(0.3-3.9)
Heart rate at admission, bpm*†	76.0	(63.0-90.0)	80.0	(68.0-98.0)
Systolic BP at admission, mmHg*†	138.0	(120.0-157.0)	140.0	(121.0-160.0)

STEMI indicates ST-elevation MI; NSTEMI, non ST-elevation MI; BP, blood pressure.

*Continuous variables are expressed as medians, with 25th and 75th percentiles.

†Completeness in peak troponin, heart rate and systolic BP 85, 77 and 77%, respectively.

Table 2. Prevalence (unstandardized and age- and sex- standardized) and duration of diagnosed atherosclerotic disease in patients with first STEMI and NSTEMI, recorded over a median 8.7 years follow up before MI. This includes patients with atherosclerotic disease at more than one site.

	STEMI (N=3780)						NSTEMI (N=4394)						P*
	n	(%)	Standardized prevalence	(95% CI)	Median disease duration	(IQR)	n	(%)	Standardized prevalence	(95% CI)	Median disease duration	(IQR)	
Any atherosclerotic disease	1112	(29.4)	32.0	(30.5-33.5)	6.2	(2.2-11.7)	2214	(50.4)	47.2	(45.8-48.5)	7.6	(3.2-13.4)	<0.001
Coronary disease	788	(20.8)	22.7	(21.3-24)	4.5	(1-8.9)	1795	(40.9)	38.2	(36.8-39.5)	4.2	(1.1-9.3)	<0.001
Stable angina	587	(15.5)	16.9	(15.7-18.2)	6.3	(1.4-11.4)	1442	(32.8)	30.8	(29.5-32.1)	7.2	(2.5-13.2)	<0.001
Unstable angina	46	(1.2)	1.4	(1.0-1.9)	4.6	(1.8-7.9)	172	(3.9)	3.8	(3.2-4.3)	2.7	(0.3-6.9)	<0.001
PCI or CABG	99	(2.6)	2.6	(2.1-3.1)	6.5	(1.5-10.7)	281	(6.4)	6.4	(5.7-7.2)	7.4	(2.0-13.1)	<0.001
CHD not otherwise specified	404	(10.7)	11.7	(10.6-12.7)	7.3	(2.8-12.2)	969	(22.1)	20.5	(19.4-21.7)	8.1	(3.5-13.7)	<0.001
Heart failure	142	(3.8)	4.6	(3.9-5.4)	4.5	(1.5-9.5)	498	(11.3)	9.9	(9.1-10.7)	4.1	(1.2-7.9)	<0.001
Cardiac arrest	3	(0.1)	0.1	(0-0.1)	0.1	(0-8.3)	7	(0.2)	0.2	(0-0.3)	2.3	(0.4-18.8)	0.277
Other atherosclerotic disease	537	(13.9)	15.6	(14.4-16.8)	4.8	(1.8-9.3)	1036	(23.6)	21.7	(20.5-22.8)	5.6	(2.6-9.7)	<0.001
Cerebrovascular disease	276	(7.3)	9.5	(8.5-10.5)	5.3	(2.2-11.3)	554	(12.6)	12.6	(11.7-13.5)	6.1	(2.8-10.9)	<0.001
Peripheral arterial disease	261	(6.9)	7.7	(6.8-8.6)	4.4	(1.7-8.4)	565	(12.9)	12.0	(11.1-13.0)	6.1	(2.9-10.5)	<0.001
Unknown initial presentation†	6	(0.2)	0.2	(0-0.3)	15.8	(12.7-17.6)	23	(0.5)	0.5	(0.3-0.8)	4.4	(2.1-8.1)	0.009

STEMI: ST-elevation MI; NSTEMI, non ST-elevation MI; CHD: coronary heart disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft.

*Age and sex adjusted P value for the association between MI subtype and each presentation.

†Where the only code indicating atherosclerotic disease was unspecific.

Table 3. Prospectively collected evaluation of the prevalence (unstandardized and standardized) of cardiovascular risk factors and cardiovascular medications in STEMI (N=2268) and NSTEMI (N=2180) patients without previous atherosclerotic disease.

	STEMI (N=2668)		NSTEMI (N=2180)		
	n (%)	Age and sex standardized prevalence (95% CI)	n (%)	Age and sex standardized prevalence (95% CI)	P*
Smoking, %					
Non	339 (12.7)	13.4 (12.1-14.6)	338 (15.5)	15.0 (13.5-16.5)	
Former	1261 (47.3)	48.8 (47-50.5)	1219 (55.9)	54.0 (52-56)	<0.001
Current	1063 (39.8)	37.4 (35.7-39)	616 (28.3)	30.5 (28.6-32.3)	
Unknown	5 (0.2)	0.2 (0-0.4)	7 (0.3)	0.3 (0.1-0.5)	
Hypertension, %	1083 (40.6)	41.9 (40.1-43.7)	1082 (49.6)	47.7 (45.7-49.7)	<0.001
Dyslipidaemia, %	569 (21.3)	21.4 (19.9-22.9)	459 (21.1)	21.4 (19.7-23.1)	0.913
Diabetes, %	276 (10.3)	10.6 (9.4-11.7)	302 (13.9)	13.4 (12-14.7)	0.002
Blood pressure lowering†, %	806 (30.2)	31.8 (30.1-33.5)	880 (40.4)	38.3 (36.4-40.2)	<0.001
Statins†, %	430 (16.1)	16.3 (14.9-17.6)	404 (18.5)	18.4 (16.8-20)	0.043
Antiplatelets†, %	420 (15.7)	16.3 (14.9-17.7)	509 (23.3)	22.9 (21.1-24.6)	<0.001
Chest pain consultation in 90 days before MI, %	122 (4.6)	4.7 (3.9-5.4)	158 (7.2)	7.4 (6.3-8.5)	<0.001
Without any of these risk factors or cardiovascular medications†, % of unheralded MI	567 (21.3)	21.4 (19.8-22.9)	443 (20.3)	20.3 (18.6-22)	0.318
Without any of these risk factors or cardiovascular medications†, % of all MI	567 (15)	14.7 (13.6-15.8)	443 (10.1)	10.8 (9.8-11.7)	<0.001

STEMI indicates ST-elevation myocardial infarction; NSTEMI indicates non ST-elevation myocardial infarction

* Age and sex adjusted P value for the association of risk factor with MI subtype

† Prescribed in the 6 months before MI

Figure 1

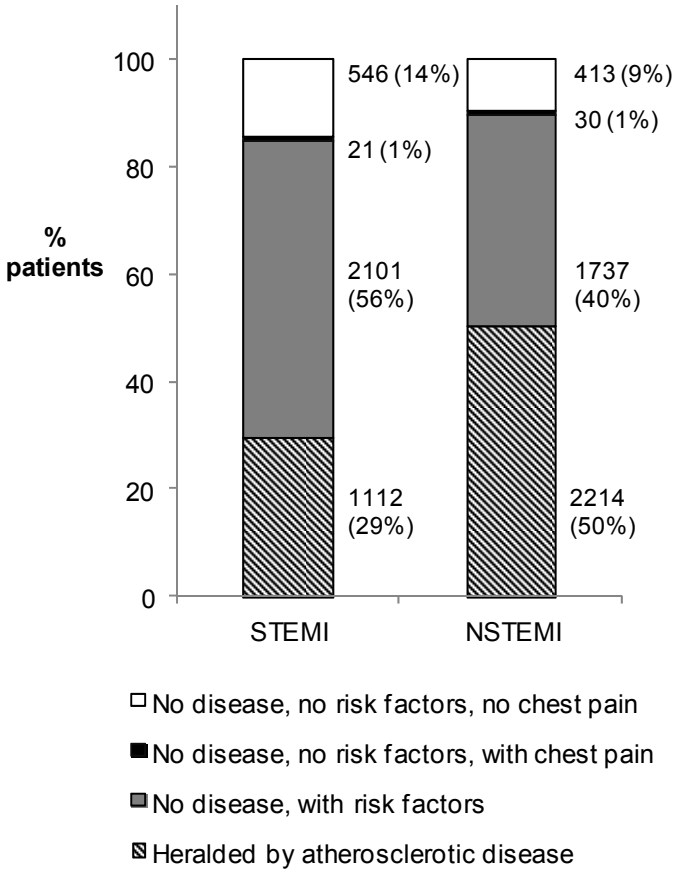

100
80
60
40
20
0
% patients
546 (14%)
21 (1%)
2101 (56%)
1112 (29%)
413 (9%)
30 (1%)
1737 (40%)
2214 (50%)
STEMI
NSTEMI
No disease, no risk factors, no chest pain
No disease, no risk factors, with chest pain
No disease, with risk factors
Heralded by atherosclerotic disease

Figure 2

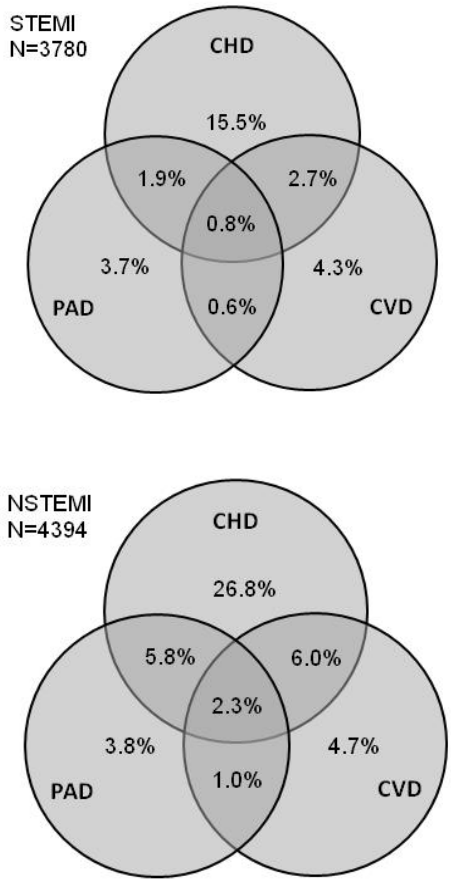

STEMI
N=3780
CHD
15.5%
1.9%
2.7%
0.8%
3.7%
4.3%
PAD
0.6%
CVD
NSTEMI
N=4394
CHD
26.8%
5.8%
6.0%
2.3%
3.8%
4.7%
PAD
1.0%
CVD

Figure 3

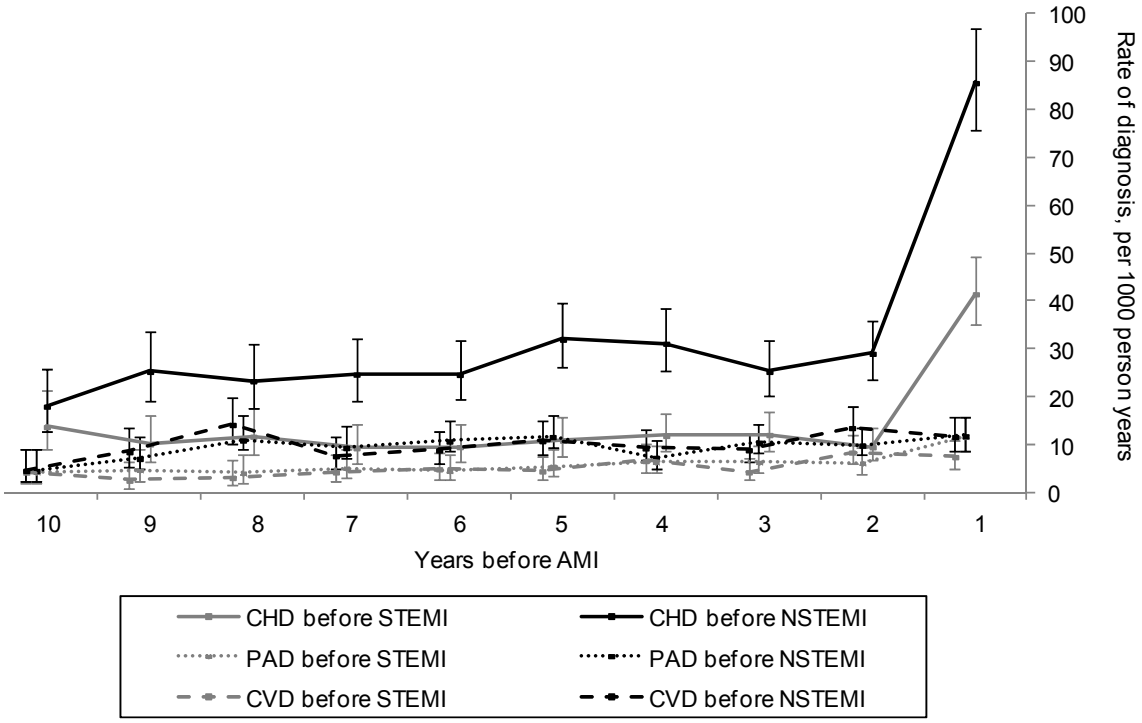
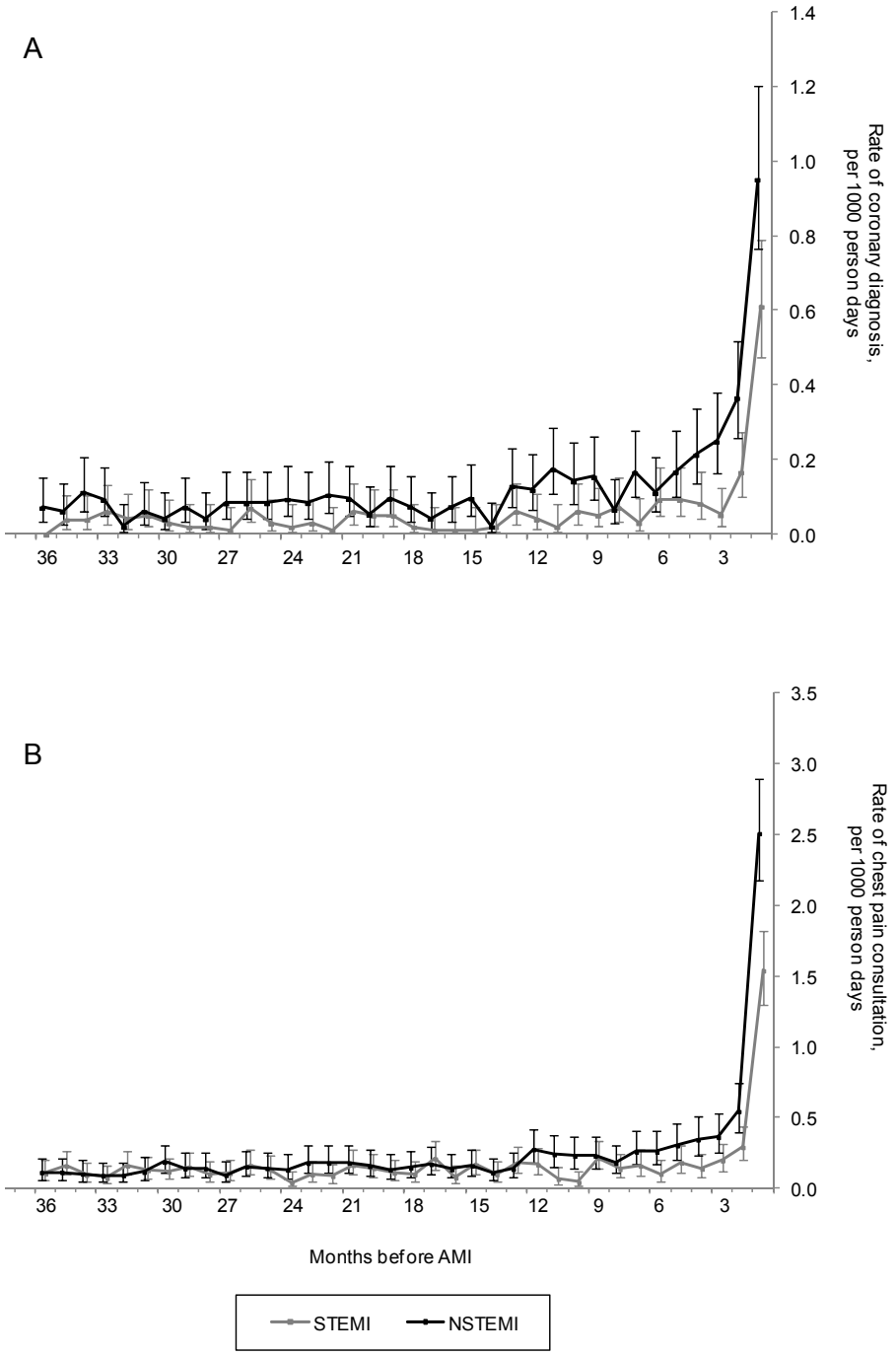

100
90
80
70
60
50
40
30
20
10
0
Rate of diagnosis, per 1000 person years
10
9
8
7
6
5
4
3
2
1
Years before AMI
CHD before STEMI
CHD before NSTEMI
PAD before STEMI
PAD before NSTEMI
CVD before STEMI
CVD before NSTEMI

Figure 4


A
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Rate of coronary diagnosis, per 1000 person days
36 33 30 27 24 21 18 15 12 9 6 3
B
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Rate of chest pain consultation, per 1000 person days
36 33 30 27 24 21 18 15 12 9 6 3
Months before AMI
STEMI
NSTEMI

10.5 Appendices for Chapter 6

10.5.1 Literature review search strategy

Table 10.20 Search terms and search strategy used in identifying studies

Search number	Terms included
1. Myocardial infarction	MYOCARDIAL INFARCTION (as a Medical Subject Heading, with all subheadings included and all sub-terms in the MeSH tree) in the keywords. OR The following MI synonyms in the keywords, title or abstract: myocardial infarct* OR stemi OR heart attack OR cardiac infarct* OR acute infarct* OR coronary attack OR myocardial thrombosis OR coronary thrombosis OR coronary infarct* OR heart infarct* OR Q wave infarct* OR acute coronary
2. Preinfarction angina or ischaemic preconditioning	The following terms in the keywords, title or abstract: ischaemic precond* OR ischemic precond* OR preinfarct* OR pre-infarct* OR ISCHEMIC PRECONDITONING (as a Medical Subject Heading)
3.	1 & 2, restricted to studies in humans and in the English language

10.5.2 Directed acyclic graph for Chapter 6

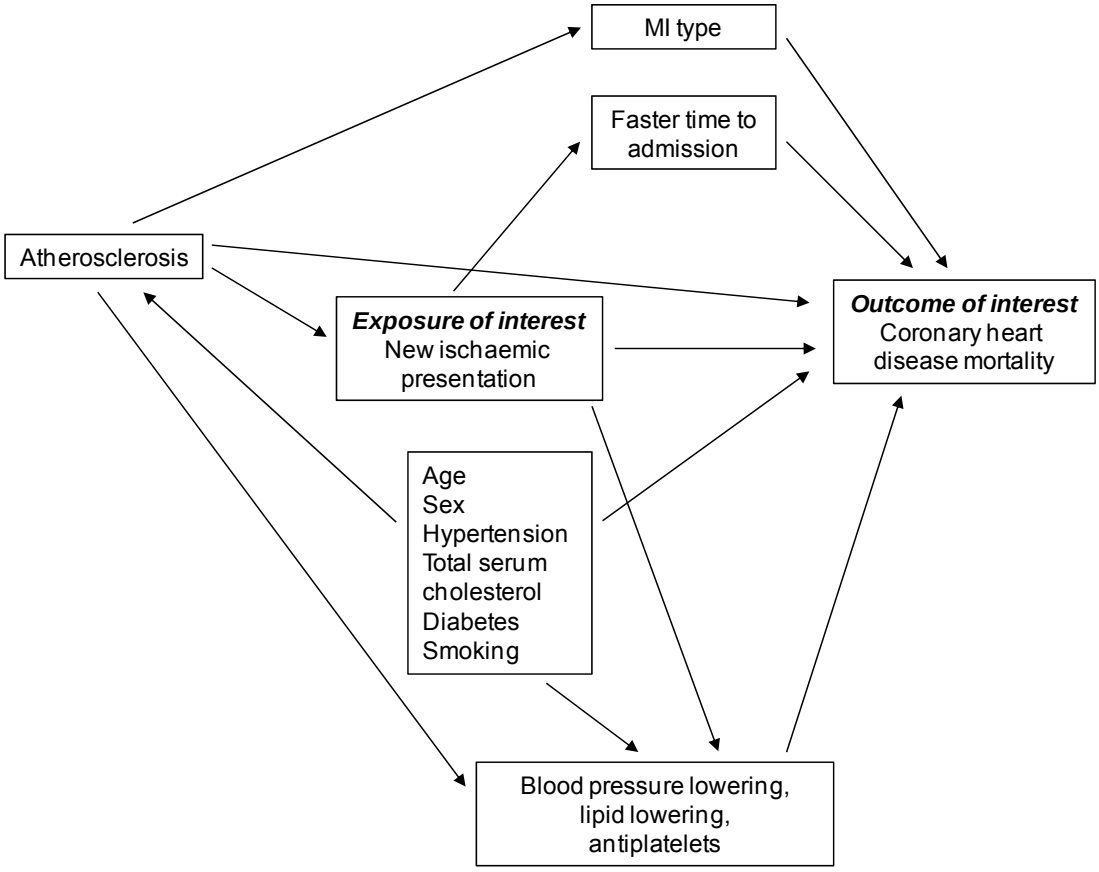


Figure 10.6 Directed acyclic graph to describe the analysis in Chapter 6

In this analysis, the exposure of interest was a new ischaemic presentation in the 90 days prior to MI. The outcome of interest was coronary heart disease mortality. The cardiovascular disease risk factors were included in the analysis to account for the underlying level of atherosclerotic disease (unmeasured), which was associated with experiencing a new ischaemic presentation and with subsequent post-MI mortality. Analyses were also undertaken to account for the possibility of faster time to admission in patients with new ischaemic presentations, the prescription of cardiovascular drugs, and for the potential association with MI type,

10.5.3 Cox regression model diagnostics

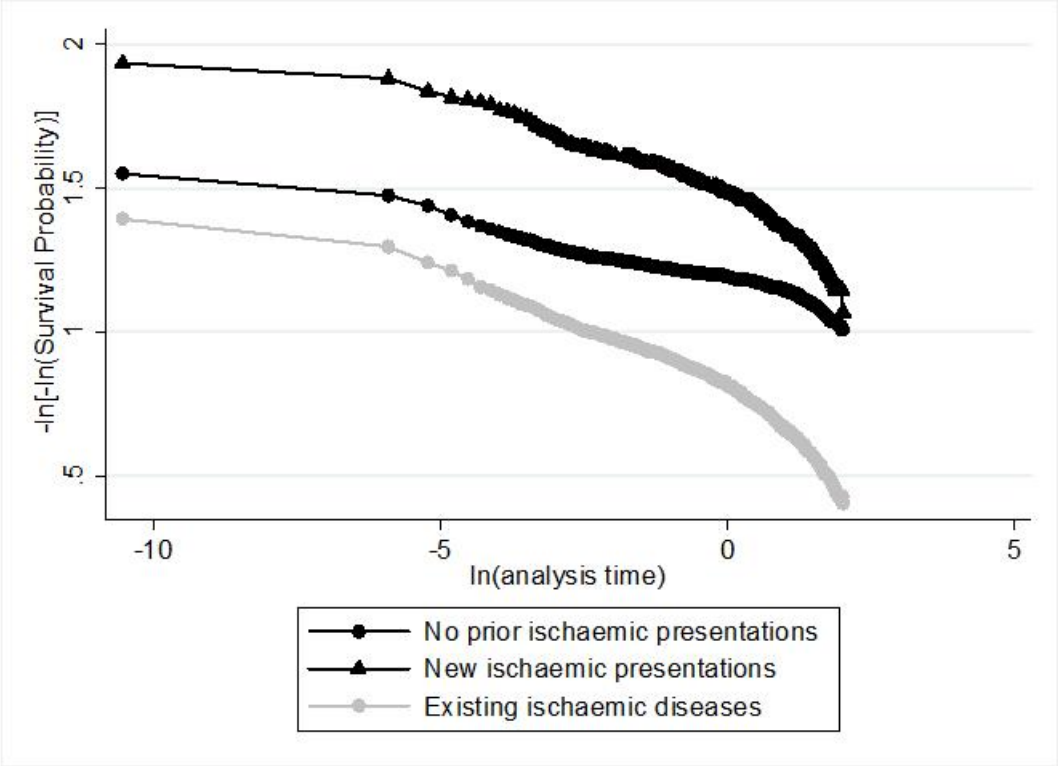


Figure 10.7 Log log plot of the hazards, in patients with no prior ischaemic presentations, new ischaemic presentations in the 90 days before myocardial infarction (MI), and existing ischaemic diseases with no new presentations in the 90 days before MI (N=16,439)

10.6 Appendices for Chapter 7

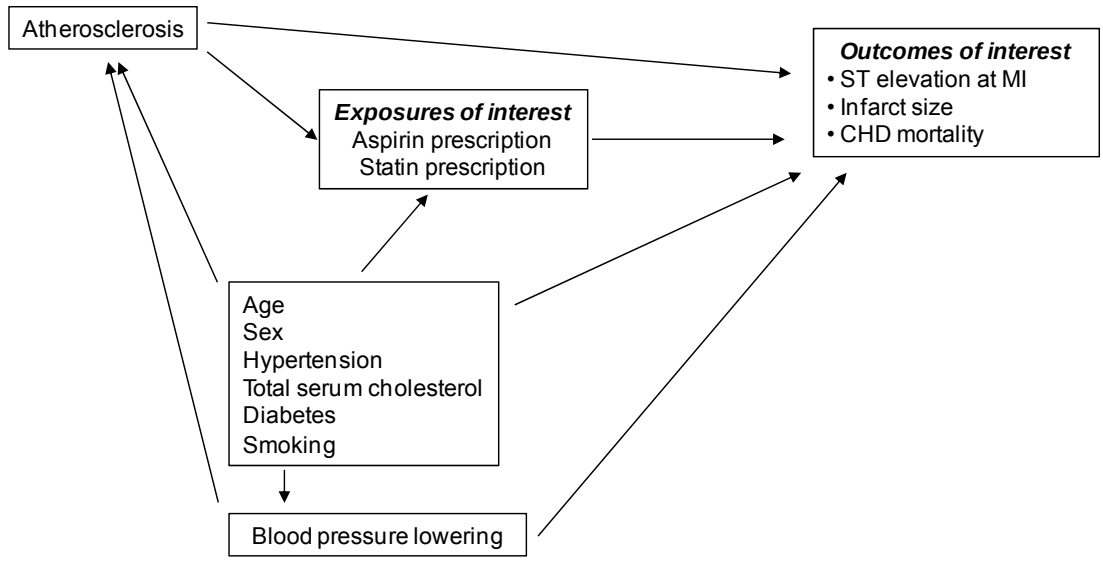
10.6.1 Literature review search strategy

Table 10.21 Search terms for literature review

Search number	Terms included
1. Myocardial infarction	MYOCARDIAL INFARCTION (as a Medical Subject Heading, with all subheadings included and all sub-terms in the MeSH tree) in the keywords. OR The following MI synonyms in the title or keywords: myocardial infarct* OR stemi OR heart attack OR cardiac infarct* OR acute infarct* OR STEAMI OR coronary attack OR myocardial thrombosis OR coronary thrombosis OR coronary infarct* OR heart infarct* OR Q wave infarct* OR acute coronary
2. Therapies	The following terms as Medical Subject headings, where possible, in the keywords: Therapeutics (MeSH) Hydroxymethylglutaryl-CoA Reductase Inhibitors Pravastatin (MeSH) Lovastatin (MeSH) Aspirin (MeSH) Ticlopidine (MeSH) statin (keyword) antiplatelet (keyword) lipid-lowering (keyword)
3. Synonyms to indicate use before infarction	The following in the title: [before OR preced* OR herald* OR previous* OR prior OR earlier OR advance former OR ahead OR sooner OR pre-exist* OR exist* OR precurs* OR prodrom* OR anteced* OR presence OR history OR prevalen* OR recogni* OR document* OR record*]

* Indicates any ending to the term is searched for.

10.6.2 Directed acyclic graph for Chapter 7



MI: myocardial infarction; CHD: coronary heart disease

Figure 10.8 Directed acyclic graph for the analysis in Chapter 7

In this analysis, the exposure of interest was prescription of aspirin or statins prior to MI. The outcomes of interest were ST-elevation at MI, infarct size and coronary heart disease mortality. The cardiovascular disease risk factors were included in the analysis to account for the underlying level of atherosclerotic disease (unmeasured), which was associated with receipt of aspirin or statins and with the outcome. Therefore blood pressure lowering medication, age, sex, hypertension, total serum cholesterol, diabetes and smoking (as the most important cardiovascular disease risk factors) were included in the analysis as confounders.

10.6.3 Raw peak troponin and log-transformed peak troponin

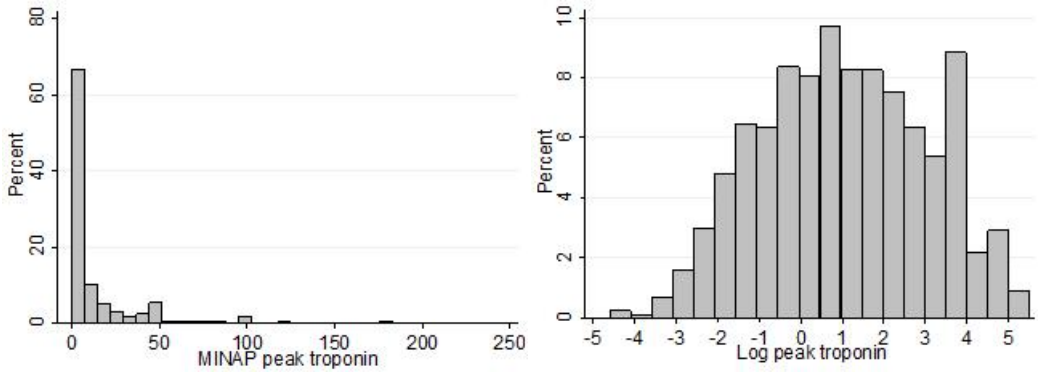


Figure 10.9 Peak troponin values in µg/L(left) and log-transformed peak troponin values (right) for all patients without previously diagnosed atherosclerotic disease (N=2,964)

10.6.4 Additional aspirin results

Duration of aspirin use

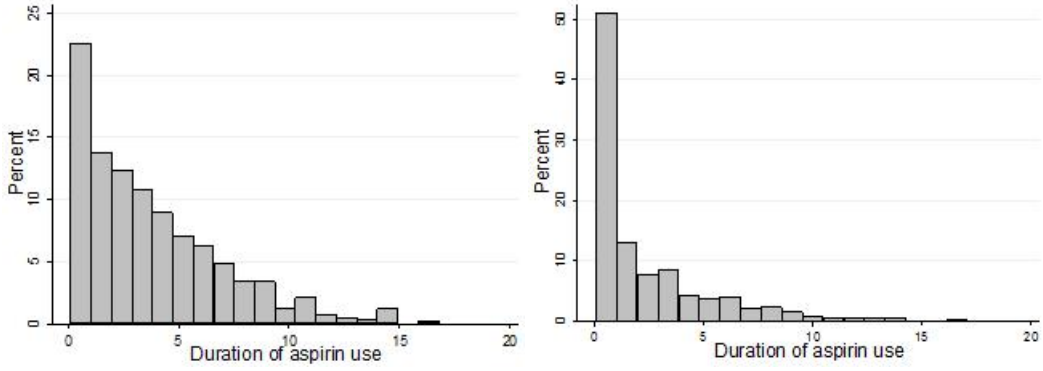


Figure 10.10 Histograms describing the duration of aspirin use prior to MI in patients who were current users (left, N=761) and previous users (right, N=563)

Frequency of aspirin prescription

Histograms describing the number of prescriptions issued per user per year are shown in Figure 10.11 for current users and Figure 10.12 for previous users. Most patients defined as current users received prescriptions between 3 and 14 times per year, reflecting the most common aspirin pack sizes of 100, 56 and 28. Previous users most commonly had less than one prescription per year, indicating one off prescribing which is unlikely to reflect aspirin use for primary prevention.

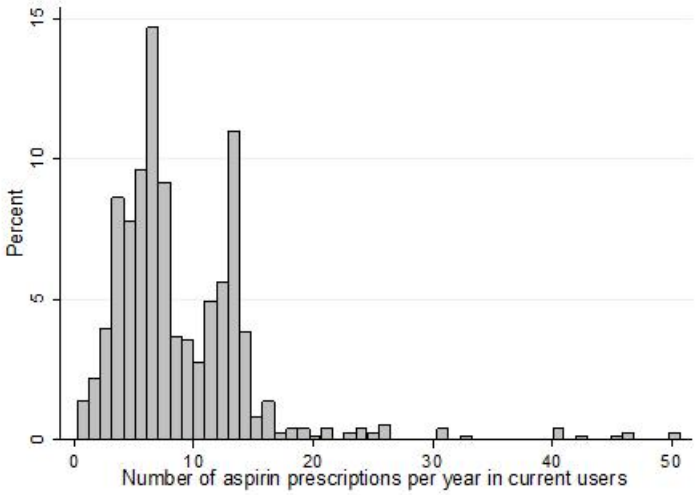


Figure 10.11 Histogram describing the number of aspirin prescriptions per year in patients defined as current aspirin users (N=761)

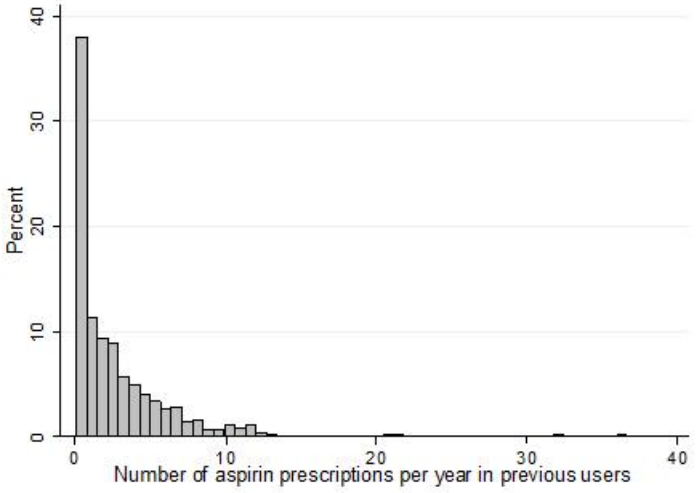


Figure 10.12 Histogram describing the number of aspirin prescriptions per year in patients defined as previous aspirin users (N=563)

Stratification of MI presentation by aspirin use and Framingham risk

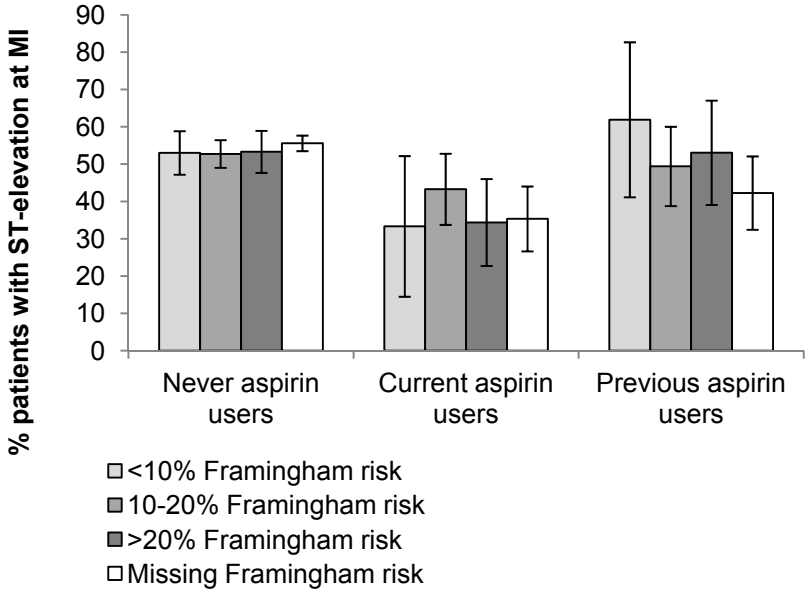


Figure 10.13 Proportion of patients with ST-elevation at myocardial infarction in never, current and previous aspirin users at different levels of Framingham risk, with 95% confidence intervals (N=4,010)

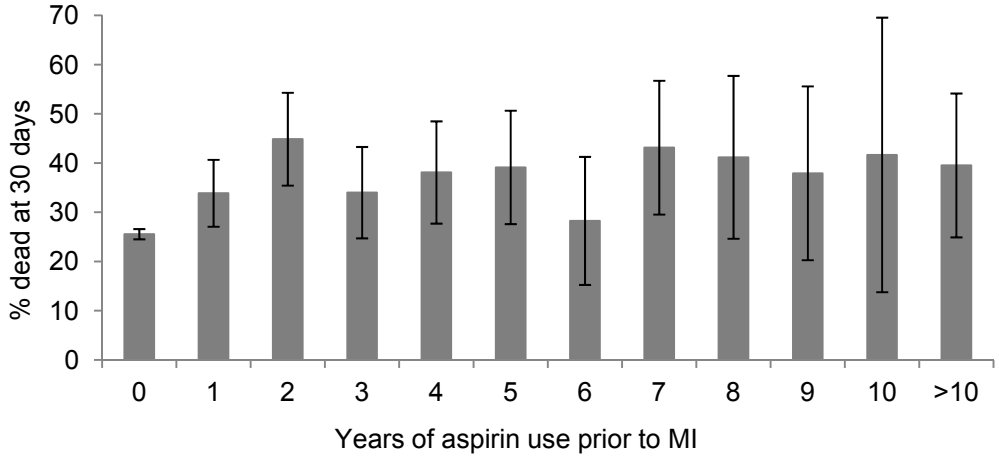


Figure 10.14 Thirty day all-cause mortality in patients, stratified by duration of aspirin use (none versus years of current use (with 95% confidence intervals) (N=7,451)

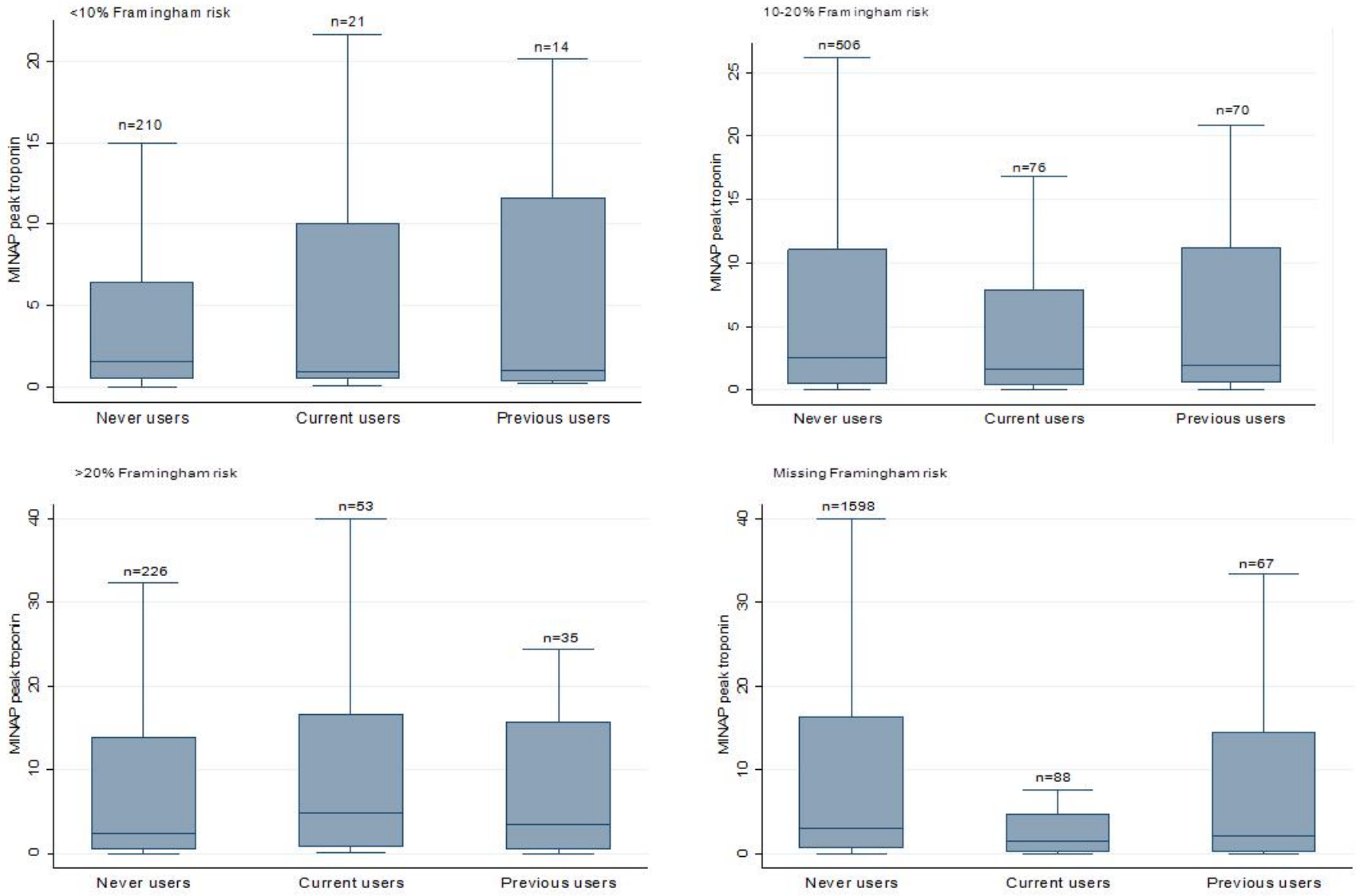


Figure 10.15 Box plots to describe the median and inter-quartile range of peak troponin values at each level of Framingham risk, by aspirin use (N=2,964)

10.6.5 Additional statin results

Duration of statin use

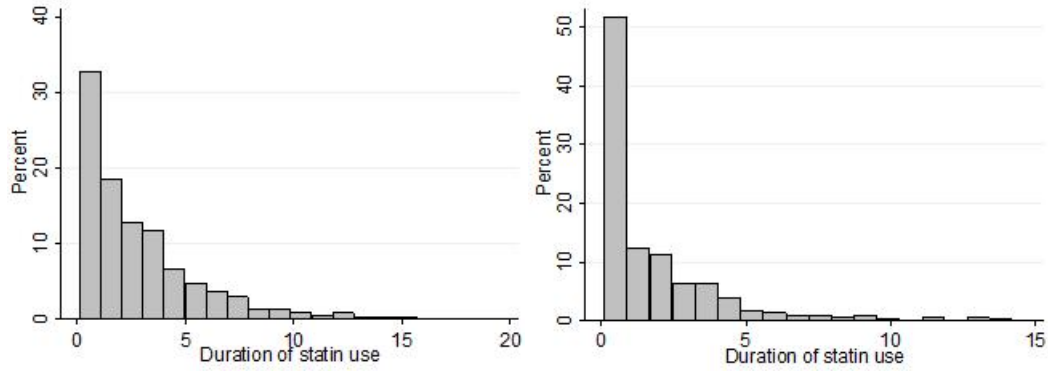


Figure 10.16 Histograms describing the duration (in years) of statin use prior to MI in patients who were current users (left, N=804) and previous users (right, N=356)

Frequency of statin prescription

Histograms describing the number of statin prescriptions per patient year in current and previous statin users are shown in Figure 10.17 and Figure 10.18. For current users there are two large peaks in the number of prescriptions issued per year. One of these is at 13, corresponding to patients receiving a prescription every 28 days. The other peak is at 7, corresponding to patients receiving prescriptions every 56 days. Pack quantities of 28 and 56 were the most frequently prescribed in this population. The frequency in previous users indicates that many patients had frequently received statin prescriptions prior to MI.

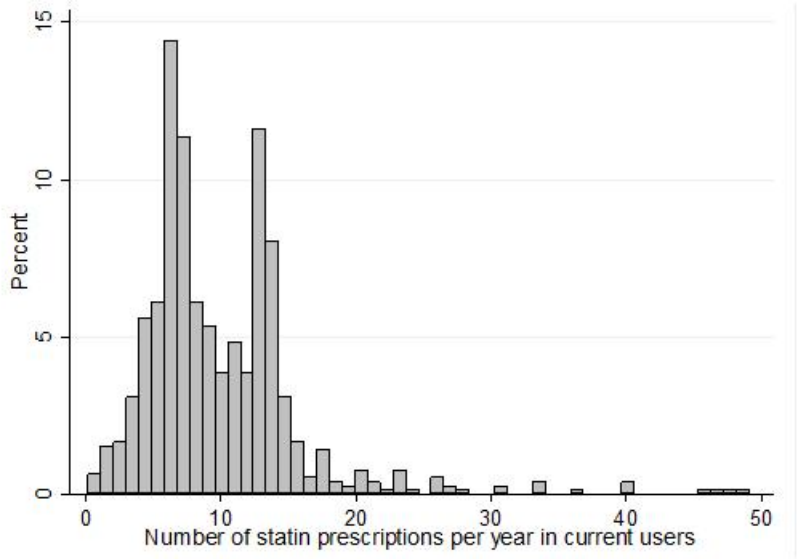


Figure 10.17 Histogram describing the number of statin prescriptions per patient year in current statin users (N=804)

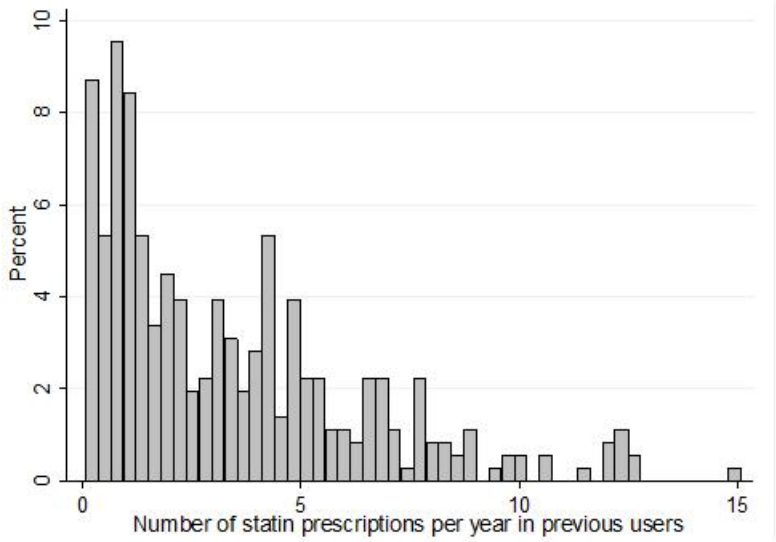


Figure 10.18 Histogram describing the number of statin prescriptions per patient year in previous statin users (N=356)

ST-elevation at MI by statin use, at different levels of vascular disease risk

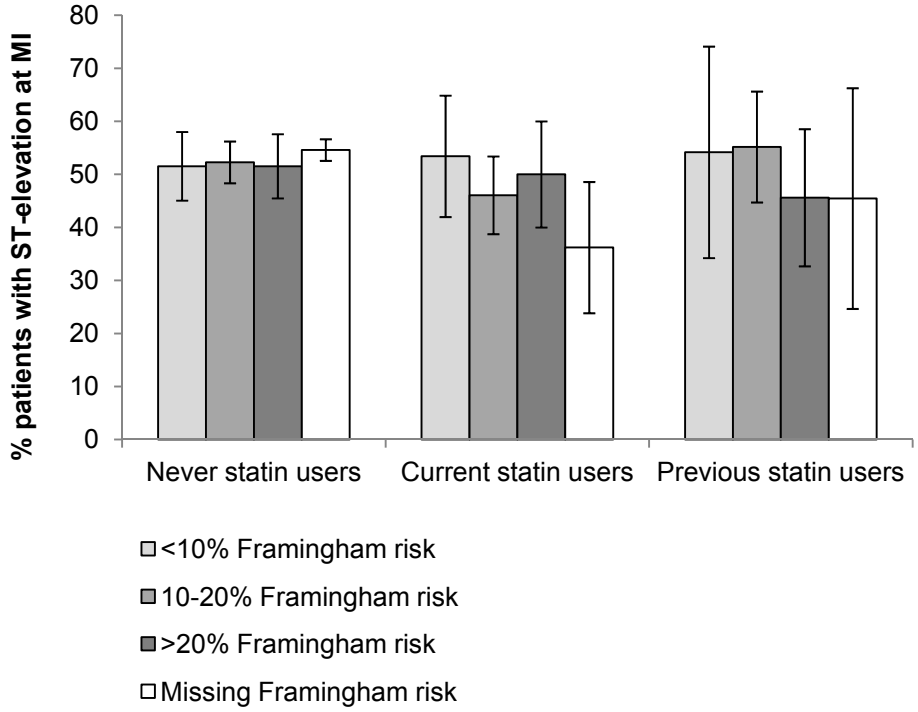


Figure 10.19 Proportion of patients with ST-elevation at myocardial infarction, in never, current and previous users of statins, at each level of Framingham risk (with 95% confidence intervals) (N=4,010)

Infarct size by statin use, at different levels of vascular disease risk

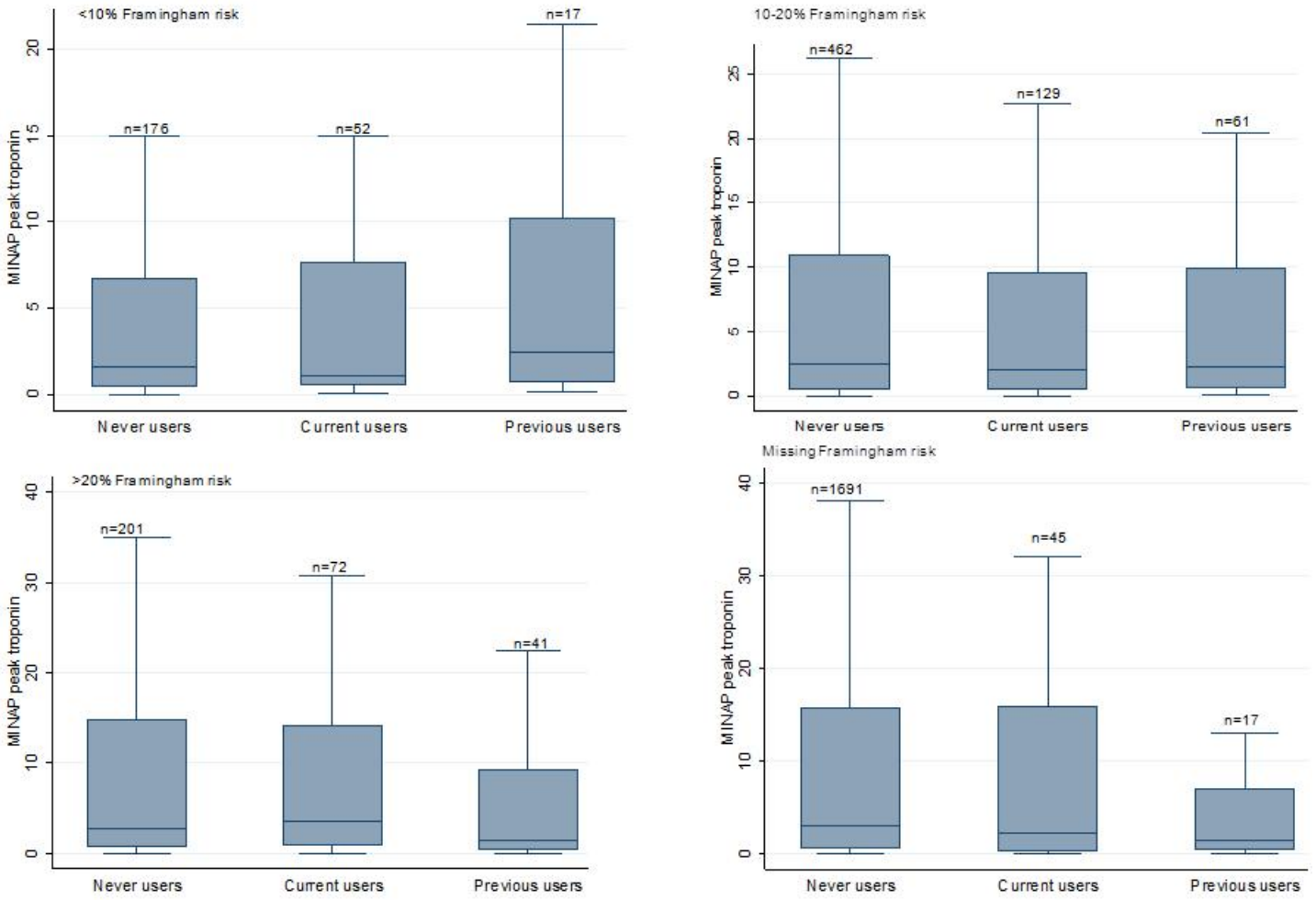


Figure 10.20 Box plots of peak troponin (in µg/L) for never, current and previous statin users, by Framingham risk category (N=2,964)

Demographic distribution by statin dosage

Table 10.22 Demographic and risk factor characteristics in patients with first MI and no previous atherosclerotic disease, stratified by dose of statins prior to MI (N=804)

	≤10mg		20mg		40mg		80mg	
N patients	96	(11.9)	353	(43.9)	293	(36.4)	62	(7.7)
Duration of use, median years (IQR)	1.5	(0.5-3.8)	1.7	(0.7-3.8)	1.8	(0.6-3.6)	4.1	(2.3-6.1)
Age, median (IQR)	69	(58-76)	69	(60-75)	66	(59-74)	66	(57-74)
Sex, n female (%)	35	(36.5)	145	(41.1)	112	(38.2)	26	(41.9)
Smoking, n (%)								
Non-smoker	12	(12.5)	54	(15.3)	43	(14.7)	8	(12.9)
Ex-smoker	57	(59.4)	209	(59.2)	166	(56.7)	39	(62.9)
Current smoker	26	(27.1)	89	(25.2)	84	(28.7)	15	(24.2)
Unknown	1	(1)	1	(0.3)	0	(0)	0	(0)
Hypertension, n (%)	73.0	(76)	268.0	(75.9)	221.0	(75.4)	50.0	(80.6)
Blood pressure lowering	71	(74)	272	(77.1)	234	(79.9)	50	(80.6)
Total serum cholesterol in mmol/L, mean (SD)	5.6	(1)	5.6	(1)	5.8	(1)	6.0	(1.4)
Diabetes, n (%)	43	(44.8)	154	(43.6)	128	(43.7)	39	(62.9)
Framingham risk, n (%)								
<10%	17	(17.7)	69	(19.5)	51	(17.4)	14	(22.6)
10-20%	44	(45.8)	178	(50.4)	156	(53.2)	36	(58.1)
>20%	35	(36.5)	106	(30)	86	(29.4)	12	(19.4)
Consultation rate per year, median (IQR)	6.7	(4.5-10.4)	7.2	(4.2-11.3)	7.3	(4.7-10.7)	9.5	(5.5-13.4)
Years of pre-MI GPRD registration, median (IQR)	6.5	(4-10.1)	8.5	(5.7-12)	9.3	(6.3-14)	8.3	(5-13.3)

10.6.6 Chapter 7 regression model diagnostics

Age and cholesterol were initially fitted in all regression models as linear variables. The assumption of linearity in the effects of these variables was checked by adding them as quadratic and cubic terms, and comparing models with likelihood ratio tests. If the models with quadratic or cubic terms indicated a better fit, then these were retained in the model.

Multiple linear regression model diagnostics

Residuals from each multiple linear regression model were plotted on a histogram to check for normality.

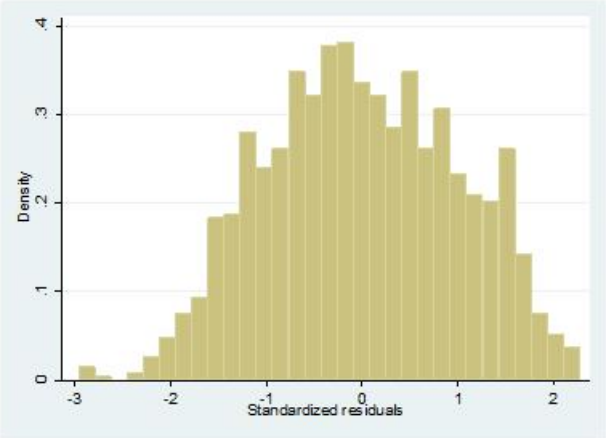


Figure 10.21 Multivariable adjusted model examining effects of aspirin and statin on infarct size

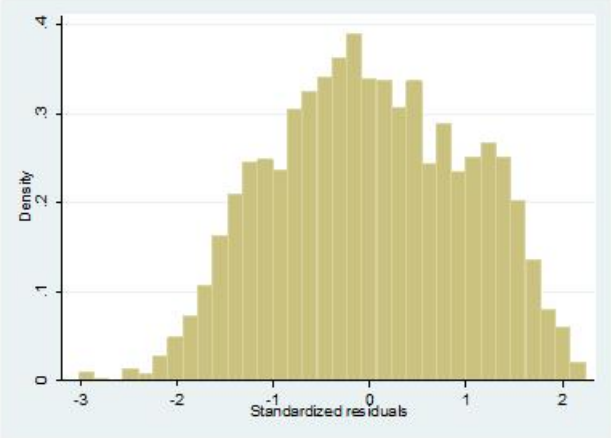


Figure 10.22 Multivariable adjusted model examining effects of statin dose on infarct size

Cox regression model diagnostics

Crude log-log plots of survival by aspirin use and by statin use were produced to check the proportional hazards assumption of the Cox model. For aspirin (below), the survival curves were roughly parallel in each stratum of aspirin use. Additionally, the proportional hazards assumption was checked in the multivariable-adjusted model using Schoenfeld residuals. If there was evidence against the assumption of proportional hazards, an interaction with time was fitted. After fitting an interaction with time at 7 days where required, there was no evidence against the assumption of proportional hazards in any model (P>0.1).

The crude log-log survival plot by statin use showed some potential for non-proportionality. However, there was no evidence of non-proportionality in the final model (global test of proportional hazards, P=0.8010). Test of proportional hazards for the statin duration Cox model also showed no evidence against the assumption of proportional hazards (P=0.7381).

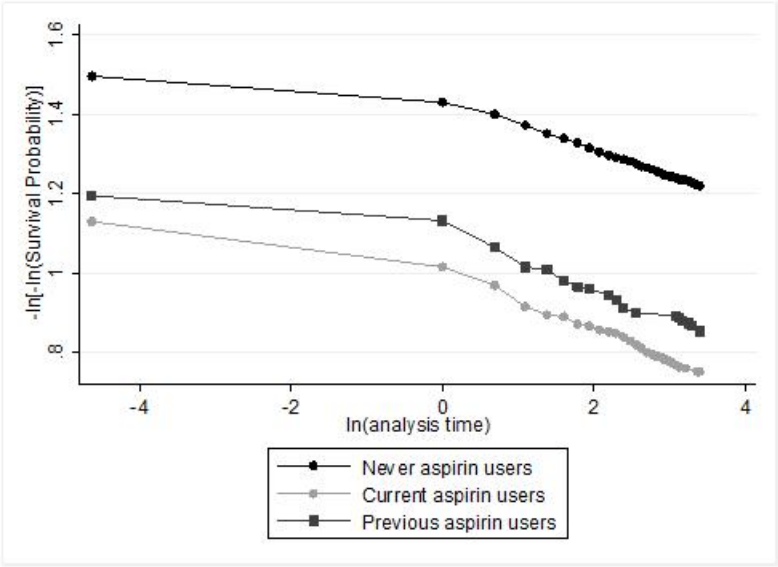


Figure 10.23 Log-log survival plot for aspirin use on 30 day all-cause mortality (N=8,104)

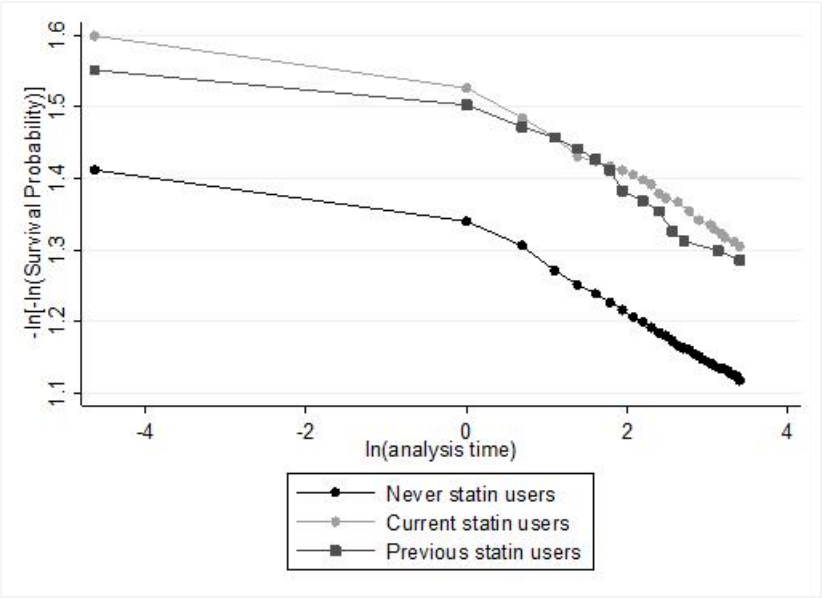


Figure 10.24 Log-log plot for statin use on 30 day all-cause mortality (N=8,104)

10.6.7 Sensitivity analysis

Adjusting for further risk factors

Table 10.23 OR for ST-elevation in patients with MI, from the main analysis, and further adjusted for BMI, family history and socioeconomic status

		Main analysis multivariable adjusted OR (95% CI)± (N=4,001)	Further adjusted OR (95% CI)† (N=2,144)
Aspirin	Never	1 -	1 -
	Current	0.66 (0.49-0.89) **	0.65 (0.48-0.88)
	Previous	1.02 (0.74-1.42)	1.03 (0.74-1.42)
Statins	Never	1 -	1 -
	Current	0.95 (0.75-1.21)	0.94 (0.74-1.20)
	Previous	0.96 (0.70-1.33)	0.93 (0.68-1.29)

± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol

† Additionally adjusted for BMI, family history and socioeconomic status

*** P<0.001, ** P<0.01, * P<0.05

Table 10.24 Estimated relative infarct size in the main analysis, and further adjusted for BMI, family history and socioeconomic status

		Main analysis multivariable adjusted estimated relative infarct size (95% CI)± (N=2,912)	Further adjusted estimated relative infarct size (95% CI)† (N=1,575)
Aspirin	Never	1 -	1 -
	Current	0.99 (0.72-1.38)	1.01 (0.72-1.40)
	Previous	1.01 (0.69-1.46)	1.04 (0.72-1.51)
Statins	Never	1 -	1 -
	Current	0.98 (0.74-1.30)	0.96 (0.73-1.27)
	Previous	0.82 (0.56-1.19)	0.80 (0.55-1.17)

Note: estimated relative infarct size was calculated by exponentiating the coefficients from the multiple linear regression model. ± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol

† Additionally adjusted for BMI, family history and socioeconomic status

*** P<0.001, ** P<0.01, * P<0.05

Table 10.25 Hazard ratios for 30 day mortality from the main analysis, and further adjusted for BMI, family history and socioeconomic status

		Main analysis multivariable adjusted HR (95% CI)± (N=4,088)	Further adjusted HR (95% CI)† (N=2,231)
Aspirin	Never	1 -	1 -
	Current	1.05 (0.87-1.25)	1.01 (0.84-1.21)
	Previous	1.00 (0.81-1.24)	0.99 (0.80-1.23)
Statins	Never	1 -	1 -
	Current	0.97 (0.81-1.16)	1.03 (0.86-1.23)
	Previous	0.98 (0.77-1.24)	1.01 (0.80-1.29)

± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol

† Additionally adjusted for BMI, family history and socioeconomic status

*** P<0.001, ** P<0.01, * P<0.05

Using possible and definite diagnoses

Table 10.26 OR for ST-elevation in patients with MI, from the main analysis, and in an analysis excluding possible atherosclerotic disease

		Main analysis multivariable adjusted OR (95% CI)± (N=4,001)	Multivariable adjusted OR, including possible diagnoses (95% CI) (N=4,001)
Aspirin	**Never**	1 -	1 -
	Current	0.66 (0.49-0.89) **	0.69 (0.51-0.95) *
	Previous	1.02 (0.74-1.42)	1.03 (0.73-1.44)
Statins	**Never**	1 -	1 -
	Current	0.95 (0.75-1.21)	1.00 (0.78-1.29)
	Previous	0.96 (0.70-1.33)	0.96 (0.69-1.34)

± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol

*** P<0.001, ** P<0.01, * P<0.05

Table 10.27 Estimated relative infarct size in the main analysis and in an analysis excluding possible atherosclerotic disease

		Main analysis multivariable adjusted estimated relative infarct size (95% CI)± (N=2,912)	Multivariable adjusted estimated relative infarct size, including possible diagnoses (95% CI) (N=2,912)
Aspirin	**Never**	1 -	1 -
	Current	0.99 (0.72-1.38)	1.05 (0.74-1.50)
	Previous	1.01 (0.69-1.46)	1.04 (0.70-1.53)
Statins	**Never**	1 -	1 -
	Current	0.98 (0.74-1.30)	1.02 (0.76-1.36)
	Previous	0.82 (0.56-1.19)	0.86 (0.58-1.26)

Note: estimated relative infarct size was calculated by exponentiating the coefficients from the multiple linear regression model. ± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol

*** P<0.001, ** P<0.01, * P<0.05

Table 10.28 Hazard ratios for 30 day mortality from the main analysis, and in an analysis excluding possible atherosclerotic disease

		Main analysis multivariable adjusted HR (95% CI)± (N=4,088)	Multivariable adjusted HR, including possible diagnoses (95% CI) (N=4,088)
Aspirin	**Never**	1 -	1 -
	Current	1.05 (0.87-1.25)	1.07 (0.88-1.29)
	Previous	1.00 (0.81-1.24)	1.00 (0.80-1.25)
Statins	**Never**	1 -	1 -
	Current	0.97 (0.81-1.16)	0.93 (0.77-1.13)
	Previous	0.98 (0.77-1.24)	0.97 (0.75-1.25)

± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol

*** P<0.001, ** P<0.01, * P<0.05

Other definitions of 'current' use

Table 10.29 OR for ST-elevation in patients with MI, from the main analysis, and in an analysis where current use was defined as two or more prescriptions in the six months prior to MI

		Main analysis multivariable adjusted OR (95% CI)± (N=4,001)	Multivariable adjusted OR, using alternative definition of 'current' use (95% CI) (N=4,001)
Aspirin	Never	1 -	1 -
	Current	0.66 (0.49-0.89) **	0.71 (0.52-0.96) *
	Previous	1.02 (0.74-1.42)	0.92 (0.67-1.26)
Statins	Never	1 -	1 -
	Current	0.95 (0.75-1.21)	0.97 (0.76-1.24)
	Previous	0.96 (0.70-1.33)	0.96 (0.70-1.32)

± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol

*** P<0.001, ** P<0.01, * P<0.05

Table 10.30 Estimated relative infarct size in the main analysis, and in an analysis where current use was defined as two or more prescriptions in the six months prior to MI

		Main analysis multivariable adjusted estimated relative infarct size (95% CI)± (N=2,912)	Multivariable adjusted estimated relative infarct size, using alternative definition of 'current' use (95% CI) (N=2,912)
Aspirin	Never	1 -	1 -
	Current	0.99 (0.72-1.38)	1.12 (0.80-1.57)
	Previous	1.01 (0.69-1.46)	0.87 (0.60-1.25)
Statins	Never	1 -	1 -
	Current	0.98 (0.74-1.30)	0.97 (0.73-1.28)
	Previous	0.82 (0.56-1.19)	0.83 (0.57-1.21)

Note: estimated relative infarct size was calculated by exponentiating the coefficients from the multiple linear regression model. ± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol

*** P<0.001, ** P<0.01, * P<0.05

Table 10.31 Hazard ratios for 30 day mortality from the main analysis, and in an analysis where current use was defined as two or more prescriptions in the six months prior to MI

		Main analysis multivariable adjusted HR (95% CI)± (N=4,088)	Multivariable adjusted HR, using alternative definition of 'current' use (95% CI) (N=4,088)
Aspirin	Never	1 -	1 -
	Current	1.05 (0.87-1.25)	1.06 (0.88-1.28)
	Previous	1.00 (0.81-1.24)	0.98 (0.79-1.21)
Statins	Never	1 -	1 -
	Current	0.97 (0.81-1.16)	0.97 (0.81-1.16)
	Previous	0.98 (0.77-1.24)	0.96 (0.75-1.22)

± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol

*** P<0.001, ** P<0.01, * P<0.05

Table 10.32 OR for ST-elevation in patients with MI, from the main analysis, and in an analysis where current use had a zero day buffer

		Main analysis multivariable adjusted OR (95% CI)± (N=4,001)	Multivariable adjusted OR, using alternative definition of 'current' use (95% CI) (N=4,001)
Aspirin	**Never**	1 -	1 -
	Current	0.66 (0.49-0.89) **	0.69 (0.51-0.93) *
	Previous	1.02 (0.74-1.42)	0.95 (0.69-1.29)
Statins	**Never**	1 -	1 -
	Current	0.95 (0.75-1.21)	0.93 (0.72-1.19)
	Previous	0.96 (0.70-1.33)	1.00 (0.75-1.35)

± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol
*** P<0.001, ** P<0.01, * P<0.05

Table 10.33 Estimated relative infarct size in the main analysis, and in an analysis where current use had a zero day buffer

		Main analysis multivariable adjusted estimated relative infarct size (95% CI)± (N=2,912)	Multivariable adjusted estimated relative infarct size, using alternative definition of 'current' use (95% CI) (N=2,912)
Aspirin	**Never**	1 -	1 -
	Current	0.99 (0.72-1.38)	1.03 (0.73-1.45)
	Previous	1.01 (0.69-1.46)	0.95 (0.67-1.37)
Statins	**Never**	1 -	1 -
	Current	0.98 (0.74-1.30)	0.92 (0.68-1.23)
	Previous	0.82 (0.56-1.19)	0.94 (0.67-1.32)

Note: estimated relative infarct size was calculated by exponentiating the coefficients from the multiple linear regression model. ± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol
*** P<0.001, ** P<0.01, * P<0.05

Table 10.34 Hazard ratios for 30 day mortality from the main analysis, and in an analysis where current use had a zero day buffer

		Main analysis multivariable adjusted HR (95% CI)± (N=4,088)	Multivariable adjusted HR, using alternative definition of 'current' use (95% CI) (N=4,088)
Aspirin	**Never**	1 -	1 -
	Current	1.05 (0.87-1.25)	1.02 (0.84-1.23)
	Previous	1.00 (0.81-1.24)	1.04 (0.85-1.27)
Statins	**Never**	1 -	1 -
	Current	0.97 (0.81-1.16)	1.00 (0.83-1.21)
	Previous	0.98 (0.77-1.24)	0.92 (0.74-1.16)

± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol
*** P<0.001, ** P<0.01, * P<0.05

Table 10.35 OR for ST-elevation in patients with MI, from the main analysis, and in an analysis where current use had a 28 day buffer

		Main analysis multivariable adjusted OR (95% CI)± (N=4,001)	Multivariable adjusted OR, using alternative definition of 'current' use (95% CI) (N=4,001)
Aspirin	**Never**	1 -	1 -
	Current	0.66 (0.49-0.89) **	0.66 (0.49-0.88) **
	Previous	1.02 (0.74-1.42)	1.06 (0.76-1.48)
Statins	**Never**	1 -	1 -
	Current	0.95 (0.75-1.21)	0.96 (0.76-1.22)
	Previous	0.96 (0.70-1.33)	0.95 (0.68-1.33)

± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol
*** P<0.001, ** P<0.01, * P<0.05

Table 10.36 Estimated relative infarct size in the main analysis, and in an analysis where current use had a 28 day buffer

		Main analysis multivariable adjusted estimated relative infarct size (95% CI)± (N=2,912)	Multivariable adjusted estimated relative infarct size, using alternative definition of 'current' use (95% CI) (N=2,912)
Aspirin	**Never**	1 -	1 -
	Current	0.99 (0.72-1.38)	1.04 (0.75-1.43)
	Previous	1.01 (0.69-1.46)	0.95 (0.65-1.39)
Statins	**Never**	1 -	1 -
	Current	0.98 (0.74-1.30)	1.00 (0.76-1.32)
	Previous	0.82 (0.56-1.19)	0.78 (0.52-1.14)

Note: estimated relative infarct size was calculated by exponentiating the coefficients from the multiple linear regression model. ± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol
*** P<0.001, ** P<0.01, * P<0.05

Table 10.37 Hazard ratios for 30 day mortality from the main analysis, and in an analysis where current use had a 28 day buffer

		Main analysis multivariable adjusted HR (95% CI)± (N=4,088)	Multivariable adjusted HR, using alternative definition of 'current' use (95% CI) (N=4,088)
Aspirin	**Never**	1 -	1 -
	Current	1.05 (0.87-1.25)	1.05 (0.88-1.25)
	Previous	1.00 (0.81-1.24)	0.99 (0.79-1.24)
Statins	**Never**	1 -	1 -
	Current	0.97 (0.81-1.16)	0.97 (0.81-1.16)
	Previous	0.98 (0.77-1.24)	0.97 (0.75-1.25)

± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol
*** P<0.001, ** P<0.01, * P<0.05

Adjusting for consultation rate

Table 10.38 OR for ST-elevation in patients with MI, from the main analysis, and in an analysis adjusting for consultation rate

		Main analysis multivariable adjusted OR (95% CI)± (N=4,001)	Multivariable adjusted OR, with adjustment for consultation rate (95% CI) (N=4,001)
Aspirin	Never	1 -	1 -
	Current	0.66 (0.49-0.89) **	0.67 (0.50-0.90) **
	Previous	1.02 (0.74-1.42)	1.05 (0.76-1.46)
Statins	Never	1 -	1 -
	Current	0.95 (0.75-1.21)	0.97 (0.76-1.23)
	Previous	0.96 (0.70-1.33)	0.98 (0.71-1.36)

± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol
*** P<0.001, ** P<0.01, * P<0.05

Table 10.39 Estimated relative infarct size in the main analysis, and in an analysis adjusting for consultation rate

		Main analysis multivariable adjusted estimated relative infarct size (95% CI)± (N=2,912)	Multivariable adjusted estimated relative infarct size, with adjustment for consultation rate (95% CI) (N=2,912)
Aspirin	Never	1 -	1 -
	Current	0.99 (0.72-1.38)	1.12 (0.80-1.57)
	Previous	1.01 (0.69-1.46)	0.88 (0.61-1.28)
Statins	Never	1 -	1 -
	Current	0.98 (0.74-1.30)	0.98 (0.74-1.30)
	Previous	0.82 (0.56-1.19)	0.84 (0.58-1.22)

Note: estimated relative infarct size was calculated by exponentiating the coefficients from the multiple linear regression model. ± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol
*** P<0.001, ** P<0.01, * P<0.05

Table 10.40 Hazard ratios for 30 day mortality from the main analysis, and in an analysis adjusting for consultation rate

		Main analysis multivariable adjusted HR (95% CI)± (N=4,088)	Multivariable adjusted HR, with adjustment for consultation rate (95% CI) (N=4,088)
Aspirin	Never	1 -	1 -
	Current	1.05 (0.87-1.25)	1.04 (0.87-1.25)
	Previous	1.00 (0.81-1.24)	1.00 (0.81-1.24)
Statins	Never	1 -	1 -
	Current	0.97 (0.81-1.16)	0.97 (0.81-1.16)
	Previous	0.98 (0.77-1.24)	0.98 (0.77-1.24)

± Adjusted for all other drug use, age, sex, hypertension, diabetes, smoking, total cholesterol
*** P<0.001, ** P<0.01, * P<0.05

Chapter 11 Appendix B (CD)

11.1 Code lists

11.1.1 Read code lists for GPRD

11.1.2 ICD-10 code lists for HES and ONS

11.1.3 OPCS-4 codes for HES

11.2 CALIBER data manual

11.3 Analytic protocols for the analyses in this thesis

11.4 Approvals for the analyses in this thesis