Studies in cardiovascular epidemiology in Scotland

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SUMMARY

Aim:

The aim of this study was to describe the epidemiology of important cardiovascular diseases (including angina, AMI, acute coronary syndromes, heart failure, atrial fibrillation and obesity) in Scotland using routinely available sources of data as well as data available from the Renfrew Paisley study.

Objectives:

- To report on the incidence, prevalence, primary care burden and prescribing practices of heart failure, angina and atrial fibrillation in Scotland and explore socioeconomic disparities.
- To examine trends in population hospitalisation rates for suspected acute coronary syndromes and short and long-term outcome following a hospitalisation with an acute coronary syndromes between 1990 and 2000
- To examine between hospital variability in 30 day survival following an admission to hospital in Scotland with an acute myocardial infarction.
- To examine the long-term cardiovascular consequences of angina and of obesity in the Renfrew Paisley study.

Methods:

Data was obtained from primary care (Continuous Morbidity Recording in General Practice Scheme), secondary care (Linked Scottish Morbidity Recording Scheme) and from a prospective cohort study (Renfrew-Paisley Study).

Prescribing and morbidity data were obtained from a representative sample of all General Practices in Scotland participating in the Continuous Morbidity Recording in General Practice Scheme for the years 1999-2000 (for heart failure) and 2001-2002 (for angina and atrial fibrillation).

The Linked Scottish Morbidity Recording Scheme was used to identify all 225,221 first-ever emergency admissions for suspected acute coronary syndromes in Scotland between

1990 and 2000. All emergency admissions for acute myocardial infarction to hospitals in Scotland during two time periods 1988-1991 and 1998-2001 were also identified using the Linked Scottish Morbidity Recording Scheme.

The Renfrew-Paisley study was used to examine the long-term cardiovascular consequences of obesity and angina. In the Renfrew-Paisley study, 15,406 men and women aged 45-64 years, living in the two industrialised towns of Renfrew and Paisley in the West of Scotland underwent comprehensive cardiovascular screening between 1972 and 1976. All deaths and hospitalisations for cardiovascular reasons occurring over the subsequent 20 years were analysed according to baseline body mass index (BMI) category and the presence or absence of Rose angina.

Results:

I have shown that angina is a common condition, more so in men than in women. Deprived individuals are more likely to have angina but are less likely to consult their general practitioner. Guideline recommended treatments for angina are underused in women and the elderly. I also showed that heart failure is a common condition especially in older people. In the elderly, the community burden of heart failure is at least as great as that of angina or hypertension. People with heart failure have a high rate of concomitant respiratory tract infection. Compared with affluent patients, socioeconomically deprived individuals are 44% more likely to develop heart failure, but 23% less likely to see their general practitioner on an ongoing basis. Drugs proven to improve survival in heart failure are used less frequently in elderly patients and in women however prescribed therapy does not differ across socioeconomic gradients. I similarly showed that atrial fibrillation is a common condition, more so in men than in women. In contrast with heart failure and angina deprived individuals are less likely to have atrial fibrillation. As for heart failure and angina, recommended treatments for atrial fibrillation are underused in women and the elderly.

I have also shown that the pattern of emergency admissions with heart disease to Scottish hospitals has changed dramatically over recent years. While population hospitalisation rates for acute myocardial infarction have declined by a third between 1990 and 2000, hospitalisation rates for angina and chest pain have nearly doubled. The long term prognosis following an admission for myocardial infarction or angina is similar, when

deaths within the first 30 days are excluded. The average 30 day case-fatality rate following admission with an AMI has fallen substantially over the past 10 years. Between-hospital variation in 30 day survival is also considerably less marked during the time period 1998-2001 than it was during the time period 1988-1991 due to better survival in the previously poorly performing hospitals.

Using the Renfrew Paisley study, I found that compared with normal weight individuals (BMI 18.5-24.9), obesity (BMI ≥30) was associated with an increased adjusted risk of coronary heart disease, heart failure, stroke, venous thromboembolism and atrial fibrillation. Obesity was associated with 8 additional cardiovascular deaths and 30 additional cardiovascular hospital admissions for every 100 affected middle-aged individuals over the subsequent 20 years. Assuming no change in cardiovascular risk profile, the increase in prevalence of obesity in 1998, when compared to 1972, is projected to lead to an additional 4 cardiovascular deaths and 14 admissions per 100 middle-aged men and women over the next 20 years. Again using the Renfrew-Paisley study, I found that individuals with Rose angina had an increased risk of cardiovascular death or hospitalisation, myocardial infarction and heart failure relative to individuals without angina. An abnormal ECG increased the risk further and both angina and an abnormal ECG further again when compared to those with neither angina nor an ischaemic ECG. Compared to men, women with Rose angina were less likely to have a cardiovascular event, or myocardial infarction, though there was no sex difference in the risk of stroke, atrial fibrillation or heart failure.

Conclusion:

I have demonstrated the potential of using data from the Continuous Morbidity Recording in General Practice Scheme to examine the epidemiology and prescribing practices of conditions in primary care and explore socioeconomic discrepancies. I have also demonstrated the potential of using data from the Linked Scottish Morbidity Recording Scheme to examine trends in hospitalisations and outcome for diseases and explore inter-hospital variability in outcome. I have also used the Renfrew-Paisley study to examine the effect of baseline obesity or angina on long term cardiovascular hospitalisations and deaths.

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ABBREVIATIONS

ACS	Acute coronary syndrome
AF	Atrial fibrillation
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ARIC	Atherosclerosis Risk in Communities Study
ATRIA	AnTicoagulation and Risk Factors in Atrial Fibrillation Study
BMI	Body mass index
CHD	Coronary heart disease
CHS	Cardiovascular Health Study
CMR	Continuous Morbidity Recording
CSA	Common Services Agency
CV	Cardiovascular
ECG	Electrocardiogram
EPESE	Established Populations for Epidemiologic Studies of the Elderly
EPICA	Epidemiologica da Insuficiencia Cardiaca e Aprendizagem
FEV_1	Forced expiratory volume in 1 second
GP	General Practitioner
GPASS	General Practice Administration System for Scotland
GPRD	General Practice Research Database
HF	Heart failure
HR	Hazard ratio
ICD	International Classification of Disease
IN-CHF	Registry of Italian Network on Congestive Heart Failure
ISD	Information and Statistics Division
LV	Left ventricular
MIDAS	Myocardial Infarction Data Acquisition System Study Group
MITI	Myocardial Infarction Triage and Intervention Registry
MONICA	Multinational Monitoring of Trends and Determinants of Cardiovascular Disease
NA	Not available
NHANES	National Health and Nutrition Examination Survey

95% CI	95% confidence interval
OR	Odd's ratio
PCCIU-R	Primary Care Clinical Informatics Research Unit
PACT	Prescribing Analysis and Cost
PATAF	Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation
PRAIS-UK	Prospective Registry of Acute Ischaemic Syndromes
PRIME	Prospective Epidemiological Study of Myocardial Infarction STudy
PTI	Practice Team Information
REACH	Resource Utilization Among Congestive Heart Failure
REGICOR	Registre Gironi del Cor, Gerona Heart Registry
RR	Relative risk
SIMD	Scottish Index of Multiple Deprivation
SMR	Scottish Morbidity Records
VTE	Venous thromboembolism
WHO	World Health Organisation

1 INTRODUCTION

In this thesis I will examine the epidemiology of cardiovascular disease in Scotland using data from primary care (Continuous Morbidity Recording in General Practice Scheme), secondary care (Linked Scottish Morbidity Recording Scheme) as well as data available from a prospective cohort study, the Renfrew Paisley study. In this chapter, I will review the literature on the prevalence, incidence, morbidity and mortality of angina, acute myocardial infarction, heart failure, atrial fibrillation and obesity. In chapter 2, I will outline the aims of my thesis. In chapter 3, I will discuss the Continuous Morbidity Recording in General Practice Scheme, the Linked Scottish Morbidity Recording Scheme and the Renfrew Paisley study and explore the methods employed in the various studies I have performed. In Chapters 4, 5 and 6, I will discuss the prevalence, incidence, primary care burden and pharmacological treatment of angina, heart failure and atrial fibrillation and also explore socioeconomic disparities. Chapters 7 and 8, address temporal trends in hospitalisation rates for suspected acute coronary syndromes and the short and long-term prognosis following admission with a suspected acute coronary syndrome. Chapter 9 explores between hospital variation in 30 day survival following an admission with an acute myocardial infarction. Chapters 10 and 11, examine the long-term cardiovascular consequences of angina and obesity. Finally in chapter 12, I will summarise the findings of this thesis and discuss limitations of the data and the possible avenues for further research.

1.1 Epidemiology of angina

1.1.1 Prevalence of angina

The prevalence of angina has been estimated in studies by using a number of different methods, mainly; the Rose angina questionnaire, a self reported angina diagnosis, a physician diagnosis or a general practitioner diagnosis. (Table 1)

1.1.1.1 Prevalence of angina in population studies using Rose angina questionnaire

The majority of population studies examining the prevalence of angina have used the World Health Organisation (Rose) questionnaire.[1] This questionnaire was introduced by Rose in 1962 and has since been widely used for determining the prevalence of angina in epidemiological studies. The subject is asked if they ever get chest pain or discomfort when walking uphill or hurrying. The chest pain is defined as either "definite" or "possible" angina depending on whether four additional criteria are fulfilled. These additional criteria are 1) the pain must be sited in the sternum or the left anterior chest and arm, 2) when it occurs on walking it must make the subject to stop or slow down, 3) it must go away if the person stops or slows down and 4) resolve within 10 minutes from the time when the subject stands still. Grade I angina is chest pain or discomfort when walking uphill or hurrying. Grade II angina is if in addition the subject also reports chest pain or discomfort when walking at an ordinary pace on the level. The Rose angina questionnaire is an accepted technique with good, population based, repeatability and validity for the detection of coronary heart disease.[2-4] The validity of the Rose angina questionnaire has been tested in studies comparing it to a clinical diagnosis of angina, electrocardiogram (ECG) abnormality, thallium scanning and as a predictor of coronary artery disease events and mortality.[2;3;5 8] The Rose angina questionnaire has been shown to have a 81% sensitivity and a 97% specificity when compared to clinical judgement[2] and a 26% sensitivity and 79% specificity when compared to exercise thallium testing[6]. Because the questionnaire is standardised it can be used to estimate disease prevalence in different large populations. Its' limited sensitivity and specificity are outweighed by its' ease of use, repeatability when applied to the same group of people, and proven validity in identifying groups of people at risk of developing the consequences of coronary heart disease.[4] There has been debate about which Rose categories should be included in epidemiological studies. Most epidemiological studies exclude possible angina.[9-15] However, in the British Regional Heart Study men with 'possible' angina were as likely to have an ischaemic ECG at rest and had a similar risk of acute myocardial infarction during follow-up as those with 'definite' angina.[16] Men with 'possible' angina have also been shown to have a greater risk of dying from coronary heart disease, having an acute myocardial infarct, or needing a CABG than age matched counterparts with no symptoms of angina.[17]

In the 1998 Health Survey for England, a nationally representative sample of 15,908 persons, aged 16 and over, was interviewed.[9] The overall prevalence of definite angina

symptoms by the Rose Questionnaire was 2.6% in men and 3.1% in women. It was higher in women than in men in all age groups except for those aged 75 and over, where 7.3% of men and 5.9% of women reported the symptoms. In the Scottish Heart Health Study[18], the self-administered Rose angina questionnaire was given to a representative sample of 10,359 men and women between 1984 and 1986. Grade 1 and 2 angina was included but it is not clear if possible angina was excluded. The prevalence of angina was higher in women (8.5%) than in men (6.3%). The British Regional Heart Study[19] is a prospective study of 7,735 men who were randomly selected from one general practice in each of 24 British towns. The prevalence of definite angina at entry (1978-1980) in men aged 40-59 years was 4.8%. An additional postal questionnaire was sent to surviving men in 1996 (age 56-77) and the prevalence of definite and possible angina was 13.8%.[20] Men belonging to the manual social class at baseline had almost double the prevalence of angina compared to those from the non-manual group. The prevalence of angina in women in the UK was examined in the Royal College of General Practitioners' Oral Contraception Study in 1994-1995.[14] The prevalence of definite angina in 11797 women, mean age 55.9 years, using a postal questionnaire was 7.4% increasing to 9.9% in women over 65 years. The prevalence of angina increased with manual social class. Another UK study conducted in 1967 in the Rhondda Fach in South Wales found a much higher prevalence of angina in women (17.8% aged 45-74 years).[21] In the original Whitehall Study carried out between 1967 and 1969 among male London civil servants aged 40-64 years, the prevalence of definite and possible angina was 4.8%.[22] In Whitehall II, the prevalence of definite angina in government employees between 1985 and 1988 was 2.4% in men and 4.0% in women aged 35-55 years.[15] The prevalence of angina in middle aged men was found to be similar (7.7% and 7.8%) in two community studies carried out in South Wales (Caerphilly) and the West of England (Speedwell).[23]

Two European population studies have examined the prevalence of angina. In the Northern Sweden MONICA Project unlike all other studies using the Rose questionnaire the prevalence of definite angina was higher in men than in women. The prevalence of angina declined significantly in women aged 35-64 years from 5.9% in 1986 to 2.8% in 1994.[11]. In the Reykjavik study which took place between 1983 and 1987 the prevalence of angina was 6.1% in 1,142 Icelandic men aged 50-79 years.[24] Prior myocardial infarction was excluded and Rose angina was not defined. The Multifactorial trial in prevention of Coronary Heart Disease [25] compared the prevalence of angina in five European countries in the 1970s. The prevalence of angina varied significantly between countries and ranged

from 2.3% in Spain up to 5.1% in Poland with an overall average of 4.3%. In the UK the prevalence of angina was 3.6% in 18210 men aged 40-59 years.

Two US studies using the Rose questionnaire have also found a higher prevalence of angina in women compared to men. The prevalence of definite angina was 6.2% in women and 5.2% in women over 40 years in NHANES III[10] and 4.1% in women and 3.2% in men over 30 years in the Lipid Research Program Prevalence Study[12;26]. In a Canadian population-based cross-sectional survey the prevalence of definite angina in 2167 individuals aged 18 to 74 years was 3.1% in men and 4.1% in women.[27] Possible angina was more prevalent among those with less education, lower income and those who were unemployed.

The prevalence of angina has been shown in these studies to increase with age. A direct comparison between the different studies is difficult due to the different age profiles of patients studied. Most studies have found a higher prevalence of Rose angina in women than men. We do not know whether this difference reflects true difference in the prevalence of angina between the sexes or whether it is a difference in the perception or description of chest pain between sexes highlighted by the Rose questionnaire. All-cause mortality rates are higher in women with Rose angina compared to women without.[14] Coronary artery disease risk has shown to be raised in women with Rose angina even when they have high levels of general symptom reporting.[15] Variation in symptom reliability between sexes has not been shown to explain the higher prevalence of Rose angina in women.[26] The variability of angina symptoms over a 5-year period was examined in the British Regional Heart Study and whilst there was considerable variability in response to the Rose questionnaire at the two time points, it was shown that persistently reported symptoms were associated with severe disease and a poor prognosis.[28]

1.1.1.2 Prevalence of angina in population studies based on a self-report of angina.

Both the Health Survey for England[9] and the Scottish Heart Health Study[18], in addition to the Rose questionnaire, estimated the prevalence of angina based on self reported angina. In the Health Survey for England in contrast to the prevalence of Rose angina, more men (5.3%) than women (3.9%) reported having ever had angina. Similarly in the Scottish Heart Health Study, the prevalence of a history of angina was higher in men (5.5%) than in women (3.9%).

1.1.1.3 Prevalence of angina in population studies using a physician diagnoses.

In the Primary Prevention Study subjects judged to have definite or suspected angina on Rose angina questionnaire were then interviewed and examined by a single physician to confirm the diagnosis. At the second screening visit, which took place between 1974 and 1977, the prevalence of angina in men aged 51-59 years was 4.4%.[13] In the Cardiovascular Health Study[29] the prevalence of angina was ascertained in 5,201 adults aged 65 years and older. A diagnosis of angina was based on a self-report of angina in combination with either use of nitrates, revascularisation, hospital diagnosis of angina or physician diagnosis of angina. The prevalence of angina was 15.4% in men and 9.8% in women over 65 years. In the Framingham Study[30] the prevalence of physician diagnosed angina was 5.9% during 14 years of biennial cardiovascular surveillance in a cohort (aged 30-62 at entry) who were free of clinical manifestations of coronary heart disease at initial screening 1949-1952. From 1951 through 1986 in the Framingham Study angina was the initial presenting manifestation of coronary disease in 39% of subjects.[31]

1.1.1.4 Prevalence of angina based on general practitioner reported diagnoses.

Studies estimating prevalence based on general practitioner (GP) diagnosis of angina have strengths and weaknesses compared to the more commonly used alternative of administration of a questionnaire. There have been concerns that the questionnaire approach may overestimate the prevalence of angina, especially in women. Conversely, reliance on a medical diagnosis may underestimate prevalence as individuals with unrecognised angina or very mild symptoms might not attend (or be correctly identified by) their general practitioner. In addition there is concern that GP coding of angina in the UK may be different since the introduction of the new General Medical Services (GMS) contract in 2004 which provides financial incentives for the correct management of patients with angina.[32]

Two studies used an analysis of nitrate prescribing to establish the prevalence of angina. Nitrates are mostly used for the treatment of angina.[33] Prescription analysis has the advantage that it is cheap and can be done quickly and by few staff. In the Nottingham nitrate study[33] the prevalence as estimated using nitrate prescriptions in 1984 was 2.6% in patients over 30 years.

The prevalence of angina in 1992 was determined by using GPs' records from 21 general practices in the Wakefield region of northern England[34] of patients who are regularly taking nitrates. 3.2% of men and 3.0% of women had angina. The prevalence of angina was higher in men than in women in all age groups and rose steeply with age. The Newcastle General Practice survey[35], carried out in 1979, reported a prevalence of 1.1% in subjects aged 30-59 years which is lower than other studies. This survey was conducted by 51 general practitioners and identified 336 patients with angina through either repeat prescriptions, recent consultations or recall. Case-ascertainment therefore may not have been complete.

1.1.1.5 Secular trends in prevalence of angina

Trends in the prevalence of angina have been examined using data from the British Regional Heart Study.[20] The Rose angina questionnaire was used to ascertain the prevalence of current angina symptoms at four time points between 1978 and 1996. They found that over this time period middle-aged British men with and without a diagnosis of coronary heart disease were less likely to experience symptoms of angina. In a separate study of the same cohort the incidence of diagnosed angina (ascertained from general practice record reviews) seems to have increased by 2.6% per year between 1978 and 2000.[36] A possible explanation for the differences between these two studies may be that a greater proportion of angina cases are now formally diagnosed. This may result from general practitioners prioritising the early identification and treatment of coronary heart disease and an increase in availability of diagnostic investigations for suspected angina. The prevalence of angina also increased in England and Wales in the 1990s compared to the 1980's using data from the general practice morbidity survey.[37] The Minnesota Heart Survey reported a 56% increase in the discharge rate for angina in men and a 30% increase in women between 1985 and 1995 (with a 20% decline in the discharge rate for acute myocardial infarction (AMI) in both men and women).[38]

Table 1 Prevalence of angina in men and women

Study	Location	Type of study Definition of angina	Year of study	No of subjects (proportion of men)	Age group (years)	Overall prevalence (%)	Overall prevalence in men (%)	Overall prevalence in women (%)	Prevalence in older age group (%)
Health Survey for England[9]	England	Cross sectional study Definite Rose angina and self reported diagnosis	1998	15908 (45%)	≥16	NA	2.6	3.1	7.3 in men and 5.9 in women (≥75 years)
British Regional Heart Study[19;20]	UK	Prospective cohort study Definite and possible Rose angina	1978-1980 1996	7735 (100%) 5263 (100%)	40-59 (1978-80) 56-77 (1996)	NA	4.8 (definite 1978-80) 13.8 (definite and possible 1996)	NA	18.3 (75-79 years)
RCGP Oral Contraception Study[14]	UK	Prospective cohort study Definite Rose angina	1994-1995	11797 (0%)	Mean age 56	NA	NA	7.4	9.9 (>65 years)
Whitehall II[15]	London, England	Prospective cohort study Definite Rose angina	1985-1999	10191 (67%)	35-55	2.9	2.4	4.0	NA
Saskatchewan Heart Health Survey[27]	Saskatchewan, Canada	Cross sectional study Definite and possible Rose angina	1990	2167 (50%)	18-74	NA	3.1 (definite) 8.2 (possible)	4.1 (definite) 8.8 (possible)	4.8 in men and 7.1 in women (definite Rose angina) (55-74 years)
Scottish Heart Health Study[18]	Scotland	Cross sectional study Rose angina (not defined) and self reported diagnosis	1984-1986	10,359 (not available)	40-59	NA	6.3 (Rose) 5.5 (self-reported)	8.5 (Rose) 3.9 (self-reported)	NA
Caerphilly and Speedwell Survey[23]	Wales and England	Prospective cohort study Definite and possible Rose angina	1978-1982	4860 (100%)	45-63	NA	7.7 in Caerphilly 7.8 in Speedwell	NA	14.8 (60-63 years)
Whitehall Study[22]	UK	Prospective cohort study Definite and possible Rose angina	1967-1969	18403 (100%)	40-64	NA	4.8	NA	8.3 (60-64 years)
Rhondda Valley Study[21]	South Wales	Prospective cohort study Definite Rose angina	1967	1428 (0%)	45-74	NA	NA	17.8	NA
Nottingham nitrate study[33]	UK	Cross sectional study Nitrate prescription	1984-1985	344,700 (49%)	>30	2.6	NA	NA	7.1 in men (≥65 years) and 4.4 in women (≥60 years)
Wakefield Study[34]	Wakefield, northern England[34]	Cross sectional study Nitrate prescription	1992-1993	164,796 (57%)	All ages	3.1	3.2	3.0	16.0 (≥ 75 years)

NA=not available

Continued over...

Table 1 continued

Study	Location	Type of study Definition of angina	Year of study	No of subjects (proportion of men)	Age group (years)	Overall prevalence (%)	Overall prevalence in men (%)	Overall prevalence in women (%)	Prevalence in older age group (%)
Newcastle General Practice survey[35]	UK	Cross sectional study Angina prescription or recent consultation	1979	336 identified with angina (not available)	30-59	1.1	1.6	NA	NA
Northern Sweden Monica Project[11]	Sweden	Coronary event register Definite Rose angina	1994	1196 (49%)	35-64	2.9	3.1	2.8	NA
Reykjavik Study[24]	Iceland	Prospective cohort study Rose angina (not defined)	1983-1987	1142 (100%)	50-79	NA	6.1	NA	8.1 (75-79 years)
Multifactor Primary Prevention Study[13]	Göteborg, Sweden	Prospective population study/ randomised controlled trial Definite Rose angina and physician diagnosis	1974-1977	7100 (100%)	51-59	NA	4.4	NA	NA
Multifactorial trial in prevention of CHD [25]	5 European countries	Randomised controlled trial. Rose angina (not defined)	1971-1977 (1971-1973 in UK)	63732 (18210 in UK) (100%)	40-59	NA	4.3 (3.6 in UK)	NA	NA
NHANES III[10]	US	Cross sectional study Definite Rose angina	1988-1994	9255 (47%)	≥40	5.8	5.2	6.2	7.7 (≥65 years)
Cardiovascular Health Study[29]	US	Prospective cohort study Self reports **and** nitrate prescription *or* revascularisation *or* physician diagnosis	1989-1990	5201 (43%)	≥65	NA	NA	NA	15.4% in men and 9.8% in women (>65 years) 17.4 in men and 12.8 in women (80-84 years)
Lipid Research Program Prevalence Study[12;26]	US	Cross sectional study Definite Rose angina	1972-1976	4661 (53%)	≥30	NA	3.2	4.1	12.4 in men and 6.0 in women (70-79 years)
Framingham Study[30]	Framingham, US	Prospective cohort study Physician diagnosis	1952-1966	5127 (45%)	44-76	5.9	NA	NA	NA

NA=not available

1.1.2 Incidence of angina

Table 2 shows studies reporting the incidence of angina. There are fewer studies that have examined the incidence of angina in men and women as it is more difficult to examine. The best information on incidence comes from cohort studies.

In a study of referrals to a chest pain clinic at the Royal South Hants Hospital in Southampton the incidence of angina was 0.8 per 1,000 in persons aged 31-70 years.[39] All general practitioners in Southampton agreed to refer any patient presenting for the first time with chest pain, which in their opinion could be stable angina. The denominator was all men and women in the practice population. The incidence in this study is lower than other studies and may reflect the methods employed. The incidence of angina in men aged 50-59 years was compared between France and Northern Ireland in the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study.[40] This was carried out between 1991 and 1994. Angina was defined by the presence of chest pain at rest and/or on exertion and one of the following criteria: angiographic stenosis or positive functional test (if no angiographic data) or ECG changes at rest (if no angiographic or functional test data). The incidence was higher in Northern Ireland (5.4 per 1,000 per year) than in France (2.6 per 1,000 per year). During a 10-year follow-up of the Seven Countries Studies cohorts, the average annual incidence of angina as the only manifestation of coronary heart disease in men aged 40-59 years was 0.1% in Japan, Greece and Croatia, 0.2-0.4% in Italy, Serbia, Netherlands and USA and 0.6-1.1% in Finland.[41]

The Framingham Heart Study is a longitudinal study in which 5,127 persons free of clinical manifestations of coronary heart disease at initial screening between 1949 and 1952 were followed for 14 years.[30;42] The annual incidence of angina was 3.1 per 1,000 in men and 2.8 per 1,000 in women. The Framingham Cardiovascular Disease Survey was a 1 year survey in which all new cases of angina in patients over 30 years of age were identified in the town of Framingham between 1970 and 1971 using hospital, GP and pharmacist records and death certificate data.[42;43] The annual incidence of angina was lower at 1.8 per 1,000 in men and 0.4 per 1,000 in women. A possible explanation is that the Framingham Heart Study used periodic direct examination of a population sample whereas short-term population studies like the Cardiovascular Disease Survey are dependent upon patient-initiated contacts and therefore are likely to miss mild angina

pectoris. In both these studies the incidence of angina was higher in men than in women in most age groups and increased with age. Two other older US studies with similar methodology reported similar incidence rates to the Cardiovascular Disease Survey.[44;45] The incidence of angina in older patients was examined in a US study of members of the Kaiser Foundation Health Plan.[46] The incidence of angina in those over 80 years in the 1980-1981 cohort was 12.6 per 1,000 person years in men and 5.1 per 1,000 person years in women.

The annual incidence of angina in Japanese American men aged 45-68 years in the Honolulu Heart Program was 2.1 per 1,000.[47] In the Israel Ischaemic Heart Disease Project male civil service employees aged 40 years and over were followed between 1963 and 1968. The annual age-adjusted incidence of angina was 7.2 per 1,000, which is higher than other studies.

Table 2 Incidence of angina in men and women

Study	Location	Type o f Study Definition of angina	Year	No of subjects (proportion of men)	Age group (years)	Overall incidence (per 1000 per year)	Overall incidence in men (per 1000 per year)	Overall incidence in women (per 1000 per year)	Incidence in older age group (per 1000 per year)
PRIME study[40]	France and N. Ireland	Prospective cohort study Chest pain **and** CAD on angiogram *or* positive functional test *or* ECG changes at rest	1991-1994	7359 in France 2399 in Belfast (100%)	50-59	NA	2.6 in France 5.4 in Belfast	NA	NA
Southampton Study[39]	UK	Prospective survey Referrals to a chest pain clinic	1990-1992	110 new angina patients (64%)	31-70	0.8	1.1	0.5	2.6 in men and 0.9 in women (61-70 years)
Kaiser Foundation Health Plan [46]	US	Retrospective cohort study Hospitalisation data	1980-1988	3032 (52%)	≥65	NA	NA	NA	12.6 in men and 5.1 in women (≥80 years)
Honolulu Heart Program[47]	Japanese Americans, Hawaii	Prospective cohort study Reexamination and hospital surveillance	1965-1975	8,006 (100%)	45-68	NA	2.1	NA	2.4 (60-68 years)
Framingham Cardiovascular Disease Survey[42;43]	Framingham , US	Cross sectional study Hospital, GP and pharmacist records and death certificate data	1970-1971	29,158 (46%)	≥30	NA	1.8	0.4	4.3 in men and 0.7 in women (65-74 years)
Seven Countries Study[41]	Seven countries*	Prospective cohort study Physician diagnosis at baseline screening	1958-1964	2571(100%) US Railroad Companies	40-59	NA	33 US Railroad Companies	NA	NA
Israel Ischemic Heart Disease Project[48]	Israel	Prospective cohort study Definite angina on a modified Rose questionnaire	1963-1968	10,059 (100%)	≥40	NA	7.2	NA	8 (≥60 years)
Framingham Heart Study[30;42]	Framingham, US	Prospective cohort study Physician diagnosis	1949-1964	5,127 (45%)	30-62 at entry between 1949-1952	NA	3.1	2.8	5.6 in men and 6.5 in women (65-74 years)
Health Insurance Plan study[45;49]	New York, US	Cross sectional study Physician reports, hospital claims and death records	1961-1965	110,000 (69%)	35-64	NA	2.0	0.9	NA

*** Yugoslavia, Italy, Greece, Finland, Netherlands, United States and Japan; NA=not available**

1.1.3 Angina morbidity

1.1.3.1 Risk of non-fatal events associated with angina

In contrast to case-fatality there are relatively few studies, which have reported non-fatal events in patients with angina (Table 3). The British Regional Heart Study[50] examined the combined outcome of coronary heart disease death or non-fatal myocardial infarction. They showed that men with angina were twice as likely to have a coronary heart disease death or non-fatal myocardial infarction over 10 years when compared to men without angina.

The Framingham study looked at non-fatal myocardial infarction alone.[31] 33.4% of men and 17.8% of women with angina had a myocardial infarction over a 10 year follow-up. The Framingham study also looked at the risk of coronary heart disease events in subjects reporting chest discomfort.[51] Men with definite angina had a threefold increased risk (OR 3.7, 95% CI 2.1, 6.6) and women a fivefold increased risk (5.4 (3.1, 9.3)) of developing unstable angina, myocardial infarction or cardiac death within two years of first presentation. An excess risk was also present for individuals with possible angina (men 3.0 (1.3, 6.7); women 2.9 (1.1, 7.2)) however there was no increase in risk associated with non-anginal chest discomfort.

During a median follow-up of 15.8 months, 7.5% of patients aged 31-70 years with newly diagnosed typical angina referred to a chest pain clinic in Southhampton experienced a myocardial infarction and 18.7% underwent coronary revascularisation.[39] The Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK) examined outcome following hospitalisation with an acute coronary syndrome without ST segment elevation between 1998 and 1999.[52] Patients presenting with acute chest pain and an ischaemic ECG or a prior history of coronary heart disease were included. This study therefore included both patients with unstable angina and those with non-ST elevation myocardial infarction. These two groups were not analysed separately however, and creatinine kinase was not a predictor of an adverse outcome. The risk of subsequent myocardial infarction was 7.3% during the 6-month follow-up.

In the Rochester Coronary Heart Disease Project[53], women with angina were 53% less likely than men to have a cardiac death or non-fatal myocardial infarction.

Patients with angina are likely to be at increased risk of other complications of coronary heart disease (e.g. heart failure) and non-cardiac vascular events (e.g. stroke). The British Regional Heart Study[50] found that 5% of men with angina developed a stroke (identified from general practitioner records), a relative risk 2.6 times that of men without angina. There is however very little information on the risk of other non-fatal outcomes in patients with angina.

Table 3 Prior studies reporting morbidity outcomes in patients with angina.

	Type of study Location	Definition of angina N with angina (% men)	Age group (years)	Era of screening	Follow-up (years)	Non-fatal myocardial infarction			Other morbidity outcomes		
						Both sexes	Men	Women	Both sexes	Men	Women
Southhampton chest pain clinic[39]	Prospective survey, Royal South Hants Hospital, Southhampton, UK	Physician diagnosis 110 (74%)	31-70	1990-1992	1.3 (0.6-2.5)	7.5%	8.7%	5.2%	18.7% for revascularisation	24.6% for revascularisation	7.9% for revascularisation
Framingham[51]	Prospective cohort study Framingham, US	Physician diagnosis 601 (48%)	Mean age 61 (men) 64 (women)	1951-1986	10	NA	33.4% Multivariable adjusted hazard ratio relative to women 2.2 (1.5,3.3)	17.8%	NA	NA	NA
British Regional Heart Study[50]	Prospective cohort study 24 British towns	Diagnosed angina and Rose angina 607 (100%)	40-59	1978-1980	15	NA	14.2% for CHD death or non-fatal AMI (10 years). Age adjusted hazard ratio 2.1 (1.5,2.8) for Rose angina excluding prior CHD	NA	NA	5.0% for stroke (10 years). Age adjusted hazard ratio 2.6 (1.5,4.4) for Rose angina excluding prior CHD	NA
Rochester Coronary Heart Disease project[53]	Retrospective cohort study Rochester, US	Review of medical records 1033 (49%)	≥30	1960-1979	3-22	NA	NA	Multivariable adjusted hazard ratio for cardiac death or non-fatal AMI relative to men 0.5 (0.2,0.6)	NA	NA	NA

AMI = acute myocardial infarction; CHD= coronary heart disease; NA=not available

1.1.4 Angina mortality

Studies reporting on mortality outcomes in patients with angina are shown in Table 4. In the Framingham Study[31] 291 men and 319 women who were free at baseline screening of coronary artery disease, developed angina between 1951 and 1986. Their mean age was 61 and 64 years in men and women respectively. During a mean follow-up of 10 years 41.5% of men and 31.5% of women died and 28.2% of men and 16.7% of women died from coronary heart disease. In the Rochester Coronary Heart Disease Project[53] the diagnosis of angina was identified through review of medical records from physicians offices and hospitals in Rochester between 1960 and 1979. Angina was diagnosed in 529 women and 504 men aged ≥30 years (33% over 70 years) and they were followed up until 1982. 10-year mortality was 29.6% for women and 40.8% for men. Women were 55% less likely to die at 1 year compared to men (RR 0.45 95% CI 0.37, 0.55).

In the Reykjavik Study[54], 9141 men aged 34-79 at entry (1967-1987) were followed for 4-20 years. There were 3 different angina groups a) definite angina by Rose questionnaire with ECG manifestation of myocardial ischaemia; b) definite angina by Rose questionnaire with normal ECG and physician's diagnosis; c) definite angina by Rose questionnaire only. Ten year mortality was 11-13% in the three groups. Those with angina had a 1.7- to 2.2-fold risk of all cause mortality and a 2.5- to 3.2-fold risk of CHD mortality depending on the subgroup of angina over the follow-up period. In the Primary Prevention Study[13] 7,100 men, aged 51-59 years, and living in Göteborg, Sweden were screened between 1974 and 1977 and followed for at least 16 years. Angina was identified by questionnaire and confirmed by examination by a physician, in 314 men with no prior myocardial infarction. In men with angina there were 33.0 deaths per 1000 observation years and 17.6 coronary heart disease deaths per 1000 observation years. The adjusted risk of all cause death was 1.63 (1.38, 1.93) and coronary heart disease death was 2.60 (2.04, 3.31) relative to no coronary heart disease.

In the British Regional Heart Study[50] 7,735 men, aged 40-59 years at entry (1978-1980) were followed up for 15 years. There were two angina groups, those with diagnosed angina (n=123) and those with angina symptoms (n=349) (defined as definite or possible on Rose angina questionnaire with no prior history of ischaemic heart disease). The 10 year risk of death was 3.0 (2.1, 4.2) and of cardiovascular mortality was 4.3 (2.7, 6.9) for the diagnosed

angina group when compared to men with no coronary heart disease. The equivalent hazard ratios for the angina symptoms group was 2.0 (1.5, 2.6) and 2.6 (1.8, 3.8). In the Whitehall Study[22] angina was classified according to Rose angina questionnaire however they do not define whether possible Rose angina was included. The 5 year coronary heart disease mortality rate in 40-64 year old men was 7.1%. In the Whitehall II study[53] 6,895 men and 3413 women, aged 35-55 years, were followed up for a mean of 11 years. Angina was defined as a GP or hospital diagnosis of angina and the presence of angina on Rose angina questionnaire. The mortality rate, adjusted for age and sex, was 3.4 per 1000 person years at risk.

In the Royal College of General Practitioners' Oral Contraception Study [14], angina as defined as definite angina on the Rose Angina Questionnaire was identified in 640 women. The 5-year mortality rate was 6.3%. In a study by Campbell *et al*[21] 1428 women aged 45-74 years living in Wales, were followed for 12 years. Angina was defined as definite angina on Rose Angina Questionnaire. The 12-year mortality rate for 45-74 year olds with angina was 22.8%.

The mortality of patients hospitalised with unstable angina was examined using population data from Alberta, Canada and the outcome in men and women compared.[56] Between 1993 and 2000 there were 8,441 admissions with unstable angina. Five-year mortality was similar in men and women (19.7% versus 21.6%). After multivariable adjustment women with unstable angina had a survival advantage over men (HR 0.81, 95% CI 0.72, 0.92). The risk of death following admission with unstable angina increased with age.[56;57]

Table 4 Prior studies reporting mortality outcomes in patients with angina.

	Type of Study Location	N with angina (% men) Definition of angina	Age group (years)	Era of screening	Follow-up (years)	All-cause mortality			Coronary heart disease mortality	
						Both sexes	Men	Women	Men	Women
Chang *et al*[56]	Retrospective cohort study. Alberta, Canada.	8441 (60%) Hospitalisation with unstable angina	>18 Mean age 65	1993-2000	5	0.8 (0.7-0.9) for women versus men	19.7%	21.6%	-	-
RCGP oral contraception study[14]	Prospective cohort study. UK.	640 (0%) Rose angina	Mean age 56	1994-1995	5	-	-	6.3% (5 years) Adjusted odds ratio grade I 1.5 (0.7, 3.4) and grade II Rose angina 3.9 (1.6, 9.8) relative to no angina	-	
Whitehall II[55]	Prospective cohort study. London, UK.	1158 (-) Rose angina and clinical records	35-55	1985-1988	11	3.4 per 1000 patient years	-	-	-	-
Reykjavik[54]	Prospective cohort study. Reykjavik, Iceland.	1053 (100%) Rose angina and physician diagnosis	34-79	1968-1986	4-20	-	11-13% (10 years) Multivariable adjusted hazard ratio 1.7 (1.3, 2.3) relative to no CHD	-	Multivariable adjusted hazard ratio 2.5 (1.6, 3.9) relative to no CHD	-
Framingham study[31]	Prospective cohort study. Framingham, USA.	601 (48%) Physician diagnosis	Mean age 61 (men) 64 (women)	1951-1986	10	-	41.5% (10 years) Multivariable adjusted hazard ratio 1.6 (1.1, 2.2) relative to women	31.5% (10 years)	28.2% (10 years) Multivariable adjusted hazard ratio 2.1 (1.3, 3.4) relative to women	16.7% (10 years)
British Regional Heart Study[50]	Prospective cohort study. 24 British towns.	472 (100%) Diagnosed angina and Rose angina	40-59	1978-1980	15	-	16.8% (10 years) Age adjusted hazard ratio 2.0 (1.5, 2.6) relative to no CHD	-	-	-
Rochester Coronary Heart Disease project[53]	Retrospective cohort study. Rochester, USA.	1033 (49%) Review of medical records	≥30	1960-1979	3-22	-	40.8% (10 years)	29.6% (10 years) Multivariable adjusted hazard ratio 0.5 (0.4, 0.6) relative to men	-	-

CHD= coronary heart disease; NA=not available

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Table 4 continued

	Type of Study Location	N with angina (% men) Definition of angina	Age group (years)	Era of screening	Follow-up (years)	All-cause mortality			Coronary heart disease mortality	
						Both sexes	Men	Both sexes	Men	Both sexes
Multifactor Primary Prevention Study[13]	Retrospective cohort study/ Randomised controlled trial. Gothenburg, Sweden.	314 (100%) Physician diagnosis	51-59	1974-1977	16	-	33 per 1000 patient years. Multivariable adjusted hazard ratio 1.6 (1.4, 1.9) relative to no CHD	-	17.6 per 1000 patient years. Multivariable adjusted hazard ratio 2.6 (2.0, 3.3) relative to no CHD	-
Whitehall[22]	Prospective cohort study. London, UK.	886 (100%) Rose angina	40-64	1967-1969	5	-	-	-	7.1% (5 years)	-
Rhondda Valley Study[21]	Prospective cohort study. Rhondda Fach, South Wales, UK.	228 (0%) Rose angina	45-74	1967	12	-	-	22.8% (12 years) Age-adjusted odds ratio for Rose angina grade I 1.4 (1.0, 2.0) grade II 1.8 (1.2, 2.9) relative to no angina	-	5.5% (12 years) Age-adjusted odds ratio for Rose angina grade I 1.1 (0.5, 2.5) grade II 2.4 (1.0, 5.5) relative to no angina
British Norwegian Migrant Study[58]	Prospective cohort study. UK, Norway, US.	5532 (45.5%) Rose angina	35-69	1962-1963	5	-	14.5%	6.2%	-	-
Health Insurance Plan study[45;49]	Retrospective cohort study. New York, US.	412 (67%) Physician diagnosis	35-64	1961-1965	4.5	-	17.5%	11.9%	12.0% (cardiac death)	8.5% (cardiac death)

CHD= coronary heart disease; NA=not available

1.2 Epidemiology of acute myocardial infarction

1.2.1 Incidence of acute myocardial infarction

Studies reporting the incidence of acute myocardial infarction (AMI) are shown in Table 5. The methodology employed differs between studies. Some studies use hospitalised patient registries to report the incidence of AMI. However these do not include approximately 40% of AMI which occur as out of hospital cardiac deaths. Alternatively some studies report both fatal and non fatal AMI by including both AMI which are admitted to hospital and out of hospital cardiac deaths. Studies also differ as to whether they look at first events only, or include individuals with first or subsequent AMI or look at AMI attack rates (which may include the same individual on more than one occasion). Different diagnostic criteria between different studies occur and this determines whether mild cases are included as AMI or not. In addition measurements of more sensitive biomarkers for myocardial damage such as cardiac troponins were introduced around 2000. This is likely to result in individuals with a mild troponin leak being labelled as AMI that would previously have been labelled as unstable angina.[59] Another potential problem with myocardial infarction registries is that unrecognised AMI are not included. AMI are more likely to be unrecognised in women.[60] In the Reykjavik study 33% of non-fatal AMI in women were unrecognised. More unrecognised events occurred in the younger age groups (40%) than in the older (27%).[61]

1.2.1.1 Incidence of acute myocardial infarction in hospitalised patient registries

Using the resources of the Rochester Epidemiology Project[62] all individuals hospitalised with a first AMI between 1979 and 1994 were identified. The diagnosis of AMI was validated by review of case notes. In 1994, the age adjusted annual incidence was 260 per 100,000 in men and 180 per 100,000 in women. The Minnesota Heart Survey[38] randomly selected a sample of all case notes of individuals aged 30-74 years discharged from hospital with a diagnosis of acute CHD in the Twin Cities of Minneapolis and St Paul in 1985, 1990 and 1995. Standardised criteria were use to validate a diagnosis of AMI. First and recurrent events were distinguished by examining medical records. The age adjusted annual incidence of first AMI was 272 per 100,000 in men and 105 per 100,000 in women in 1995. The Worcester Heart Attack Study[63] included all 3,148 individuals hospitalised

with a first AMI in Worcester, Massachusetts between 1975 and 1988. In 1988, the age-adjusted incidence rate of first AMI was 240 per 100,000 in men and 137 per 100,000 in women. The Atherosclerosis Risk in Communities Study (ARIC)[64] examined incidence of coronary heart disease in individuals aged 35 to 74 years in four communities in the United States. In 1994, the age adjusted incidence of first AMI was 180 per 100,000 in women and 410 per 100,000 in men. The Corpus Christi Heart Project[65] examined all residents aged 25-74 years in Nueces County, Texas hospitalised with a first AMI between 1988 and 1992. There was a greater incidence of hospitalised first AMI among Mexican Americans (367 per 100,000 in men and 205 per 100,000 in women in 1991/92) than among non-Hispanic whites (342 in men and 150 in women). The age adjusted rate of hospitalisation for AMI in 1997 was 482 per 100,000 using data from the National Hospital Discharge Survey[66]. All discharges from non-institutional hospitals in Columbia were included and no distinction was made between first and recurrent AMI.

1.2.1.2 Incidence of acute myocardial infarction including out of hospital deaths

The World Health Organization MONICA project is a study that consists of 39 collaborative centres in 26 countries and monitors deaths from coronary heart disease, myocardial infarction, coronary care and risk factors.[67-69] The Toulouse MONICA Study[70] reported on the incidence of first AMI in men and women aged 35 to 64 years living in the French department of Haute-Garonne in south-western France. Out of hospital deaths were included. In 1993, the age adjusted incidence for first AMI was 162 per 100,000 in men and 29 per 100,000 in women. In the Oxford myocardial infarction incidence study[71], all patients with AMI in Oxfordshire, England in 1994-95, were identified using WHO MONICA diagnostic criteria. The annual rate for a first or recurrent coronary event (fatal and non-fatal) per 100,000 was 273 for men and 66 for women aged <65 years and 1350 for men and 677 for women aged 65-74 years.

Using the National AMI Register for Sweden[72;73], all 303,324 Swedes discharged from hospitals, or deceased with a diagnosis of AMI between 1987 and 1995 were identified. The age standardised attack rate of AMI in 1995 was 881 per 100,000 in men and 381 per 100,000 in women. These studies have been consistent in their findings that the incidence of AMI increases with age and is higher in men than in women in all age groups. The Regicor Study[74] used a community based registry to determine the incidence of AMI in the province of Gerona, Spain from 1990 to 1992. Age standardised incidence rates (first AMI

cases only) for definite and fatal possible AMI were 130.4 per 100000 men and 27.1 per 100000 women aged 25-74 years.

In the NHANES Epidemiologic Follow-up Study[75] the incidence of first AMI including out of hospital deaths in 9,774 participants aged 35-74 years, was 492 per 100,000 in the 1982-92 cohort.

In the Hunter Valley Heart Attack Study[76] the AMI attack rate (all AMI including out of hospital deaths) in 1979 in a well-defined area in New South Wales, Australia was 258 per 100,000.

Table 5 Incidence of acute myocardial infarction

Study	Location	Type of study	Years of study	No of subjects (proportion of men)	Age (years)	Overall incidence per 100,000 per year	Incidence per 100,000 in men per year	Incidence per 100,000 in women per year
National Hospital Discharge Survey[66]	Non-institutional hospitals, US	Retrospective cross sectional study. All AMI.	1988-1997	746000 in 1997 (60%)	Mean age 67	482* (1997)	NA	NA
Minnesota Heart Survey[38]	Minneapolis-St-Paul, Minnesota, US	Retrospective case note study. All AMI including out of hospital deaths.	1995	3615 (NA)	30-74	NA	491*	168*
Oxford Myocardial Incidence Study[71]	Oxford, UK	Coronary event register. All AMI including out of hospital deaths	1994-1995	476 (72%)	<80	-	292 * (35-64 years)	94 * (35-64 years)
National AMI Register in Sweden[72]	Sweden	Retrospective study using routine data. All AMI including out of hospital deaths.	1987-1995	303324 (NA)	All ages	NA	881* (1995)	400* (1995)
Worcester Heart Attack Study[63]	Massachusetts, US	Nonconcurrent prospective population-based study. All AMI.	1975-1995	5270 (NA)	All ages	184 (1995)	NA	NA
ARIC Study[64]	4 communities, US	Retrospective observational study. First AMI.	1987-1994	7637 (64%)	35-74	NA	410* (1994)	180* (1994)
Rochester Epidemiology Project[62]	Olmsted County, Minnesota, US	Retrospective population-based cohort study. First AMI	1979-1994	1820 (56%)	All ages	218 * (1994)	260 * (1994)	180 * (1994)
Toulouse MONICA Study[70]	France	Coronary event register. All AMI including out of hospital deaths.	1985-1993	3839 events (85%)	35-64	NA	162* (first AMI) 206* (all events) (1993)	29* (first AMI) 32* (all events) (1993)
WHO MONICA Project[68]	37 population in 21 countries across 4 continents	Coronary event register. All AMI including out of hospital deaths.	1985-1993	166000 events (80%)	35-64	NA	434*	103*
Regicor Study[74]	Gerona, Spain	Hospitalised AMI register. All AMI including out of hospital deaths.	1990-1992	1169 (78%)	25-74	NA	130* (first definite and fatal possible AMI)	27** (first definite and fatal possible AMI)

*** Age standardised; AMI= acute myocardial infarction; NA=not available**

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Table 5 continued

Study	Location	Type of study	Years of study	No of subjects (proportion of men)	Age (years)	Overall incidence per 100,000 per year	Incidence per 100,000 in men per year	Incidence per 100,000 in women per year
Corpus Christi Heart Project[65]	Neuces County, Texas, US	Hospitalised AMI register. First AMI.	1988-1992	1805 (60%)	25-74	NA	367* (Mexican Americans) 342* (non-Hispanic whites) (1991/92)	205* (Mexican Americans) 150* (non-Hispanic whites) (1991/92)
NHANES I Epidemiological Follow up Study[75]	US	Prospective cohort study. First AMI including out of hospital deaths.	One cohort, 1971-1982 Second cohort, 1982-1992	9774 in 1982-92 cohort. 358 first AMI (55%)	35-74	492*	734* (white men)	363* (white women)
Hunter Valley Heart Attack Study[76]	Hunter region of New South Wales, Australia	Coronary event register. All AMI including out of hospital deaths.	1979	1271 (77%) definite AMI	20-69	258	400	120

*** Age standardised; AMI= acute myocardial infarction; NA=not available**

1.2.1.3 Trends in incidence of acute myocardial infarction

Many studies have looked at trends in AMI event rates. (Table 6) Some studies have reported a decline in the incidence of AMI[38;63;68;72;77;78] while others have shown that the incidence has remained stable[66;75;79;80]. In several studies the direction of the trend has been different in men and women.[62;71] Changes in the incidence of AMI are postulated to be driven by changes in known coronary risk factors.

Examination of trends in the incidence of AMI over 10 years from the mid 1980s in 37 populations in 21 countries across four continents in the WHO MONICA Project[68] showed that non-fatal definite AMI fell by 2.1% in men and 0.8% in women per year. When fatal events were included there was a similar decline (2.1% and 1.4% in women). Using routine data, all deaths and discharges with AMI in Denmark and Sweden were extracted for the period 1978-98 for Denmark and 1987-1999 for Sweden.[77] Between 1991 and 1998 there was an average annual relative decrease in the incidence of first AMI of 6% in men and 5.9% in women in Denmark. This was significantly higher than in Sweden where the incidence declined by 2.3% in men and 1.8% in women per year between 1991 and 1998. Analyses based on the National AMI Register in Sweden[72] showed that between 1987 and 1995, the age-standardised attack rate of AMI declined by 11% for men and 10% for women. Attack rates include all AMI discharges (principal or secondary coding) or AMI deaths, and a recurrent AMI after 28 days was included as a new event. The attack rate decreased more in younger than in older people and the magnitude of this decline was much greater in younger men than in younger women. The incidence of first AMI in Stockholm County, Sweden[78] declined between 1984 and 1996 in both men and women. The average yearly decline of first AMI was 2% in men and 1.4% in women. The decline was seen in all ages above 44 years in men and above 54 years in women.

In the Worcester Heart Attack Study[63], the incidence of first AMI in Worcester, Massachusetts decreased by 25% between 1975 and 1995. Temporal trends however show an increase initially in age-adjusted incidence rates between 1975 and 1981 after which time these rates declined through 1990 and then slightly increased after this period up to 1995. In the Minnesota Heart Survey[38] AMI discharges for the years 1985, 1990 and 1995 were identified from discharge diagnoses from the Twin Cities metropolitan area hospitals and then validated. The rate of all AMI hospital discharges, declined by almost 20%, between 1985 and 1995.

The incidence of AMI in Perth, Western Australia, declined by 24% in men and 37% in women between 1971 and 1982.[81] Fatal and non-fatal AMI were included using MONICA definitions.

The Atherosclerosis Risk in Communities (ARIC) Study[79] showed that the age-adjusted rate of first hospitalised AMI remained relatively stable between 1987 and 1996 in four US communities. These results differed from MONICA although the study was carried out at the same time and in association with MONICA. Possible explanations may include use of different age groups and diagnostic criteria in the two studies.[68] In ARIC there was a modest decline in attack rates of recurrent hospitalised AMI. Between 1986 and 1996, all AMI discharges and all death records with CHD listed as the cause of death among New Jersey residents ≥ 15 years were analysed.[80] Both first and recurrent events are included in the analysis. The age-adjusted rate for AMI hospitalisation remained stable, whereas the out-of-hospital death rate increased. There was a non-significant mean annual decline in age-adjusted rates of hospitalisation for AMI of 0.8% between 1988 and 1997 using data from the National Hospital Discharge Survey.[66] In NHANES Epidemiologic Follow-up Study[75], between 1971-1982 and 1982-1992, age standardised incidence of fatal and non-fatal AMI increased slightly however this did not reach statistical significance. In a community surveillance study of all AMI from the Pee Dee area of South Carolina, US[82], there was a 22.7% reduction in period prevalence of AMI (including hospitalisations and out-of-hospital deaths) from 1978 to 1985 in individuals aged 35 to 74 years. Period prevalence was defined as a first AMI within one year or an out-of-hospital AMI death. The Oxford myocardial infarction incidence study[71], reported a non-significant decline in non-fatal, definite, AMI in men and a non-significant increase in women. Between 1966-7 and 1994-5 when out of hospital deaths were included, there was a decline in both sexes over the time period, however this only reached significance in men. In Olmsted County, Minnesota[62] between 1979 and 1994 the incidence of hospitalised infarction increased in women but decreased slightly in men. The incidence of AMI increased over time in older persons compared to younger persons.

In summary the incidence of AMI is higher in men than in women and the majority of studies have reported a decrease in the incidence of AMI over time especially in men. Changes in prevalence of known coronary risk factors in the population are most probably responsible for this change. Whilst improved medical intervention and secondary prevention are factors in the reduction of recurrent events.

Table 6 Trends in hospitalisations for acute myocardial infarction in men and women

Study	Location	Type	Years of study	No of AMI (% men)	Age (years)	Change in both sexes	Change in men [% change per year (95% confidence intervals)]	Change in women [% change per year (95% confidence intervals)]
Abildstrom *et al*[77]	Denmark and Sweden	Retrospective routine data. First AMI.	1978-98 (Denmark) 1987-98 (Sweden)	567752 (NA)	All ages	NA	-6% (Denmark) -2.3% (Sweden) (1991-98)	-5.9% (Denmark) -2.3% (Sweden) (1991-98)
National Hospital Discharge Survey[66]	Noninstitutional hospitals, US	Cross sectional study. All AMI.	1988-97	746000 in 1997 (60%)	≥35 Mean 67	-0.8% (-5.1, 3.5) per year	NA	NA
ARIC Study[79]	4 communities, US	Retrospective observational study. First AMI.	1987-1996	9647	35-74	NA	+1.1% (0.0, 2.1)* per year (definite and probable AMI)	+1.7% (-0.1, 3.4)* per year (definite and probable AMI)
MIDAS Database[80]	New Jersey, US	Retrospective population based cross sectional study. All AMI including out of hospital deaths.	1986-96	270,091 (NA)	>15	-2.3% (-3.0, -1.7) per year (fatal events). +2% (1.5, 2.4) per year (non fatal events)	NA	NA
Stockholm Study[78]	Stockholm County, Sweden	Retrospective hospital discharge AMI register. First AMI.	1984-1996	50,850 (61%)	30-89	NA	-18%* -2.0% (-1.7, -2.2) per year	-13%* -1.4% (-1.1, -1.8) per year
National AMI Register in Sweden[72]	Sweden	Retrospective study using routine data. All AMI including out of hospital deaths.	1987-1995	303324	All ages	-10%	-11%	-10%
Oxford Myocardial Incidence Study[71]	Oxford, UK	Coronary event register. All AMI including out of hospital deaths	1966-1967 1994-1995	476 (72%) in 1994-5 No data for 1966-7.	<80	NA	-33% (-44, -21)* (30-69 years)	-8% (-33, 17)* (30-69 years)
Minnesota Heart Survey[38]	Minneapolis-St-Paul, Minnesota, US	Retrospective cross sectional study. First AMI.	1985-1995	3615 (NA)	30-74	NA	-21%* (all) -21%* (first) (ICD code 410)	-21%* (all) -18%* (first) (ICD code 410)

*** Age standardised; AMI=acute myocardial infarction; NA=not available**

Continued over...

Table 6 continued

Study	Location	Type	Years of study	No of AMI (% men)	Age (years)	Change in both sexes	Change in men [% change per year (95% confidence intervals)]	Change in women [% change per year (95% confidence intervals)]
Worcester Heart Attack Study[63]	Massachusetts, US	Non concurrent prospective population-based study. All AMI.	1975-1995	5270 (NA)	All ages	-25%*	NA	NA
Keil *et al*[82]	Pee Dee area of South Carolina, US	Cross sectional study. All AMI	1978 and 1995	NA	35-74	NA	-13.7 (Non-significant)	+32.5 (Non-significant)
Rochester Epidemiology Project[62]	Olmsted County, Minnesota, US	Retrospective population-based cohort study. First AMI	1979-1994	1820 (56%)	All ages	NA	-8% -0.5% per year* (non-significant)	+36% +2.1% per year* (significant)
Toulouse MONICA Study[70]	France	Coronary event register. First AMI	1985-1993	3,174 events (85%)	35-64	NA	-2.0% (-4.1, -0.1) per year	-2.0% (-6.5, 2.5) per year
WHO MONICA Project[68]	37 population in 21 countries across 4 continents	Coronary event register. All AMI including out of hospital deaths.	1985-1993	166000 events (80%)	35-64	NA	-2.1% (-6.9, 2.8) per year for non-fatal definite AMI	-0.8% (-9.8, 6.8)* per year for non-fatal definite AMI
NHANES I Epidemiological Follow up Study[75]	United States	Prospective cohort study. First AMI including out of hospital deaths.	One cohort, 1971-1982 Second cohort, 1982-1992	20,643 individuals in cohorts. 941 first AMI (60%)	35-74	+2% (age race and sex adjusted) (Non-significant)	-7.8%* in white men. (Non-significant)	+21%* in white women. (Significant)
Western Australia Study[81]	Perth, Western Australia	Cross-sectional study. All AMI including out of hospital deaths	1971-1982	381,899 individuals	25-64	NA	-24%* (19, 28%)	-37%* (29, 44%)

*** Age standardised; AMI=acute myocardial infarction; NA=not available**

1.2.2 Acute myocardial infarction morbidity

1.2.2.1 Re-infarction

The Framingham Heart Study showed a second AMI rate of 6% at one year following a Q wave AMI and 13% following a non-Q wave AMI[17] whilst Gilpin et al reported a one year recurrent AMI rate of 6.7%[18]. As expected, patients with a second AMI were older (3 years on average) and had more cardiovascular risk factors (e.g. diabetes and hypertension), presumably demonstrating the potential of these factors to increase the likelihood of a recurrent event. Patients with a second AMI also had more cardiovascular co-morbidity, probably reflecting the consequences of greater cardiac injury. For example, these patients had more atrial fibrillation and a particularly notable excess of heart failure. In addition, individuals with a recurrent AMI had more *non-cardiovascular* co-morbidity, presumably reflecting common aetiological factors (e.g. COPD in relation to smoking) and the older age of these patients.

1.2.2.2 Heart Failure

Following an AMI heart failure can occur due to left ventricular systolic dysfunction as a consequence of myocardial damage. In the Yorkshire AMI Study, 9% of men and 11% of women hospitalised with AMI (either first or recurrent) had a previous history of heart failure.[83] In the Northern Sweden MONICA Project, 6.5% of men and 7.6% of women aged 35-64 years hospitalised with an AMI, had a clinical diagnosis of heart failure at the time of discharge.[84] In the Göteborg Study, 18% of men and 29% of women with AMI had a history of congestive heart failure.[85]In the REGICOR Study 8% of men and 19% of women hospitalised with a first AMI in Spain had a history of heart failure.[86] The prevalence increased substantially with age in both sexes. The National Registry of Myocardial Infarction 2[87] was a prospective observational study of patients admitted to participating hospitals in the US with an AMI. Data was collected on 384,878 men and women admitted to hospital with an AMI between 1994 and 1998. 13% of men and 21% of women had a history of heart failure. In the Alberta Health and Wellness database, 26% of women and 17% of men had a diagnosis of previous heart failure on their discharge record.[56]

1.2.3 Acute myocardial infarction mortality

1.2.3.1 Short-term survival of patients with acute myocardial infarction

Short term survival following AMI has been reported in many studies (Table 7). Comparison between different studies is difficult as some studies do not distinguish between first and recurrent AMI and age specific rates are not always reported. In addition some studies use 28 or 30 day survival end-points where as others use in-hospital survival as a proxy for short term survival.

In the UK the Oxford Myocardial Infarction Incidence Study[71] carried out between 1994-95 the 28 day case fatality for hospitalised AMI was 12.2% in men and 14% in women aged <65 years. If out-of-hospital deaths from AMI were included 28 day case fatality rose to 38.6% in men and 36.1% in women.

A number of European studies have examined short term survival after an AMI. In the REGICOR Study[86] unadjusted 28 day case fatality after a Q wave AMI was 18.8% in women and 9.3% in men aged <75 years. Between 1989 and 1995, definite AMI was monitored in people aged 35-64 years in nine hospitals in Northern Sweden as part of the Northern Sweden MONICA Project.[84] A definite AMI was identified in 2,483 men and 669 women. Pre-hospital case-fatality was significantly higher in men (24.1 vs. 19.3%) but in patients treated in hospital, the case-fatality was significantly lower in men (12.7% vs. 21.2% respectively). Between 1987 and 1995 crude case fatality was 22.6% in men and 27.5% in women aged 30 to 89 years hospitalised with a first or recurrent AMI using data from the Swedish National Acute Myocardial Infarction Register.[73] After adjusting for age women were less likely than men to die at 28 days (odds ratio 0.98; 95% CI 0.96-1.00). In the MONICA Bremen Study[88], 2273 German men and women aged 25-69 years with an admission for a first AMI were identified. The unadjusted 28 day case fatality rate was 23.1% in women and 16.1% in men. Adjusting for the older age of women did not eliminate the difference in case-fatality between men and women completely. The in-hospital case-fatality rate of 921 individuals admitted to a single hospital in Göteborg[85] with AMI, was 12% in men and 19% in women ($p<0.01$). Women were older than men (76 vs. 69 years). In a multivariable analysis, female sex did not appear as an independent risk factor for death.

In the National Registry of Myocardial Infarction 2[87] in-hospital case fatality was 16.7% in women and 11.5% in men in participating hospitals across the US between 1994 and 1998. Similarly in another US study, using data from the National Hospital Discharge Survey[66], in-hospital case fatality in individuals aged ≥35 years between 1988 and 1997 was 11.1%. Case fatality was higher among women than men in all age groups except in those above age 85 years. Using the resources of the Rochester Epidemiology Project[62], case fatality rates for first hospitalised AMI in Olmsted County, Minnesota were examined. In 1994, 28 day case fatality rates were 7% in men and 15% in women. In the Minnesota Heart Survey[89] in 1990, age adjusted 28 day case fatality was 10% in men and 12% in women in the Twin Cities of Minneapolis and St. Paul. The Myocardial Infarction Triage and Intervention (MITI) registry database[90] contains information on 4255 women and 8076 men who developed an AMI in 19 Seattle, Washington area hospitals between 1988 and 1994. In-hospital case fatality was 13.7% in women and 7.8% in men. After adjusting for age women were 20% more likely to die in hospital than men. The EPESE Study[91] was a prospective cohort study of 2182 individuals aged ≥65 years who were living in New Haven, Connecticut in 1982. Over the next 10 years 223 individuals were hospitalised with an AMI. Overall 30 day case fatality did not differ significantly between men (25.0%) and women (21.4%). The Worcester Heart Attack Study[92] examined survival in 3,148 patients hospitalised with a first AMI between 1975 and 1988. The age adjusted in-hospital case fatality rates were 17.9% in women and 15.2% in men.

Table 7 Short-term case fatality following acute myocardial infarction in men and women

Study	Location	Type	Year of study	No of subjects (proportion of men)	Age-group	Case-fatality in men (time)	Age-specific case-fatality in men	Case-fatality in women	Age-specific case-fatality in women
National Registry of Myocardial Infarction 2[87]	US	Prospective observational study. All AMI.	1994-1998	384,878 (60%).	30-89	11.5% (in-hospital) (1998)	<50 years, 3% 65-69 years, 11% 85-89 years, 25%	16.7% (in-hospital) (1998)	<50 years, 6% 65-69 years, 13% 85-89 years, 24%
National Hospital Discharge Survey[66]	US	Retrospective cross sectional study. All AMI.	1988-1997	NA.	≥ 35	3.4%* (in-hospital) (1997)	Only in figure format	4.4%* (in-hospital) (1997)	Only in figure format
REGICOR Study[86]	Gerona, Spain	Hospitalised AMI register. First AMI.	1978-1997	2769 (84%)	25 -74	9.3% (28 days)	< 65 years, 7% 65-74 years, 14%	18.8% (28 days)	< 65 years, 7% 65-74 years, 27%
Oxford Myocardial Incidence Study[71]	Oxford, UK	Coronary event register. All AMI.	1994-1995	476 events (72%)	<80	12% *(<65years) (1 month)	30-49 years, 2% 50-69 years, 18%	14% *(<65years) (1 month)	30-49 years, 25% 50-69 years, 48%
Northern Sweden MONICA Study[84]	Northern Sweden	Coronary event register. All AMI.	1989-1995	3,152 (79%)	35-64	12.7% (28 days)	NA	21.2% (28 days)	NA
Swedish National AMI Register[73]	Sweden	Coronary event register. First AMI in that time period.	1987-1995	353,905 (63%)	30-89	22.6% (28 days)	30-49 years, 6% 65-69 years, 18% 85-89 years, 43%	27.5% (28 days)	30-49 years, 10% 65-69 years, 19% 85-89 years, 40%
Rochester (Minnesota) Epidemiology Project[62]	Olmsted County, Minnesota, US	Retrospective population based cohort study. First AMI.	1994	1820 (56%)	All ages	7% (28 days)	NA	15% (28 days)	NA
MITI Registry[90]	Washington, US	Prospective observational study. All AMI admitted to CCU.	1988-1994	12,331 (66%)	All ages	7.8% (in-hospital)	NA	13.7% (in-hospital)	NA
EPESE Project[91]	New Haven, Connecticut, US	Prospective cohort study. All AMI.	1982-1992	223 (46%)	≥65	25% (30 days)	NA	21.4% (30 days)	NA
Minnesota Heart Survey[89]	Minneapolis-St-Paul, Minnesota, US	Retrospective cross sectional study. First AMI.	1985-1990	7,032 (70%) All AMI (Not available for first AMI)	30-74	10%* (28 days) (1990)	NA	12%* (28 days) (1990)	NA
MONICA Bremen Study[88]	Bremen, Germany	Coronary event register. First AMI.	1985-1990	2,273 (75%)	25-69	17%* (28 days)	35-39 years, 8% 65-69 years, 24%	21% * (28 days)	35-39 years, 8% 65-69 years, 24%
Worcester Heart Attack Study[92]	Massachusetts, US	Non concurrent prospective population-based study. First AMI.	1975- 1988 (6 one year periods)	3148 (61%)	All ages	15.2%* (in-hospital)	NA	17.9%* (in-hospital)	NA
Göteborg AMI Study[85]	Sweden	Prospective observational study. All AMI.	1986-1987	921 (67%)	All ages	12% (30 days)	NA	19% (30 days)	NA

*** Age standardised; AMI=acute myocardial infarction; NA=not available**

1.2.3.2 Trends in short-term survival following acute myocardial infarction

Trends in short-term survival following an AMI are shown in Table 8. Whilst it is postulated that changes in the incidence of AMI are driven by changes in known coronary risk factors[93] it is thought that changes in survival rates are determined by changes in medical care (improvements in the immediate management of an AMI and improvements in secondary prevention). Comparison between different studies is hindered by differences in methodology. Many of the studies do not distinguish between first and subsequent AMI. Many studies including the MONICA studies have included out-of-hospital deaths in their analysis. Not all studies have adjusted for prognostic factors which may influence changes in survival over time.

Using routine data in Scotland, 117,718 patients admitted to hospital in Scotland with a first AMI between 1986 and 1995 were identified.[94] Over the time period 30 day case-fatality fell by 16% in men and 27% in women after multivariable adjustment. In the Oxford myocardial infarction incidence study[71] there was also a significant reduction in 30 day case-fatality between 1966-7 and 1994-5 in both sexes however the decline was greater in women (53%) compared to men (43%).

Other European studies have also demonstrated a reduction in short-term case fatality following AMI. Using routine data Abildstrom et al[77] showed a significant reduction in 28 day case-fatality following an AMI hospitalisation in men and women, in different age groups, in Denmark (1978-98) and in Sweden (1987-98). Deaths occurring on the day of the infarct were excluded. Improvements in short-term survival following an AMI have also been reported by two other Swedish studies up to 1995.[72;84] The National AMI Register in Sweden[72] examined case-fatality in all 303,324 Swedes with an AMI admission or death between 1987 and 1995. Age standardised 28 day case-fatality declined from 49% to 45% in men and from 45% to 42% in women. The improvement in short-term case fatality was even more marked for patients alive on admission i.e. from 30 to 23% in men and from 28 to 23% in women. In the Northern Sweden MONICA Project[84] over the period 1989 to 1995, age standardised 28 day case fatality following an admission with an AMI declined significantly in both men and women. The Toulouse-MONICA Study[70] showed a significant decline in 28 day case-fatality following a first AMI between 1985 and 1993 however like many of the MONICA studies deaths in individuals who die before reaching hospital with an AMI were included.

In-hospital case-fatality for all AMI in the Worcester Heart Attack Study[95] was 19.9% in 1975 and 12.0% in 2001 (p value for trend <0.001). After controlling for age and sex there was a 63% decline in case-fatality during the 25 year period. The National Hospital Discharge Survey[66] also demonstrated a significant decline in in-hospital case fatality following AMI. Age adjusted in-hospital case fatality decreased by nearly half, from 7.6% in1988 to 3.9% in 1997. The average annual percentage decline was significantly higher among older patients in both men and women. In the Ontario Myocardial Infarction Database[96], there was a modest improvement in short term survival after an AMI in 89,456 individuals hospitalised between 1992 and 1996. The 30-day risk-adjusted case fatality rate declined from 15.5% in 1992 to 14.0% in 1996. In New Jersey, between 1986 and 1996, 30 day case fatality after an AMI admission decreased by 17.3%.[80] The Minnesota Heart Survey[89] demonstrated an improvement in short term case fatality in men and women. Between 1985 and 1990 there was a 26% reduction in 28-day case fatality in men and a 16% reduction in women. In the ARIC Study[64], between 1987 and 1994, age-adjusted 28 day case fatality rate fell by 4.1% per year in men and 9.8% per year in women. This decline was statistically significant only among women. In contrast the Rochester Epidemiology Project[62], demonstrated no significant temporal trend in 28 day case-fatality rates for AMI. Unadjusted case fatality rates for first AMI in men were 10% in 1979 and 7% in 1994 (14% and 15% respectively in women). The case-fatality rate decreased over time in persons younger than 75 years of age, but did not change in persons 75 years of age or older.

Table 8 Trends in short-term survival following acute myocardial infarction

Study	Location	Type of study	Years	No of subjects with AMI (proportion of men)	Age (years)	Case-fatality in men at start of study (time)	Case-fatality in men at end of study (time)	Change in case-fatality in men	Case-fatality in women at start of study	Case-fatality in women at end of study	Change in case-fatality in women
Worcester Heart Attack Study[95]	Massachusetts, US	Prospective observational population-based study. All AMI.	1975- 2001 (13 one year periods)	10440 (61%)	All ages	19.9% (in-hospital) Both sexes	12.0% (in-hospital) Both sexes	Both sexes Yes 0.4 (0.3, 0.5) for 2001 relative to 1975-8 adjusted for age, and sex	NA	NA	NA
Abildstrom *et al*[77]	Denmark and Sweden	Retrospective study using routine data. First AMI.	1978-98 (Denmark) 1987-98 (Sweden)	567752 (NA)	All ages	NA (1-28 days)	NA (1-28 days)	Yes Denmark 30-54 years -5.8 (-6.8,-4.8) 75-94 years -5.9 (-6.5,-5.2) Sweden 30-54 years -2.4 (-3.2, -1.5) 75-94 years -3.8 (-4.3,-3.3)	NA (1-28 days)	NA (1-28 days)	Yes Denmark 30-54 years -5.6 (-7.3,-3.8) 75-94 years -5.8 (-6.6,-4.9) Sweden 30-54 years -4.2 (-5.5, -2.8) 75-94 years -3.4 (-3.9,-2.9)
National Hospital Discharge Survey[66]	US	Retrospective cross sectional study. All AMI.	1988-1997	NA	≥ 35	7.0%* (in-hospital)	3.4%* (in-hospital)	Yes. (p=0.005)	8.2%* (in-hospital)	4.4%* (in-hospital)	Yes. (p=0.02)
Ontario Study[96]	Canada	Retrospective study using routine data. All AMI.	1992-1996	89,456 (64%)	All ages	12.8% (30 days)	11.6% (30 days)	Yes. (p<0.05)	20.1% (30 days)	19.1% (30 days)	No
ARIC[79] **Study**	US	Retrospective observational study. All AMI.	1987-1996	14,842 (66%)	35-74	NA (28 days)	NA (28 days)	No -4.1%* per year (-10.5, +2.8)	NA (28 days)	NA (28 days)	Yes -9.8%* per year (-2.3, -16.7)
MIDAS Database[80]	New Jersey, US	Retrospective cross sectional study. All AMI.	1986-96	270,091 (NA)	>15	NA (30 days)	NA (30 days)	Both sexes Yes -17.3%	NA	NA	NA

***Age standardised; AMI= acute myocardial infarction; NA=not available**

Continued over…

Table 8 continued

Study	Location	Type of study	Years	No of subjects with AMI (proportion of men)	Age (years)	Case-fatality in men at start of study (time)	Case-fatality in men at end of study (time)	Change in case-fatality in men	Case-fatality in women at start of study	Case-fatality in women at end of study	Change in case-fatality in women
Oxford Myocardial Infarction Incidence Study[71]	Oxford, UK	Coronary event register. All non-fatal definite AMI	1994-1995	476 (72%) AMI events	<80	27% * (30 days)	15% * (28 days)	Yes -43% * (-73, -14)	46% * (30 days)	22% * (28 days)	Yes - 53% * (-87,-19)
Northern Sweden MONICA Study[84]	Northern Sweden	Coronary event register. All AMI.	1989-1995	3,152 (79%)	35-64	15% * (28 days)	10% * (28 days)	Yes -5% * per year	26% * (28 days)	18% * (28 days)	Yes -8% * per year
Swedish National AMI Register[73]	Sweden	Retrospective study using routine data. First AMI in that time period.	1987-1995	353,905 (63%)	>19	30% * (28 days)	23%* (28 days)	NA	28%* (28 days)	23%* (28 days)	NA
Linked Scottish Morbidity Record Database[94]	Scotland, UK	Retrospective study using routine data. First AMI.	1986-1995	117,718 (58%)	All ages	Both sexes 25.1 % (30 days)	Both sexes 19.4 % (30 days)	Yes -46% (multivariable adjusted)			Yes -27% (MV adjusted)
Worcester Heart Attack Study[63]	Massachusetts, US	Nonconcurrent prospective study. All AMI.	1975-1995	5270 (NA)	All ages	Both sexes 17.8 (in-hospital)	Both sexes 11.7% (in-hospital)	Both sexes Yes Relative risk 0.43 (0.32,0.58) Adjusted for age, sex and co-morbidity.	NA	NA	NA
Rochester (Minnesota) Epidemiology Project[62]	Olmsted County, Minnesota, US	Retrospective population-based cohort study. First AMI.	1979-1994	1820 (56%)	All ages	10% (28 days)	7% (28 days)	No	14% (28 days)	15% (28 days)	No
Toulouse-MONICA Study[70]	Haute-Garonne, France	Coronary event register. First AMI including out-of-hospital deaths	1985-1993	3839 (85%) All AMI (number of first AMI not reported)	35-64	43.4%* (28 days)	31.8%* (28 days)	Yes -3.2% (-4.1, -2.3)	67.9%* (28 days)	33.6%* (28 days)	No -33% (-13.2, 6.6)
Minnesota Heart Survey[89]	Minneapolis-St-Paul, Minnesota, US	Retrospective cross sectional study. First AMI.	1985-1990	7,032 (70%) All AMI (number of first AMI not reported)	30-74	13%* (28 days)	10%* (28 days)	Yes. Relative risk 0.74 (0.58-0.96) Adjusted for age and prior AMI	15%* (28 days)	12%* (28 days)	No. Relative risk 0.84 (0.62-1.13). Adjusted for age and prior AMI

***Age standardised; AMI= acute myocardial infarction; NA=not available**

1.2.3.3 Longer term survival of patients with acute myocardial infarction

Table 9 shows studies examining the longer term prognosis following AMI. The REGICOR Study[86] examined the risk of death in individuals aged 25-74 years who were admitted to a tertiary hospital in Gerona, Spain with a first AMI between 1978 and 1997. Unadjusted three year case fatality in those who had survived the first 30 days was 12%. Women had a worse three year case-fatality compared to men (21.8% versus 10.3%). Another European study using the Helsinki Coronary Registry[97] included information on 388 men and 178 women with a first AMI between 1970 and 1971. Among 28 day survivors, age adjusted five year case fatality was 17.3% in women and 26.3% in men.

The Alberta Health and Wellness databases[56] examined longer-term case-fatality in 7,158 women and 15,809 men admitted to hospital following an AMI between 1993 and 2000 in the Western Canadian province of Alberta. Five year crude case fatality was 38.8% in women and 26.8% in men.

In the Worcester Heart Attack Study[98], two year case fatality rate in persons hospitalised with a confirmed AMI between 1975 and 1995 in Worcester, Massachusetts, was 28.9% in women and 19.6% in men. Similarly, two year case fatality was 20% in men and 29% in women hospitalised with an AMI from the MITI Registry in Washington.[90] In the Minnesota Heart Survey[89], three year age-adjusted case fatality following a first AMI was 18% in men and 24% in women aged 30 to 74 years in 1990.

Table 9 Longer-term case fatality following acute myocardial infarction in men and women

Study	Location	Type of study	Year of study	No of subjects (proportion of men)	Age (years)	Case-fatality in men (time)	Age-specific case-fatality in men	Case-fatality in women	Age-specific case-fatality in women	Adjusted relative risk
Alberta Health and Wellness Databases[56]	Canada	Retrospective study using routine data. All AMI.	1993-2000	22967 (69%)	≥ 18	26.8% (5 years)	NA	38.8% (5 years)	NA	1.0 (0.9, 1.1) Multivariable adjusted men relative to women
REGICOR Study[86]	Gerona, Spain	Coronary event register. First AMI.	1978-1997	2769 (84%)	25-74	22% (3 years excluding first 28 days)	NA	10% (3 years excluding first 28 days)	NA	1.3 (0.9, 1.9) Multivariable adjusted women relative to men
Worcester Heart Attack Study[92]	Massachusetts, US	Noconcurrent prospective study. First AMI.	1975-1988 (6 one year periods)	6826 (62%)	All ages	19.6% (2 years)	<50 years, 6.0% 60-69 years, 17.2% ≥80 years, 51.3%	28.9% (2 years)	<50 years, 8.9% 60-69 years, 18.4% ≥80 years, 46.0%	1.2 (1.0, 1.4) Multivariable adjusted men relative to women
MITI Registry[90]	Washington, US	Prospective observational study. All AMI admitted to CCU.	1988-1994	12,331(66%)	All ages	20% (2 years)	NA	29% (2 years)	NA	0.9 (0.8, 1.0) Multivariable adjusted women relative to men
Minnesota Heart Survey[89]	Minneapolis-St-Paul, Minnesota, US	Retrospective cross sectional study. First AMI.	1985-1990	7,032 (70%) All AMI (number of first AMI not reported)	30-74	18%* (3 years) (1990)	NA	24%* (3 years) (1990)	NA	NA
Perth Coronary Registry[99]	Perth, Australia	Coronary event register.	1971	1078 (NA)	25-64	Both sexes. 33% (5 years) 48% (9 years) (Excluding first 28 days)	NA	NA	NA	NA
Helsinki Coronary Registry[97]	Finland	Coronary event register. First AMI.	1970-1971	566 (69%)	<66	26.3%* (5 years excluding first 28 days)	NA	17.3%* (5 years excluding first 28 days)	NA	NA

***Age standardised; AMI= acute myocardial infarction; NA=not available**

1.2.3.4 Trends in longer term survival following AMI

There are few studies describing trends in longer term case fatality following AMI (Table 10). In Scotland, 5 year case-fatality fell from 52.3% in 1985 to 46.3% in 1991.[94] The relative risk of death fell by 34% in men and 30% in women using multivariable analysis to adjust for age and co-morbidities. In the Minnesota Heart Survey[89] age adjusted three-year case fatality after a first AMI declined from 21% to 18% in men and from 29% to 24% in women between 1985 and 1990, however neither of these falls was statistically significant.

In summary in recent years there has been a decrease in the incidence of AMI and a decreased occurrence of recurrent coronary events. In addition case-fatality following an AMI has improved. Improvements in primary prevention, the acute management of AMI and secondary prevention have contributed to these improvements. To further improve mortality however we need to tackle the large proportion of AMI which do not survive to reach hospital.

Table 10 Trends in longer-term case fatality following acute myocardial infarction

Study	Location	Type of study	Years	No of subjects (proportion of men)	Age (years)	Case-fatality in men at start of study (time)	Case-fatality in men at end of study (time)	Significant change in case-fatality in men	Case-fatality in women at start of study	Case-fatality in women at end of study	Significant change in case-fatality in women
Linked Scottish Morbidity Record Database[94]	Scotland, UK	Retrospective cohort study using routine data. First AMI.	1986-1991	117,718 (58%)	All ages	Both sexes 52.3 % (5 years excluding first 30 days)	Both sexes 46.3 % (5 years excluding first 30 days)	Yes -34% (multivariable adjusted)	NA	NA	Yes -30% (multivariable adjusted)
Minnesota Heart Survey[89]	Minneapolis-St-Paul, Minnesota, USA	Retrospective case note study. First events.	1985-1990	7,032 (70%) All AMI (number of first AMI not reported)	30-74	21%* (3 years)	18%* (3 years)	No. Relative risk 0.85 (0.67, 1.08)	29%* (3 years)	24%* (3 years)	No. Relative risk 0.81 (0.63, 1.03)

*** Age standardised; AMI= acute myocardial infarction; NA=not available**

1.3 Epidemiology of heart failure

1.3.1 Prevalence of heart failure

The prevalence of the clinical syndrome of heart failure in population studies primarily comes from two sources. Firstly, studies based on physician records or prescriptions for heart failure medications and secondly, cross-sectional or cohort studies where individuals are screened for heart failure. In addition a number of studies have reported on the prevalence of left ventricular systolic dysfunction (both symptomatic and asymptomatic) and the prevalence of heart failure with preserved systolic function.

1.3.1.1 Population studies based on physician records and prescriptions

The prevalence of heart failure in population studies based on physician records is shown in Table 11. The prevalence of heart failure in 211 general practices in England and Wales covering 2.6% of the population was examined using the General Practice Research Database.[100] Diagnosis and treatment data were recorded by general practitioners participating in the General Practice Research Database in the course of their clinical work based on clinical judgement or on information given to them by hospital or other medical personnel. Diagnostic data were recorded using OXMIS (based on ICD-8) and/or READ (based on ICD 9) code terms and submitted to the database on a regular basis. The prevalence of heart failure was 1.2% in men and 1.6% in women increasing to 19% in those over 85 years in 1998. The morbidity statistics from General Practice also recorded diagnostic information from all face-to-face contacts between a General Practitioner or a practice nurse and a patient in 60 General Practices in England and Wales during an earlier time period, 1st September 1991 to 31st August 1992.[101] Data was entered on a computer in the practice using READ codes. The prevalence of heart failure was lower at 0.8% in men and 1.0% in women but also increased dramatically with age.

The REACH study was a retrospective study using administrative databases of outpatient visits and hospitalisations within the Henry Ford Health System.[102] 29,686 patients with heart failure were identified between 1989 and 1999. The prevalence in 1999 was 14.5 per 1,000 in men and 14.3 per 1,000 in women. There was an annual increase in prevalence of 1 per 1,000 in men and 0.9 per 1,000 in women. In the Rochester Epidemiology Project[103],

the overall prevalence of heart failure was 2.7 per 1000 in persons 25 through 74 years of age in 1981. Patients who had a diagnosis of heart failure made at an inpatient or outpatient visit in Rochester Minnesota were identified and the diagnosis of heart failure confirmed through a review of medical records. Again using the resources of the Rochester Epidemiology Project[104] in 1997 a random sample of 2,042 residents who were at least 45 years old were identified. Each participant's medical records were reviewed to see if any diagnosis of heart failure had been made and checked to see if the documented clinical information fulfilled Framingham criteria. The overall prevalence of heart failure was 2.2% increasing to 8.4% in those over 75 years.

There are 4 retrospective studies of heart failure prevalence in the UK, which used drug prescriptions as a surrogate for heart failure. Lip et al[105] reported an overall prevalence of heart failure of 24 per 1000 in three GP practices in Birmingham in patients over 40 years of age. Mair et al[106] reported a prevalence of 80.5 per 1000 among patients over 65 years attending 2 general practices in Liverpool in 1994. Clarke et al[107] found the prevalence of heart failure in six general practices in Nottinghamshire in 1992 was 2.4 per 1000 among those under 60 years increasing to 32 per 1000 in those over 60 years. Parameshwar et al[108] found the prevalence of heart failure in three general practices in North West London in 1988 was 0.6 per 1000 among patients under 65 years of age rising to 27.7 per 1000 in those over 65 years. In these studies patients were identified through prescriptions for heart failure medications (either diuretics alone[107;108] or heart failure medication[105;106]) and a diagnosis of heart failure was confirmed using the clinical case notes. Patients had to satisfy one of the four clinical diagnostic criteria: symptomatic response to diuretic treatment with evidence of heart disease clinically, on electrocardiogram or on echocardiogram; dyspnoea with clinical signs of heart failure on examination; dyspnoea with evidence of cardiomegaly or pulmonary oedema on chest X-ray; dyspnoea with left ventricular dysfunction on echocardiogram or left ventriculogram.[105;107;108]

Table 11 Prevalence of heart failure in population studies based on physician records and prescriptions

Study	Location	Type of study	Year of study	Number of subjects with HF (proportion men)	Age (years)	Overall prevalence per 1,000	Prevalence in men per 1,000	Prevalence in women per 1,000	Prevalence in older age group
Rochester Epidemiology Project[103;104]	Olmsted County, Rochester, Minnesota, US	Cross sectional study. Clinical criteria	1997-2000 1982	2042 (NA) subjects screened 113 (50%)	≥45 0-74	22 2.6	27 3.3	17 2.1	84 (≥75 years) NA
General Practice Research Database[100]	211 general practices in England and Wales	Retrospective cohort study using UK national data. Physician diagnosis.	1998	16094 of 1.4 million (40%)	All ages	-	12.2	15.8	191 in men and 189 in women (≥85 years)
REACH study[102]	Michigan, US	Retrospective study using administrative databases of outpatient visits and hospitalisations	1989-1999	29,686 (47%)	All ages Mean age men 69 and women 74	NA	14.5 (1999)	14.3 (1999)	NA
Lip *et al* [105]	3 group general practices, West Birmingham, UK	Retrospective cross sectional study. Prescribing data, computerised and clinical records.	Published 1997	188 of 7555 (45%)	≥40 Mean age 72	24	NA	NA	NA
Mair *et al* [106]	2 group general practices, Liverpool, UK	Retrospective cross sectional study. Prescribing data, computerised and clinical records.	1994	266 of 17405 (40%)	All ages	15.3	26.6 (>35 years)	34.5 (>35 years)	80.5 (≥65 years)
PACT (Prescribing Analysis and Cost)[107]	Nottinghamshire, UK	Observational study. Diuretic prescriptions.	1991-1992	281 (NA)	All ages	8-16	NA	NA	44 (≥70 years)
Morbidity statistics from General Practice[101]	60 general practices in England and Wales	Retrospective cross sectional study using UK national data.	1991-1992	502,493 practice population	All ages	8.9	7.7	10.1	158 in men and 135 in women (≥85 years)
Parameshwar *et al* [108]	3 general practices, north west London, UK	Retrospective cross sectional study. Diuretic prescriptions and clinical records.	1988	117 of 30304 (39%)	All ages Mean age 74	3.9	NA	NA	27.7 (>65 years)
Gibson *et al* [109]	2 rural communities in North Carolina and Vermont, US	Cross sectional study. Physician questionnaire.	1962-1964	352 (44%)	All ages	9-10	8	9-11	65 (>65 years)

HF=heart failure; NA=not available

1.3.1.2 Population studies based on clinical criteria

The prevalence of heart failure in cross sectional or cohort studies is shown in Table 12. The EPICA study[110] is a cross-sectional observational study where 5,434 individuals attending 365 general practitioners in mainland Portugal in 1998 were recruited consecutively and stratified by age. Patients with 3 or more points on the Boston questionnaire or on any heart failure medication underwent further cardiovascular investigations and heart failure cases were identified according to the Guidelines of the European Society of Cardiology. The prevalence of heart failure in subjects over 25 years of age was 4.4% and increased to 7.6% in subjects aged 60-69 years. The presence of heart failure in 5,540 participants of the Rotterdam Study[111] which took place between 1990 and 1993 was determined by assessment of symptoms and signs and use of heart failure medications. In this population based cohort study the prevalence of heart failure was 39 per 1000 in subjects aged 55-94 years. In 1990-91, 501 randomly selected individuals in Helsinki born in 1904, 1909 and 1914 were examined clinically and with cardiac ultrasound as part of the Helsinki Ageing Study.[112] Heart failure was diagnosed by criteria based on symptoms, clinical examination and chest radiography. The prevalence of heart failure was 8.2% in men and women aged 75-86 years. In the study of men born in 1913[113], a sample of 973 men, 50 years old, born in Gőteborg, Sweden, were initially identified in 1963 and followed for 17 years. Heart failure diagnosis was based on a scoring system which included dyspnoea, cardiac disease, heart failure treatment or death from heart failure. The prevalence of 'manifest' heart failure was 2.1% at 50 years, 4.3% at 60 year and 13% at 67 years. In another Swedish population study[114] the prevalence of heart failure diagnosed on clinical history, examination and chest X-ray, was 11-17% in men and 8-11% in women aged 70-75 years. In an earlier study of a random sample of 476 persons over 62 years of age from Sheffield, England the prevalence of heart failure was 3% increasing to 5% if hypertensive heart disease was included.[115]

In the US in the Cardiovascular Health Study[29], 5,201 individuals aged 65 years and older underwent baseline screening in 1989-90. Self report of heart failure required confirmation by the use of heart failure medications or a physician diagnosis of heart failure or a heart failure discharge diagnosis. The overall prevalence of heart failure was 2.0% in those ≥65 years and 2.6% in those >85 years which is much lower than other studies. The discrepancy could be a consequence of healthy participant bias that resulted in a healthier than average study sample. 687 predominantly African-American participants were added to the Cardiovascular Health Study in 1992. In 1994-95 clinic visit (n=4,942)

echocardiograms were recorded along with examinations and interviews.[116] The prevalence of heart failure was 8.8% (mean age 77 ± 5 years). The prevalence of heart failure increased even in the very old age range and this was particularly striking in women in whom it increased more than twofold from 6.6% at age 65-69 to 14% at age >85 years. The authors do not address why the prevalence is so different between these two studies – the later time period and the inclusion of African-American participants are unlikely to explain the huge discrepancies. In the Framingham Study[117] during the 1980s, among individuals aged ≥ 45 years, the age-adjusted prevalence of heart failure was 2.4% in men and 2.5% in women. Using data collected from the National Health and Nutrition Examination Survey[118] (NHANES-1, 1971-1975) the prevalence of heart failure was 20 per 1000 in subjects under 74 years based on self reporting and a clinical scoring system. In an earlier survey of residents of Evans County, Georgia, US the prevalence of heart failure was 21 per 1000 in persons aged 45-74 years.[119]

The prevalence of heart failure varies substantially between the various studies and this could be due to the different diagnostic criteria and the different age groups studied. In most of these studies heart failure was diagnosed clinically and no objective evidence of left ventricular dysfunction, apart from chest X-ray, was obtained.

Table 12 Prevalence of heart failure in population studies based on clinical criteria

Study	Location	Type of study Definition of HF	Year of study	Number of subjects with HF (proportion men)	Age (years)	Overall prevalence per 1000	Prevalence in men per 1000	Prevalence in women per 1000	Prevalence per 1000 in older age group
EPICA Study[110]	Portugal	Cross sectional observational study of patients attending 365 primary care practices. ESC clinical criteria for HF.	1998	551 of 5434 (37%)	>25 Mean age 68	44.6	43.3	43.8	127 (70-79 years)
Cardiovascular Health Study[29;116]	US	Prospective cohort study. Self report and confirmation by physician diagnosis or heart failure medication.	1994-1995 1989-1990	425 of 4842 (40%) 5201 (43%)	≥65	NA	NA	NA	88 (≥65 years) 25 in men and 17 in women (≥65 years) 29 in men and 22 in women (≥85 years)
Rotterdam Study[111]	Rotterdam, The Netherlands	Prospective cohort study. Clinical criteria and medications.	1990-1993	5540 assessed (41%)	55-95 Mean age 69	39 (>55 years)	37 (>55 years)	40 (>55 years)	130 (75-84 years)
Helsinki Ageing study[112]	Helsinki, Finland	Prospective population study. Clinical and radiological criteria	1990-1991	501 (27%)	75-86	NA	NA	NA	82 in both sexes, 93 in men and 52 in women (75-86 years)
70 year old people in Göteborg[114]	Göteborg, Sweden	Prospective cohort study Clinical criteria and CXR	Screened 1971-1972 Re-screened 1976-1977	1148 (39%)	70 and 75 years	NA	NA	NA	110 in men and 80 in women (70 years) 170 in men and 110 in women (75 years)
Framingham heart study[117]	Framingham, US	Prospective cohort study. Clinical score for HF diagnosis	1948-1988	652 of 9504 (51%)	≥45	NA	24 (1980s)	25 (1980s)	66 in men and 79 in women (80-89 years)
Study of men born in 1913[113]	Göteborg, Sweden	Prospective cohort study. Heart failure scoring system.	1963-1980	855 (100%)	50-67	NA	21 (50 years)	NA	130 (67 years)
NHANES-I[118]	US national data	Prospective cohort study. Clinical criteria for HF diagnosis	1971-1975	14,407	25-74	20	19	20	45 (65-74 years)
Garrison *et al*[119]	Evans Country, Georgia, US	Cross sectional study. Clinical criteria for HF.	1960-1962	3102 (NA)	15-74	21.2 (45-74 years)	24.8 (45-74 years)	17.8 (45-74 years)	34.7 (65-74 years)

HF= heart failure; NA=not available

1.3.1.3 Prevalence of left ventricular systolic dysfunction based on echocardiographic surveys

In the UK in the Echocardiographic Heart of England Screening study[120], 3960 patients aged 45 years and older from primary care practices in the West Midlands region of England were assessed by history, examination, electrocardiography and echocardiography between 1995 and 1999.(Table 13) The prevalence of left ventricular systolic dysfunction defined as an ejection fraction ≤40% was 2.9% in men and 0.7% in women increasing to 3.6% in those aged over 75 years. 58% of patients with heart failure had preserved systolic function and 47% of patients with left ventricular systolic dysfunction were asymptomatic. In the Glasgow study[121] 1,640 persons aged 25-74 years who had taken part in the Glasgow MONICA study were assessed with questionnaires, electrocardiography and echocardiography. The prevalence of definite left ventricular systolic dysfunction defined as a left ventricular ejection fraction ≤30% was 2.9%, was higher in men than in women (4.0% versus 2.0%) and increased with age. If participants with an ejection fraction of ≤35% were included the prevalence was 7.7%. The prevalence of asymptomatic left ventricular systolic dysfunction was 1.4%. In another UK study, 817 elderly patients aged 70-84 years, from a four centre group general practice in Poole Dorset underwent echocardiographic qualitative assessment of left ventricular systolic function.[122] The overall prevalence of left ventricular systolic dysfunction was 7.5% and was higher in men than in women (12.8% versus 2.9%). Prevalence was more than twice as high at age ≥ 80 than at ages 70-74 years (20.5% in men and 5.4% in women).

A random sample of 433 men and women aged 75 years from the city of Vasteras, Sweden were assessed by a single physician for the presence or absence of heart failure using clinical history, examination and electrocardiogram.[123] All patients underwent an echocardiogram to which the physician was blinded. The prevalence of left ventricular systolic dysfunction (defined as an ejection fraction <43% or a wall motion index <1.7) was 6.8%. The prevalence of left ventricular systolic dysfunction was significantly higher in men (10.2%) than in women (3.4%). 46% of patients with left ventricular systolic dysfunction were asymptomatic and 46% of patients with heart failure had preserved left ventricular function. In the EPICA study[110] the prevalence of heart failure due to systolic dysfunction was 1.3% and the prevalence of heart failure with normal systolic function was 1.7%. A higher proportion of women (2.4%) than men (0.9%) had preserved systolic function and a higher proportion of men than women had systolic dysfunction (1.9% versus 0.8%). In the Rotterdam study[111] the prevalence of left ventricular systolic

dysfunction (fractional shortening ≥25%) was 2.5 times higher in men than in women (5.5% versus 2.2%) however in contrast with other studies the prevalence did not increase with age. 60% of persons with left ventricular systolic dysfunction were asymptomatic. In a cross sectional survey of a random sample of 2158 patients ≥ 50 years from three general practices in Copenhagen, Denmark, 357 patients with definite or suspected heart disease were identified through review of case notes and questionnaires and an echocardiogram was performed in 126 of these patients.[124] The prevalence of left ventricular systolic dysfunction was 2.9%. 34% of patients with left ventricular systolic dysfunction were asymptomatic and 56% of patients with heart failure had preserved systolic function. The prevalence of left ventricular systolic dysfunction was 11.3% in elderly persons in the Helsinki Ageing Study[112] and 51% of patients had heart failure with preserved systolic function.

In the Rochester Epidemiology Project[104] the prevalence of left ventricular systolic dysfunction was 2.0% in individuals ≥ 45 years and 4.4% in those ≥ 75 years. 44% of patients with left ventricular systolic dysfunction were asymptomatic and 55% of patients with heart failure had preserved left ventricular function. In the Cardiovascular Health Study[116], 42% of men and 67% of women with heart failure had normal left ventricular function (ejection fraction ≥55%) and 80% had normal or mildly reduced left ventricular systolic function (ejection fraction ≥45%).

Table 13 Population prevalence of echocardiographic left ventricular systolic dysfunction

Study	Location	Type of study and definition of LV systolic dysfunction	Year of study	Number of subjects undergoing echo (proportion men)	Age (years)	Overall prevalence per 1,000	Prevalence per 1,000 in men	Prevalence per 1,000 in women	Prevalence per 1,000 in older age group	Proportion of HF patients with preserved LV function	Proportion of patients with LVSD who are asymptomatic
Hedberg *et al*[123]	Västerås, Sweden	Cross sectional population study. Wall motion index <1.7 or EF <43%.	Published 2001	433 (49%)	75	NA	NA	NA	68 in both sexes, 102 in men and 34 in women (75 years)	46%	46%
Rochester Epidemiology Project[104]	Olmsted County, Minnesota, US	Cross sectional survey. Ejection fraction ≤40%	1997-2000	2042 (NA)	≥45 Mean age 63	20	36	10	44 (≥75 years)	44%	55%
Echocardiographic Heart of England Screening study[120]	16 general practices, West Midlands, UK	Cross sectional survey. Ejection fraction <40%	1995-1999	3960 (50%)	≥45	18	29	7	36 (>75 years)	58%	47%
EPICA Study[110]	Portugal	Cross sectional study of patients attending 365 primary care practices. Fractional shortening <28%	1998	551 of 5434 (37%)	>25 Mean age 68	NA	NA	NA	NA	40%	NA
Glasgow study[121]	Glasgow, UK	Cross sectional survey. Ejection fraction ≤30%	1997	1467 (48%)	25-74 Mean age 50	29	40	20	64 in men and 49 in women (65-74 years)	NA	48%

LV= left ventricular; LVSD= left ventricular systolic dysfunction; NA=not available

Continued over...

Table 13 continued

Study	Location	Type of study and definition of LV systolic dysfunction	Year of study	Number of subjects undergoing echo (proportion men)	Age (years)	Overall prevalence per 1,000	Prevalence per 1,000 in men	Prevalence per 1,000 in women	Prevalence per 1,000 in older age group	Proportion of HF patients with preserved LV function	Proportion of patients with LVSD who are asymptomatic
Cardiovascular Health Study[116]	US	Prospective cohort study	1994-1995	4025 (40%)	≥65	NA	NA	NA	NA	55% in both sexes, 42% in men and 67% in women	NA
Nielsen *et al*[124]	3 general practices, Copenhagen, Denmark	Cross sectional survey. Ejection fraction ≤45%	1993-1995	126 (NA)	≥50	29 (>50 years)	NA	NA	NA	56%	34%
Rotterdam Study[111]	Rotterdam, The Netherlands	Prospective cohort study. Fractional shortening ≤25%	1990-1993	2267 (45%)	55-95 Mean age 69	37 (>55 years)	55 (>55 years)	22 (>55 years)	103 (85-94 years)	71%	60%
Morgan *et al* [122]	4 general practices Poole, Dorset, UK	Cross sectional survey. Qualitative assessment of left ventricular function	1992	817 (46%)	70-84	NA	NA	NA	75 in both sexes, 128 in men and 29 in women (70-84 years)	NA	50%
Helsinki ageing study[112]	Helsinki, Finland	Prospective cohort study. Fractional shortening ≤25%	1990-1991	501 (27%)	75-86	NA	NA	NA	113 (75-86 years)	51%	NA

LV= left ventricular; LVSD= left ventricular systolic dysfunction; NA=not available

1.3.2 Incidence of heart failure

In the UK, two general practitioner studies have reported on the incidence of heart failure. (Table 14) Cowie et al[125] identified new cases of heart failure from a population of 151,000 served by 82 general practitioners in Hillingdon, West London through surveillance of acute hospital admissions and through a rapid access clinic to which general practitioners referred all new cases of suspected heart failure. The diagnosis of heart failure was confirmed by a panel of three cardiologists on the basis of clinical assessment, electrocardiography, chest X-ray and echocardiogram. The incidence of heart failure was 1.3 cases per 1,000 population per year for those over 25 years and was higher in men (1.4 per 1,000 person years) than in women (1.2 per 1,000 person years). The incidence increased from 0.02 cases per 1,000 population per year in those aged 25-34 years to 11.6 in those aged 85 years and over. The incidence of heart failure for the year 1996 in individuals 40-84 years using the General Practice Research Database[126] was 4.2 per 1,000 person-years (4.4 in men and 3.9 in women). Heart failure cases were identified from the database and for a random sample of 1,200 patients a questionnaire was sent to the general practitioner to confirm the diagnosis of an incident case of heart failure. The lower incidence in the Hillingdon study in similar age groups presumably reflected the difference in the criteria for case definition used in the two studies.

In the Study of men born in 1913[113] the incidence of 'manifest' heart failure was 1.5, 4.3 and 10.2 per 1,000 person years in men aged 50-54 years, 55-60 years and 61-67 years respectively. In a population based surveillance study from four rural communities in Eastern Finland[127] the incidence of heart failure was 4 per 1,000 per year in men and 1 per 1,000 per year in women increasing to 8 per 1,000 person per year in those over 65 years.

In the REACH study[102] the incidence of heart failure in 1999 was 3.7 per 1,000 in men and 4.2 per 1,000 in women of all ages. Incidence rates were higher in men and African Americans across all age groups. There were no secular trends from 1989-1999. The annual incidence during the 1980s in the Framingham study[117] among persons ≥45 years was 7.2 cases/1,000 in men and 4.7 cases/1,000 in women. In a more recent analysis of the Framingham data[128] the incidence of heat failure was examined in four periods 1950-69, 1970-79, 1980-89 and 1990-99. As compared with the rate for the period from 1950 through 1969, the incidence of heart failure remained virtually unchanged among men in the three subsequent periods but declined by 31% to 40% among women (rate ratio for the

period from 1990 through 1999, 0.69). Using the resources of the Rochester Epidemiology Project[129] the incidence of heart failure was 2.8 per 1,000 in 1981 and 1991. The incidence was higher in men than in women and increased with dramatically with age to 60 per 1,000 person years in those over 79 years. There was no difference in incidence rates between the 1981 and 1991 cohorts.

Table 14 Incidence of heart failure

Study	Location	Type of study Definition of HF	Year of study	Number of subjects with HF (proportion men)	Age (years)	Overall incidence per 1,000 per year	Incidence in men per 1,000 per year	Incidence in women per 1,000 per year	Incidence per 1,000 per year in older age group
REACH study[102]	Michigan, US	Retrospective study using administrative databases of outpatient visits and hospitalisations.	1989-1999	29,686 (47%)	All ages. Mean age men 69 and women 74	NA	3.7 (1999)	4.2 (1999)	46 in men and 40 in women (> 85 years)
Rochester Epidemiology Project[103;129]	Rochester, US	Cross sectional study. Clinical criteria.	1991/1981 1982	248 (52%) 113 (50%)	All ages Mean age 77 <75	2.8 (1991) 1.1	3.4 (1991) 1.6	2.4 (1991) 0.7	60 (>79 years) NA
Study of men born in 1913[113]	Göteborg, Sweden	Prospective cohort study. Heart failure scoring system.	1963-1980	855 (100%)	50-67	NA	1.5 (50 years) 5.5 (50-67 years)	NA	10.2 (67 years)
Remes *et al*[127]	4 rural communities, Eastern Finland	Population based surveillance study. Boston and Framingham HF criteria	1986-1988	51 (75%) of 11,000	45-74	2.3-2.7	4*	1*	4.4-4.8 (65-74 years)
Cowie *et al* [125]	Hillingdon, London, UK	Cross sectional study. Rapid access HF clinic and hospital admission	1995-1996	220 of 151,000 (54%)	>25	1.3	1.4	1.2	11.6 in both sexes, 16.8 in men and 9.6 in women (≥85 years)
General Practice Research database[126]	2000 general practitioners in England and Wales	Retrospective cohort study using UK national data GP diagnosis.	1996	938 of 689,467 (52%)	40-84	4.2	4.4	3.9	15-19 (75-79 years)
Framingham[117]	Framingham, US	Prospective cohort study. Clinical score for HF diagnosis	1948-1988	652 of 9504 (51%)	70	NA	7.2 (≥45 years) (1980s)	4.7 (≥45 years) (1980s)	27 in men and 22 in women (80-89 years)

*** Age standardised; HF=heart failure; NA=not available**

1.3.3 Heart failure morbidity

1.3.3.1 Hospitalisations for heart failure

Rates of hospitalisations for heart failure have been increasing in recent years.[130-136] In the Leicestershire study[130], between 1993/94 and 2000/01, rates of first hospitalisations for heart failure increased by 62% from 29 to 47/10,000 population. Record linked discharge and mortality data were used to identify 12,220 residents aged ≥40 years who were admitted for a first heart failure in any coding position to any of the hospitals serving the population of Leicestershire, England. In Scotland[131], using routine data, the number of hospitalisations with a principal diagnosis of heart failure increased by 16% in men and 12% in women between 1990 and 1996. The highest numbers of hospitalisations for heart failure were recorded in 1993 for men and 1994 in women suggesting that the epidemic of increasing rates of hospitalisations for heart failure seems to have peaked.

Using the Swedish Hospital Discharge Registry[132], 156,919 hospital discharges with heart failure in men and women aged 45-84 years from 19 Swedish counties (population 2.9 million) were identified between 1988 and 2000. Hospitalisations for heart failure increased until 1993 in both men and women and in all age groups, after which a yearly decrease in hospitalisations was observed. In 2000, 24 men and 17 women per 10,000 inhabitants were discharged with heart failure. In the Netherlands[133], from 1980 to 1993 age adjusted discharge rates with a principal diagnosis of heart failure rose by 48% for men and 40% for women.

In the US, in the Medicare population[134], patients over 65 years with an initial hospital admission for heart failure in 1986 (n=631,306) and 1993 (n=803,506) were identified. An initial hospital admission for heart failure was defined as no prior admission for heart failure in the previous two years. Age standardised hospitalisation rates for any diagnosis of heart failure were higher in 1993 compared to 1986. The number of hospitalisations for heart failure in patients over 35 years between 1995 and 1995 were estimated from the National Hospital Discharge Survey.[135] The number of hospitalisations for heart failure increased by 49.1% in men and 52.5% in women between 1985 and 1995. Almost 78% of men and 85% of women hospitalised with heart failure were ≥65 years.

Trends in admissions to hospital in Montreal, Canada[136] between 1990 and 1997, were examined for individuals aged 65 years or greater. The annual rate of admission to hospital for heart failure increased from 92 per 10,000 population in 1990/91 to 124 per 10,000 population in 1997/98.

1.3.3.2 Quality of life

Heart failure impairs self-reported quality of life more so than any other common chronic medical condition.[137;138]

1.3.3.3 Other morbidity

Patients with heart failure have an increased risk of myocardial infarction (as a consequence of an ischaemic aetiology), atrial fibrillation and consequently stroke.[139;140]

1.3.4 Heart failure mortality

1.3.4.1 Prognosis of heart failure in community based studies

Table 15 shows the prognosis of heart failure in community based studies from Europe, Canada and US. The IN-CHF registry[141] prospectively collected information on 3327 outpatients with heart failure referred to 133 cardiology centres throughout Italy between 1995 and 1998. One year case fatality was 16.3% and was significantly higher in patients over 70 years (22% versus 13.7%). Age was an independent predictor of 1-year case fatality, increasing by 2.8% for each year of age. In the Helsinki Ageing Study[112], in 1990, 46% of individuals aged 75-86 with heart failure died within 4 years. This corresponded to an age and sex adjusted relative risk of all-cause mortality of 2.1.

In a study using death certificate data from Quebec, Canada[136] death rates from heart failure was 10.4-10.6 per 10,000 population ≥65 years between 1990 and 1997, and increased with age.

Using the resources of the Rochester Epidemiology Project[62] 4537 Olmsted County residents with a diagnosis of heart failure between 1979 and 2000 were identified and a sample was validated using clinical and Framingham criteria. Case-fatality at 30 days, 1 year and 5 years was 6%, 21% and 50% respectively in men and 4%, 17% and 46% respectively in women. The case-fatality in patients with heart failure at 30 days, 1 year and 5 years in the Framingham 1990-99 cohort[128] was 11%, 28% and 59% in men and 10%, 24% and 45% in women respectively. The Framingham cohort was slightly older than Rochester (mean age 80 years versus 74). In both these studies men had a higher age adjusted risk of death than women. In NHANES I (1971-1975)[118], the 10 year case-fatality was 49.8% for men and 36.0% for women aged 25-74 years with heart failure.

Table 15 Prognosis of heart failure in community based studies

Study	Location	Type	Year of study	No of subjects (proportion of men)	Mean age (years)	Case-fatality in men (time)	Age-specific case-fatality in men	Case-fatality in women (time)	Age-specific case-fatality in women	Adjusted relative risk of death	Adjusted risk of death for sex
Rochester Epidemiology Project[62]	Olmsted County, Minnesota	Retrospective population based cohort study. Clinical criteria for HF diagnosis.	1979-2000	4537 (43%)	74	6% (30 day) 21% (1 year) 50% (5 years) (1996-2000 cohort)	NA	4% (30 day) 17% (1 year) 46% (5 years) (1996-2000 cohort)	NA	NA	1.33 (1.24, 1.43)* Men relative to women.
Framingham Heart Study[128;142]	USA	Prospective cohort study. Clinical score for HF diagnosis	1948-1999	1075 (49%)	80	11% (30 day)* 28% (1 year)* 59% (5 years)* (1990-1999 cohort)	1.27 (1.09, 1.47) per decade of age	10% (30 day)* 24% (1 year)* 45% (5 years)* (1990-1999 cohort)	1.61 (1.37, 1.90) per decade of age		0.64 (0.54, 0.77)* Women relative to men.
IN-CHF Registry[141]	Italy	National registry of outpatients with heart failure. ESC criteria for HF diagnosis.	1995-1998	3327 (74%)	63	16.3% (1 year) Both sexes	22% ≥75 years 13.7% <70 years (1 year) 2.8% increase per year of age Both sexes	NA	NA	NA	0.86 (not significant) Women relative to men (>70 years)
Montreal study[136]	Quebec, Canada	Retrospective population study. Death certificate data and HF hospitalisation.	1990-1997	239-300 HF deaths per year	≥65 years	10.6/10,000 population	3.1/10,000 65-74 years 62.4/10,000 ≥85 years Both sexes (1997)	10.4/10,000 population	NA	NA	NA
Helsinki Ageing Study[112]	Finland	Prospective cohort study. Clinical and radiological criteria.	1990	41 (17%)	75-86	46% (4 years) Both sexes	NA	NA	NA	2.1 (1.3, 3.4) (4 years versus general population) Age and sex adjusted	NA
NHANES-I[118]	US	Prospective population based cohort study. Clinical criteria for HF diagnosis	1971-1975	288 (NA)	25-74	49.8% (10 years)	72% 65-74 years (10 years)	36.0% (10 years)	59% 65-74 years (10 years)	NA	NA

*** Age adjusted; HF heart failure; NA=not available**

1.3.4.2 Prognosis of patients hospitalised with heart failure

Hospital based studies reporting the prognosis of heart failure is shown in Table 16. In the Leicestershire study[130] one and five year case fatality following a first hospitalisation for heart failure, between 1993 and 2001, was 43% and 73% respectively. There was a 43-45% increase in risk of death for each decade of age at admission and a 14-17% increase associated with male sex. One and four month case fatality was higher in patients with heart failure associated with an acute myocardial infarction. All patients admitted to hospital in Scotland with a principal diagnosis of heart failure between 1986 and 1995 were examined.[143] Crude case fatality rates at 30 days, 1 year and 5 years were 19.9%, 44.5% and 76.5%. Median survival was 1.47 years in men and 1.39 years in women.

In Sweden one year case fatality following a first hospitalisation with heart failure, between 1988-2000, was 9% in men and 8% in women aged 45-54 years, increasing to 35% in men and 30% in women aged 75-84 years.[132] In the Multifactor Primary Prevention study[144], a random population sample of 7495 men were examined in 1970-73 and followed until 1996. 937 men were hospitalised for heart failure during the 27 years of follow-up. A diagnosis of heart failure increased the risk of death by more than eight times. In another earlier study from Western Sweden[145], all hospital records of patients with heart failure aged 16-65 years between 1980 and 1987, were examined in all hospitals in the region. The five year case fatality rate was 50%. All heart failure cases (principal or secondary diagnosis; first or recurrent admission) admitted to hospital in Lombardy, Italy were identified using a database of hospital records.[146] In-hospital case fatality was 10.9% in 1997 and was lower in women than in men and increased with age. In the Netherlands[133], 15.3% of all patients with a principal discharge diagnosis of heart failure in 1993 died in hospital. In-hospital case fatality was higher in men than in women in all age groups.

Crude 30-day and 1-year case-fatality rates after first admissions for heart failure were 11.6% and 33.1% respectively in Ontario, Canada between 1994 and 1997.[147] Case-fatality rates increased with age. Patients ≥75 years were 4 times more likely to die at 30 days and one year compared to those aged 20-49 years. After adjusting for age men showed a higher 30 day and one year case fatality rate than women.

Medicare patients hospitalised with a first admission for heart failure at 29 Northeast Ohio Hospitals were identified between 1991 and 1997.[148] Crude 30 day and 1-year case fatality

rates were 8.6% and 36.5% respectively. In the Post-Acute Care study[149], in 519 Medicare patients, aged ≥65 years, from Minneapolis, Pittsburgh and Houston, who were discharged alive after a hospitalisation for heart failure during 1988 and 1999, 1 year case fatality was higher in men (48%) than in women (35%). In an earlier study of first heart failure hospitalisations of a national cohort of Medicare patients aged ≥67years[150] only 19% of black men, 16% of white men, 25% of black women and 23% of white women survived 6 years.

Table 16 Prognosis of heart failure in hospital based studies

Study	Location	Type	Year of study	No of subjects (proportion of men)	Mean age (years)	Case-fatality in men (time)	Age-specific case-fatality in men	Case-fatality in women	Age-specific case-fatality in women	Adjusted relative risk of death	Adjusted risk of death for sex
Leicestershire Study[130]	UK	Retrospective cohort study. First HF hospitalisation.	1993-2001	4335 (51%) Primary diagnosis	≥40	19.2% (1 month) 41.4% (1 year) 75.6% (5 years) Both sexes	1.4 (1.4, 1.5) for each decade of age Multivariable Both sexes	NA	NA	NA	0.9 (0.8, 0.9) Women relative to men
Swedish Hospital Discharge Registry[132]	Sweden	Retrospective population based cohort study. First HF hospitalisation.	1988-2000	156919 (NA)	45-84	NA	4% (30 day) 9% (1 year) 45-54 years 14% (30 day) 35% (1 year) 75-84 years	NA	4% (30 day) 8% (1 year) 45-54 years 12% (30 day) 30% (1 year) 75-84 years	NA	NA
Canadian Institute for Health Information database[147]	Ontario, Canada	Retrospective population-based cohort study. First HF hospitalisation.	1994-1997	38702 (49%)	≥20	11.4% (30 day) 34% (1 year)	4.6% (30 day) 15% (1 year) 20-49 years 15.6% (30 day) 43.1% (1 year) ≥75 years	11.8% (30 day) 32.3% (1 year)	4.3% (30 day) 10.9% (1 year) 20-49 years 14.7% (30 day) 37.9% (1 year) ≥75 years	3.6 (2.6, 4.8) (30 days) 4.2 (3.5, 5.1) (1 year) (≥75 years versus <50 years)	1.0 (0.9, 1.0) (30 days) 0.8 (0.8, 0.9) (1 year) Women versus men
Lombardy study[146]	Lombardy, Italy	Retrospective population based cohort study. All HF hospitalisations (principal and secondary coding)	1996-1997	67041 (49.4%)	72 for men and 78 for women	10.9% (in hospital) (1997) Both sexes	4.5 (3.1, 6.3) >80 years versus <61 years Multivariable Both sexes	NA	NA	NA	0.8 (0.7, 0.9) Women versus men
Cleveland Health Quality Choice Program[148]	Cleveland, Ohio, US	Retrospective cohort study. First hospitalisation.	1991-1997	23,505 (43%)	78 (1997)	6.4% (in hospital) 8.6% (30 day) 36.5% (1 year) Both sexes	NA	NA	NA	NA	NA

NA not available; HF heart failure

Continued over...

Table 16 continued

Study	Location	Type	Year of study	No of subjects (proportion of men)	Mean age (years)	Case-fatality in men (time)	Age-specific case-fatality in men	Case-fatality in women	Age-specific case-fatality in women	Adjusted relative risk of death	Adjusted risk of death for sex
Multifactor Primary Prevention study [144]	Sweden	Retrospective cohort study/ randomised controlled trial. Hospitalisations for heart failure	Screened 1970-73 and followed to 1996 for HF hospitalisations	937 (100%)	55-79	NA	NA	NA	NA	8.1 (7.5, 9.0)	NA
Linked Scottish Morbidity Record database[143]	Scotland	Retrospective cohort study using routine data. First hospitalisation	1986-1995	66547 (47%)	72 for men and 78 for women	19.4% (30 day) 44.0% (1 year) 87.8% (10 years)	2.8 (2.4, 3.2) (30 days) 75-84 versus <55 years. Multivariable	20.3% (30 day) 45.0% (1 year) 88.4% (10 years)	1.9 (1.6, 2.3) (30 days) 75-84 versus <55 years. Multivariable	NA	0.9 (0.9, 0.9) (longer-term) Women versus men
National Medical Register, Netherlands [133]	Netherlands	Retrospective population based cohort study. Episode based hospitalisations	1980-1993	14423 (51%) in 1980. 25966 (50%) in 1993	All ages	15.5% (in hospital) (1993)	NA	14.9% (in hospital) (1993)	NA	NA	NA
Post acute care study[149]	Minneapolis, Pittsburgh and Houston, US	Prospective cohort study. Discharged alive with heart failure	1988-1989	519 (39%)	≥65	48% (1 year)	NA	35% (1 year)	NA	NA	Men significantly higher case fatality than women
Western Sweden study[145]	Western Sweden	Retrospective cohort study. Clinical criteria for heart failure	1980-87	2711 (68%)	16-65	50% (5 years) Both sexes	NA	NA	NA	NA	NA
Medicare[150]	US	Retrospective cohort study. First HF hospitalisations	1986	170239 (42%)	≥67	84% (6 years) white men	NA	77% (6 years) white women	NA	NA	Men significantly higher case fatality than women

NA=not available; HF=heart failure

1.3.4.3 Trends in survival of patients with heart failure

In the Leicestershire study[130] between 1993/94 and 2000/01 there was a 35% reduction in the adjusted risk of death and a 50% reduction in the risk of cardiovascular death.(Table 17) In Scotland[143], 30 day case-fatality rates fell between 1986 and 1995 by 26% in men and 17% in women. Longer term case-fatality rates fell by 18% in men and 14% in women.

In Sweden 30 day and 1 year case fatality following a heart failure hospitalisation decreased between 1988 and 2000 in both men and women.[132] The decrease was more pronounced in the younger age groups. There was a yearly decrease in one year case fatality of 9% in men and 10% in women aged 45-54 years and 4% in men and 5% in women aged 75-84 years. In the Netherlands[133], age adjusted in-hospital case fatality decreased from 19.9% in 1980 to 15.5% in 1993 in men and from 17.8% to 14.9% in women.

In Ontario, Canada from 1992-2000, there was a 2.8% reduction in age-, sex- and co morbidity-adjusted 1 year case fatality but no change in 30 day case fatality.[151] In Montreal, Canada[136] between 1990 and 1997, in individuals aged 65 years or more age-adjusted case fatality rates did not change significantly. From the IN-CHF registry[152] of outpatients with heart failure in Italy, there was a 30% increased adjusted risk of death in 1995 compared to 1999.

Using the resources of the Rochester Epidemiology Project[62], age adjusted 5-year survival after heart failure diagnosis improved over time from 43% in 1979-84 to 52% in 1996-2000. There were age and sex differences in the degree of improvement in survival. Survival improved more in younger men than older men. In women survival improved in younger women but to a lesser extent than men and did not change in older age groups. In the Framingham study[128], the 30 day, 1-year, and 5-year age-adjusted case fatality rates among men declined from 12%, 30%, and 70% respectively, in the period from 1950 through 1969 to 11%, 28% and 59%, respectively, in the period from 1990 through 1999. The corresponding rates among women were 18%, 28% and 57% for the period from 1950 through 1969 and 10%, 24% and 45% for the period from 1990 through 1999. Overall, there was an improvement in the survival rate after the onset of heart failure of 12% per decade. Among Medicare patients hospitalised with heart failure in Northeast Ohio there

was a 15.3% decrease in 30-day case fatality and a 14.6% decrease in 1-year case fatality between 1991 and 1997.[148]

In summary heart failure is a common condition affecting approximately 1% of the population. The prevalence of heart failure increases with age to approximately 10% of the population over 75 years of age. Around 50% of patients with heart failure have preserved systolic function and 50% of patients with left ventricular systolic dysfunction are asymptomatic. Hospitalisations for heart failure are common and have increased over time. The prognosis for heart failure is poor however there is evidence that survival has improved in recent years.

Table 17 Trends in survival of men and women with heart failure

Study	Location	Type of study	Years	No of subjects (proportion of men)	Case-fatality in men at start of study (time)	Case-fatality in men at end of study (time)	Significant change in case-fatality in men	Adjusted change in case-fatality in men	Case-fatality in women at start of study	Case-fatality in women at end of study	Significant change in case-fatality in women	Multivariate Adjusted change in case-fatality in women
Leicestershire Study[130]	UK	Retrospective cohort study. First hospitalisation.	1993-2001	12,220 (49%) Diagnosis in any position. ≥40 years	28% (1 month) 55% (1 year) *	18% (1 month) 38% (1 year) *	Yes*	0.7 (0.6, 0.7) in 2000/1 compared to 1993/4*	NA	NA	NA	NA
Swedish Hospital Discharge Registry[132]	Sweden	Retrospective population-based cohort study. First hospitalisation.	1988-2000	156919 (NA)	15% (30 days) 40% (1 year)	11% (30 days) 27% (1 year)	Yes	NA	16% (30 days) 42% (1 year)	11% (30 days) 28% (1 year)	Yes	NA
Rochester Epidemiology Project[62]	Olmsted County, Minnesota	Retrospective population based cohort study	1979-2000	4537 (43%)	57% (5 year) *	48% (5 year) *	Yes	0.5 (0.4, 0.6) (60 years) 0.7 (0.6, 0.9) (80 years) Age adjusted	NA	NA	Yes	0.7 (0.5, 0.9) (60 years) 0.9 (0.8, 1.1) (80 years) Age adjusted
Canadian Institute for Health Information database[151]	Ontario, Canada	Retrospective cohort study. All heart failure (not first). ≥65 years	1992-2000	88440 (47%)	36.5% (1 year) *	35.2% (1 year) *	Yes*	-2.8% Risk adjusted 1 year case fatality. No change in in-hospital case fatality.*	NA	NA	NA	NA
IN-CHF[152]	Italy	National registry of outpatients with heart failure	1995-1999	1315 (77%)	15% (1 year)*	9% (1 year)*	Yes*	1.3 (1.2, 1.5) 1995 relative to 1999*	NA	NA	NA	NA
Framingham Heart Study[128]	US	Prospective cohort study	1948-1999	1075 (49%)	12% (30 days) 30% (1 year) 70% (5 years)	11% (30 days) 28% (1 year) 59% (5 years)	Yes	0.7 (0.5, 1.0) 1990/99 relative to 1950/69	18% (30 days) 28% (1 year) 57% (5 years)	10% (30 days) 24% (1 year) 45% (5 years)	Yes	0.7 (0.5, 1.0) 1990/99 relative to 1950/69

*** Both sexes together (not available for men and women separately); NA= not available**

Continued over...

Table 17 continued

Study	Location	Type of study	Years	No of subjects (proportion of men)	Case-fatality in men at start of study (time)	Case-fatality in men at end of study (time)	Significant change in case-fatality in men	Multivariate adjusted change in case-fatality in men	Case-fatality in women at start of study	Case-fatality in women at end of study	Significant change in case-fatality in women	Multivariate adjusted change in case-fatality in women
IN-CHF[152]	Italy	National registry of outpatients with heart failure	1995-1999	1315 (77%)	15% (1 year)*	9% (1 year)*	Yes*	1.3 (1.2, 1.5) 1995 relative to 1999*	NA	NA	NA	NA
Framingham Heart Study[128]	US	Prospective cohort study	1948-1999	1075 (49%)	12% (30 days) 30% (1 year) 70% (5 years)	11% (30 days) 28% (1 year) 59% (5 years)	Yes	0.7 (0.5, 1.0) 1990/99 relative to 1950/69	18% (30 days) 28% (1 year) 57% (5 years)	10% (30 days) 24% (1 year) 45% (5 years)	Yes	0.7 (0.5, 1.0) 1990/99 relative to 1950/69
Cleveland Health Quality Choice Program[148]	Cleveland, Ohio, US	Retrospective cohort study. First hospitalisation.	1991-1997	23505 (43%)	36.6% (1 year) *	32.5% (1 year) *	Yes	-4.3% (1 year)	NA	NA	Yes	-6.1% (1 year)
Montreal study[136]	Quebec, Canada	Retrospective population based cohort study. ≥65 years	1990-1997	239-300 CHF deaths per year	12.2/10,000 population	10.6/10,000 population	No	NA	10.8/10,000 population	10.4/10,000 population	No	NA
Linked Scottish Morbidity Record database[143]	Scotland	Retrospective population based cohort study. Population based. First hospitalisation	1986-1995	66547 (47%)	19.9% (30 day) *	18.6% (30 day) *	Yes	-26% (30 day) -18% (longer term)	NA	NA	Yes	-17% (30 day) -15% (longer term)
National Medical Register, Netherlands *133*	Netherlands	Retrospective population based cohort study. Episode based hospitalisations	1980-1993	14423 (51%) in 1980. 25966 (50%) in 1993	19.9% (in hospital)	15.5% (in hospital)	NA	NA	17.8% (in hospital)	14.9% (in hospital)	NA	NA

*** Both sexes together (not available for men and women separately); NA= not available**

1.4 Epidemiology of atrial fibrillation

1.4.1 Prevalence of atrial fibrillation

Atrial fibrillation is the most common sustained cardiac arrhythmia.[153;154] It is estimated that 2.2 million adults in the United States have atrial fibrillation.[155] The prevalence of atrial fibrillation is increasing because the population is ageing and survival from conditions predisposing to atrial fibrillation (such as coronary heart disease and heart failure) is improving.[143;156] This prompted Braunwald in his Shattuck Lecture to refer to the growing 'epidemic' of atrial fibrillation.[157]

Four UK primary care studies[158-161] and one primary care study from the Netherlands[162] have reported the prevalence of atrial fibrillation in recent years. (Table 18) The SAFE trial was a multicentred randomised controlled trial involving patients ≥ 65 years from 50 primary care practices across the West Midlands.[161] They were randomised to 25 interventional practices and 25 control practices. GPs and practice nurses in the interventional practices received education on the importance of atrial fibrillation detection and ECG interpretation. The overall prevalence of atrial fibrillation was 7.2% and was higher in men than in women. The prevalence increased with age to 10.3% in those over 75 years. Analysis of electronic data from 131 general practices in the UK was performed using the DIN-LINK database for the period 1994-2003.[158] Read codes were used to identify patients with atrial fibrillation. All ages prevalence of atrial fibrillation increased steadily over time (0.84% in men in 1994 compared to 1.49% in 2003, compared with 0.83% and 1.29% in women). Prevalence rose steadily with increasing age (13.2% in men and 11.0% in women ≥85 years). The prevalence of atrial fibrillation in 211 general practices in England and Wales between 1994 and 1998 was examined using the General Practice Research Database.[159] Atrial fibrillation was identified by a clinical diagnosis on the practice computer system. The prevalence of atrial fibrillation in all ages in 1998 was 1.21% in men and 1.27% in women and again increased dramatically with age to 10.6% in men and 10.9% in women over 85 years old. Unlike other studies the prevalence of atrial fibrillation was similar in men and women. The prevalence of atrial fibrillation increased by 22% in men and 14% in women between 1994 and 1998. In another UK primary care study 4843 older patients, registered with 26 general practices in Northumberland, UK had

electrocardiographic screening for atrial fibrillation.[160] The prevalence of atrial fibrillation was 10.0% in men and 5.6% in women ≥ 75 years.

In the Netherlands all patients over 60 years attending 10 GP practices were screened for the PATAF (primary prevention of arterial thromboembolism in patients with atrial fibrillation) study.[162] Patients with atrial fibrillation were identified by an irregular pulse on examination followed by an ECG. Medical records were also searched for patients with atrial fibrillation. The prevalence of atrial fibrillation in those 60 years and over was 5.1% and in those 80 years and over was 10.0%. The prevalence was higher in men than in women in all ages.

In a study from the US the prevalence of atrial fibrillation was 0.95% in an adult cohort over 19 years and 9% in those >80 years who received care within Kaiser Permanente of Northern California, a large group-model health maintenance organisation.[163] As with most other studies the prevalence of atrial fibrillation was greater in men than in women. To identify patients with atrial fibrillation, as well as searching a clinical database containing all ambulatory visits, they also searched an electrocardiographic and hospital discharge diagnosis database.

The prevalence of atrial fibrillation has also been reported in a number of large European[164-168] and US[169-171] population based cohort studies.

In the Renfrew Paisley study[167] 15406 men and women aged 45-64 years, living in two industrialised towns in the west of Scotland, were screened between 1972 and 1976. The prevalence of atrial fibrillation was 0.75% in men and 0.56% in women. In the Reykjavik study[168], 0.27% of a randomly selected population of 9,067 Icelandic individuals aged 32-64 years and screened between 1967 and 1970 had chronic atrial fibrillation. This lower prevalence is partially explained by the earlier era studied and the younger age group of patients included. Three more recent European studies have also reported on the prevalence of atrial fibrillation.[164-166] In the Copenhagen City Heart Study the prevalence of atrial fibrillation diagnosed from electrocardiograms was determined in 8,606 patients examined in 1976-1978, in 8,943 patients examined in 1981 to 1983 and in 6,733 subjects examined in 1991-1994 aged 50-89 years.[165] The age-standardised prevalence of atrial fibrillation was 3.3% in men and 1.1% in women in 1991-1994. Looking at secular changes in prevalence over time the prevalence of atrial fibrillation more than doubled in men from the 1970s to the 1990s but remained unchanged in women. A similar prevalence

in men of 3.3% and a higher prevalence in women of 2.7% were reported in the Rotterdam Study of 6,584 individuals' aged ≥55 years which also used an electrocardiographic diagnosis of atrial fibrillation.[166] In both these studies a diagnosis of atrial fibrillation was made on a single ECG recording and therefore may underestimate the presence of paroxysmal atrial fibrillation. In the Multifactor Primary Prevention Study the prevalence of atrial fibrillation in a random sample of 7,495 men from Göteborg in the age groups 55-64, 65-74 and 75-79 years was 1.2, 4.2 and 8.0% respectively.[164] These men were first examined in 1970-73 and followed for a mean of 25.2 years. A diagnosis of atrial fibrillation was based on a hospital diagnosis of atrial fibrillation, which differs from other studies reported here.

A higher prevalence of atrial fibrillation has been reported in three US longitudinal population based studies.[169 171] Differences in prevalence could be related to the differences in study criteria including inclusion of younger patients in some of the European studies, methods of ascertainment, and techniques of age adjustment for the estimation of prevalence and geographical variations. In the Cardiovascular Health Study atrial fibrillation was identified in a sample of 5,201 men and women aged ≥65 years by ECG and self-report of a physician diagnosis. The prevalence was 6.2% in men and 4.8% in women increasing to 8.0% in men and 6.7% in women over 79 years.[165] In the Framingham Study the prevalence of atrial fibrillation was 9.1% in men and 4.7% in women aged 65-84 years.[170] Atrial fibrillation was determined by biennial clinical examinations and electrocardiograms, and interim hospitalisations. Age adjusted prevalence increased in men but not women in the Framingham study. In the Rochester Epidemiology Project the prevalence of atrial fibrillation increased significantly in ischaemic stroke patients and their controls from 1960 to 1989 in Rochester, Minnesota, independent of age and gender. [171] The rate of increase did not differ significantly between men and women. In this study age was a potent risk factor for the development of atrial fibrillation: each decade of age was associated with a doubling of the odds of atrial fibrillation.

The prevalence of atrial fibrillation is higher in patients with clinical cardiovascular disease.[169;172;173] In addition cardiovascular risk factors are independent predictors of atrial fibrillation.[169;172;174]

The increase in prevalence of atrial fibrillation with advancing age coupled with the steadily increasing numbers of persons reaching very old age, most certainly contributes to

the growing epidemic of atrial fibrillation. Hypertension, coronary artery disease, diabetes mellitus and heart failure are among the age-related co-morbid conditions that are likely to play a central role in the propagation of the atrial fibrillation epidemic i.e. a significant proportion of the elderly population have survived these conditions which in themselves are risk factors for the development of atrial fibrillation.

In summary the prevalence of atrial fibrillation is approximately 1.3% increasing dramatically with age to approximately 10% in those over 80 years. The prevalence in most studies is higher in men than in women however the overall number of female patients with atrial fibrillation exceeds the number of men with this condition because of greater longevity in women compared with men[175].The prevalence of atrial fibrillation is increasing rapidly in industrialised nations.

Table 18 Prevalence of atrial fibrillation

Study	Location	Type of study and definition of atrial fibrillation	Year	No of subjects (proportion of men)	Age group (years)	Overall prevalence (per 1,000)	Overall prevalence (per 1,000) in men	Overall prevalence (per 1,000) in women	Prevalence (per 1,000) in older age group
SAFE study[161]	50 general practices, West Midlands. UK	Randomised controlled trial. Computer search and review of notes.	2001	14802 (42.6%)	>65	72	78	68	103 (≥75 years)
DIN-LINK database[158]	131 general practices, UK	Retrospective cross-sectional study. Read codes for AF.	1994-2003	~ 1 million registered patients	All ages	NA	14.9 (2003)	12.9 (2003)	132 in men and 110 in women (≥85 years for 'active' AF)
General Practice Research Database[159]	211 general practices, England and Wales	UK national data. Retrospective cross-sectional study	1994-1998	7748 patients with AF 1998	All ages	12.4 (1998)	12.1 (1998)	12.7 (1998)	106 in men and 109 in women (≥85 years) (1998)
Sudlow *et al*[160]	26 general practices, Northumberland, UK	Retrospective cross-sectional study. AF on ECG.	Published 1998	3678 (NA)	≥65	NA	NA	NA	100 in men and 56 in women (≥75 years)
ATRIA Study [163]	Kaiser Permanente of Northern California, US, (health maintenance organisation)	Cross-sectional study. AF hospitalisation and outpatient visits.	1996-1997	17974 (56.6%) with AF	≥20 Mean age 71	9.5	11	8	90 (≥80 years)
West Birmingham atrial fibrillation project[176]	2 General Practices, Birmingham, UK	Retrospective cross-sectional study. Prescription data and GP records.	Published 1997	4522 (38% of 111 with AF)	≥50	24	NA	NA	NA
Multifactor Primary Prevention Study[164]	Göteborg, Sweden	Retrospective cohort study/ randomised controlled trial. AF hospitalisations.	Screened 1970-1973 and followed 1996	7495 (100%)	55-79	NA	12 (55-64 years)	NA	42 in men (65-74 years) and 80 in men (75-79 years)
PATAF study[162]	10 general practices, Netherlands	Cross-sectional screening study. AF on clinical examination and ECG.	Published 1996	1234 (NA) with AF	≥60	28 (60-69 years)	33 (60-69 years)	23 (60-69 years)	51 (≥60 years) 121 in men and 87 in women (≥80 years)
Copenhagen City Heart Study[165]	Denmark	Population based prospective cohort study. AF on ECG.	1991-1994	6733 (NA)	50-89	NA	33	11	Relative risk 3.6 (2.5, 4.8) for each decade of age (50-69 years)
Rotterdam Study[166]	Netherlands	Population based prospective cohort study. AF on ECG.	1990-1993	6584 (41%)	≥55	30	33	27	132 in men and 106 in women (≥85 years)

AF= atrial fibrillation; NA= not available

Continued over...

Table 18 continued

Study	Location	Type of study and definition of angina	Year	No of subjects (proportion of men)	Age group (years)	Overall prevalence (per 1,000)	Overall prevalence (per 1,000) in men	Overall prevalence (per 1,000) in women	Prevalence (per 1,000) in older age group
Cardiovascular Health Study[169]	4 US communities	Prospective cohort study. AF on ECG and self-report of physician diagnosis.	1990	5151 (43%)	≥65	54	62	48	80 in men and 67 in women (≥80 years)
Framingham Study[170]	Framingham, US	Prospective cohort study. AF on ECG, clinics and hospitalisations for AF	1968-1989	5070 (NA)	65-84	NA	91	47	117 in men and 52 in women (75-84 years)
Rochester Epidemiology Project[171]	Minnesota, US	Longitudinal case-control study of ischaemic strokes. AF in medical records documented on ECG	1960-1989	3742 (45%)	Mean age 76	220 in ischaemic stroke cases and 130 in control subjects (1980-89)	160 in ischaemic stroke cases and 120 in control subjects (1980-89) Age adjusted	200 in ischaemic stroke cases and 80 in control subjects (1980-89) Age adjusted	390 in ischaemic stroke cases and 220 in control subjects ≥85 years (1980-89)
Renfrew-Paisley Study[167]	Scotland, UK	Prospective cohort study. AF on ECG at baseline screening.	1972-1976	15406 (46%)	45-64	6.5	7.5	5.6	NA
Western Australia study[177]	Busselton, Western Australia	Triennial population survey. AF on ECG.	1966-1981	1770 (52%)	>60	NA	NA	NA	177 in men and 70 in women (≥70 years)
Reykjavik Study[168]	Iceland	Prospective cohort study. AF on ECG at baseline screening.	1967-1970	9067 (48%)	32-64	2.8	4.1	1.5	NA
Hill et al[178]	1 General Practice, Tamworth, Staffordshire, UK	Retrospective cross-sectional study.	1984-1985	819 (NA)	>65	NA	NA	NA	37 (>65) 59 (≥85)

AF= atrial fibrillation; NA= not available

1.4.2 Incidence of atrial fibrillation

In studies examining the incidence of atrial fibrillation there are differences in case ascertainment. (Table 19) Several studies have examined the incidence of a first hospitalisation for atrial fibrillation.[164;167;179] This may potentially underestimate the incidence of atrial fibrillation as a diagnosis of atrial fibrillation can be made in primary care and often does not require hospitalisation.

In a study from Denmark using routine data 131,728 subjects with an incident hospital diagnosis (either inpatient or outpatient) of atrial fibrillation or flutter were identified between 1980 and 1999.[179] The incidence of atrial fibrillation was 4.38 per 1000 in individuals aged 40-89 years in 1999. The number of subjects with a diagnosis of atrial fibrillation more than doubled during the study period in both men and women. Another study using hospitalisations for atrial fibrillation to identify incident atrial fibrillation cases was the Multifactor Primary Prevention Study. During the 27 years of follow-up the incidence of atrial fibrillation in men was 2.0, 5.8 and 17.3 per 1,000 person years in the age groups 55-64, 65-74 and 75-79 years respectively.[164] In the Renfrew-Paisley study subjects aged 45-64 years were screened initially between 1972 and 1976 and again between 1977 and 1979.[167] During the 20 year follow up, the rate of incident hospitalisation for atrial fibrillation was 1.9 per 1,000 person years. The four-year incidence of atrial fibrillation between the first and second screening was also reported and this was 0.54 per 1,000 person years.

In a study of all adult residents in Olmsted County, Minnesota between 1980 and 2000, atrial fibrillation was identified from medical records.[180] The age and sex adjusted incidence of atrial fibrillation was 3.4 per 1,000. There was a relative increase of 12.6% in the age adjusted incidence of atrial fibrillation over 21 years.

The General Practice Research Database and the SAFE trial used a general practitioner diagnosis of atrial fibrillation.[161;181] In the SAFE trial the incidence of atrial fibrillation in patients over 65 years in the control group was 1.04%, and was higher in women (1.18%) than in men (0.85%).[161] This is higher than the incidence of chronic atrial fibrillation in the

General Practice Research Database which was 1.7 per 1000 person-years in patients 40-89 years.[181] The incidence increased markedly with age from 0.05 per 1,000 among patients 40-49 years to 8.6 per 1,000 in patients aged 80-89 years. The incidence was lower in women especially in younger age.

The incidence of atrial fibrillation has also been reported in several longitudinal population studies. The Framingham Study, used electrocardiograms from biennial visits, hospital records and outside physician records to identify patients with atrial fibrillation.[182] The incidence of atrial fibrillation was 3.1 per 1000 person years in men and 1.9 in women aged 55-64 years and the incidence increased with age to 38.0 per 1000 person years in men and 31.4 in women aged 85-94 years. Men were 1.5 times more likely to develop atrial fibrillation than women even after adjusting for other risk factors for atrial fibrillation. The Manitoba Follow-Up Study in Canada examined 3,983 male air crew recruits with an average age of 31 years in 1948 and followed them for 44 years.[172] Atrial fibrillation was identified on electrocardiograms performed at periodic medical examinations or if the subject reported contact with a physician. In the Manitoba Follow-Up Study in Canada the incidence of atrial fibrillation was 2 per 1,000 patient years. The incidence of atrial fibrillation increased with age from less than 0.5 per 1,000 person years before age 50 to 2.3 per 1,000 person-years by age 60, and rose further to 16.9 per 1,000 person-years by age 85. [172;182;183] In the Cardiovascular Health Study atrial fibrillation was identified from three sources, annual electrocardiography, self reported atrial fibrillation and hospital discharge diagnosis.[183] The incidence of atrial fibrillation was 26.4 per 1,000 in men and 14.1 per 1,000 in women 65 years and over. Paroxysmal as well as chronic atrial fibrillation was included. The incidence of atrial fibrillation in the Cardiovascular Health Study is much higher than other studies. Including self-reported episodes of atrial fibrillation and conducting electrocardiographs yearly may partly explain the differences. In addition the other US studies covered an earlier time period and the incidence and the importance of recognition of atrial fibrillation has increased over time. The low incidence of atrial fibrillation in the Manitoba Follow-Up Study is partly explained by a selection bias of young healthy fit recruits.

In summary the incidence of atrial fibrillation varies from 1.7-20 per 1,000 person years and as with prevalence is higher in men than in women and increases dramatically with age.

Table 19 Incidence of atrial fibrillation

Study	Location	Type of study and definition of atrial fibrillation	Year	No of subjects (proportion of men)	Age group (years)	Overall incidence (per 1000 per year)	Overall incidence (per 1000 per year) in men	Overall incidence (per 1000 per year) in women	Incidence (per 1000 per year) in older age group
SAFE study[161]	50 general practices, West Midlands. UK	Randomised controlled trial. Computer search and review of notes.	2001	4936 (42.1%) in control group	>65	10.4	8.5	11.8	14.2 (≥75 years)
Olmsted County Study[180]	Olmsted County, Minnesota, US	Retrospective cohort study. AF in medical records documented on ECG	1980-2000	4618 (51%)	≥18	3.4*	4.5*	2.6*	39.7 in men and 27.7 in women (≥85 years)
Danish National Registry of Patients[179]	Denmark	Population study using routine data. Incident AF hospitalisation	1980-1999	131,728 (52%) with AF	40-89	4.38 (1999)	NA	NA	NA
General Practice Research Database[181]	2000 general practitioners in England and Wales	UK national data Retrospective cohort study. GP diagnosis of AF.	1996	703730 (NA)	40-89	1.7	Relative risk men versus women 1.4 (1.2-1.6)	NA	8.6 (80-89 years)
Multifactor Primary Prevention Study[164]	Göteborg, Sweden	Prospective population study. AF hospitalisations.	Screened 1970-73 and followed to1996	7495 (100%)	55-79	NA	2.0 (55-64 years) 5.8 (65-74 years)	NA	17.3 in men (75-79 years)
Renfrew-Paisley Study[167]	Scotland, UK	Prospective cohort study. AF on ECG at a re-screening visit and hospitalisations for AF.	Screened 1972-76 and followed for 20 years	15406 (46%)	45-64 at entry	0.5 (re-screening) 1.9 (incident hospitalisation)	0.9 (re-screening) 2.0 (incident hospitalisation)	0.2 (re-screening) 1.7 (incident hospitalisation)	NA
Cardiovascular Health Study[183]	4 US communities	Population based Prospective cohort study. AF on ECG, self-report of physician diagnosis and hospital discharge diagnosis.	1990-1993	4844 (42%)	≥65	NA	26.4	14.1	58.7 in men and 25.1 in women (≥80 years)
Manitoba Follow-up Study[172]	Royal Canadian Air Force	Prospective cohort study. AF on ECG or physician report.	Screened 1948 and followed for 44 years	3983 (100%)	18-62 at entry. Mean age at onset of AF 66 (33-93)	NA	2	NA	9.7 in men (>70 years)
Framingham Study[182]	Framingham, US	Prospective cohort study. AF on ECG, clinics and hospitalisations for AF	Screened 1948 and followed for 38 years	4731 (44%)	55-94	NA	3.1 (55-64 years)	1.9 (55-64 years)	38.0 in men and 31.4 in women (85-94 years)
Western Australia study[177]	Busselton, Western Australia	Triennial population survey	1966-1981	1770 (52%)	>60	NA	NA	NA	5 (≥60 years)

*** Age and sex adjusted; AF= atrial fibrillation; NA= not available**

1.4.3 Atrial fibrillation morbidity

1.4.3.1 Stroke

Many studies have shown that atrial fibrillation is an independent predictor of stroke. (Table 20) The relative risk for stroke was 6.9 (3.0, 13.5) in the Whitehall Study and 2.3 (0.1, 12.7) in the British Regional Heart Study in individuals with atrial fibrillation.[184] In the Renfrew-Paisley study women with atrial fibrillation had a higher risk of stroke than men.[185] Other studies have also shown that women with atrial fibrillation may be more likely than men to have a stroke. [170;186;187] In a study of all hospitalisations with atrial fibrillation in Scotland, the total number of strokes associated with atrial fibrillation increased between 1986 and 1996.[186]

In the Reykjavik Study fatal or non-fatal stroke occurred in 24% of patients with atrial fibrillation at the end of the 14-year follow up period compared to 4.3% of controls ($P<0.05$, RR 7.1).[168] The relative risk of fatal stroke was 12.3 ($p<0.05$). Atrial fibrillation was also a strong predictor of stroke in men in the Multifactor Primary Prevention Study.[164;188] However in a more recent analysis extending follow-up through 28 years, atrial fibrillation was no longer a significant predictor of stroke after 21 years of follow-up[189].

In the Framingham study atrial fibrillation was a major independent risk factor for embolic stroke or transient ischaemic attack and was associated with a 4-5 fold increased risk compared to the unaffected population.[190] The attributable risk associated with atrial fibrillation increased with age, in contrast to many stroke risk factors where the attributable risk of stroke decreases with age. Thus older patients are not only more prone to atrial fibrillation but their risk of stroke is considerably increased when compared with younger patients with atrial fibrillation.[191] Atrial fibrillation was also a risk factor for stroke in the Rochester Epidemiology Project[192] and in men in the Manitoba Follow-Up Study[172]. It was significantly associated with stroke in individuals over 65 years in the Cardiovascular Health Study[169].

In the Western Australia study[177] the adjusted risk of fatal stroke (HR 3.8) was increased in individuals aged ≥ 60 years with atrial fibrillation. In the Dubbo Study of the Elderly[193], a cohort of 2805 Australian men and women aged ≥60 years were first examined in 1988

and followed for 8 years. 306 men and women manifested an ischaemic stroke and atrial fibrillation was a significant independent predictor of stroke increasing the risk by 58%.

1.4.3.2 Heart Failure

Atrial fibrillation was an independent predictor of heart failure in women and men in the Renfrew-Paisley study.[185] In the Reykjavik Study 36% of patients with atrial fibrillation and 2.1% of controls had heart failure at the end of the study period (P<0.001, RR 24.7).[168] In the Multifactor Primary Prevention Study heart failure was also more common in those who had atrial fibrillation compared with those without. In this study heart failure hospitalisations prior to, during and after the hospitalisation for atrial fibrillation were included in the analysis.[164] In the Manitoba Follow-Up Study[172] men with atrial fibrillation had a 2.98 times risk of heart failure.

1.4.3.3 Myocardial infarction

Ischaemic heart disease often precedes atrial fibrillation and is an independent predictor for developing AF. In the Renfrew-Paisley study[185], the Manitoba follow-up study[172], and the Reykjavik Study [168] the risk of myocardial infarction was not increased following a diagnosis of atrial fibrillation. In the Multifactor Primary Prevention Study[164] patients with a hospitalisation for atrial fibrillation had an increased risk of hospitalisation for myocardial infarction however this included myocardial infarctions prior to, during and after the hospitalisation for atrial fibrillation.

1.4.3.4 Hospitalisations for atrial fibrillation

Atrial fibrillation is a common cause of hospitalisation[194] and rates of hospitalisations for atrial fibrillation are increasing.[170;186;195 197] Between 1986 and 1995 the numbers of patients admitted to hospital in Scotland with a principal diagnosis of atrial fibrillation for the first time increased by 125% in men and 105% in women.[186] Average length of stay fell during this period but because of the overall increase in hospitalisations, atrial fibrillation contributed to a growing proportion of cardiovascular-related bed-days utilised (from 18% to 37% with atrial fibrillation coded in any diagnostic position).[196] Similarly in Denmark between 1980-1993 hospitalisation rates for atrial fibrillation increased.[195] In the US, using data from the National Hospital Discharge Survey, hospitalisations for atrial fibrillation increased 2-3 fold between 1982 and 1993.[197]

1.4.3.5 Cost of atrial fibrillation

In the UK in 2000, the cost of atrial fibrillation was 459 million which was equivalent to 1% of total NHS expenditure.[198] Hospitalisations for atrial fibrillation are a major determinant of the cost.

1.4.3.6 Summary

Atrial fibrillation is an extremely costly public health problem. It is an independent risk factor for stroke and heart failure. It is one of the most common causes of hospitalisation and hospitalisation rates for atrial fibrillation are increasing.

Table 20 Prior studies reporting morbidity outcomes in patients with atrial fibrillation

Study	Location	n / n with AF (% men)	Age group (years)	Era of screening	Follow-up (years)	Stroke RR (95%CI)	Heart failure (95%CI)	Other morbidity (95%CI)
Rotterdam Study[166]	Rotterdam, The Netherlands	6584 / 195 9 (40.8%)	≥55	1990-1993	-	NA	NA	Dementia 2.0 (1.2, 3.4)
Dubbo Study of the Elderly[193]	Australia	2805 / 66 (44%)	≥60	1988-1989	8	1.6 (0.9, 2.8) (fatal or non fatal) 3.1 (1.4, 7.0) (fatal)	NA	NA
Multifactor Primary Prevention Study[164]	Göteborg, Sweden	7495 / 754 atrial fibrillation hospitalisations during follow up period (100%)	47-55 (at screening)	1970-1973	25.2	3.0 (2.5, 3.6) men (non fatal) (age-adjusted)	7.0 (5.8, 8.2) men (age-adjusted)	Myocardial infarction 1.9 (1.6, 2.3) men (age-adjusted)
Renfrew-Paisley Study[185]	Scotland, UK	15406 / 100 (53%)	45-64 (at screening)	1972-1976	20	2.5 (1.3, 4.8) men 3.2 (1.0, 5.0) women (fatal or non fatal)	3.4 (1.7, 6.8) men 3.4 (1.9, 6.2) women	Risk of myocardial infarction not increased
Manitoba Follow-Up Study[172]	Royal Canadian Air Force	3983 / 300 (100%)	18-62 at entry. Mean age at onset of atrial fibrillation 66	1948	44	2.1 men (fatal or non fatal)	3.0 men	Risk of myocardial infarction not increased
Whitehall Study[184]	London Civil Servants, UK	19018 / 63 (100%)	40-69	1967-1969	18	6.9	NA	NA
British Regional Heart Study[178]	UK	7727 / 48 (100%)	40-59	1979-1980	5	2.3 (non significant)	NA	NA
Rochester Epidemiology Project[192]	Minnesota, US	1444 stroke cases / NA (NA)	NA	1960-1984	-	2.0 Unadjusted	NA	NA
Framingham Study[190]	Framingham, US	5070 / 303 (48%)	30-62	1948-1952	34	4.0 (50-59 years) 4.5 (80-89 years) (fatal and non fatal) Unadjusted	NA	NA
Reykjavik Study[168]	Iceland	9067 / 25 (72%)	32-64	1967-1970	14	7.1 (fatal or non fatal) 12.3 (fatal) (Unadjusted)	25.9	Risk of myocardial infarction not increased
Western Australia study[177]	Busselton, Western Australia	1770 / 87 (48%)	>60	1966-1981	2-17	3.8 (fatal)	NA	NA

AF= atrial fibrillation; NA= not available

1.4.4 Atrial fibrillation mortality

1.4.4.1 Risk of death in patients with atrial fibrillation

The prognosis of individuals with atrial fibrillation has been examined in two distinct groups of individuals. (Table 21) Firstly, in cohort studies, atrial fibrillation was identified at screening and individuals were followed prospectively for mortality outcomes.[168;172;177;184;185;199] Secondly, in several studies the prognosis of patients following an incident hospitalisation or outpatient encounter for atrial fibrillation was examined.[164;173;179;186;195]

The mortality rate of subjects aged 55-94 years who developed atrial fibrillation during 40 year follow-up of the Framingham Heart Study[199] cohort was approximately twice that of age and sex matched controls. After adjustment for cardiovascular risk factors and pre-existing cardiovascular disease atrial fibrillation was still associated with a significant increased risk of death in men (OR 1.5, 95% CI 1.2, 1.8) and in women (1.9 (1.5, 2.2)). In the Manitoba Follow-Up Study[172] atrial fibrillation increased the total mortality rate 1.31 times after multivariable adjustment. Cardiovascular mortality including and excluding fatal stroke was also increased (adjusted RR 1.41 and 1.37, respectively).

The Whitehall Study[184] was a prospective cohort study of 19,063 male civil servants, aged 40-69 years, who were screened between 1967 and 1969 and followed for 18 years. There was a 2.6 times increased risk of death in the 63 patients with atrial fibrillation compared to those without atrial fibrillation. In a population study from Western Australia[177] the adjusted risk of all-cause death (HR 1.9) and cardiovascular death excluding stroke (HR 1.8) were increased in individuals aged $\geq$ 60 years with atrial fibrillation. In the Reykjavik Study[168] individuals with atrial fibrillation had an increased risk of cardiac death (RR 6.1, $p<0.05$) and whilst there was an increase in all-cause mortality (32% in the atrial fibrillation group compared with 20% in the control group during 14 year follow-up), unlike other studies this was not statistically significant. Atrial fibrillation was also an independent predictor of all-cause mortality (men RR 1.5, 95% CI 1.2, 2.2; women 2.2 (1.5, 3.2)) and cardiovascular mortality (men 1.8 (1.3, 2.8); women 2.8 (1.9, 4.2)) in the Renfrew-Paisley study.[185] Both heart failure and stroke contributed to this excess mortality. In the Multifactor Primary Prevention Study (Göteborg Study)[164] of the group of 754 men hospitalised with atrial fibrillation during the 27 year follow-up period mortality was

increased by 3.3 times. Amongst men with atrial fibrillation at first screening (n=37) mortality during follow-up was 79% compared to 44.3% in men without atrial fibrillation (OR 4.71, 95% CI 2.16, 10.28).

In a more contemporary population study using the Marshfield Epidemiologic Study Area database[173], 577 patients with a first episode of atrial fibrillation or flutter were identified between 1991 and 1995. They were followed prospectively until 1998. Compared with controls, mortality among patients with atrial fibrillation or flutter was nearly 7.8-fold higher at 6 months and 2.5 fold higher at the end of the follow-up period after adjusting for other risk factors.

Within subsets of patients with heart failure[200-202], acute myocardial infarction[203-206] or acute stroke[207-209], atrial fibrillation has been found to increase mortality in some studies[200;202;203;207;208] but not in others[201;204-206;209].

1.4.4.2 Secular trends in mortality

Trends in the risk of death following a hospitalisation with atrial fibrillation between 1980 and 1999 were examined using the Danish National Hospital Discharge data.[179] There was a 20% reduction in the adjusted risk of death in men and an 18% reduction in women during the last five-year period compared to the first five-year period. There is no mention in this study as to whether different durations of follow-up were taken into account.
In Scotland, the risk of short term (30-day) and medium term (31 days-2 years) case fatality in patients hospitalised with atrial fibrillation between 1986 and 1995 was examined.[186] After adjusting for age, sex, deprivation and co-morbidities the risk of short-term case-fatality in 1995 significantly declined by 21% in men and 24% in women in comparison to 1986. The medium term case-fatality also declined significantly in men by 30% and in women by 20% over this period.
Despite the proven efficacy and more widespread use of anticoagulation both of these studies still demonstrate an excess mortality associated with atrial fibrillation in recent years.

1.4.4.3 Sex and age differences in mortality

The risk of death in individuals with atrial fibrillation varied by sex in the Framingham Study, although this finding was not significant (OR 1.2, 95% CI 0.98, 1.49) for men

versus women with atrial fibrillation.[199] The risk of death was greater in men compared to women without a diagnosis of atrial fibrillation (1.69 (1.4, 1.7)) and it appears therefore that the presence of atrial fibrillation attenuates the survival advantage of women. There was no evidence of an age sex interaction in individuals with atrial fibrillation.
In the Danish study the elevated mortality risk associated with atrial fibrillation diminished with age.[195] Persons aged 50-59 years had a 4 fold increased risk of death from any cause and a 6-8 fold increased risk of cardiovascular death compared to the Danish population. This is in comparison to persons aged 80-89 years with atrial fibrillation having a 2-3 fold increased risk of death and a 3-4 fold risk of cardiovascular death compared to the general population. In contrast in the Scottish hospitalisation data the adjusted risk of death in the short and medium term increased with increasing age.[186]

1.4.4.4 Mortality in lone atrial fibrillation

Atrial fibrillation in the absence of structural heart disease is termed lone atrial fibrillation. In the Renfrew-Paisley study, lone atrial fibrillation conferred a non-significant 1.8 fold (95% CI 0.9, 3.8) increased risk of death.[185] In the Marshfield Epidemiologic Study Area patients with lone atrial fibrillation had a mortality twice that of controls (p=0.06).[173] Likewise in the Framingham Study lone atrial fibrillation was associated with a doubling in mortality (multivariate OR 2.4, 95%CI 1.8, 3.3 in men and 2.2 (1.6, 3.1) in women).[199]

1.4.4.5 Summary

A number of studies have confirmed that atrial fibrillation is an independent predictor of mortality. There is a temporal trend towards a reduction in the risk of death associated with atrial fibrillation in recent years. However, the excess mortality associated with atrial fibrillation demonstrated in more recent studies emphasises the need for improved prevention of atrial fibrillation and improved therapeutic modalities for treating and curing atrial fibrillation.

Table 21 The prognosis of atrial fibrillation (AF)

Study	Location	Study design	Year of study	N / N with AF (proportion men)	Mean age (years)	Case-fatality in men (time)	Case-fatality in women (time)	Adjusted relative risk for death	Adjusted risk of death for sex
Danish National Registry of Patients[179;195]	Denmark	Population study using routine data. Incident AF hospitalisation	1980-1999	131,728 (52%)	40-89	45% (5 years) (1995-99) (Kaplan-Meier survival curve estimate)	47% (5 years) (1995-99) (Kaplan-Meier survival curve estimate)	Death men 3.8 (3.2, 4.4) women 4.2 (3.4, 5.4) Cardiovascular death men 5.8 (4.7, 7.1) women 8.0 (5.0, 11.6) (50-59 years)	NA
Marshfield Epidemiologic Study Area[173]	Wisconsin, US	Prospective case-control study. AF on ECG, rhythm strips, holter or event recorders.	1991-1995 and followed up until 1998	577 (56%)	21-96 Mean age 71	15% with AF compared to 2% without AF (6 months) men and women	NA	7.8 (4.1, 15) (6 months) 2.5 (2.0, 3.1) (end of follow-up)	NA
Scottish Morbidity Record Scheme[186]	Scotland, UK	Population study using routine data. First AF hospitalisation.	1986-1995	22968 (49%)	71 70 in 1986 72 in 1995	3.1% (30-day) (1995) 22% (2-year) (1995)	3.8% (30-day) (1995) 25% (2-year) (1995)	1995 versus 1986 0.79 men, 0.76 women (30-day) 0.70 men, 0.80 women (2-year)	NA
Renfrew-Paisley Study[185]	Scotland, UK	Population based prospective cohort study. AF on ECG.	Screened 1972-1976 and followed for 20 years	15406 / 100 (53%)	45-64	72% with AF compared to 46% without AF (20 years)	86% with AF compared to 29% without AF (20 years)	1.5 (1.2, 2.2) in men and 2.2 (1.5, 3.2) in women	No difference
Multifactor Primary Prevention Study[164]	Göteborg, Sweden	Prospective population study. AF hospitalisations.	Screened 1970-1973 and followed 1996 (mean 25 years)	7495 / 37 (100%) at screening 7495 / 754 (100%) AF hospitalisations	47-55 and followed for 27 years	51% with AF compared to 44% without AF	NA	3.3 (2.9, 3.8) in men hospitalised AF 4.7 (2.2, 10.3) in men with AF at screening	NA
Manitoba Follow-up Study[172]	Royal Canadian Air Force	Prospective cohort study. AF on ECG or physician report during 44 year follow-up.	Screened 1948 and followed for 44 years	3983 / 300 (100%)	18-62 at entry. Mean age at onset of AF 66 (33-93)	NA	NA	1.31 in men (total mortality) 1.41 (cardiovascular mortality)	NA

AF= atrial fibrillation; NA not available

Continued over...

Table 21 continued

Study	Location	Study design	Year of study	N / N with AF (proportion men)	Mean age (years)	Case-fatality in men (time)	Case-fatality in women (time)	Adjusted relative risk for death	Adjusted risk of death for sex
Framingham Heart Study[199]	Framingham, US	Prospective cohort study. AF on ECG.	Screened 1948 and followed for 40 years	5209 / 621 (47.7%)	55-94	61.5% with AF compared to 30.0% without AF (10 years) in 55-74 year olds	57.6% with AF compared to 20.9% without AF (10 years) in 55-74 year olds	1.5 (1.2, 1.8) in men and 1.9 (1.5, 2.2) in women	OR 1.2 (0.98, 1.5) for men versus women
Reykjavik Study[168]	Iceland	Prospective cohort study. AF on ECG at baseline screening	1967-1970 and followed for 14 years	9,067 / 25 (72%)	32-64 at baseline screening	32% with AF compared to 20% without AF RR 1.9 (not significant) (men and women)	NA	Cardiac death; 6.1 ($p<0.05$) Unadjusted	NA
Western Australia study[177]	Busselton, Western Australia	Triennial population survey	1966-1981 and followed for 2-17 years	1770 / 87 (48%)	>60	NA	NA	All cause 1.9 Cardiovascular (non-stroke) 1.8	NA

AF= atrial fibrillation; NA= not available

1.5 Obesity and cardiovascular outcomes

The World Health Organisation defines overweight as a body mass index (BMI) of 25 to 29.9kg/m^2, obesity as a BMI $\geq$ 30 kg/m^2 and morbid obesity as a BMI $\geq$ 40 kg/m^2. BMI is calculated as the weight in kilograms divided by the square of the height in metres.

1.5.1 Prevalence of obesity

The prevalence of obesity has reached unprecedented proportions.[210] Nearly one third of Americans are obese.[211;212] It is estimated that there are up to 200 million obese citizens in the recently expanded European Union. The obesity epidemic is also afflicting developing countries. [210] There is appropriate concern that this alarming trend will have major public health consequences globally, with evidence linking obesity to an increased risk of more than 30 medical conditions.[210]

According to the last Scottish Health Survey in 2003, 65.4% of Scottish men and 59.7% of Scottish women were classified as either overweight or obese.[213] Men were more likely than women to be overweight (43.0% versus 33.8%). However, women were more likely than men to be obese (26% versus 22.4%) or morbidly obese (3.4% versus 1.6%). There has been a steady upward trend in mean BMI since 1995 in men and women (men; 26.0 in 1995, 26.4 in 1998, 26.9 in 2003 and women; 25.7 in 1995, 26.3 in 1998, 26.9 in 2003). The proportion of individuals who are classified as overweight or obese has risen from 55.6% in 1995 to 64% in 2003 in men and 47.2% in 1995 to 57.3% in 2003 in women and the proportion morbidly obese tripled during this time period.

The increased prevalence of obesity is thought to result from a decline in physical activity and rising fat intake.[210] People now have increasingly sedentary life styles and consume high fat, energy dense diets. There is also a genetic or other biological predisposition to gain weight more readily when exposed to an unfavourable environment.[214] Behavioural aspects may also play a role.

Obesity should be regarded as today's largely neglected health problem with projections for the next decade that are so serious that public health action is urgently required. Merely concentrating on children and adults who are obese and have associated health problems is not sufficient. What is required are preventative public health strategies, which affect the entire society including dietary change (such as easy access to cheap healthy food, provision of healthy food to children in schools and health education), alterations in physical activity (such as physical activity programs in schools) and behaviour modification.[215]

1.5.2 Cardiovascular morbidity associated with obesity

Obesity is associated with a broad range of metabolic and mechanical disorders including sleep apnoea, respiratory problems, osteoarthritis, gastrointestinal and gallbladder disease, and cancers such as endometrial, breast, prostate and colon cancer. [210] For the purpose of this literature review I will focus on the cardiovascular risk factors and cardiovascular diseases associated with obesity.

1.5.2.1 Cardiovascular risk factors

The importance of obesity alone in predicting adverse cardiovascular outcomes has been a subject of debate because obesity influences the development of other established cardiovascular risk factors. Obesity has an adverse effect on several coronary risk factors including hypertension[216-220], type II diabetes mellitus[216;218;221;222] and dyslipidaemia[223]. Risk estimates from population studies suggest that ≥75% of hypertension can be directly attributed to obesity.[224]

The relationship between body mass index and cardiovascular disease risk factors was examined prospectively in the Framingham Heart Study[216] participants aged 35 to 75 years, who were followed for 44 years. Relative to normal weight men, obese men had a multivariable adjusted relative risk of 2.23 for hypertension and 1.85 for diabetes (in women 2.63 and 1.36 respectively). During follow-up, overweight participants (but not those who were obese) experienced an increased risk for new hypercholesterolaemia. In the Framingham Offspring Study[223], obesity was significantly and linearly associated with low-density lipoprotein cholesterol levels. In NHANES III the risk of developing diabetes and hypertension increases dramatically with increasing BMI in men and women.[225] While

men and women with BMI≥25 kg/m^2 were more likely than persons of normal weight to have high cholesterol levels, the prevalence of high cholesterol did not increase with increasing weight category. BMI was also positively associated with systolic and diastolic blood pressure in 4780 men and women from nine North American populations who participated in the Lipid Research Clinic Prevention Study.[226] In another relatively large US study[227], of 886 men and 1114 women who were aged 50 years and older when examined in 1984-1987, those who gained 10 pounds or more between ages 40 and 60 years had an increased risk for developing diabetes. The relative risk for diabetes was 1.4 for every 17% to 31% increase in body weight after age 18 years. In an earlier cross-sectional study in the US, more than one million people were screened for hypertension as part of the Community Hypertension Evaluation Clinic.[220] The overweight group had a prevalence of hypertension which was 50% to 300% (in different age groups) higher than other participants. The relationship between obesity, fat and the risk of non-insulin-dependent diabetes mellitus was examined in the cohort of 51,529 U.S. male health professionals aged 40-75 years of age in 1986.[228] During the five year follow-up here was a strong positive association between overall BMI and the risk of diabetes. Men with a BMI of ≥35 kg/m^2 had a multivariate RR of 42.1 (95% CI 22.0, 80.6) compared with men with a BMI < 23.0 kg/m^2.

Two other American studies examined the association between obesity and cardiovascular risk factors in women. The Iowa Women's Health Study[218] was a prospective cohort study of 31,702 Iowa women, aged 55 to 69 years. Body mass index was independently associated with self reported diabetes (age-adjusted relative risk 13.8) and hypertension (age-adjusted relative risk 2.2). In the Nurses Health Study[229] the relationship between obesity and diabetes was examined in a cohort of 114824 female nurses aged 30-55 years who were initially screened in 1976 in the US. After adjusting for age, BMI was a strong predictor of the risk of developing diabetes during the 14 year follow-up. Women with a BMI of 31 kg/m2 or greater had an age-adjusted relative risk of 40 or more compared to women with a BMI of less than 22 kg/m2.

Two Swedish studies examined the relationship between obesity and risk of diabetes.[221;230] In a 12 year longitudinal study of women in Göteborg, BMI, sum of two skinfolds and waist-to-hip circumference ratio, were significantly associated with an increasing incidence of diabetes even after multivariable adjustement.[230] In the study of Men Born in 1913, 792 54 year old men who were resident in Göteborg, Sweden, were followed for 13.5 years for the development of diabetes.[221] Even when the confounding effect of body mass index, as a

measure of the total body fat mass, was accounted for, the waist-to-hip ratio was positively and significantly associated with the risk for diabetes.

In the INTERSALT study[231], the relationship between body mass index and blood pressure was studied in 10,079 men and women aged 20-59, sampled from 52 centres around the world. Overall, a 10 kg higher body weight was associated on average with a 3.0 mmHg increase in systolic and a 2.2 mmHg increase in diastolic pressure. The relationship between obesity as measured by the ponderal index (height in inches / weight in $lb^{1/3}$) and blood pressure was measured in 637 men and 835 women who attended the Glasgow Blood Pressure Clinic with untreated hypertension. There was an association between obesity and blood pressure only in non-smoking men. The associations of obesity with blood pressure were studied in 5,550 male and female subjects aged 25 to 64 years, surveyed in the National Heart Foundation of Australia 1980 Risk Factor Prevalence Study.[232] BMI was significantly and independently associated with blood pressure levels in both sexes. 30% of hypertension in the study population could be attributed to overweight.

1.5.2.2 Metabolic syndrome

It is now recognized that overweight and obese persons without diabetes, particularly those with abdominal obesity often have a cluster of clinical and metabolic findings that is termed the metabolic syndrome.[233] This syndrome is characterised by insulin resistance and a particularly atherogenic dyslipidaemia (high levels of low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, and triglycerides and low levels of high-density lipoprotein cholesterol) but it is also associated with elevated C-reactive protein levels, increased propensity to thrombosis and activation of the sympathetic nervous system. The metabolic syndrome is a major risk factor for cardiovascular events.[234]

1.5.2.3 Coronary heart disease and acute myocardial infarction

One of the first medical consequences of obesity to be recognised was coronary heart disease.[224;235-237] In response to the emerging body of scientific, medical and behavioural data about the link between excess adiposity and coronary heart disease the American Heart Association has reclassified obesity is a major modifiable risk factor for coronary heart disease.[238]

Obesity is associated with hypertension, hypercholesterolaemia and hyperglycaemia which accelerate atherogenesis. However, obesity has also been shown to be an independent risk factor for coronary heart disease. In the Framingham Study[237], obesity on initial examination in persons aged 28-62 years, as measured by Metropolitan Relative Weight (the percentage of desirable weight), was a significant independent predictor of 26-year incidence of coronary disease. In a more recent analysis of the Framingham cohort[216], participants aged 35-75 years were followed for 44 years for the development of coronary heart disease. Obesity was defined as a body mass index ≥ 30. After adjusting for age, smoking, hypertension, cholesterol and diabetes, the relative risk for angina was increased among those who were obese (men 1.8, 95% CI 1.3, 2.6; women 1.6 (1.2, 2.3)) relative to normal weight individuals. Whilst the age-adjusted relative risk for myocardial infarction was increased in obese women, there was no greater risk in obese men or women in the multivariable model (men 1.2 (0.8, 1.7); women 1.5 (0.9, 2.3)).

The Nurses' Health Study[235] cohort of 115,818 women aged 30-55, all without cardiovascular disease at study inception, was followed for 14 years. In a multivariable analysis (not controlling for diabetes, hypertension and hypercholesterolaemia) comparing women with a body mass index of ≥29kg/m^2 to those with a body mass index of <21kg/m^2 the relative risk was 2.90 for coronary heart disease, 3.15 for non fatal myocardial infarction and 2.73 for fatal coronary heart disease.

In the Manitoba Study[239], of a cohort of 3,983 men with a mean age of 31 at entry, body mass index significantly predicted myocardial infarction and coronary heart disease during a 26 year follow-up, after adjusting for age and blood pressure.

In the Study of Men Born in 1913[240] a cohort of 792 men aged 54 years were screened in 1967. There was no correlation between BMI and ischaemic heart disease during the 13 year follow up period.

1.5.2.4 Heart failure

There has been debate as to whether obesity is an independent predictor of heart failure or whether the risk is mediated through other physiological and metabolic abnormalities.

In the Framingham study[241] 5881 participants were followed up for 14 years. 496 subjects (258 women and 238 men) developed heart failure. The hazard ratio for obesity relative to

normal weight was 2.12 (1.51, 2.97) for women and 1.90 (1.30, 2.79) for men. There was an increase in the risk of heart failure of 5% in men and 7% in women for each increment of 1 unit in body mass index. Models were adjusted for age, alcohol consumption, cholesterol, smoking, valve disease, hypertension, diabetes, electrocardiographic evidence of left ventricular hypertrophy and myocardial infarction. In NHANES I[242] 1382 heart failure cases were documented during a follow-up of 19 years (13,643 individuals screened between 1971-1975) from medical records and death certificates. The relative risk of heart failure for overweight (BMI $\geq$27.8 kg/m^2 in men and $\geq$27.3 kg/m^2 in women) was 1.24 (1.01, 1.51) for men and 1.43 (1.19, 1.72) for women after adjusting for age, race and coronary heart disease and 1.23 (1.00, 1.52) in men and 1.34 (1.10, 1.64) in women after adjusting for age, race, high school education, smoking, alcohol, physical activity, hypertension, cholesterol, diabetes, valvular heart disease and coronary heart disease. In the New Haven, Connecticut cohort of the Established Population for Epidemiologic Studies of the Elderly program[243] 1749 subjects aged 65 years and over were evaluated in 1982 and 173 subjects developed incident heart failure (determined by chart review) during 13,811 person-years of follow up. The hazard ratio for a BMI $\geq$ 28 kg/m^2 compared with <24 kg/m^2 was 1.6 (1.0, 2.4) after adjusting for age, sex, diabetes, pulse pressure. In the Multifactor Primary Prevention Study (Göteborg)[144] 7495 men were examined at baseline in 1970-73 and followed for 27 years. During this time 937 men were hospitalised for heart failure. The relative risk for a BMI $\geq$27 kg/m^2 compared to a BMI $\leq$23.99 kg/m^2 was 1.50 (1.26, 1.78) in a bivariable analysis. Body weight was also related to incident heart failure in 973 Swedish men born in 1913.[113] With the exception of the Framingham study these studies do not use conventional definitions of obesity.

There are a number of possible mechanisms given in these studies for the association between obesity and heart failure. Obesity is a recognised risk factor for coronary artery disease and coronary risk factors such as hypertension, hyperglycaemia, and hyperlipidaemia, which increase the risk of myocardial infarction and therefore heart failure. Elevated body mass index is also associated with altered left ventricular remodelling possibly due to increased haemodynamic load (i.e. increasing cardiac output and intravascular volume, thereby causing elevated left ventricular filling pressure and end-diastolic volume leading to subsequent cardiac dilation and left ventricular hypertrophy thereby increasing the risk for developing heart failure), increased oxidative stress and neurohumoral activation. There is also the possibility of a direct effect of

obesity on the myocardium - cardiac steatosis and lipoapoptosis was recently demonstrated in an animal model of obesity.[244]

1.5.2.5 Stroke

There have been conflicting results on the effect of obesity on stroke with some studies showing a positive association[237;245-250] and others showing no association[240;251-254]. The risk of stroke related to obesity has been shown to be different in men and women.[237;245]

In the Physicians' Health Study of 21,414 male physicians, the adjusted relative risk for stroke (not including hypertension, diabetes and cholesterol) was 2.00 (1.48, 2.71) in participants with BMI ≥30 kg/m^2 compared to those with BMI <23 kg/m^2.[248] They also evaluated BMI as a continuous variable and found that each unit increase in BMI was associated with a 6% increased risk of stroke and this reduced to 4% when diabetes, cholesterol and hypertension were included in the model. In the Honolulu Heart Program[246] 1663 non-smoking Japanese-American men (55-68 years) (screened 1965-68) with no hypertension, diabetes or left ventricular hypertrophy were followed for 22 years. The risk of stroke after adjusting for age and other risk factors (including systolic BP, glucose and cholesterol) for the average body mass index in the top tertile (26.6 kg/m^2) compared with that in the bottom tertile (20.3 kg/m^2) was 2.1 (1.1, 4.1). In a prospective population study a total of 234,863 Korean men aged 40-64 years were screened in 1986 and followed up between 1991 and 2000 for fatal and nonfatal stroke events. [249] The hazard ratio after adjusting for age, alcohol, smoking, exercise and monthly salary level for a BMI ≥30 kg/m^2 relative to a BMI 22-23.9 kg/m^2 was 1.7 (1.4, 2.3) for all stroke, 1.4 (0.9, 2.0) for ischaemic stroke and 2.6 (1.7, 4.0) for haemorrhagic stroke. After full adjustment for confounders and variables potentially on causal pathway (i.e. blood pressure, glucose and cholesterol) the association between body mass index and stroke subtype was attenuated (1.2(1.0, 1.6) for all stroke, 1.0 (0.6, 1.4) for ischaemic stroke and 1.8 (1.1, 2.7) for haemorrhagic stroke). In the Whitehall study[250] in 17,753 male civil servants, aged 40 to 64 years, there was a two fold increased risk of death from stroke among men with BMI ≥24 kg/m^2 compared with those with BMI<24 kg/m^2. In the Nurses' Health Study[247] 116759 women screened in 1976 aged 30-55 years. During 16 years of follow-up for women with increased BMI (≥32 kg/m^2) the relative risk of ischaemic stroke was 2.37 (1.60, 3.50) as compared with those with a BMI <21 kg/m^2 after adjusting for age,

smoking, postmenopausal hormone use, and menopausal status. The equivalent RR for haemorrhagic stroke was 0.73 (0.42, 1.26) and for total stroke was 1.59 (1.22, 2.08).

Dey et al[245] looked at risk factors for stroke in 2,287 individuals aged 70 years old and examined between 1971-1981 in Sweden. In men the relative risk for stroke in the highest BMI quartile (≥28) was 1.68 (1.12, 2.53) after adjusting for smoking, CHD, diabetes, cholesterol and SBP. There was no significant association between BMI and risk of stroke in women. In contrast in the Framingham study[237] Metropolitan Relative Weight (percentage of desired weight) was positively and independently associated with stroke in women but not in men.

In a study of 28,643 US male health professionals, abdominal obesity, but not elevated body mass index (age adjusted relative risk 1.29 (0.73, 2.27)), predicted risk of stroke in men.[252] In the Study of Men Born in 1913[255], 789 men aged 54 at baseline were followed for 18.5 years for the development of stroke. Increased waist circumference, but not body mass index, was independently associated with the risk of stroke.

In the Copenhagen City Heart Study[253] 7,060 women, ≥ 35 years, were initially investigated between 1976-1978, and followed up to 1988. There was no significant effect of BMI (1.02 (0.99, 1.05) per unit of BMI) on risk of cerebrovascular disease after adjusting for age, length of school education, household income, smoking, alcohol, daily consumption of tranquilizers and physical inactivity. In the British Regional Heart Study[256], 7,735 men aged 40-59 years from 24 General practices in the UK were followed for eight years for the development of fatal and non-fatal strokes. There was no association between obesity and stroke. In the Chicago Stroke Study[251] 3,141 subjects were screened between 1965-67 and followed up for a median of 32.1 months. They examined the association between adiposity (as measured by ponderal index and chest skinfold) and risk of stroke. Ponderal index was associated with risk of stroke in a race-age-sex stratification however on a multivariate analysis neither variable was significantly associated with stroke. In the Finnmark study, 13,266 men and women aged 35-52 years were followed for 14 years.[254] There were 241 first stroke events. BMI was a highly significant predictor of stroke in a univariate but not multivariate model. The model however included height as well as body mass index.

In a random sample of 41,837 women aged 55-69 years from Iowa, women who developed a stroke were 2.1 times more likely to be in the upper tertile of waste-hip circumference

ratio.[219] Multivariable adjustment including body mass index in the model reduced the risk ratio to 1.6 and including diabetes and hypertension reduced the risk ratio to 1.3 which was no longer significant. This suggests that abdominal obesity increases the risk of stroke, even after accounting for overall body mass index and that the association between abdominal obesity and the risk of stroke is in part related to the association of abdominal obesity with hypertension and diabetes.

The fact that the association between BMI and risk of stroke is attenuated by adjustment for cholesterol, glucose and blood pressure indicates that obesity may have its effect on stroke in part through these mechanisms. Other possible reasons are an increase in prothrombic factors observed among overweight and obese individuals.[248] Increased levels of C-reactive protein in overweight and obese individuals may also play a role since an association between increased levels of inflammatory markers and risk of ischaemic stroke has been previously documented.

1.5.2.6 Atrial fibrillation

Obesity increases the risk of arrhythmias and sudden death, even in the absence of cardiac dysfunction.[257;258]

In the Multifactor Primary prevention study the adjusted HR for atrial fibrillation was 1.07 (1.04, 1.10) per unit of BMI.[164] In the Framingham cohort[259], 5,282 participants without baseline atrial fibrillation were followed for a mean of 13.7 years for the development of new onset atrial fibrillation. There was a 4% increase in atrial fibrillation risk per one unit increase in body mass index in men and women. The adjusted hazard ratio for atrial fibrillation associated with obesity was 1.52 in men and 1.46 in women.

1.5.2.7 Venous thromboembolic disease

The Longitudinal Investigation of Thromboembolism Aetiology was a prospective study of 19,293 individuals in 6 US communities between 1987 and 1998.[260] There were 215 venous thromboembolic events during a median of 8 years of follow up. The age-, race- and sex-adjusted hazard ratio (relative to a BMI<25) was 2.27 (1.57, 3.28) for obesity and 1.51 (1.06, 2.14) for overweight. Possible mechanisms suggested in this study include venous stasis and higher levels of prothrombotic factors, such as fibrinogen, plasminogen activator inhibitor I, and factor VII in obese individuals. In addition it is possible that obese

individuals are more likely to be hospitalised (and therefore subject to precipitating factors such as surgery and immobilization).

Two other studies have looked at body mass index and risk of pulmonary embolism and one of these was confined to fatal events. The Framingham study showed that women but not men who had a fatal pulmonary embolism had higher Metropolitan relative weights (percentage of desirable weight) compared with participants who died of other causes.[261] In the Nurses' Health Survey of 121,700 female nurses, a BMI of 29 or higher was an independent risk factor for pulmonary embolism (HR 3.0 [2.0, 4.7] relative to a BMI <21 adjusted for age, oral contraceptive pill, post menopausal hormone use, parity, diabetes, high blood pressure, cholesterol, smoking and time period).[262] In an autopsy study, morbid obesity was an independent risk factor for death from pulmonary emboslism.[263]

Another study found an association between abdominal circumference and venous thromboembolism. In the Study of Men Born in 1913, 855 men screened at 50 years old and followed for 30 years, abdominal obesity was an independent risk factor for venous thromboembolic events.[264]

1.5.3 All-cause and cardiovascular mortality associated with obesity

1.5.3.1 All cause mortality

Many studies have reported on the association between obesity and mortality with most studies showing an increased risk of death associated with obesity.(Table 22) Using data from US life tables, NHANES III, NHANES follow-up study and NHANES II Mortality Study, Fontaine *et al* estimated the expected number of years of life lost due to overweight and obesity.[265] Years of life lost is defined as the difference between the number of years that one would be expected to live if one were not obese and life expectancy if one were obese. They showed that obesity reduces life expectancy substantially especially among younger adults. Even a moderate amount of excess weight confers a noticeable diminution in life expectancy.

The Cancer Prevention Study II[266] was a prospective study of more than 1 million adults in the US who completed a questionnaire in 1982. Families were enrolled if at least one household member was ≥45 years and all household members ≥30 years were included.

There was an increased risk of death associated with obesity and a gradient of increasing risk associated with increasing BMI above the normal range. For example among non-smoking men who had no history of disease the relative risk of death compared to those with a BMI between 23.5 and 24.9, increased from 1.09 in men with a BMI 26.5-27.9 to 1.32 in those with a BMI 30.0-31.9 to 2.58 in men with a BMI ≥40 (the equivalent RR for women 1.10 (1.30, 2.00)). Over 750,000 adults participated in an earlier study, the Cancer Prevention Study I[267;268] which had similar methodology. The relative weight was calculated by dividing the person's weight by the average weight for his or her group and multiplying by 100. Men and women who were more than 40% overweight had a mortality rate nearly twice as high as average weight people. In another analysis of Cancer Prevention Study I[269] the association between BMI and death was examined in different age groups. The increase in risk of death from all causes associated with a higher body-mass index tended to be greater among younger subjects.

In the NHANES I Epidemiologic Follow-up Study[270] there was an increased mortality risk associated with the highest 15th percentile of the BMI distribution which only reached statistical significance in white women. In another paper, data from the NHANES I Epidemiologic Follow-up study was compared to another national representative sample of the US population, the National Health Interview Survey[271]. In the National Health Interview Survey each week a probability sample of households in the US was interviewed by trained personnel of the US Bureau of census to obtain information about health. There was a U shaped mortality curve associated with obesity. In both these studies the shape of the BMI mortality curves in men and women were similar in blacks and whites.

In the Adventist Health Study, the relationship between BMI and mortality was examined in a cohort of 20,346 non-Hispanic white, Seventh-day Adventist men and women aged 25-84 years who never smoked.[272] The cohort was screened in 1976 by mailed questionnaire and followed prospectively for 12 years. There was an increased risk of death associated with obesity in middle aged (25-54 years) and older aged (55-84 years) men and women both during earlier follow-up (1-6 years) and longer follow-up (7-12 years). The Adventist Mortality Study was an earlier study in which Californian Seventh-day Adventists aged 30-74 years were screened in 1960 and followed for 26 years. In the cohort of 12,576 women[273] during the later years of follow-up (years 15-26) there was an elevated risk of mortality, in those with a BMI >27.4 compared to those with a BMI < 21.3. In 5,062 men[274] there was also an increased risk of all-cause death in those with a

BMI ≥ 27.5 compared to those with a BMI 22.6-27.4 however this was only significant in younger (30-54 years) men.

An association between obesity and mortality was also shown in the Harvard Alumni Health Study[275]. 21,582 Harvard University male Alumni responded to a mailed questionnaire in 1962 or 1966 and were followed until 1988. Men with a BMI ≥ 26 had nearly a 20% increased risk of death relative to those with a BMI <22.5. There was also an excess mortality in participants of the Honolulu Heart Study[276] who were in the highest BMI quintile.

The relationship between BMI and mortality was also examined in a prospective population study from the Social Insurance Institution of Finland.[277;278] In 22,995 men aged 25 years and over there was a 1.5 fold increased risk of death for those with a BMI≥34.0 as compared with men of normal weight.[277] In a separate analysis of 17,519 Finnish women aged 25-79 years, the population was divided into quintiles of BMI by 10-year age groups. In those women aged 25-64 years there was an increased risk of death in the top quintile compared to the 2nd quintile (RR=1.5).[278] However, among women over 65 years of age BMI was not an important predictor of mortality. Data from compulsory army medical examinations of 78,612 Dutch men aged 18 years, were linked to death registration data over a follow-up period of 32 years.[279] An elevated BMI at aged 18 was associated with an increased risk of death.

In the Cardiovascular Health Study[280] the relationship of body mass index to 5-year mortality was examined in a cohort of 4,317 non-smoking men and women aged ≥65 years. There was no association between higher body mass index and mortality in this cohort of older adults. Likewise in the Established Populations for Epidemiologic Studies of the Elderly study[281] there was no excess risk of death associated with obesity in a cohort of 6,387 whites aged 70 years or older during the period 1982-1987. In contrast in the Framingham Heart Study[282]there was an increased risk of mortality for non-smoking men and women at age 65 years in relationship to body mass index. After adjusting for cholesterol and glucose levels, systolic blood pressure and prior cardiovascular disease this excess risk however was only significant in women. The Longitudinal Study of Ageing[283] examined the relationship between BMI and mortality in a large nationally representative sample of 7,260 US adults aged ≥70 years. Individuals were initially interviewed in 1984 and were followed through to 1990. Using Cox proportional hazard model and adjusting for age, sex, education and several health related questions they found that the relationship

between BMI and mortality was U-shaped for both men and women. The minimum mortality in this elderly cohort occurred at a BMI of 31.7 for women and 28.8 for men. In the Whitehall Study[284] the relationship between mortality and BMI in middle aged men differed within age bands. In the 40-49 year age group mortality increased with increasing quintile of BMI, however the excess risk of death for the heaviest quintile disappeared with advancing age.

The association between BMI and overall mortality was examined in a cohort of 115,195 U.S. women aged 30-55 years who were enrolled in the prospective Nurses' Health Study in 1976 and followed for 16 years.[285] When women who had never smoked were examined separately, there was a direct association between BMI and obesity (p for trend < 0.001). In women who had never smoked and had recently had stable weight, mortality among obese women (BMI≥29 kg/m^2) was more than twice that among leanest women. Mortality did not increase substantially until BMI reached 27.6 kg/m^2. A weight gain of 10 kg (22 lb) or more since the age of 18 was associated with increased mortality in middle adulthood. The relationship between BMI and mortality in women was also investigated in the Iowa Women's Health Study.[218] A mailed questionnaire was completed in 1986 by 31,702 Iowa women aged 55 to 69 years who were free of cancer, diabetes or heart disease and who held a valid Iowa driver's licence. Over a 12 year follow-up BMI showed a U-shaped association with all-cause mortality in the age-adjusted models. However after adjustment for other risk factors, there was no association between BMI and mortality (RR for fifth versus first quintiles 0.91 (95% CI, 0.8, 1.0)).

Several studies have failed to show an association between BMI and death. In the Study of Men Born in 1913[240], 792 men aged 54 years, were screened in 1967. There was no significant difference in mean BMI between those who died and those who remained alive over the 13 year follow-up period. In another study from Gőteborg, Sweden 1,462 women aged 38, 46, 50, 54 or 60 years were screened in 1968-69 and followed for 20 years.[286] There was no correlation between BMI and death. In both these studies Pitman's permutation test was used for correlation and multivariable modelling was not performed. In a study from eastern Finland the risk of death from all causes was examined in 3,786 men and 4,120 women aged 30-59 at outset in 1972 and followed for 9 years.[287] In a multivariable analysis adjusting for age and smoking, BMI was not an independent predictor of the risk of death from all causes in men or women. In the Seven Countries study[41] all cause mortality was not related to BMI.

Table 22 Prior studies reporting an association between obesity and all-cause mortality

	Location	Type of study	N (% men)	Age group (years)	Era of screening	Follow-up (years)	Multivariable model		All-cause mortality	
							BMI reference group	Adjustment	Men	Women
National Health Interview Survey[271]	US	Cross-sectional study	114954	All ages	1987-1990	December 1991	28.0-30.9	Age	1.2 (BMI 31.0-33.9) 1.7 (BMI ≥34.0) (White) (No CI given)	1.4 (BMI 31.0-33.9) 1.5 (BMI ≥34.0) (White) (No CI given)
Cardiovascular Health Study[280]	US	Prospective cohort study	4317	>65	1989	5	20-22 Mortality Men 20.4% Women 6.9%	Smokers excluded.	14.2% (BMI 30-32) 18.2% (BMI 32-34)	7.8% (BMI 30-32) 10.1% (BMI 32-34) 9.1% (BMI≥34)
Established Populations for Epidemiologic Studies of the Elderly[281]	4 communities in US	Prospective cohort study	6387 (38.3%)	≥70	1982-1987	3-6	Men 24.4-26.2 Women 23.7-25.8	Adjusted for age, smoking	1.0 (0.8, 1.1) (BMI ≥ 28.4)	1.0 (0.9, 1.2) (BMI ≥ 29.2)
Iowa Women's Health Study[288]	Iowa, US	Prospective cohort study	41177 (0%)	55-69	1986	5	<22.9	Smokers excluded. Age-adjusted	NA	1.23 (>30.7) (No CI given)
Longitudinal Study of Ageing[283]	US	Prospective cohort study	7260 (38.1%)	≥70	1984	6	Men 28.8 Women 31.7	Multivariable excluding DM, HTN, cholesterol and smoking	1.4 (no confidence intervals given) (BMI 40)	2.1 (no confidence interval given) (BMI 40)
Cancer Prevention Study II[266]	US	Prospective cohort study	1046154 (42.8%)	≥30	1982	14	23.5-24.9	Smokers excluded. Multivariable excluding DM, HTN and cholesterol	1.3 (1.2,1.5) (BMI 30.0-31.9) 1.7 (1.5,1.9) (BMI 32.0-34.9) 2.2 (1.8,2.6) (BMI 35.0-39.9) 2.6 (1.6,4.1)(BMI ≥40.0)	1.3 (1.2,1.4) (BMI 30.0-31.9) 1.5 (1.5,1.7) (BMI 32.0-34.9) 1.8 (1.6,1.9) (BMI 35.0-39.9) 2.0 (1.7,2.4) (BMI ≥40.0)
Nurses Health Study[285]	US	Prospective cohort study	115192 (0%)	30-55	1976	16	<19.0	Smokers excluded. Multivariable excluding DM, HTN and cholesterol	NA	2.1 (1.4, 3.2) (BMI 29.0-31.9) 2.2 (1.4, 3.4) (BMI≥32)
Adventist Health Study[272]	California, US	Prospective cohort study	20346 (34.4%)	25-84	1976	7-12	Men 22.4-27.3* 23.8-25.3† Women 20.7-27.4* 22.5-24.2†	Smokers excluded. Age	1.5 (0.8, 2.6)* 1.8 (1.3, 2.5)† (BMI≥27.4)	1.9 (1.2, 3.0)* 1.5 (1.2, 1.8)† (BMI≥27.5)

***25-54 years; † 55-84 years; CI= confidence interval; BMI= body mass index**

Continued over…

Table 22 continued

	Location	Type of study	N (% men)	Age group (years)	Era of screening	Follow-up (years)	Multivariable model		All-cause mortality	
							BMI reference group	Adjustment	BMI reference group	Adjustment
NHANES I Follow-up Study[270]	US	Prospective cohort study	3339 (47.5%)	65-74	1971-1975	10	Men 24.4-26.3 Women 24.4-26.9	Multivariable	1.0 (0.8, 1.3) (BMI ≥29.3)	1.3 (1.0, 1.7)(BMI ≥31.3)
Social Insurance Institute of Finland Survey[277;278]	Finland	Prospective cohort study	40114 (57.3%)	≥25 (≥80 excluded in women)	1966-1972	12	Men 22.0-24.9 Women Quintile II	Heart disease, cancer (and diabetes in men) excluded Age, geographical region and smoking	1.4 (p<0.01) (BMI ≥ 34)	1.6 (1.2, 1.8) (25-64 years) 1.0 (0.8, 1.2) (65-79 years) (BMI Quintile V)
Honolulu Heart Study[276]	Honolulu, Japan	Prospective cohort study	8006 (100%)	45-68	1965-1968	10	23.0-24.5 Mortality 8.1/1000	Not adjusted	Mortality 9.7/1000 (BMI >26.3)	NA
Harvard Alumni Health Study[275]	US	Prospective cohort study	19297 (100%)	Mean 46.6	1962/1966	22/26	< 22.5	Adjusted for age, smoking and physical activity	1.2 (1.1, 1.3) (BMI ≥ 26)	NA
Adventist Mortality Study[273;274]	California, US	Prospective cohort study	17638 (40.2%)	30-74	1960	26	Men 22.6-27.4 Women <21.3	Smokers excluded. Age adjusted in men. Multivariable excluding DM, HTN and cholesterol in women	1.7 (1.2, 1.3) (30-54 years) 1.1 (0.9, 1.4) (55-74 years) (BMI≥27.5)	1.6 (1.2, 2.3) (30-54 years) 1.3 (1.1, 1.5) (55-74 years) (BMI≥27.4)
Cancer Prevention Study I[267;268]	US	Prospective cohort study	755502 (44.5%)	≥30	1959	12	Relative weight index 90-109	Not adjusted	1.87 (Relative weight index ≥140)	1.89 (Relative weight index ≥140)
Framingham Heart Study[282]	US	Prospective cohort study	1723 (34.6%)	65	1957-1981	1-23	Men 23.0-25.2 Women 24.1-26.1	Smokers excluded. Multivariable.	1.4 (0.9, 2.2) (BMI ≥ 28.5)	1.6 (1.1, 2.3) (BMI ≥ 28.7)
Hoffmans *et al*[279]	The Netherlands	Retrospective cohort study	78612 (100%)	18	1950	32	19	Not adjusted.	2.0 (1.4, 2.7) (BMI ≥ 26)	NA

***25-54 years; † 55-84 years; CI= confidence interval; BMI= body mass index**

1.5.3.2 Cardiovascular mortality

As discussed earlier there is debate as to whether obesity exerts its affect on cardiovascular disease through its influence on established cardiovascular risk factors or whether obesity is an independent risk factor for cardiovascular disease. There are three potential methodological problems that can distort studies investigating the relationship between obesity and the risk of cardiovascular mortality.[236] Firstly, reverse causation, which is the effect of patients losing weight during chronic illnesses that are ultimately fatal, there by creating the appearance that persons with a lower weight have an increased mortality. Secondly, the issue of confounding variables such as not adjusting for smoking because smokers weigh less and have a higher mortality than non smokers. Thirdly, statistical adjustments for conditions related to obesity in the study population, for example hypertension and diabetes, which remove some of the adverse effects of obesity and give a false impression that the effect of obesity on the risk of death is neutral.

In the Cancer Prevention Study I, excess body weight increases the risk of death from cardiovascular disease in adults between 30 and 74 years of age.[269] The relative risk associated with greater body weight was higher among younger subjects. In another analysis of data from the Cancer Prevention Study I, men and women who were more than 40% overweight had a coronary heart disease mortality rate nearly twice as high as average weight people (men 1.95; women 2.07).[267;268] In the Cancer Prevention Study II, significantly increased risks of death from cardiovascular disease were found with a BMI of more than 25 in women and 26.5 in men.[266]

In the Nurses Health Study[285], rates of death due to cardiovascular disease among obese women (BMI $\geq$29 kg/m^2) were four times higher than those among the leanest women. The risk of coronary heart disease mortality was also increased with increasing BMI (p for trend <0.001). In the Iowa Women's Health Study[218] BMI was associated positively with coronary heart disease related mortality (multivariable adjusted RR for the fifth versus first quintiles of 1.7). In the Honolulu Heart Study[276] most of the excess deaths in the fifth quintile of BMI were due to coronary heart disease.

In the Whitehall Study, a 2-fold increase in risk of stroke mortality was observed among men with BMI > 24kg/m2 compared with those with BMI<24kg/m2.[250]

Obesity was also shown to increase the risk of premature coronary heart disease mortality in 84,910 men discharged from the US Army in 1946-47 and followed for 23 years.[289] In the Social Insurance Institution of Finland population survey, men aged ≥25 years, with a BMI ≥34, had a 1.8 times ($p<0.001$) increased risk of death from cardiovascular disease compared to men with a normal BMI (22.0-24.9) over a 12 year median follow-up.[277] In non-smoking women, aged 25-64 years, there was also an increased risk of mortality from cardiovascular diseases in the highest BMI quintile relative to the second quintile of BMI (RR 1.6, 95% CI 1.1-2.3).[278] However, there was no excess cardiovascular mortality in older obese women.

There was a correlation between BMI and cardiovascular death in the study of 1462 women from Göteborg, Sweden who were screened in 1968-69 and followed for 20 years after adjusting for age.[286]

In the Seventh-day Adventist study[290], 12,576 women who had never smoked completed a questionnaire in 1960. There was an increased risk of death from cardiovascular causes in women with a BMI >27.4 relative to those with a BMI 21.3-27.4 between 9 and 26 years of follow-up.

1.5.3.3 Mortality from heart failure

Obese people with heart failure seem to have a more favourable prognosis and this is referred to as the 'obesity paradox'. [291-299] The role of obesity in the prognosis of patients with heart failure was examined in 1,203 patients with advanced heart failure followed in a comprehensive heart failure management program.[291] In this study obesity was associated with a better five-year survival rate in patients with advanced heart failure and in multivariable analysis there was an inverse association between body mass index and mortality. In a UK study of 525 non-cachectic patients with chronic heart failure increasing body mass index was not an adverse prognostic factor.[292] In 522 patients with a history and clinical findings of heart failure referred to two Veteran Affairs Medical Centres in California, a lower body mass index was an independent predictor of death over a six-year follow-up period.[293] In a study of 181 patients with heart failure from The Netherlands a higher body mass index was an independent predictor of a more favourable prognosis.[294] Higher body mass index was also associated with better survival in a study of 209 patients with mostly class II and III heart failure who were followed at the Cardiomyopathy and Heart Transplant Centre in New Orleans.[295] In the Systolic Hypertension in the Elderly

Program study, overweight status was associated with a decreased stroke risk and reduced total mortality, as compared with lean subjects with heart failure.[296] Increasing body mass index was also associated with a lower mortality in a study of 4,700 patients hospitalised with heart failure.[297] Compared with normal weight, and adjusted for age and sex, the risk ratio for obese was 0.77 (0.70, 0.86). In the Digitalis Investigation Group trial[298], in 7,767 patients with stable heart failure, overweight and obese patients were at lower risk for death (Hazard Ratio 0.88 and 0.81 respectively), compared with patients at a healthy weight.

In summary, the prevalence of obesity is growing and obesity is associated with many adverse outcomes. Although clearly a risk factor, the evidence surrounding the mechanism and magnitude of associated risks is not consistent and appears to vary according to the outcome studied.

2 AIMS

To describe the epidemiology of cardiovascular disease (including angina, AMI, acute coronary syndromes, heart failure, atrial fibrillation and obesity) in Scotland using routinely available sources of data as well as data available from the MIDSPAN study.

3 METHODS

For this thesis I used data from primary care (Continuous Morbidity Recording in General Practice Scheme), secondary care (Linked Scottish Morbidity Recording Scheme) and a prospective cohort study (the Renfrew Paisley study). For each of these I will describe the source of the data and the quality, organisation and extraction of the data. In addition I will describe the specific data extracted and statistical analysis performed for each of the studies in chapters 4-11.

3.1 Continuous Morbidity Recording (CMR) in General Practice Scheme

3.1.1 Data sources

Primary care morbidity statistics from a sample of General Practices in Scotland were collected using the Continuous Morbidity Recording (CMR) scheme. Since April 2003, CMR has been superseded by Practice Team Information (PTI). CMR collected data on General medical Practitioner contacts only. PTI includes data recording by the broader practice team (general practitioners, practice nurses, district nurses and health visitors). Currently 44 practices contribute full Practice Team Information to PTI, covering around 5 per cent of the Scottish population. In April 1998 CMR was included as part of the national dataset. Any computerised General Practice could volunteer to take part in CMR. Practices were weighted to form a national sample that is broadly representative of the Scottish population as a whole in terms of age, sex, deprivation and rural/urban mix. All individuals resident in Scotland (including children) are registered with primary care, which is free at the point of contact and manages the treatment of patients once they are discharged from hospital. Access to secondary care is usually obtained through a General Practitioner (GP) based within a primary care practice.

General Practices partipating in the CMR scheme collected data from every face-to-face patient contact with a GP. In 1999, 53 practices participated in CMR covering 6% of the Scottish population. This increased to 55 General Practices contributing in 2001 (7% of the Scottish population). All contacts with practice patients (including temporary residents) were captured and recorded by every doctor (including locums and co-operative doctors). Data was collected from face-to-face doctor patient contacts only and not from telephone contacts or hospital episodes.

For each doctor-patient contact the following information is recorded; patient identifier, date of birth, sex, postcode, diagnosis, modifier, date of consultation, type of encounter and clinician I.D. These will be discussed in more detail below. The patient identifier is generated by General Practice Administration System for Scotland (GPASS) software, is practice specific and allows analysis of the data at the individual level. The diagnosis is the underlying morbidity the patient has presented with. It can be a diagnosis, or if the diagnosis is not clear, a symptom or sign. As patients can present with multiple problems, information is collected on the index condition and up to ten concomitant medical problems. General practitioners are asked to only record a problem if the patient presented with that condition or if the consultation was relevant to the condition in question (e.g. involving a change of medication for the condition). Each diagnosis is given a Read code. Read codes are the recommended national standard coding system in General Practice and can be mapped onto other coding systems including ICD-9, ICD-10 and British National Formulary (BNF) formulary. Read codes are arranged hierarchically, with the level of detail increasing down the hierarchy. For example G.... refers to circulatory system disease, G3... ischaemic heart disease, G30.. acute myocardial infarction, G301. acute myocardial infarction not otherwise specified, G3011 acute anteroseptal infarction. Each diagnosis is also given an appropriate modifier of "first", "recurrence" or "persistent". A 'first' modifier is defined by the first ever occurrence in primary care of a newly diagnosed condition or symptom for this patients with any doctor. A 'recurrence' modifier refers to a new occurrence of an illness or symptom, which has been previously diagnosed for that patient but has been inactive. 'Recurrence' also includes an acute exacerbation of an on-going morbidity. A 'persistent' modifier is defined as a follow-up, review or other consultation of an on-going symptom or condition. Modifiers allow calculation of incidence and prevalence of conditions. The type of encounter identifies what type of contact took place such as a home visit, out of hours contact or a surgery or clinic contact.

The data are entered onto the practice GPASS system and an extract is sent every month to the Information and Statistics division of the National Health Service in Scotland (ISD Scotland) for analysis. Data from all CMR practices is combined to form a national sample. The Primary Care Clinical Informatics Research Unit (PCCIU-R) based at the University of Aberdeen collates the prescribing and morbidity data.

CMR practices are located throughout Scotland with the highest concentration of practices in the more densely populated central areas of Scotland. (Figure 1) CMR practices are recruited on a continual basis so that the dataset is representative by age and sex of the Scottish population. The age distribution in the CMR practice population is comparable to the general Scottish population. The proportion of men and women in different age groups in the CMR practice population and in the Scottish population in the years ending March 2000 and March 2002 is shown in Figure 2. The CMR practice population is based on CMR practices which returned complete GP data for the years ending March 2000 and 2002 respectively. The source of the CMR practice population figures is the General Medical Practitioner Database (as at 1 October 1999 and 2001), while the source of the Scottish population figures is the General Register's Office, Scotland (mid year population estimates for 1999 and 2001). The overall proportion of men was slightly higher in the CMR population compared to the Scottish population in both time periods (1999-2000 49.4% versus 48.6% and 2001-2002 49.6% versus 48.1%). This was due to a higher ratio of younger men to women in the CMR population compared to the Scottish population.

Figure 3 gives the CMR practice population and the Scottish population stratified by Scottish Index of Multiple Deprivation (SIMD) quintiles for the years 1999-2000 and 2001-2002. The source of the CMR practice population and the Scottish population is the Community Health Index (CHI) record (as at 30 Sept 1999 and 2001). The SIMD is based on 37 indicators in seven domains: current income, employment, health, education skills and training, geographic access to services (including public transport travel times for the first time), housing and a crime domain. The SIMD is presented at data zone level, and the data zones have a median population size of 769. The first quintile is the least deprived and the fifth quintile is the most deprived. As can be seen from Figure 3 a disproportionate number of individuals in the CMR practice population are in SIMD quintiles 1 and 2.

Figure 1The location of CMR practices in Scotland

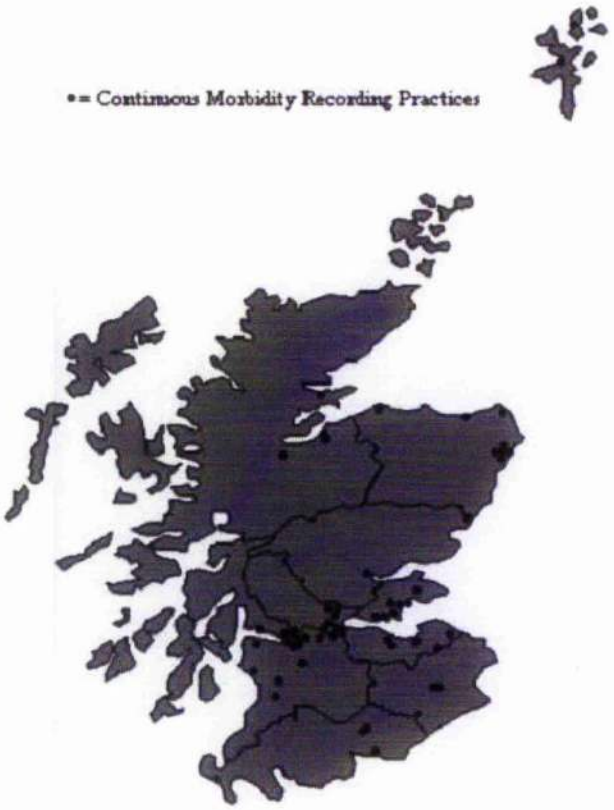
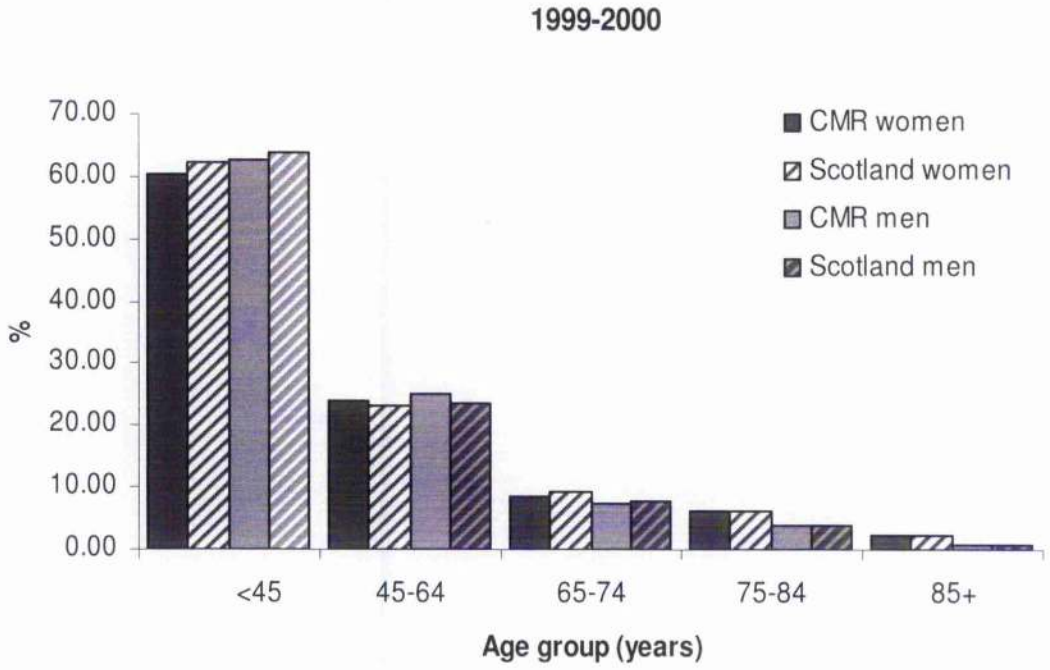


Figure 2 The proportion of men and women stratified by age group in the CMR practice population and in the Scottish population in the years ending March 2000 and March 2002



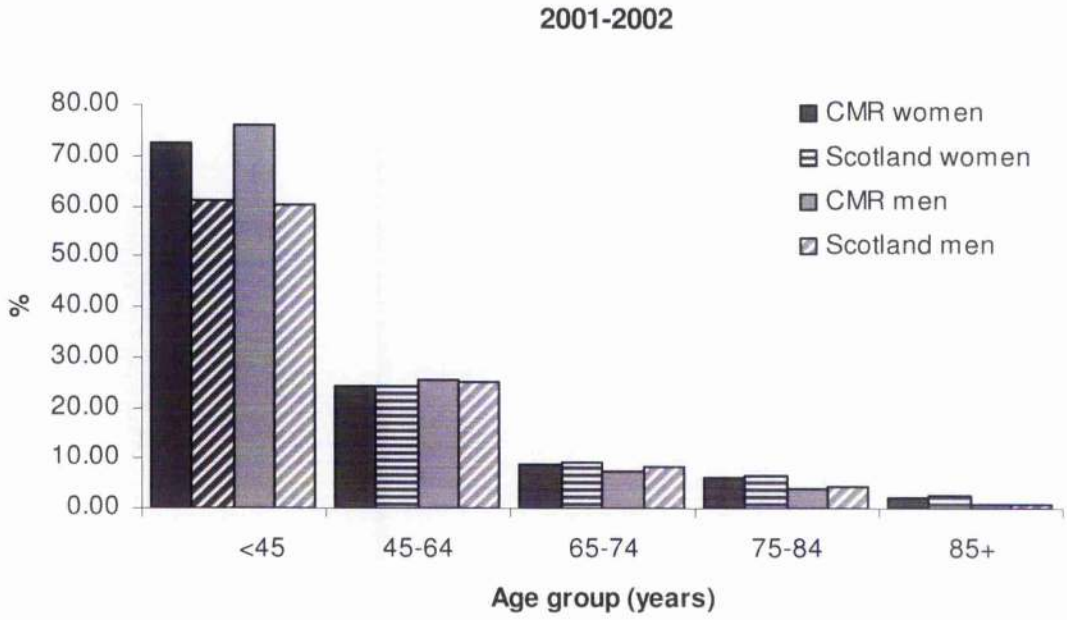
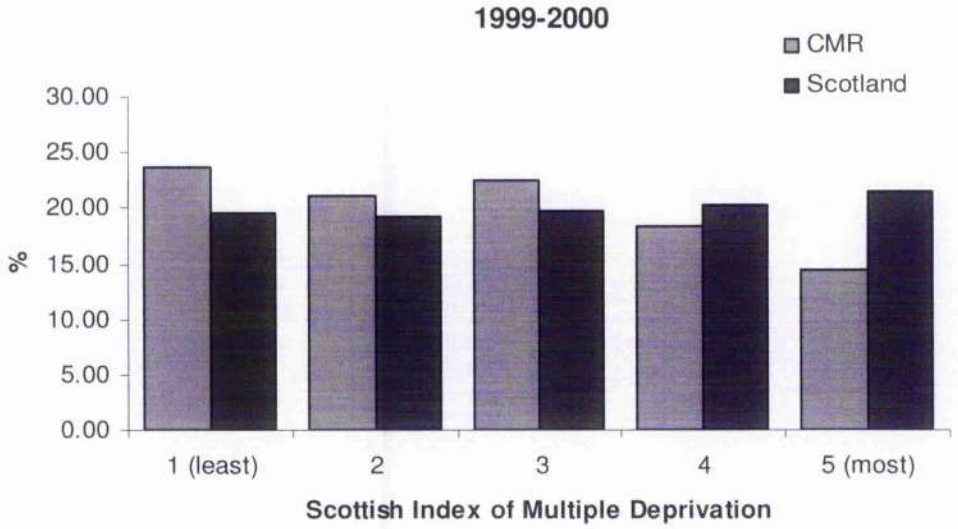
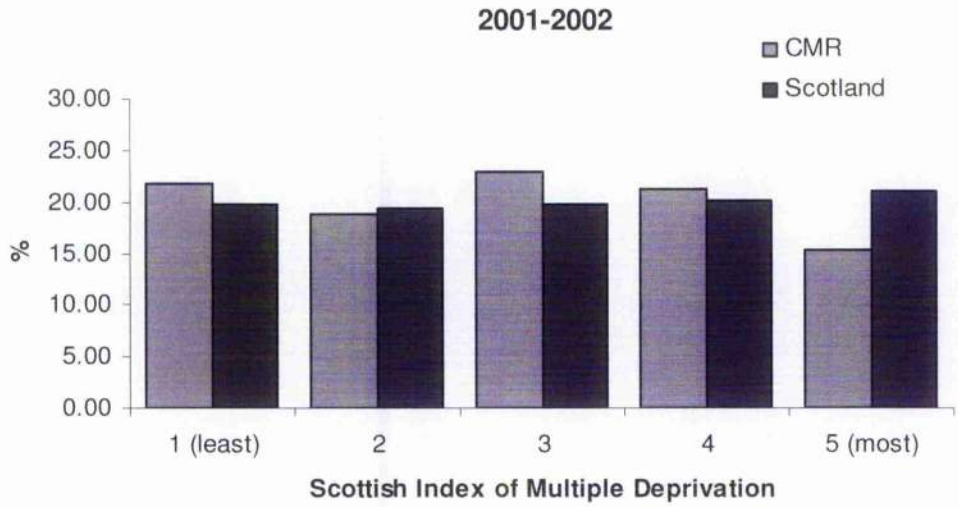


Figure 3 The proportion of the CMR practice population and the Scottish population* in the year ending March 2000 and March 2002 stratified by deprivation quintiles based on the Scottish Index of Multiple Deprivation





* The source of the CMR practice population and the Scottish population is the Community Health Index (CHI) record (as at 30 Sept 1999 and 2001)

3.1.2 Quality of the data

ISD administers the CMR project and operates a continuous quality assurance system for completeness and accuracy of entry. This involves a rolling programme of practice visits to compare CMR data with practice held records. Completeness is measured by comparing the number of contacts on the CMR database in a complete week with the number of contacts seen by the practice during that week. Accuracy is assessed by comparing clinical notes with the Read Codes held on the CMR database for a random sample of 80 contacts in each practice. Data from practices with less than 90% accuracy and 92.5% completeness are not included in the national sample. In 1999-2000 the completeness of capture of contacts was 91% and the accuracy of Read coding was 91%. The long-term nature of the database and its clinical focus ensures that initially uncertain events are confirmed or refuted over time and the diagnostic codes amended appropriately. [300;301]

3.1.3 Organisation and extraction of data

Information is extracted from CMR practices by the EQ software programme and stored in Rich Text Format. This information is then converted and stored in Microsoft SQL server software. Microsoft SQL server software uses Standard Query Language (SQL) to extract data from long lists of information ('base' tables). Several 'basic' tables exist which can be used for investigation. The 'Patient' table includes information on the patient's date of birth, sex, postcode sector, Carstairs deprivation category and the type of registration (temporary or full). The 'Clinical Events' table includes information on every diagnosis coded using Read codes, diagnosis name and diagnosis date along with a modifier code (first, recurrent or persistent). The 'Registration' table includes date of registration, date of deregistration and date of death. The 'Prescribing' table contains the names, BNF code, quantity, dose and frequency of drugs prescribed, the start and finish date of the prescription and whether the drug was prescribed as a repeat or acute script. All tables contain unique practice and patient identifier numbers. The number of patients that are live and registered in CMR stratified by age and sex is used as a measure of the population at risk to calculate age and sex specific rates. Using the database language Transact SQL queries are written to extract information from these basic tables so that a specified doctor diagnosis that any patient has received (e.g. angina, heart failure or atrial fibrillation) can

be viewed and amalgamated with patients given the same diagnosis. A single database can be created containing all patients with a specific illness and relevant demographic, clinical and prescribing information.

3.1.4 Data extracted for the present studies

CMR data was analysed to examine:

1. Prevalence, incidence, primary care burden and medical treatment of angina in Scotland (Chapter 4)
2. Prevalence, incidence, primary care burden and medical treatment of heart failure in Scotland (Chapter 5)
3. Prevalence, incidence, primary care burden and medical treatment of atrial fibrillation in Scotland (Chapter 6)

All study protocols were approved by the Scientific Advisory Group of the Primary Care Clinical Informatics Unit – Research (PCCIU-R).

3.1.4.1 Angina

For the year 1st April 2001 to 31st March 2002 prescribing and morbidity data from 55 General Practices with a total practice population of 362,155 fully registered patients (7% of the Scottish population) were obtained from the Primary Care Clinical Informatics Research Unit (PCCIU-R) based at the University of Aberdeen. All patients who had been labelled as ever having angina (includes stable and unstable angina) were included.
The following Read Codes for angina were included – G33 (angina pectoris), G3111 (unstable angina), G3112 (angina at rest), G3113 (refractory angina), G3114 (worsening angina).

Each patient record contained information on age, sex, GP practice, number of GP contacts in the year and an incidence marker. Information on medications included aspirin, clopidogrel, warfarin, statins, betablockers, nicorandil, calcium channel blockers, nitrates, ACE inhibitors and angiotensin receptor blockers. In addition the following comorbidities were included; hypertension, back pain, chest infection, upper respiratory tract infection, chronic obstructive pulmonary disease, dyspepsia, diabetes, depression, pain in limb, heart failure, ischaemic heart disease and atrial fibrillation. Postcode sectors were used to derive Carstairs socio-economic deprivation scores, which were used to categorise patients into

deprivation categories.[302] Resident postcodes were used to assign a Carstairs deprivation category from one (least deprived) to five (most deprived) to each individual. These categories are derived from 1991 census data on four variables: the proportion of persons in households without a car; the proportion of economically active males who are unemployed; proportion of persons in private households with a density of more than one person per room; the proportion of persons in households with an economically active head of household in social class 4 or 5.

3.1.4.2 Atrial fibrillation

Atrial fibrillation data for the year 1st April 2001 to 31st March 2002 was obtained from PCCIU-R. Morbidity and prescription information was available for 55 General Practices with a total practice population of 362,155 fully registered patients (7% of the Scottish population). All patients who had been labelled as ever having atrial fibrillation were included. The following Read codes for atrial fibrillation were used; 3272 (ECG: atrial fibrillation), 3273 (ECG: atrial flutter), G573 (atrial fibrillation and flutter), G5730 (atrial fibrillation), G5731 (atrial flutter), G5732 (paroxysmal atrial fibrillation), G573z (atrial fibrillation and flutter NOS).

Each patient record contained information on age, sex, GP practice, number of GP contacts in the year for atrial fibrillation, an incidence marker and comorbidities. Prescribing information on the following medications were included; aspirin, clopidogrel, warfarin, verapamil, diltiazem, betablockers, sotolol, digoxin, propafenone, disopyramide, quinidine, flecainide and amiodarone.

3.1.4.3 Heart failure

Heart failure data, from 53 practices participated in CMR between 1st April 1999 and 31st March 2000 was obtained from ISD. These practices had a total registered practice population of 307,741 patients representing 6% of the total Scottish population. Prescribing information was available from the PCCIU-R for 22 of the CMR practices with a combined list size of 140,246 patients (2.6% of the Scottish population). All patients who had a consultation generating a heart failure related Read code during the year ending 31 March 2000 were included in the analysis. The Read codes uses were; G58.. (heart failure), G580. (congestive heart failure), G5800 (acute congestive heart failure), G5801 (chroncongestive heart failure), G5802 (decompensated cardiac failure), G5803

(compensated cardiac failure), G581 (left ventricular failure), G5810 (acute left ventricular failure), G582 (acute heart failure) and G58z (heart failure not otherwise specified).

Repeat prescription data were obtained for a representative subset of the "period prevalence" group, in order to describe which medications these patients took on a regular basis. This information was obtained from the PCCIU-R based at the University of Aberdeen. It included prescribing information from 22 CMR practices with a combined list size of 140,246 patients (2.6% of the Scottish population). The age range, sex distribution and level of deprivation in these patients were comparable to those in the total Scottish population. Newly started medication (i.e. where a second prescription had not been issued) was not accounted for. The prescription rates reported may, therefore, slightly underestimate the true rate of use of the drugs concerned.

3.1.5 Statistical analysis

All tests of statistical significance were two tailed. All analyses were undertaken using the Statistical Package for Social Scientists (SPSS Inc, Version 11.5, Chicago, Illinois 60611), Confidence Interval Analysis for Windows (CIA, 1998) and Centres for Disease Control and Prevention's statistical package Epi Info (2002, Revision 2).

3.1.5.1 Descriptive analysis

Prevalence

The prevalence of a disease is the proportion of a population that have the condition at a point in time (also referred to as point prevalence). Period prevalence refers to the proportion of the population that are cases within a designated period of time (for instance per annum). Prevalence per 1000 population was calculated using the following formula:
Prevalence= (number of existing cases/ population at risk) X 1000
The denominator used in these studies to calculate prevalence was the total registered practice population for the year studied. For the atrial fibrillation and angina analyses prevalence was calculated by estimating the proportion of total registered practice population who ever had a diagnosis of atrial fibrillation or angina. For heart failure period prevalence was estimated by including all patients who had a consultation generating a

heart failure related Read code from in the 12 month period from 1st April 1999 to 31st March 2000. Any patient who died or moved away from the practice prior to 31 March 2000 was excluded. Patients not attending their GP during the year of the study were also not accounted for. While this may have led to an underestimate of prevalence, it is unlikely that many patients with heart failure will not attend their GP within a 12 month period.

Incidence

The incidence of disease is the rate at which new cases occur in a population during a specified period ie the number of patients during the period of study who present with an illness for the first time. Incidence was calculated by including all patients with a Read code for the disease being studied which had a modifier of "first" for the year studied. Incidence per 1000 population per annum was calculated using the following formula:
Incidence = number of new cases / (population at risk x time during which the cases were ascertained) X 1000
The population at risk was the total registered practice population for the year studied.

Contact rates and number of contacts per patient

Contact rates (total number of consultations/attendances for the year where that condition was indicated as relevant to the visit) were also calculated using the following formula:
Contact rate= (number of contacts/ population at risk) X 1000
The population at risk was the total registered practice population. The average number of contacts per patient was calculated by dividing the number of contacts relevant to the condition in one year by the number of patients with that condition.

As the CMR practices are age and sex representative of the Scottish population, the CMR data were used to estimate prevalence, incidence and contact rates for the whole Scottish population (5.1 million) on an age and sex specific basis, derived from the 2001 census.[303]

Chi-square tests and chi-square tests for trend were used to compare prevalence, incidence, contact rates and prescribing data between different age groups and deprivation categories. Indirect standardisation was used to adjust incidence, prevalence and contact rates for age and sex differences in the practice population in each deprivation category. Indirect standardisation was performed by applying age and sex specific prevalence, incidence and

contact rates to the CMR population in deprivation categories 1-5 to get an expected number of events. The ratio of observed to expected events was then applied to the average event rate to get age and sex standardised rates.
For comparative purposes, contact rates for other common cardiovascular conditions are also described and we examined where each condition ranks amongst all reasons for consultation with a GP. Prescription rates stratified by sex, age and deprivation category are also described.

3.1.5.2 Logistic regression

Using the drug of interest as the dependent variable, multivariable logistic regression was performed to examine the independent effects of age, sex, deprivation category and general practitioner on prescribing of different medications. The odds ratios were adjusted for potential prognostic factors including sex, age, deprivation category, general practitioner. Co-morbidity (including conditions which may influence prescribing of angina medications such as prior myocardial infarction, hypertension, heart failure, stroke, atrial fibrillation and chronic obstructive lung disease) was also adjusted for in the angina analysis.

3.2 Linked Scottish Morbidity Recording Scheme (SMR)

3.2.1 Data sources

3.2.1.1 Scottish morbidity records

Healthcare data for individual patients in Scotland is collected as a series of Scottish Morbidity Records (SMR). The record type denotes the general type of healthcare received during an episode and/or the nature or status of the patient. The hospital activity SMRs are outpatient attendances (SMR00), all discharges from acute hospitals (SMR01), maternity units (SMR02), psychiatric units (SMR04), neonatal units (SMR11) and geriatric long stay inpatients (SMR50). Analysis of SMR01 data was used for this study. An SMR01 is an episode-based patient record relating to all inpatients or day cases discharged from non-obstetric and non-psychiatric specialties. Elective and emergency admissions are included.

An SMR01 is generated when a patient is discharged home from hospital, transferred to another clinician (either at the same or a different hospital), changes specialty (either under the same or a different clinician), or dies. Data collected includes patient identifiable and demographic information as well as episode management details (such as length of stay) and general clinical information. Each patient is given a principal diagnosis and up to five secondary diagnoses and up to four operative procedures. These secondary diagnoses or comorbidities are recorded if they affect the management of the patient or are associated with the main condition or are chronic conditions. Diagnosis at discharge is coded using the World Health Organisation (WHO) International Classification of Diseases (ICD) system.[304] Diseases were coded using the ninth revision (ICD-9) up to March 31st 1996 and the tenth revision (ICD-10) thereafter. The data is abstracted from case notes and then transcribed onto an SMR01 form. The Information and Statistics Division (ISD) of the Common Services Agency (CSA) collates the data at National level.

3.2.1.2 Death certificate data

The General Register Office for Scotland records the causes of death for all Scottish residents. [305] The codes used to classify deaths are allocated using the WHO International Classification of Diseases. ICD9 was used between 1979 and 1999 and ICD10 has been used since 1st January 2000. Classification of the cause of death is based on information collected on the medical certificate of cause of death which contains information on the underlying cause of death and up to three other causes considered to have contributed to death.

3.2.1.3 Linked Database

Computerised hospital records (Scottish Morbidity Records), cancer registration records, mental health records and death registration records belonging to the same patient in Scotland are linked together in the Scottish Record Linkage System. [306] Record linkages have been carried out in Scotland since the early seventies. Initially it was a slow and laborious process. A joint project between ISD and the CSA started in May 1989 and led to the development of permanent linked data sets of Scottish health related data. The linked data set holds hospital discharge records for non-psychiatric, non-obstetric specialties (SMR01) together with Cancer Registry records (SMR6) and Registrar General's death records from 1981 until the present day. Ad hoc linkages can also be carried out dating back to 1968.

3.2.1.4 Methods of linking

Records from individual hospital episodes from different SMR schemes together with records from the Registrar General are pulled together using probability matching record linkage to provide profiles for each patient. Howard Newcombe from Canada was the pioneer and founder of probability matching techniques in the 1950s. Over the last thirty years, methods of probability matching have been developed and refined in Oxford, Scotland and Canada and are used by the Record Linkage System to allow for inaccuracies in the identifying information. [307] When records are linked, two records are compared using identifying items such as surname, first initial, sex, year, month and day of birth and postcode and a decision is made as to whether they belong to the same individual. Surnames are changed to coded format in order to avoid the effects of differences in spelling. A computer algorithm calculates a score for each pair of records that is proportional to the likelihood that they belong to the same person. The huge volume of data would mean it is be impossible to carry out probability matching on all pairs of records involved in the linkage and blocking is used to cut down the number of comparisons required. Only those records that have a minimum level of agreement in identifying items are compared. Probability matching then allows mathematically precise assessment of the implications of the levels of agreement and disagreement between records.

3.2.2 Quality of the data

The linkage process is largely automatic as a threshold score based on probability matching dictates the decision as to whether the records belong together. Clerical checking has shown that the accuracy of probability matching is 98-99%.[308]

The Quality Assessment and Accreditation (QAA) Unit of ISD monitors the quality of SMR data, by assessing accuracy, completeness, consistency and fitness for purpose. It carries out routine validation of a sample of SMR01 records where data held on the sampled records are compared with information contained in the medical case notes. An assessment of the accuracy of SMR01 data, carried out between 2000 and 2002, on a 2% sample of SMR01 data found the accuracy for recording of clinical data at the three-digit level was 88% for the main diagnosis falling to 81% at the four-digit level.[309] The accuracy of the main diagnosis was 89% from the 1997/98 audit. Coding of secondary diagnosis was less accurate at 77% and the most frequently observed omissions from secondary diagnosis

included chronic ischaemic heart disease, hypertension, asthma, diabetes and angina. The accuracy for main procedure/ operation was 91% accurate and other procedures/ operations 92% accurate. The accuracy for non-clinical data items was 97%. The accuracy of AMI, angina and chest pain coded as a principal diagnosis was shown to be 86%, 88% and 93% respectively. The accuracy of AMI coded as a principal diagnosis had been shown to be 97% in the1996/97 audit. [310]

3.2.3 Organisation and extraction of data

The linked data is stored as a conventional flat file of records. The records for each individual are stored adjacently in chronological order and marked with a unique personal identifier. Different types of record are stored in their original unlinked format and are preceded by several fields of linkage information. The dataset is complex and requires tailored FORTRAN programs to access the data. The staff in ISD use FORTAN programming to produce specific datasets. In collaboration with staff at ISD, data specs were written which detailed the nature of the data required for these studies.

3.2.4 Data extracted for present studies

All study protocols were approved by the Privacy Advisory Committee which is an independent body set up in 1990 to provide advice on requests for the release of data by ISD.

SMR data was used to examine:

1. Trends in hospital discharge rates for suspected acute coronary syndromes in Scotland between 1990 and 2000 (Chapter 7)
2. Short-term and long-term outcomes in patients admitted with suspected acute coronary syndromes in Scotland between 1990 and 2000 (Chapter 8)
3. Between-hospital variation in short-term survival following an acute myocardial infarction (Chapter 9)

3.2.4.1 Suspected acute coronary syndromes 1990-2000

All adults (16 years and over) with a *'first'* emergency hospitalisations with a "principal" discharge diagnosis (coded in the first position) of AMI (ICD 9: 410, ICD 10: I21 or I22),

"hospitalised angina" (ICD 9: 411 or 413, ICD 10: I20 or I24.9) or "other chest pain" (ICD 9: 786.5, ICD 10: R07) in Scotland between January 1990 and December 2000 were identified. In addition all subsequent deaths occurring in these individuals up until 31st December 2001 were also identified. This allowed patients to be followed up for a minimum of one year to the end of the study (31st December 2001). A "first" hospitalisation was defined as one occurring in a patient with no previous discharge diagnosis of coronary heart disease or chest pain (ICD 9: 410-414, 786.5, ICD10 I20-I25, R07) in the principal coding position, in the previous 10 years. This means there was an equal look back for all patients avoiding double counting and bias.

During a continuous inpatient stay, individuals may be coded with a number of different diagnostic codes. In the current study the principal diagnosis was based on the last cardiovascular diagnosis in this continuous inpatient stay. Therefore, individuals who are diagnosed as chest pain or angina, before a definitive diagnosis of AMI is made, are included in the study as AMI. Individuals hospitalised with an AMI who are subsequently transferred with a diagnosis of angina are included in the study as angina. Individuals, who have a non-cardiovascular diagnosis at any point during their admission, are also included in the analysis. This avoids double counting of patients as each individual can be given only one diagnosis during their inpatient stay. Each patient record contains information on the dates of admission and discharge, age, sex, postcode of residence and date of death, if it occurred. Postcode sectors were used to allocate Carstairs deprivation categories on the basis of four variables from the 1991 census, namely male unemployment, overcrowding, social class and car ownership as described previously.[302] Secondary diagnoses in positions two to six were examined in order to determine the most frequent concomitant diagnoses. These were then recoded into categorical variables. Using the record linkage system, all prior hospitalisations occurring within five years of the index hospitalisation, were identified and coded according to the principal diagnosis recorded at discharge. Co-morbidity was defined as any concomitant diagnosis or as any principle diagnosis in a prior admission within five years of the index admission, categorised as: diabetes; (ICD9 code 250); respiratory disease (480-496); cancer (140-208); cerebrovascular disease (430-438); peripheral vascular disease (440-443); hypertension (401); renal disease (463); or atrial fibrillation, (427.3) [ICD10 codes E10-E14, J10-J18, J 40-J47, C00-C99, I60-I69, G45, I70-I78, I10-I13, N17-N19, and I48 respectively]. All 32 acute hospitals in Scotland were included in the analysis, of which eight were university hospitals and six had cardiac catheterisation facilities. Following the first index admission, all subsequent admissions for non-fatal events were identified.

These included non-fatal acute myocardial infarction, stroke, heart failure, angina and revascularisation (coronary artery bypass surgery and coronary angioplasty). Primary cause of death was categorised by ICD code.

3.2.4.2 Acute myocardial infarction

All patients discharged (alive or dead) from Scottish hospitals during two periods of time: i) between October 1988 and September 1991 and ii) between October 1998 and September 2001 with a principal diagnosis of AMI (ICD 9 410, ICD 10 I21 and I22) were identified. Only discharges for a "first" AMI were analysed. A "first" AMI was defined as one where the patient had no prior hospital discharge for AMI. Only hospitals admitting patients with emergency medical problems during both study periods (n=26) were compared in this analysis.

Each patient record provided information on age, sex, postcode sector, date of discharge, hospital discharged from, previous discharges and date of death if it occurred. As discussed previously postcodes of residence were used to assign a Carstairs deprivation category ranging from one (least deprived) to five (most deprived) to each individual.[302] There is a strong concordance between Carstairs scores for postcode sectors in 1991 and 2001 (Pearson's correlation coefficient r=0.955).[311] All prior discharges within five years were identified using retrospective linkage. Secondary conditions on the index admission allowed the identification of up to five co-morbidities.

3.2.5 Statistical analysis

All tests of statistical significance were two tailed. All analyses were undertaken using the Statistical Package for Social Scientists (SPSS Inc, Version 11.5, Chicago, Illinois 60611) and Confidence Interval Analysis for Windows (CIA, 1998).

3.2.5.1 Suspected acute coronary syndromes 1990-2000

The suspected acute coronary syndrome database was used to look at

1. Trends in hospital discharge rates for suspected acute coronary syndromes in Scotland between 1990 and 2000 (Chapter 7)

2. Short-term and long-term outcomes in patients admitted with suspected acute coronary syndromes in Scotland between 1990 and 2000 (Chapter 8)

3.2.5.1.1 Descriptive statistics

Baseline data were compared using chi square tests and chi square tests for trend for categorical data and t tests for continuous data. Population denominator data were used to derive population-based discharge rates per 100,000 stratified by sex, age and year of admission. Rates were calculated using official age and sex specific population estimates obtained from the General Registrar for Scotland for each year between 1990 and 2000.[303] Linear regression was used to test the significance of the observed trends in population discharge rates and numbers. Age and sex-specific rates for non-fatal events (non-fatal acute myocardial infarction, stroke, heart failure, angina and revascularisation) were calculated for individuals following the index suspected acute coronary syndrome admission.

3.2.5.1.2 Survival analysis

Crude case-fatality rates at 30 days and five years were compared in men and women who were categorized into five age groups. Survival time was calculated as the time from first admission for suspected acute coronary syndrome, to death from any cause; or censored at 31/12/2001. Age and sex specific survival rates were calculated for the follow up periods using the actuarial life table method. This takes account of admission dates and periods of follow-up, which differ between patients.

Kaplan-Meier survival curves were drawn in order to graphically illustrate the probability of fatal or non-fatal event in men and women following an AMI or angina admission. The log rank test was used to test the null hypothesis that these two groups are samples from the same population as regards survival experience. This involves calculating the observed and expected number of deaths in both groups at separate time intervals and summing these.

Cox's proportional hazards

Cox's proportional hazards models were then used to determine whether sex, age, socio-economic deprivation, comorbidity and year of admission were independently associated

with survival at five years excluding those deaths that occurred during the first 30 days following admission. The Cox's proportional hazards model compares the hazard functions for each level of the model. This was carried out using an enter model. Cox proportional hazard models were also used to adjust for the effects of age, sex, year of admission, deprivation and co-morbidity on the risk of each subsequent non-fatal event in the two groups. All variables were entered simultaneously. For each variable entered into a model, the lowest class was set at unity. After fitting the final model, the assumptions were checked. The assumptions underlying a Cox's proportional hazards model are

- Proportional hazards, the ratio of hazard functions for two individuals with different covariates does not vary with time.
- Linearity, the relationship between the covariates and the hazard function should be linear in the log space.
- Survival times should be independent and the mechanisms giving rise to censoring of individual subjects should not be related to the probability of an event occurring.

These were checked by looking at a log-log plot for each categorical covariate in the model, which should demonstrate parallel lines if the hazards are proportional.

Logistic regression

Multiple logistic regression was used to calculate the adjusted odds ratio for the probability of death within 30 days following an admission with a suspected acute coronary syndrome and to quantify the independent effects on survival of: age, sex, socioeconomic deprivation, year of admission and comorbidity (including respiratory disease, diabetes, cancer, cerebrovascular disease, peripheral arterial disease, hypertension, heart failure, atrial fibrillation, and renal failure). Men and women were considered separately in the models, because sex was a significant predictor of outcome and because of an interaction previously seen between age and sex in short term outcome following an acute myocardial infarction.[312] All variables were entered simultaneously into the models. For each variable entered into a model, the lowest class was set at unity. Adequacy of fit was assessed using the Hosmer Lemeshow Goodness-of Fit-Test and all were statistically non-significant.

3.2.5.2 Acute myocardial infarction

The acute myocardial infarction database was used to examine

1. Between-hospital variation in short-term survival following an acute myocardial infarction (Chapter 9)

3.2.5.2.1 Descriptive statistics

Baseline characteristics of patients admitted to hospital within the two time periods were compared using chi-square test for discrete variables and Student t-test for continuously distributed variables. Crude 30 day survival was calculated for each hospital and for Scotland as a whole by use of the actuarial life table method. Indirect standardisation was then used to adjust hospital-specific 30 day survival rates for age and sex differences between the hospital population and the whole Scottish population.

3.2.5.2.2 Survival analysis

Multiple logistic regression models were used to determine the independent effect of hospital on 30 day case fatality after adjusting for the effects of age, sex, deprivation category and prior and co-morbidity. The hospitals were entered into the logistic models as one categorical variable. The 'index' hospital was set as that with a case fatality nearest the Scottish crude case fatality for that time period. All variables were entered simultaneously into the models. Each model was subject to the Hosmer-Lemeshow goodness-of-fit test, and all were statistically non-significant.

3.3 Renfrew-Paisley Study

3.3.1 Data sources

3.3.1.1 Midspan studies

The Midspan studies are four separate occupational and general population cohort studies based in Scotland; the Main and Tiree study (an industrial group of 3931 individuals from 13 factories in the central belt of Scotland), the Collaborative study (an occupational group

of 7028 individuals from 27 workplaces in the central belt of Scotland), the Renfrew-Paisley study (a general population cohort from Renfrew and Paisley in the outskirts of Glasgow) and the Family study (2238 offspring of married couples in the Renfrew-Paisley study). The use of large-scale epidemiological studies for public health research was pioneered in Scotland by Victor Hawthorne in the 1960s. The Midspan studies originated in the post war drive to control pulmonary tuberculosis using mass miniature radiography. This effective screening method of examining large numbers of apparently healthy volunteers was extended in the Midspan studies to detect and control cardiorespiratory risks and diseases in addition to improving the detection and control of tuberculosis. For this thesis data from the Renfrew-Paisley study was used and will be discussed in more detail.

3.3.1.2 Sample and Baseline Data

The Renfrew-Paisley study is a general population study of 7048 men and 8354 women living in the industrialised towns of Renfrew and Paisley, near Glasgow in the west of Scotland.[313] Eligibility for the Renfrew-Paisley study was established by a door-to-door census of all households in the two towns in 1972. Between 1972 and 1976, all persons aged 45-64 years who met residency criteria were invited to complete a questionnaire and attend for a screening examination at one of twelve nearby temporary screening centers. 78.8% of the target population in Renfrew and 77.9% of Paisley residents was examined. Approximately 60% of the cohort re-attended for repeat screening between 1977 and 1979.

The target population in the Renfrew-Paisley study was from a large urban area with high levels of socioeconomic deprivation and high mortality rates. In 1980-85 standardised mortality rates in Renfrew-Paisley for all cause death was higher than the Scottish average and Renfrew ranked 6th for ischaemic heart disease deaths and 10th for cerebrovascular deaths in Scotland out of 56 other local government districts.[302] Twelve of the 16 postcode sectors in Paisley and Renfrew were in Carstairs' deprivation categories 4-7. One sector had the highest deprivation score in Scotland. In the 1981 census 63% of households in these two towns rented their accommodation from the local authority. Thirty per cent of households were overcrowded, 44% had no car, 13% of men were unemployed and 25% of heads of households were in social class 4 or 5.[314]

Each subject's demographic profile and cardiorespiratory health status were documented. Table 23 shows the study data recorded at the screening visit. Social class was determined by occupation according to the Registrar General's classification, except for housewives and retired women whose husbands' or fathers' occupations were used instead.[315] Resident postcodes were used to assign a Carstairs deprivation category from one (least deprived) to five (most deprived) to each individual as described previously.[302] Angina pectoris (identified by the Rose angina questionnaire), possible myocardial infarction (identified by a separate question on Rose questionnaire as having ever experienced a severe pain across the front of chest lasting for half an hour or more) and chronic bronchitis (determined by the Medical Research Council's chronic bronchitis questionnaire) were noted.[1;316] Past and current medical history and risk factors for cardiorespiratory disease were documented. A smoking history was recorded including average number of cigarettes smoked per day (never smoked, 1-14, 15-24, 25-34, 35 or more), ex-smoker (less than 5 years or 5 years or more) or pipe or cigar smoker. Blood pressure was recorded as the mean of two measurements taken in the seated position and diastolic pressure was recorded at the disappearance of the fifth Korotkoff sound. Height and weight were recorded and used to calculate body mass index in kg/m^2 (weight in kg divided by height in meters squared). Forced expiratory volume in 1 second (FEV_1) was measured.[313;317] An adjusted FEV_1 was calculated as a percentage of the "expected" FEV_1 (derived from a linear regression equation of age and height for men and women separately from a healthy subset of the sample who were nonsmokers and had no respiratory symptoms) and the actual FEV_1. The cardiothoracic ratio was based on a chest radiograph and cardiomegaly was defined as a cardiothoracic ratio ≥ 0.55. Plasma cholesterol and glucose concentrations were measured in a 10ml non-fasting blood sample. Glucose concentration was not measured during the whole screening period and was, therefore, only available for 69% of the total cohort. A six-lead electrocardiogram (ECG) was also obtained (leads I, II, III, aVR, aVL and aVF) and coded using the Minnesota coding system.[313]

Table 23 Renfrew-Paisley study data recorded at screening

Questionnaire data	Clinical measurements	Derived data
Sex	Blood pressure	Social class
Marital status	Height	Deprivation category
Date of birth	Weight	Body mass index
Occupation	Sputum	
Exercise	Tine test	
Bronchitis	Chest X-ray	
Weather effect on breathing	Cardiothoracic ratio	
Detailed questions on smoking habit	Respiratory function, FEV1, FVC	
Rose angina questionnaire	ECG (Minnesota code)	
Severe chest pain	Plasma cholesterol	
Diabetes	Blood sugar*	
Past history of hospital admissions	Sodium*†,	
Stroke symptoms	Potassium*	
Asthma / hayfever	Oxygen saturation*	
Years in present home†	Haemoglobin*	
	Carboxyhaemoglobin*	

*** Only available on some subjects**
† Renfrew only

3.3.1.3 Study follow-up

Electronic linkage to hospital and death records is possible for all residents of Scotland, as previously described. The Scottish Morbidity Record Scheme was used to retrieve details of all hospital discharges (according to the eighth [a small number of initial episodes] and ninth revisions of the World Health Organisation International Classification of Diseases) over the 20 years after initial screening (i.e., surviving subjects were aged 65 to 84 years).[304] The occurrence and timing of admissions for acute myocardial infarction (ICD9 410), coronary heart disease (ICD9 410-414), heart failure (ICD9 425.4, 425.5, 428, 402), deep venous thrombosis (ICD9 451.1) and pulmonary embolism (ICD9 415) (collectively referred to as venous thromboembolism), aortic aneurysm (ICD9 441), atrial fibrillation (ICD9 427.3) and stroke (ICD9 430-438) was noted. These diagnoses, in combination with a number of other less commonly recorded diagnoses are collectively called cardiovascular hospitalisations (ICD9 390-459). Emergency, transfers and elective admissions were included in total hospital admissions. Deaths and their certified cause were obtained from the General Register office for the same period.

3.3.2 Quality of the data

The self-completed health questionnaire at baseline screening was checked by experienced interviewers at the screening examination. As discussed previously SMR data are approximately 90% accurate in identifying the correct discharge diagnosis.[310] Death certificate data has been shown previously to be virtually complete with no discrepancies in coding comparisons of causes of death by the Registrar and by independent physicians.[318]

3.3.3 Organisation and extraction of the data

The Renfrew-Paisley study is centred at the Public Health and Health Policy Division in University of Glasgow. Data pertaining to the initial and follow-up screening visits is held in SPSS file format. A copy of original questionnaires and screening visit results for each patient is also held. The cohort is updated for mortality on a three monthly basis including full checks on the status (dead/alive) of the oldest participants. At the time of this study

subsequent hospital admission data for the cohort were available for 20 years of follow-up however this has subsequently been extended. In collaboration with Midspan staff a dataspec was written which detailed the nature of the baseline and follow-up data required for the studies in this thesis.

3.3.4 Data extracted for present studies

Written consent was given at the time of the studies in the 1970s for hospital records to be looked at. Ethical permission was obtained from MREC and Argyll & Clyde LREC for linkage with the Scottish Morbidity Records system. The Midspan Steering Committee approved the studies. Permission was given by the Privacy Advisory Committee of ISD to use the linked data.

Each patient record contained all information available from the baseline questionnaire (Table 23). Date of death and cause of death until 30th June 2001 were also included. In addition the date of all hospitalisations and cause of all hospitalisations were also available up until 30th December 1995. Because of the different lengths of follow-up for death and hospitalisations, all individuals were followed up until date of death or censorship. Date of censorship was 20 years from the date of each person's initial screening visit.
Using the Renfrew-Paisley data I carried out two studies for this thesis.

1. A population study of the long-term consequences of angina: 20 year follow-up of the Renfrew-Paisley study (Chapter 10)
2. Long-term cardiovascular consequences of obesity: 20 year follow-up of more than 15,000 middle aged men and women (the Renfrew-Paisley study) (Chapter 11)

Rose angina criteria

The standard Rose angina classification was used.[16] The validity of the Rose angina questionnaire has been tested in studies comparing it to a clinical diagnosis of angina, electrocardiogram abnormality, thallium scanning and as a predictor of coronary artery disease mortality.[17-21] In this classification, Grade I angina is defined as pain or discomfort when walking uphill or hurrying. Angina is classified as Grade II angina when the subject also reports chest pain or discomfort when walking at an ordinary pace on the level. Angina is further classified as "definite" if, in addition, the pain is sited in the sternum or the left chest and arm, causes the subject to stop or slow down and resolves within 10

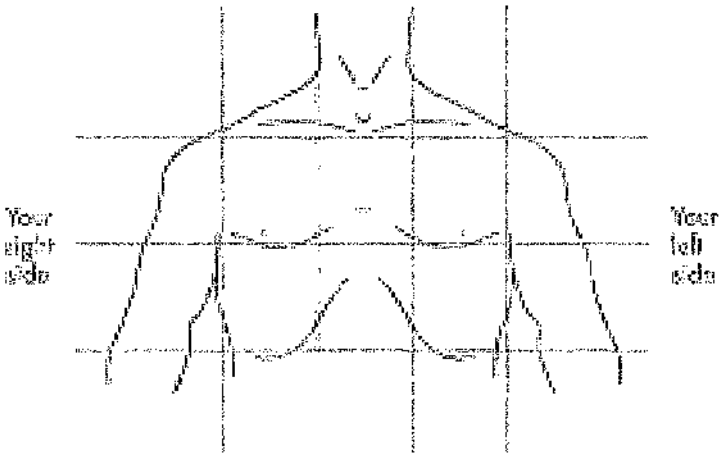
minutes of the subject stopping or slowing down. If these additional criteria are not satisfied, angina is classified as "possible". For the purpose of this study, "angina" was defined as Rose grade I and II "definite" angina and was not confirmed by further work up or evaluation. Possible myocardial infarction (identified by a separate question on Rose questionnaire as having ever experienced a severe pain across the front of chest lasting for half an hour or more) was noted. The Rose angina questionnaire is shown in Figure 4.

Figure 4 The complete Rose angina questionnaire

1 Do you ever have any pain or discomfort in your chest?

Yes/No

2 Where do you get this pain or discomfort?
Please mark ✖ on the appropriate places



3 When you walk at an ordinary pace on the level does this produce the pain?

Yes/No/Unable

4 When you walk uphill or hurry does this produce the pain?

Yes/No/Unable

5 When you get any pain or discomfort in your chest on walking, what do you do?

Stop Slow down Continue at same pace Not applicable

6 Does the pain or discomfort in your chest go away if you stand still?

Yes/No

7 How long does it take to go away?

10 minutes or less
more than 10 minutes

Ischaemic ECG criteria

The following Minnesota codes were considered to represent ECG evidence of "ischaemia", 1.1-1.3 (Q waves), 4.1-4.3 (ST junction and segment depression), 5.1-5.3 (T wave abnormalities) and 7.1 (left bundle branch block).[319]

Overweight and obesity criteria

According to baseline body mass index (BMI), subjects in the Renfrew/Paisley Study were categorised into underweight (BMI < 18.5 kg/m^2), normal (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2) and obese (BMI ≥ 30 kg/m^2). [210] Only the data for normal, overweight and obese are presented.

3.3.5 Statistical analysis

All tests of statistical significance were two tailed. All analyses were undertaken using the Statistical Package for Social Scientists (SPSS Inc, Version 11.5, Chicago, Illinois 60611). Data were missing for social class in 409 (2.7%) cases and cholesterol in 124 (0.8%) cases. Missing values for social class were replaced with the most common social class in each sex and missing values for cholesterol were replaced with the sex specific mean cholesterol. Data were missing in a small number of cases for systolic blood pressure (n=7) and adjusted FEV1 (n=11) however the availability of other variables was complete.

3.3.5.1 Angina

3.3.5.1.1 Descriptive statistics

Men and women were analyzed separately and compared. Those with angina were compared to those without angina. Because an abnormal ECG is recognised to be of prognostic importance, subjects with ischaemic ECGs were analyzed separately from those without ischaemic ECGs and the groups were compared.[320] Therefore for men and women there were four groups examined – i) angina and an ischaemic ECG, ii) angina and no evidence of ischaemia on ECG, iii) no angina and an ischaemic ECG and iv) no angina and

no evidence of ischaemia on ECG. Categorical variables were compared using chi-square test and continuous variables were compared using Student t-test.

3.3.5.1.2 Survival analysis

Case-fatality and event rates were calculated over the 20-year follow up period using the actuarial life table method. 17 (0.1%) patients were excluded from the survival analyses as they had emigrated and their vital status was unknown.

3.3.5.1.3 Cox's proportional hazards

Cox proportional-hazards regression models were used to examine the relation between Rose-positive angina (with and without an ischaemic ECG) and outcome. Outcome included all-cause death, death from cardiovascular causes, cardiovascular hospitalisations, cardiovascular death or hospitalisation. Age, blood pressure, cholesterol, prior history of diabetes, number of cigarettes smoked per day (with an additional 0/1 variable for ex-smoker), Rose myocardial infarction, adjusted FEV1 and social class were adjusted for. The adjusted risk of fatal and non-fatal outcomes in women with angina compared to men with angina was also examined. These were adjusted for age, ischaemic ECG, cholesterol, systolic blood pressure, adjusted FEV_1, smoking, social class, Rose myocardial infarction and prior history of diabetes.

3.3.5.2 Obesity

3.3.5.2.1 Descriptive statistics

Baseline characteristics in different weight categories were compared using chi-square tests for trend for categorical data and one-way analysis of variance for continuous data. The expected number of hospital admissions or cardiovascular deaths in the overweight and obese groups was calculated by applying the mean admission rate or cardiovascular case-fatality rate per person in the normal weight group to the obese and overweight group. The projected burden of obesity was estimated by applying age and sex specific rates of cardiovascular events to the obese Scottish population in 1998 using the prevalence of obesity as estimated from the 1998 Scottish Health Survey.[321] Population rates were calculated using official age and sex specific population estimates for 1972 and 1998.[303]

3.3.5.2.2 Survival analysis

Case-fatality and event rates were calculated over the 20-year follow up period using the actuarial life table method.

3.3.5.2.3 Cox's proportional hazards

Cox proportional-hazards regression models were used to examine the relation between body mass index and outcome. BMI was modelled both as a continuous and a categorical variable. The assumption of proportional hazards was tested by inspection of the log minus log survival plots and this was satisfied. The linearity assumption for BMI as a continuous variable was assessed by fitting the models with added quadratic terms. Quadratic terms were significant for death. In all other cases the linearity assumption was satisfied. As elevated body mass index can mediate its effect on cardiovascular risk by promoting atherogenic traits such as hypertension, diabetes and dyslipidaemia therefore two separate multivariable analysis were run, the first adjusting for age, sex, adjusted FEV_1, number of cigarettes smoked per day, social class and the second in addition also adjusting for systolic blood pressure, past history of diabetes and cholesterol. 17 (0.1%) patients (1 subject in the obese category) were excluded from the survival analyses as they had emigrated and their vital status was unknown.

4 PREVALENCE, INCIDENCE, PRIMARY CARE BURDEN AND MEDICAL TREATMENT OF ANGINA IN SCOTLAND: AGE, SEX AND SOCIOECONOMIC DISPARITIES

4.1 Introduction

Angina is an important clinical manifestation of coronary heart disease. In addition in patients with angina, the risk of future cardiovascular events can be reduced with aggressive secondary prevention.[322;323] Despite this, both the contemporary epidemiology and primary care burden of this condition are remarkably poorly described. As evident from chapter 1 most existing studies were conducted at least a decade ago. In addition the majority examined selected cohorts (e.g. male civil servants, with resultant under-representation of women and the elderly) and used patient questionnaires to diagnose angina.[14;15;18;19;22;23;25] One study, carried out in 1984, used nitrate prescriptions as a proxy for the diagnosis of angina.[33] Another study, conducted by the Northern Region Faculty of the Royal College of General Practitioners, did try and identify patients with a physician reported diagnosis of angina.[35] This survey, however, which took place in 1979 and involved 51 general practitioners in the Newcastle region in England, focussed only on subjects aged 30-59 years.

Not only is the contemporary public health burden of angina poorly described but so is its treatment. With the emergence of new evidence-based treatments,[322;323] publication of guidelines [324;325] and government directed national health-improvement programmes in coronary heart disease[326], the analysis of current prescribing patterns for angina is relevant and topical. The CMR in General Practice scheme was used to give a more contemporary picture of the epidemiology, primary care burden and treatment of angina than existing studies.

4.2 Methods

The CMR angina database was used as described in chapter 3.

4.3 Results

4.3.1 Prevalence

The overall prevalence of angina was 28 per 1000 in men and 25 per 1000 in women. The prevalence of angina was lower in women than men at all ages ($p<0.05$). In men the prevalence was extremely low in those under 45 (1 per 1,000) increasing to 141 per 1,000 in those over 75 years. In women the prevalence of angina was 108 per 1,000 in those over 75 years. The highest prevalence in both sexes was in the age range 75-84 years. Though the prevalence was higher in men than women, the greater number of elderly women in the population meant that more women than men aged 75 years or above had angina and that, overall, almost as many women as men suffered from angina. (Table 24)

The prevalence of angina increased with increasing socioeconomic deprivation from 18 per 1,000 in the least deprived group to 31 per 1,000 in the most deprived group i.e. socio-economically deprived individuals had a 72% higher prevalence of angina than affluent individuals ($p<0.001$ for trend). Similar significant trends were seen in men and women. (Table 25)

Extrapolating from the CMR practices to the whole of Scotland, the estimated number of Scots with angina in 2001 was 133,131 (67,867 men), 68% of whom were 65 years and over and 32% of whom were 75 years and over.

4.3.2 Incidence

The overall incidence of angina for the year 2001/2002 was 1.6 per 1,000. The incidence was higher in men (1.8 per 1,000) than in women (1.4 per 1,000). As with prevalence, the

incidence of angina markedly increased with age from 0.1 per 1,000 in men less than 45 years, to 6.5 per 1,000 in men aged 65-74 years, and thereafter declined by 50% to 3.1 per 1,000 in men over 85 years. In women the incidence of angina also increased with age, although it peaked in the 75-84 year age group (5.8 per 1,000) and thereafter declined to 3.2 per 1,000 in those over 85 years. In those over 65 years, the incidence of angina was 6.1 per 1,000 in men and 4.7 per 1,000 in women. (Table 24)

The incidence of angina increased with increasing socioeconomic deprivation from 0.8 per 1,000 in the least deprived stratum to 2.2 per 1,000 in the most deprived stratum ($p<0.001$ for trend) i.e. socio-economically deprived men were twice as likely to develop angina and socio-economically deprived women were three times more likely to develop angina compared to affluent men and women. (Table 25)
The estimated number of Scots presenting with angina for the first time in the year 2001 was, therefore, 8,099 (4,378 men), 53% of whom were aged 65 years or older and 23% of whom were 75 years or older.

4.3.3 Contact rates

One year contact rates for angina were higher in men (15.7 per 1,000) than in women (12.3 per 1,000). Contact rates increased with age. These were extremely low in those under 45 years, increased 48-fold in men and 44-fold in women from less than 45 years to 45-64 years and more than doubled again between 45-64 years and 65 years or older. Contact rates per 1000 population were highest in both sexes in the age group 75-84 years. (Table 24) Men and women with angina had about 3 times as many GP contacts per year as those without angina and, for men and women with angina, contacts for angina (as opposed to other reasons) accounted for approximately 1 in 20 of all GP contacts made.

On average, patients with angina saw their general practitioner 0.5 times per annum.
For both men and women, the highest number of contacts per patient with angina was in the 45-54 year age band (0.8 in men and 0.7 in women), and after this, in contrast with prevalence and incidence, the number of contacts declined with age. Women aged 45-64 years and over 85 years had less contacts per patient per year than men ($p<0.05$).

The number of contacts per patient with angina declined with increasing socio-economic deprivation so that patients in the most deprived group were 33% less likely to see their general practitioner on an ongoing basis compared to affluent patients. (Table 25)

Table 24 Contact rates, incidence and prevalence per 1,000 population by sex and age group for all CMR practices in Scotland; April 2001 - March 2002

	Age group	Practice population 2001/2002	Number of patients with angina ever	Prevalence	Number of first diagnoses of angina	Incidence	Number of contacts for angina (April 2001-March 2002)	Contact rate	Number of contacts per patient
Men	<45	110080	137	1.2	16	0.1	71	0.6	0.52
	45 – 54	25763	566	22.0	63	2.4	463	18.0	0.82
	55 – 64	19929	1313	65.9	98	4.9	859	43.1	0.65
	65 – 74	13740	1713	124.7	89	6.5	784	57.1	0.46
	75 – 84	7256	1061	146.2	44	6.1	540	74.4	0.51
	85+	1628	187	114.9	5	3.1	83	51.0	0.44
	65+	**22624**	**2961**	**130.9**	**138**	**6.1**	**1407**	**62.2**	0.48
	75+	**8884**	**1248**	**140.5**	**49**	**5.5**	**623**	**70.1**	0.50
	All ages	178396	4977	27.9	315	1.8	2800	15.7	0.56
Women	<45	106743	69	0.6	7	0.1	48	0.4	0.70
	45 – 54	25185	364	14.5	39	1.5	264	10.5	0.73
	55 – 64	20304	965	47.5	60	3.0	541	26.6	0.56
	65 - 74	15959	1454	91.1	70	4.4	668	41.9	0.46
	75 - 84	11241	1294	115.1	65	5.8	612	54.4	0.47
	85+	4327	385	89.0	14	3.2	121	28.0	0.31
	65+	**31527**	**3133**	**99.4**	**149**	**4.7**	**1401**	**44.4**	0.45
	75+	**15568**	**1679**	**107.8**	**79**	**5.1**	**733**	**47.1**	0.44
	All ages	183759	4531	24.7	255	1.4	2254	12.3	0.50
both	<45	216823	206	1.0	23	0.1	119	0.5	0.58
	45 – 54	50948	930	18.3	102	2.0	727	14.3	0.78
	55 – 64	40233	2278	56.6	158	3.9	1400	34.8	0.61
	65 - 74	29699	3167	106.6	159	5.4	1452	48.9	0.46
	75 – 84	18497	2355	127.3	109	5.9	1152	62.3	0.49
	85+	5955	572	96.1	19	3.2	204	34.3	0.36
	65+	**54151**	**6094**	**112.5**	**287**	**5.3**	**2808**	**51.9**	0.46
	75+	**24452**	**2927**	**119.7**	**128**	**5.2**	**1356**	**55.5**	0.46
	All ages	362155	9508	26.3	570	1.6	5054	14.0	0.53

Table 25 Incidence, prevalence, and contact rates (per 1,000 population), stratified by socioeconomic status for year ending March 2002

	Deprivation category	Practice population	Number of patients with angina	Prevalence	Number of first diagnoses of angina	Incidence	Number of contacts for angina	Contact rate	Number of contacts per patient
Men	1 (least)	39277	768	19.6	36	0.9	491	12.5	0.64
	2	34298	898	26.2	57	1.7	448	13.1	0.50
	3	54240	1622	29.9	102	1.9	884	16.3	0.55
	4	34221	1163	34.0	89	2.6	718	21.0	0.62
	5 (most)	15612	511	32.7	31	2.0	255	16.3	0.50
	Odds ratio between category 1 and 5			*1.70 (1.51-1.90)*		*2.17 (1.34-3.51)*		*1.31 (1.13-1.53)*	*0.56 (0.45-0.71)*
	P for trend			*<0.001*		*<0.001*		*<0.001*	*0.142*
Women	1 (least)	40488	677	16.7	30	0.7	343	8.5	0.51
	2	36070	815	22.6	42	1.2	429	11.9	0.53
	3	55976	1501	26.8	86	1.5	759	13.6	0.51
	4	34614	1067	30.8	60	1.7	511	14.8	0.48
	5 (most)	15908	458	28.8	37	2.3	207	13.0	0.45
	Odds ratio between category 1 and 5			*1.74 (1.55-1.97)*		*3.14 (1.94-5.09)*		*1.54 (1.30-1.84)*	*0.80 (0.63-1.02)*
	P for trend			*<0.001*		*<0.001*		*<0.001*	*0.015*
Both sexes	1 (least)	79765	1445	18.1	66	0.8	834	10.5	0.58
	2	70368	1713	24.3	99	1.4	877	12.5	0.51
	3	110216	3123	28.3	188	1.7	1643	14.9	0.53
	4	68835	2230	32.4	149	2.2	1229	17.9	0.55
	5 (most)	31520	969	30.7	68	2.2	462	14.7	0.48
	Odds ratio between category 1 and 5			*1.72 (1.58-1.87)*		*2.61 (1.86-3.66)*		*1.41 (1.26-1.58)*	*0.67 (0.57-0.79)*
	P for trend			*<0.001*		*<0.001*		*<0.001*	*0.006*

4.3.4 Concomitant medical conditions

The top ten concomitant medical problems in patients consulting with angina are shown in Table 26. In both sexes, upper respiratory tract infection was the commonest reason for general practitioner consultation and the most common concomitant diagnostic coding in patients with angina (39% of men and 49% of women). Hypertension was the second most frequently coded, reported in 34% of men and 42% of women. After adjusting for age, women were more likely than men to have concomitant respiratory problems (upper respiratory tract infection $p<0.001$, chest infection $p<0.001$, chronic obstructive airways disease $p=0.035$), hypertension ($p<0.001$), backache ($p<0.001$), dyspepsia ($p<0.001$) and depression ($p<0.001$) and men were more likely than women to have diabetes ($p=0.003$), pain in limb ($p<0.001$) and myocardial infarction ($p<0.001$).

Table 26 Proportion of angina patients seen with specified condition/illness; year ending March 2002

Condition/illness	CMR angina patients		Total CMR practice population	
	Men (n=4977)	Women (n=4531)	Men (n=178396)	Women (n=183759)
	N (%)			
Upper respiratory tract infection	1915 (38.5)	2224 (49.1)	57620 (32.3)	76901 (41.9)
Hypertension	1685 (33.9)	1904 (42.0)	14232 (8.0)	19283 (10.5)
Pain in limb	1330 (26.7)	1564 (34.5)	18323 (10.3)	25670 (14.0)
Backache	1279 (25.7)	1570 (34.7)	31071 (16.9)	23254 (13.0)
Chest Infection	1291 (25.9)	1458 (32.2)	10945 (6.1)	14809 (8.1)
Dyspepsia	1142 (22.9)	1243 (27.4)	13270 (7.4)	15600 (8.5)
Depressive disorder	474 (9.5)	816 (18.0)	8096 (4.5)	18437 (10.0)
Chronic obstructive airways disease	609 (12.2)	629 (13.9)	3949 (2.2)	4461 (2.4)
Diabetes	661 (13.3)	501 (11.1)	4538 (2.5)	3936 (2.1)
Myocardial infarction	647 (13.0)	357 (7.9)	1470 (0.8)	745 (0.4)

4.3.5 Pharmacological treatment

Table 27 shows the medications prescribed for patients with angina, stratified by age and sex. A β-blocker was prescribed for 49%, a calcium channel blocker for 43%, a nitrate for 56%, an ACE inhibitor, an angiotensin receptor blocker or both for 33%, a statin for 50% and an antiplatelet agent for 71%.

There were significant sex differences in prescribing. Of men, 52% were prescribed a β-blocker, 44% a calcium channel blockers, 72% aspirin, 54% a statin, 36% an ACE inhibitor or an angiotensin receptor blocker and 20% "optimal evidence-based medication" (i.e. all of an antiplatelet medication, statin and an ACE inhibitor). The corresponding prescription rates for women were 46% (p<0.001), 41% (p=0.02), 69% (p<0.001), 45% (p<0.001), 30% (p<0.001) and 14% (p<0.001). The prescription rates were lower if prior history of myocardial infarction was excluded with 17.3% of men and 12.0% of women receiving optimal evidence-based medication, compared to 35.8% (36.5% men and 34.5% women) with a previous myocardial infarction. On multivariable analysis after adjusting for age, deprivation, GP practice and co-morbidity, compared to men, women were less likely to be prescribed a β-blocker (OR 0.86 95%CI 0.78, 0.93), a calcium channel blocker (OR 0.85 95%CI 0.78, 0.93), an antiplatelet agent (OR 0.82 95%CI 0.74, 0.90), a statin (OR 0.83 95%CI 0.76, 0.91), an ACE inhibitor and/or angiotensin receptor blocker (OR 0.69 95%CI 0.63, 0.76) and optimal evidence based medications (OR 0.68 95%CI 0.60, 0.76).

There were also significant age-related differences in prescribing. A β-blocker was prescribed for 52% of those less than 75 years compared to 42% of those aged 75 years and over (p<0.001). Similarly, younger patients were more likely to be prescribed a statin (58% <75 years compared to 31% ≥75 years, p<0.001) and optimal evidence-based treatment (19% <75 years compared to 12% ≥75 years, p<0.001). Older patients were more likely to be prescribed a nitrate (61%) and warfarin (8%) compared to younger patients (54% [p<0.001] and 5% [p<0.001], respectively). On multivariate analysis, men, 75 years and over were less likely to be prescribed a β-blocker (OR 0.67 95%CI 0.59, 0.78), a statin (OR 0.30 95%CI 0.26, 0.34), an ACEI and/or angiotensin receptor blocker (OR 0.76 95%CI 0.65-0.89) and optimal evidence based treatment (OR 0.51 95%CI 0.42, 0.62) and were more likely to be prescribed a nitrate (OR 1.42 95%CI 1.23, 1.62).

Women, 75 years and over were also less likely to be prescribed a β-blocker (OR 0.71 95%CI 0.62, 0.81), a statin (OR 0.33 95%CI 0.29, 0.38) an ACEI and/or angiotensin receptor blocker (OR 0.78 95%CI 0.66, 0.91) and were also more likely to be prescribed a nitrate (OR 1.24 95%CI 1.08, 1.41).

With increasing socioeconomic deprivation, patients were less likely to be prescribed a β-blocker (p for trend = 0.018) and more likely to be prescribed a nitrate (p for trend =0.006) and an ACE inhibitor (p for trend = 0.02). On multivariate analysis, patients in the most deprived stratum were 25% more likely to be prescribed a nitrate or a calcium channel blocker, 51% more likely to be prescribed an ACE inhibitor and/or angiotensin receptor blocker and 81% more likely to be prescribed warfarin compared to patients in the least deprived stratum. However, there were no differences in prescribing of statins (OR 0.92 95%CI 0.77, 1.10) or antiplatelet medications (OR 1.08 95%CI 0.89, 1.32) according to socioeconomic deprivation. Socioeconomically deprived individuals with angina were 64% more likely to be prescribed optimal evidence-based medications.

Table 27 Pharmacological treatment of both men and women with angina for the year ending March 2002

Treatment	Age group								
	<45	45-54	55-64	65-74	75-84	85+	<75 yrs	≥75 yrs	all ages
n=	206	930	2278	3167	2355	572	6581	2927	9508
β-Blocker	95 (46.1)	505 (54.3)	1235 (54.2)	1585 (50.0)	1035 (43.9)	195 (34.1)	3420 (52.0)	1230 (42.0)	4650 (48.9)
Calcium channel blockers	46 (22.3)	342 (36.8)	1010 (44.3)	1385 (43.7)	1050 (44.6)	207 (36.2)	2783 (42.3)	1257 (42.9)	4040 (42.5)
Nitrates	90 (43.7)	464 (49.9)	1219 (53.5)	1751 (55.3)	1441 (61.2)	338 (59.1)	3524 (53.5)	1779 (60.8)	5303 (55.8)
Nicorandil	1 (0.5)	6 (0.6)	33 (1.4)	28 (0.9)	43 (1.8)	11 (1.9)	68 (1.0)	54 (1.8)	122 (1.3)
ACE inhibitors	42 (20.4)	246 (26.5)	686 (30.1)	1016 (32.1)	743 (31.5)	137 (24.0)	1990 (30.2)	880 (30.1)	2870 (30.2)
ARB	3 (1.5)	24 (2.6)	75 (3.3)	168 (5.3)	96 (4.1)	18 (3.1)	270 (4.1)	114 (3.9)	384 (4.0)
ACEI/ARB	43 (20.9)	264 (28.4)	735 (32.3)	1138 (35.9)	815 (34.6)	150 (26.2)	2180 (33.1)	965 (33.0)	3145 (33.1)
Statins	79 (38.3)	523 (56.2)	1353 (59.4)	1864 (58.9)	848 (36.0)	53 (9.3)	3819 (58.0)	901 (30.8)	4720 (49.6)
Aspirin	104 (50.5)	546 (58.7)	1592 (69.9)	2405 (75.9)	1698 (72.1)	375 (65.6)	4647 (70.6)	2073 (70.8)	6720 (70.7)
Clopidogrel	7 (3.4)	40 (4.3)	88 (3.9)	140 (4.4)	89 (3.8)	15 (2.6)	275 (4.2)	104 (3.65)	379 (4.0)
Antiplatelet medication *	105 (51.0)	567 (61.0)	1636 (71.8)	2483 (78.4)	1149 (74.3)	383 (67.0)	4791 (72.8)	2132 (72.8)	6923 (72.8)
Warfarin	3 (1.5)	25 (2.7)	93 (4.1)	176 (5.6)	205 (8.7)	25 (4.4)	297 (4.5)	230 (7.9)	527 (5.5)
Optimal medications †	25 (12.1)	166 (17.8)	450 (19.8)	621 (19.6)	325 (13.8)	23 (4.0)	1262 (19.2)	348 (11.9)	1610 (16.9)

ACEI= ACE inhibitor; ARB= angiotensin receptor blocker

*** Antiplatelet medication = aspirin or clopidogrel**

† Optimal medications = antiplatelet medication + statins + ACE inhibitor

Table 28 Relative risk of being prescribed various medication for women compared to men*, for men and women aged over 75 years compared to under 75 years† and for Carstairs deprivation category 5 compared to Carstairs deprivation category 1‡

	Women versus men		Men ≥75 years versus < 75 years		Women ≥75 years versus < 75 years		Carstairs deprivation category 5 versus 1	
	OR	P value	OR	P value	OR	P value	OR	P value
β-blockers	0.86 (0.78, 0.93)	<0.001	0.67 (0.59, 0.78)	<0.001	0.71 (0.62, 0.81)	<0.001	0.94 (0.78, 1.12)	0.485
Calcium channel blockers	0.85 (0.78, 0.93)	<0.001	1.03 (0.90, 1.19)	0.625	1.04 (0.91, 1.19)	0.536	1.25 (1.04, 1.48)	0.015
Nitrates	0.96 (0.88, 1.04)	0.312	1.42 (1.23, 1.62)	<0.001	1.24 (1.08, 1.41)	0.002	1.25 (1.05, 1.50)	<0.012
ACEI/ARB	0.69 (0.63, 0.76)	<0.001	0.76 (0.65, 0.89)	<0.001	0.78 (0.66, 0.91)	0.001	1.51 (1.23, 1.85)	<0.001
Statins	0.83 (0.76, 0.91)	<0.001	0.30 (0.26, 0.34)	<0.001	0.33 (0.29, 0.38)	<0.001	0.92 (0.77, 1.10)	0.368
Anti platelet medication¶	0.82 (0.74, 0.90)	<0.001	1.15 (0.98, 1.35)	0.079	0.96 (0.84, 1.11)	0.618	1.08 (0.89, 1.32)	0.439
Warfarin	0.79 (0.64, 0.94)	<0.035	0.84 (0.62, 1.14)	0.266	0.85 (0.61, 1.20)	0.363	1.81 (1.15, 2.85)	0.01
Optimal medications**	0.68 (0.60, 0.76)	<0.001	0.51 (0.42, 0.62)	<0.001	0.53 (0.43, 0.65)	<0.001	1.64 (1.29, 2.09)	<0.001

ACEI= ACE inhibitor; ARB= angiotensin receptor blocker
*** Adjusted for practice, age, deprivation category and co-morbidity**
† Adjusted for practice, deprivation category and co-morbidity
‡ Adjusted for age, sex, practice and co-morbidity
¶ Antiplatelet medication = aspirin or clopidogrel
**** Optimal medications = antiplatelet medication + statins + ACE inhibitor**

4.4 Discussion

In Scotland, in 2001/2002, the overall prevalence of angina was 2.6 per cent (6.4 per cent in individuals ≥ 45 years and 11.3 per cent in those ≥ 65 years). Both prevalence and incidence were higher in men than in women and increased steeply with age. The prevalence and incidence of angina also increased with increasing socioeconomic deprivation though deprived individuals were less likely to see their general practitioner on an ongoing basis. Women and older patients were less likely to receive evidence-based therapy.

The estimates of prevalence (and incidence) were based on general practitioner reported diagnosis. This approach has strengths and weaknesses compared to the more commonly used alternative of administration of a questionnaire (usually the Rose one).[1] There has been concerns that the questionnaire approach may overestimate the prevalence of angina, especially in women. The positive predictive value of the Rose angina questionnaire in comparison to exercise thallium testing has been reported to be 67% [6] and as low as 25% in women.[327] Conversely, reliance on a medical diagnosis may underestimate prevalence as individuals with unrecognised angina or very mild symptoms might not attend (or be correctly identified by) their general practitioner. In the Whitehall II study 70% of those who developed angina were undiagnosed at the time of their initial report.[55]

I found an overall prevalence of angina of 2.8% in men (7.1 per cent in subjects ≥ 45 years and 13.1 per cent in those ≥ 65 years) and 2.5% in women (5.8 per cent in subjects ≥ 45 years and 9.9 per cent in those ≥ 65 years). These findings, therefore, give a somewhat higher prevalence than the 7.1% prevalence in men over 65 years of age in the Nottingham nitrate study carried out 1984-85 [33] and a slightly lower prevalence than the 8.3% prevalence in individuals over 45 years reported in a more recent study of 48 general practices in the Wakefield region of northern England which used a similar investigative approach to the Nottingham study. [34] Another study, using data from the 1998 Health Survey for England, gave a self-reported prevalence of angina (recall of a doctors diagnosis) of approximately 3% in men and women 16 years or above.[328] Indeed, the only inconsistent study was the Newcastle General Practice survey, carried out in 1979, which reported a prevalence of 1.1% in subjects aged 30-59 years.[35] The survey was conducted by

51 general practitioners and identified 338 patients; I am, however uncertain about the completeness of case-ascertainment in this study.

The prevalence of angina in CMR is also comparable to that reported in some studies using a questionnaire-based approach[22;25], but lower than in others of this type.[19;20] Why the prevalence of angina in my study is lower than in those latter studies, is not entirely certain. Apart from the methodological difference discussed above, many of the other surveys were conducted in selected cohorts and up to 25 years earlier than the current study (during which time the incidence of coronary disease is known to have been declining). However, even the more recent questionnaire-based studies have reported a higher prevalence of angina than found in the current study. For example, amongst the 10,191 men and women aged 35-55 years enrolled in the Whitehall II study, the prevalence of Rose "definite" angina was 2.9%, compared to 1.8% in subjects aged 45-55 years in my study.[15] In the British Regional Heart Study, the prevalence of *"possible" or "definite"* angina on Rose angina questionnaire in 5,263 men aged 55-79 years in 1996 was 13.8%. The prevalence of angina in men aged 55-84 years was 10% in the current study.[20] The inclusion of *"possible"* angina in the former study, may, however, have inflated the prevalence rate compared to mine. The prevalence of "definite angina", in 11,797 women (mean age 56 years) screened with the Rose angina questionnaire during 1994-1995 as part of the Royal College of General Practitioners' Oral Contraception Study was 9.9% in those women over 65 years, which is the same as in the current study. [14] CMR prevalence findings are also consistent with another recent report from Sweden.[11]

Prior studies frequently reported a higher prevalence of angina in women compared to men, a finding inconsistent with the epidemiology of acute coronary syndromes, coronary deaths and the protection from coronary heart disease enjoyed by pre-menopausal women.[9-12;15;18;26] This anomaly has been attributed to an increased tendency for women to score positive for angina on the Rose questionnaire. I did not find a female preponderance of angina; indeed, I saw the opposite, as have other studies based on a physician diagnosis or prescription of anti-angina treatment.[29;33;34]

As in all prior studies, I also found that the prevalence of angina increased with age though few have explored the full age range.[101] The majority of patients (59% of men and 69% of women) were aged 65 years or above and a substantial minority were 75 years or older (25% of men and 37% of women). This is in striking contrast to the typical age range of patients enrolled in clinical trials[329] or undergoing coronary revascularisation (only

approximately 6% of patients in Scotland undergoing revascularisation in 2002/3 were older than 75 years). Also of note, although the overall prevalence of angina was lower in women than in men, prevalence in older women approached that of men and, because of the greater number of older women than men in the population generally, there were more women than men aged 75 years or above with angina.

In contrast to prevalence studies, there are very few prior surveys of the incidence of angina and most of these date from the 1970's.[42;43;47] In one more recent study, comparing coronary heart disease rates in France and Northern Ireland, the incidence of angina in French men aged 50-59 years was 2.6 per 1000 compared to 5.4 per 1000 in Irish men; in Scotland it was 3.5 per 1000 in men aged 45-64 years.[40] By contrast, an earlier study from Southampton, England reported an incidence of only 0.8 per 1000 in men and women aged 31-70 years (compared to 2.9 per 1000 in Scotland in individuals aged 45-64 years).[39] While the standardised mortality ratio (SMR) for coronary heart disease is higher in Northern Ireland and Scotland than in southern England, the Southampton incidence figure seems unusually low (and lower than in France) and probably reflects the methods employed in that study. Patient identification required referral to a special chest pain clinic, patients with any prior evidence of coronary heart disease were excluded and, where possible, patients underwent exercise electrocardiography. A rigorous definition of angina was applied. Of the 467 individuals referred, 110 (0.8 per 1000 population) had definite angina and another 63 had possible angina.

Consultation rates, reflecting the primary care burden of angina were relatively low with less than one visit per patient per year. This low rate of contact is in striking contrast to at least one other cardiac disorder, heart failure, where we have reported 2 to 3 contacts per annum.[330] Also in contrast to heart failure, where the number of contacts per patient per year increased with age, the annual number of consultations per patient per year for angina decreased with increasing age. Women also had a lower number of contacts per patient per year than men, at all ages. The reason for this is not clear, especially as women, in general, have more contacts with primary care physicians than men (approximately twice as many) i.e. more opportunities for angina to be recorded at a contact. There is some evidence that women may seek help for angina less often than men. [331] It is also possible that primary care physicians may record angina (as one of a number of problems) less often in women than in men (the general practitioner decided which medical problems were recorded as clinically important during "contacts"); there is evidence that physicians regard chest pain in women as less clinically significant than in men. [332]

The co-morbidities recorded in patients with angina are not unexpected. Respiratory problems are the commonest reason for a primary care consultation and dyspepsia and depression are also known to be common reasons for consultation. The higher proportion of co-morbidities in the angina group compared to the general population may be related to their older age and more frequent general practitioner contact. Hypertension, diabetes and myocardial infarction reflect the known relationships between these problems and angina. The prevalence of these co-morbidities is similar to that reported in other primary care studies and large angina trials. [333;334] Interestingly, I found that patients with angina were more likely to have depression than the general population. An association between a history of depression and a higher frequency of angina attacks has been shown previously.[335] Although patients with angina might be expected to have more comorbidity than those without, the difference may have been exaggerated because patients with angina have more frequent contact with their GP and therefore more opportunity for comorbidities to be recorded.

This study gives one of the most representative and up to date descriptions of treatment of patients with angina. The use of evidence-based secondary preventive treatments is higher than in most prior studies[328;336] and similar to that found in the Euro Heart Survey of Stable Angina which focused on newly diagnosed angina presenting to a cardiologist[337]. Although only 73% of patients with angina in CMR were recorded as treated with anti-platelet therapy others may be using "over the counter", self-purchased aspirin. However, only about half of patients were prescribed a statin and less than a third an ACE inhibitor when the most recent evidence supports the use of these drugs in all patients who can tolerate them.[322;323;338]. Drugs which modify lipids or reduce the risk of thrombosis substantially reduce the risk of myocardial infarction and death.[322;339] ACE inhibitors can also significantly improve outcome in patients with stable coronary artery disease.[338] I found that female sex and older age were associated with *under*-use of one or more guideline-recommended treatments (particularly beta-blockers and statins), even after multivariate adjustment. This reflects patterns previously described in the use of coronary revascularisation procedures, in the management of acute coronary syndromes and, recently, in the treatment of coronary heart disease (myocardial infarction and angina combined) in primary care. [328;333;336] I do not know of prior data on angina alone (as opposed to coronary heart disease); this is an important distinction as patients with prior myocardial infarction are more likely to be prescribed these treatments than those with angina. [328;336;340] Though it might be argued that the under-prescribing in this study might,

in part, reflect the lower number of consultations per patient per year in females and the elderly, this is not supported by examination of the pattern of prescribing in socio-economically deprived patients who appeared to suffer less under-treatment despite lower contact rates (see below).

I found a quite strong relationship between socioeconomic deprivation and the prevalence and incidence of angina, in keeping with previous reports of higher levels of a number of different manifestations of coronary heart disease in these disadvantaged individuals. Socioeconomically deprived individuals with angina had a lower rate of contacts per patient per year. Despite this lower contact rate, deprived patients were less obviously under-treated than women or older individuals. Indeed, deprived patients were *more* likely to be treated with ACE inhibitors, perhaps reflecting greater contact with secondary care where these drugs are more likely to be used. Another recent UK study has also found that, after multivariable adjustment, social deprivation was not associated with under-use of either medical treatments or cardiac procedures. [341]

A limitation to my study is that only patients who attend a physician with angina are included and it is known that there is a significant proportion of individuals with undiagnosed angina in the community [55]. Another limitation is that the diagnosis of angina is a GP diagnosis and not necessarily substantiated by definitive investigations. The CMR practices tend to be larger partnerships and are more likely to be training practices therefore the prescribing rates for whole of Scotland may be even lower than that presented here in CMR.

In summary, I have described the substantial burden of angina in primary care. It is a common condition affecting 3% of the population, with the prevalence rising to 12% in those 75 years and older. Although the incidence and prevalence of angina increases with increasing socioeconomic deprivation, deprived individuals with angina have less frequent follow-up with their general practitioner. Although, overall, the use of evidence-based treatments is better than in prior studies, there is scope for further improvement in prescribing. The overall sub-optimal use of treatments may, in part, reflect the marked age and sex discrepancies in prescribing of evidence-based treatments, with the elderly and women receiving less guideline-recommended treatment therapy. These discrepancies warrant further investigation.

5 PREVALENCE, INCIDENCE, PRIMARY CARE BURDEN AND MEDICAL TREATMENT OF HEART FAILURE IN SCOTLAND: AGE, SEX AND SOCIOECONOMIC DISPARITIES

5.1 Introduction

Though heart failure is perceived to be one of the most common, disabling, costly and deadly cardiovascular disorders encountered in clinical practice, its epidemiology and the burden which it places on health care systems are still poorly defined, especially in primary care.[342;344] In particular, as outlined in chapter 1, incidence studies are lacking. Similarly, the other problems with which patients with heart failure consult a GP have not been reported. There are also no comparisons of the community burden of heart failure and other common cardiovascular disorders. In addition, there are few contemporary data on the treatment of heart failure in primary care across a whole country.[345]
Socioeconomic deprivation is associated with higher rates of admission to hospital and case fatality in heart failure but the mechanisms are unclear- indeed, this excess risk seems to be independent of age, sex, comorbidities, disease severity, and even medication adherence.[143;346;347] It may be intriguing to speculate about socioeconomic gradients in access to general practitioners and outpatient pharmacotherapy being the key causative factors, but there is paucity of high quality research on heart failure in primary care.[348]
This question is important as heart failure accounts for almost a quarter of all admissions to hospital for cardiovascular events, has a high mortality rate (median survival around 18 months), and places a great burden on all health care systems (estimated direct costs of £905 million in the United Kingdom in 2000, 2% of total NHS expenditure).[131;143;349]
I have therefore used the Scottish CMR scheme, to give a more comprehensive picture of the national epidemiology and primary care burden, of heart failure than existing studies.

5.2 Methods

The CMR heart failure database was used as described in chapter 3.

5.3 Results

5.3.1 Heart failure Read codes used

Contacts were coded as congestive heart failure (51.0%), left ventricular failure (23.6%), heart failure – not otherwise specified (10.0%), heart failure (6.7%), acute left ventricular failure (4.1%), acute congestive heart failure (3.7%), chronic congestive heart failure (1.2%), compensated cardiac failure (0.5%) or acute heart failure (0.1%).

5.3.2 Prevalence of heart failure

The one-year CMR prevalence for men and women of differing ages with heart failure is shown in Table 29. Prevalence was extremely low in persons aged <45 years, increased 6-fold between the age ranges 45-64 years and 65-74 years and more than doubled again between the age ranges 65-74 years and 75-84 years. The prevalence of heart failure was higher in women (7.8/1000) than in men (6.4/1000). Extrapolating from the CMR practices to the whole of the country, the estimated number of Scots with heart failure in 2000 was, therefore, 37,305 (16,216 men), 87% of whom were aged 65 years or older and 60% of whom were 75 years or older (Table 30). The prevalence of heart failure differed between deprivation categories (Table, $p<0.0001$), with a non-significant 13% trend towards higher age and sex standardised prevalence rates in the more deprived groups. Table 31

5.3.3 Incidence of heart failure

The one-year incidence for men and women of differing ages with heart failure is shown in Table 29. This was extremely low in persons aged <45 years, increased 4 – 5 fold between the age ranges 45-64 years and 65-74 years and increased again 2 – 3 fold between the age ranges 65-74 years and 75-84 years. The incidence of heart failure was higher in women (2.2/1000) than in men (1.8/1000). The estimated number of Scots presenting with heart failure for the first time in the year 2000 was, therefore, 10,375 (4,504 men), 84% of whom were aged 65 years or older and 58% of whom were 75 years or older (Table 30). The incidence of heart failure significantly increased with increasing social deprivation (Table 31): socioeconomically deprived patients were 44% more likely to develop heart failure than affluent patients.

5.3.4 Contact rates for heart failure

The one-year contact rate was extremely low in persons aged <45 years, increased almost 7-fold between the age ranges 45-64 years and 65-74 years and nearly trebled again between the age ranges 65-74 years and 75-84 years (Table 29). The contact rate for heart failure was higher in women (17.9/1000) than in men (16.5/1000).

Overall, contact rates were approximately 2-3 times higher than prevalence in both men and women. The average number of contacts per patient with heart failure was 2.6 in men and 2.3 in women. The average number of contacts per patient doubled between the youngest and oldest subgroups in men (from 1.4 in those <45 years to 2.8 in those 85 years or older) and almost doubled in women (1.4 versus 2.5).

In contrast to prevalence and incidence, the association between socioeconomic deprivation and contacts/consultations was in the opposite direction: patients in the most deprived groups had 23% less follow-up visits per annum with their general practitioner (Table 31). Although the age and sex standardised contact rates differed significantly between the 5 strata ($p<0.00001$), the p value for trend was not significant ($p=0.07$) as there was little appreciable difference between categories 1, 2, 3, and 4. However, the most deprived subgroup had significantly lower standardised contact rates compared to deprivation categories 1 (OR 0.81, 95% CI 0.72, 0.90, $p=0.0002$), 2 (OR 0.72, 95% CI 0.65, 0.81, $p<0.0001$), 3 (OR 0.72, 95% CI 0.65, 0.81, $p<0.0001$), and 4 (OR 0.79, 95% CI 0.70, 0.90, $p=0.0003$). Contact rates did not differ across age groups or by sex.

Table 29 Contact rates, incidence and prevalence per 1,000 population of heart failure by sex and age group; April 1999-March 2000

	Age group	Population	Number of patients with HF	Prevalence	Number of first diagnoses of HF	Incidence	Number of contacts for HF (April 1999-March 2000)	Contact rate
Men	45 – 64	37,990	163	4.3	52	1.4	378	9.9
	65 – 74	11,446	294	25.7	69	6.0	745	65.1
	75 – 84	5,802	371	63.9	117	20.2	994	171.3
	85+	1,290	134	103.9	32	24.8	372	288.4
	65+	18,538	799	43.1	218	11.8	2111	113.9
	75+	7,092	505	71.2	149	21.0	1366	192.6
	All ages	152,033	973	6.4	271	1.8	2,504	16.5
Women	45 - 64	37,356	120	3.2	48	1.3	247	6.6
	65 - 74	13,428	278	20.7	82	6.1	587	43.7
	75 - 84	9,408	500	53.1	127	13.5	1,174	124.8
	85+	3,617	308	85.2	78	21.6	763	210.9
	65+	26,453	1,086	41.1	287	10.9	2,524	95.4
	75+	13,025	808	62.0	205	15.7	1,937	148.7
	All ages	155,708	1,213	7.8	338	2.2	2,781	17.9
Both sexes	45 - 64	75,346	283	3.8	100	1.3	625	8.3
	65 - 74	24,874	572	23.0	151	6.1	1,332	53.5
	75 – 84	15,210	871	57.3	244	16.0	2,168	142.5
	85+	4,907	442	90.1	110	22.4	1,135	231.3
	65+	44,991	1,885	41.9	505	11.2	4,635	103.0
	75+	20,117	1,313	65.3	354	17.6	3,303	164.2
	All ages	307,741	2,186	7.1	609	2.0	5,285	17.2

HF=heart failure

There were 18 patients (11 men) aged ≤ 44 years with heart failure, 4 with a first diagnosis (1 male). These patients made 25 contacts (15 male). The CMR practice population under 45 years is 187,404 (95,505 men).

Table 30 Estimated number of contacts, first diagnoses and patients with heart failure by sex and age group and percentages of totals for Scotland;* April 1999-March 2000

	Age group	Number of patients with HF	% of total patients with HF	Number of first diagnoses for HF	% of total first diagnoses for HF	Number of contacts for HF	% of total contacts for HF
Men	0 – 44	183	1.1	17	0.4	249	0.6
	45 – 64	2,510	15.5	801	17.8	5,820	13.9
	65 – 74	5,041	31.1	1,183	26.3	12,775	30.6
	75 – 84	6,238	38.5	1,967	43.7	16,713	40.0
	85+	2,244	13.8	536	11.9	6,231	14.9
	65+	13,523	83.4	3,686	81.8	35,719	85.5
	75+	8,482	52.3	2,503	55.6	22,944	54.9
	All ages	16,216		4,504		41,788	
Women	0 - 44	118	0.6	51	0.9	168	0.3
	45 - 64	1,979	9.4	792	13.5	4,073	8.4
	65 - 74	5,046	23.9	1,489	25.4	10,656	22.1
	75 - 84	8,743	41.5	2,221	37.8	20,529	42.5
	85+	5,203	24.7	1,318	22.4	12,888	26.7
	65+	18,992	90.1	5,028	85.6	44,073	91.2
	75+	13,946	66.1	3,539	60.3	33,417	69.2
	All ages	21,089		5,871		48,314	
Both sexes	0 - 44	301	0.8	68	0.7	417	0.5
	45 - 64	4,489	12.0	1,593	15.4	9,893	11.0
	65 - 74	10,087	27.0	2,672	25.8	23,431	26.0
	75 – 84	37,242	41.3	4,188	40.4	37,242	41.3
	85+	7,447	20.0	1,854	17.9	19,119	21.2
	65+	32,515	87.2	8,714	84.0	79,792	88.6
	75+	22,428	60.1	6,042	58.2	56,361	62.6
	All ages	37,305		10,375		90,102	

HF = heart failure

*** CMR age and sex specific rates extrapolated to whole of Scotland**

Table 31 Incidence, prevalence, and contact rates (per 1,000 population) of heart failure, stratified by socioeconomic status

Deprivation category	Sample size	Crude prevalence (per 1,000)	Adjusted prevalence (per 1,000)	Crude incidence (per 1,000)	Adjusted incidence (per 1,000)	Crude contact rate (per 1,000)	Adjusted contact rate (per 1,000)	Number of contacts Per patient	Implied mean survival (yrs)*
I – most affluent	70,961	6.3	6.4	1.8	1.8	16.8	17.1	2.6	3.5
2	66,633	7.5	7.4	1.7	1.6	20.0	19.6	2.7	4.4
3	93,258	7.3	7.5	1.9	1.9	17.5	19.6	2.4	3.8
4	34,627	7.3	7.5	2.6	2.7	16.6	17.9	2.3	2.8
5 – most deprived	28,633	6.7	7.2	2.4	2.6	13.4	14.3	2.0	2.8
Ratio between category 5 and 1 (p value for trend)		1.06 (p=0.27)	1.13 (p=0.06)	1.33 (p=0.002)	1.44 (p=0.0003)	0.80 (p<0.001)	0.84 (p=0.07)	0.77 (p<0.001)	0.80 (p<0.001)

Adjusted rates are age and sex standardised to the distribution found in the entire CMR practice population.

* Implied mean survival estimated by dividing the crude prevalence rate by the crude incidence rate in each deprivation category.

5.3.5 GP contact rates for heart failure compared to hypertension, angina and other conditions

For comparison, contact rates for hypertension and angina were 96.2/1000 and 21.2/1000, respectively, for men and 133.9/1000 and 19.2/1000, respectively, for women. Figure 5 shows age-specific contact rates for males and Figure 6 shows age-specific contact rates for females for hypertension, angina and heart failure. In older age groups, consultation rates for heart failure equalled or exceeded those for both hypertension and, especially, angina. Table 32 shows the most common conditions leading to contact with a GP in men and women in different age groups. Heart failure was one of the top five reasons for consultation in men aged 75 years or older and in women 85 years or older.

Figure 5 Age stratified GP consultation rates per 1000 population for heart failure, angina and hypertension in men

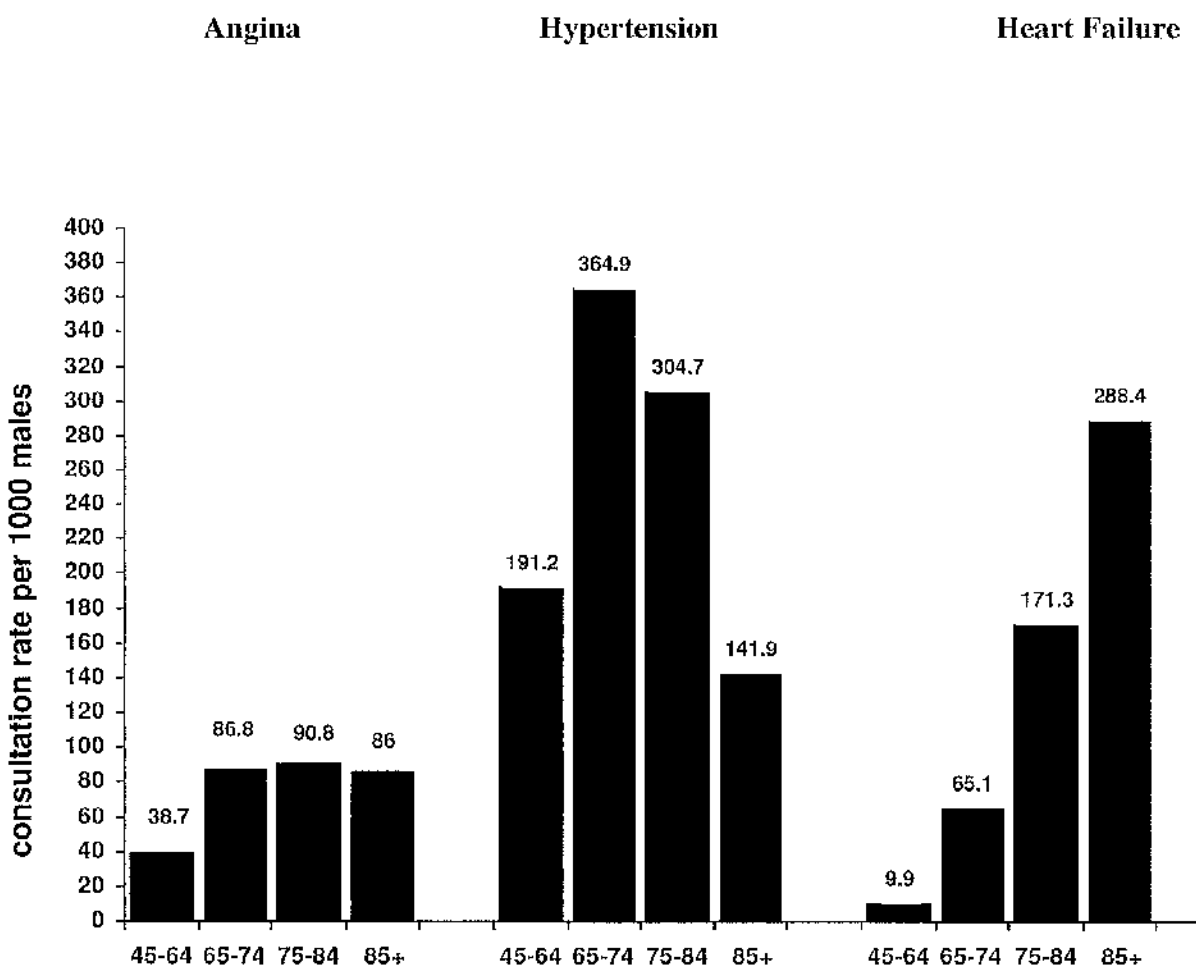


Figure 6 Age stratified GP consultation rates per 1000 population for heart failure, angina and hypertension in women

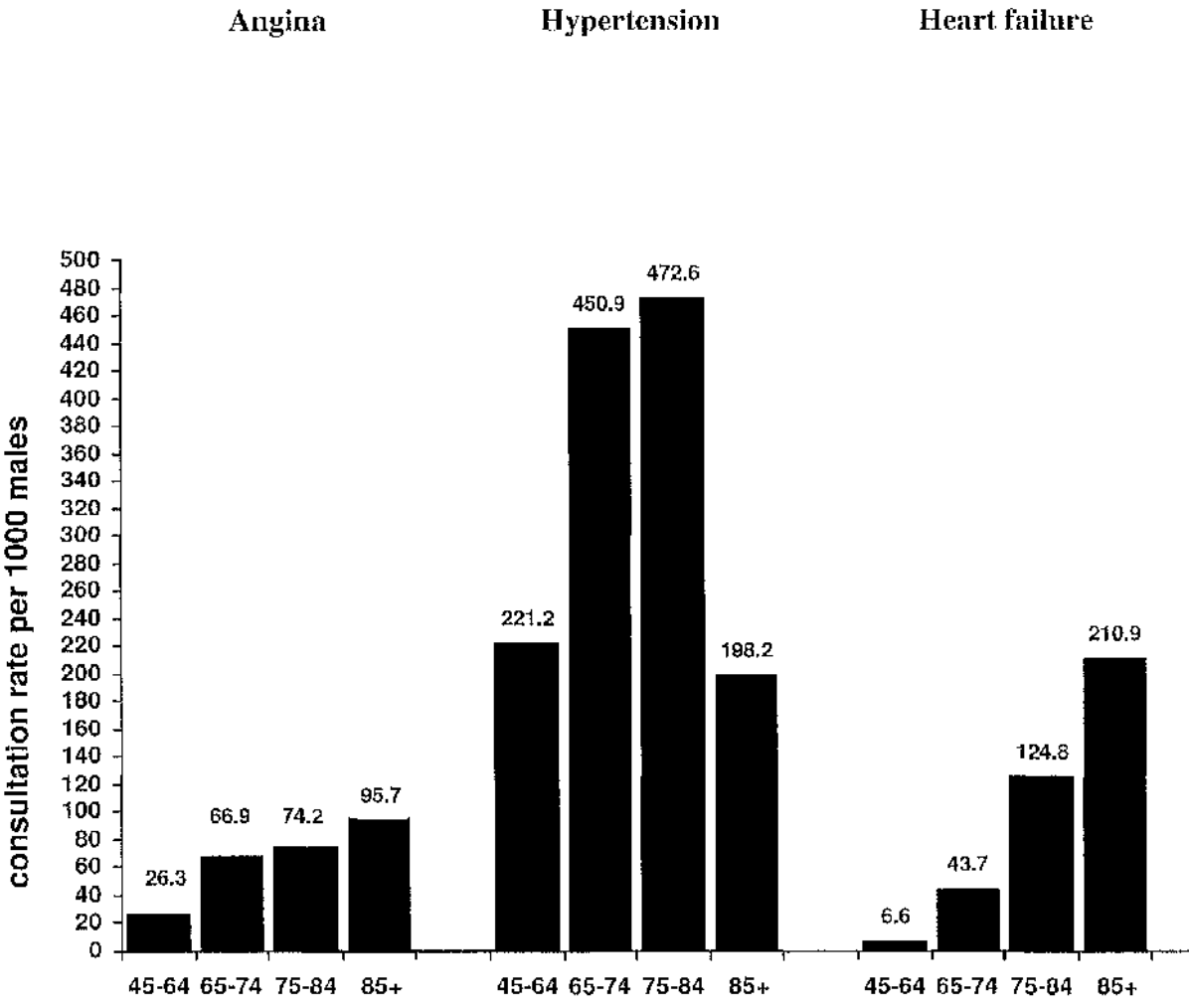


Table 32 The five most common reasons for consulting a general practitioner in Scotland by sex and age group in year 2000*

	Men				Women			
	45-64	**65-74**	**75-84**	**85+**	**45-64**	**65-74**	**75-84**	**85+**
Hypertension	1 (229)	1 (445)	1 (386)	4 (155)	3 (269)	1 (572)	1 (565)	1 (242)
Back problems	2 (148)	-	-	-	4 (177)	3 (150)	4 (169)	-
Depression	3 (125)	-	-	-	2 (275)	4 (148)	-	-
Lower RTI	4 (88)	2 (175)	2 (216)	1 (290)	-	2 (189)	2 (216)	2 (240)
Anxiety	5 (73)	-	-	-	5 (160)	-	-	-
Coronary heart disease	-	3 (156)	5 (125)		-	-	-	-
COPD	-	4 (147)	3 (198)	3 (160)	-	-	-	-
Diabetes mellitus	-	5 (143)	-	-	-	-	-	-
HEART FAILURE	**-**	**-**	**4 (136)**	**2 (248)**	**-**	**-**	**-**	**5 (169)**
Menopause	-	-	-	-	1 (313)	-	-	-
Osteoarthritis	-	-	-	-	-	5 (143)	3 (186)	-
Urinary tract infection	-	-	-	-	-	-	5 (147)	-
Dementia	-	-	-	-	-	-	-	3 (215)
General miscellaneous	-	-	-	5 (154)	-	-	-	4 (185)

COPD= chronic obstructive pulmonary disease; RTI= respiratory tract infection
***Year ending December 2000; rank (1-5) and consultation rate per 1,000 population (brackets).**

5.3.6 Concomitant diagnoses in patients with heart failure

The top ten concomitant diagnostic codings in patients consulting with heart failure are shown in Table 33. In both sexes, lower respiratory tract infection was the most common concomitant diagnostic coding (in 28% of men and women). Coronary or ischaemic heart disease was the second most frequently coded, reported in 22% of men and 13% of women. 14% of men and 16% of women had a concomitant coding for hypertension recorded and 12% of and 10% of women had a coding for atrial fibrillation (atrial fibrillation was not one of the top 10 concomitantly coded conditions in women with heart failure). The frequency of other diagnoses was generally similar in men and women.

Table 33 Proportion of heart failure patients seen with specified condition/illness; April 1999-March 2000*

Condition/illness	Men (n=973)	Women (n=1213)
Lower Respiratory Tract Infection	273 (28.1)	338 (27.9)
Coronary Heart Disease – Miscellaneous	216 (22.2)	159 (13.1)
Breathlessness	201 (20.7)	247 (20.4)
Angina	144 (14.8)	141 (11.6)
Chronic Obstructive Airways Disease	142 (14.6)	-
Upper Respiratory Tract Infection (excluding sore throat)	141 (14.5)	176 (14.5)
Hypertension	134 (13.8)	196 (16.2)
Atrial Flutter/Fibrillation	114 (11.7)	-
Oedema	111 (11.4)	177 (14.6)
Miscellaneous	108 (11.1)	144 (11.9)
Back Problems	-	153 (12.6)
Osteoarthritis	-	143 (11.8)

* number (per cent)

5.3.7 Medications taken by patients with heart failure

Prescribing information was available from 22 CMR practices with a combined list size of 140,246 patients (2.6% of the Scottish population). The age range, sex distribution and level of deprivation in these patients were comparable to those in the total Scottish population. Table 34, 35Table 36 shows the medications prescribed for patients with heart failure, stratified by sex and age. Diuretics were prescribed for 81% of these patients, ACE inhibitors for 39%, beta-blockers for 21%, digoxin for 21%, and spironolactone for 9%. Only 11% of these patients were prescribed both an ACE inhibitor and a beta-blocker, and 1% was prescribed the combination of ACE inhibitor, beta-blocker, and spironolactone.

There were significant sex differences in prescribing. Eighty per cent of men were prescribed a diuretic, 46% an ACE inhibitor, 23% a β-Blocker, 11% spironolactone and 24% digoxin. The corresponding figures for women were 81% (p=0.87), 34% (p<0.001), 20% (p=0.29), 7% (p=0.02) and 18% (p=0.02), respectively (p values for women vs. men). There were also significant age differences, with fifty per cent of patients < 75 years, but only 33% of patients ≥ 75, prescribed an ACE inhibitor (p<0.001). Twenty six per cent of patients < 75 and 19% of patients ≥ 75 years were prescribed a β-Blocker (p=0.04). These proportions for spironolactone were 19% and 9%, respectively (p=0.04). There was no difference in the rate of use of digoxin.

There was a clear association between age and sex (older patients were more often women) and multivariable analyses revealed that age was the most important factor influencing prescribing patterns. Indeed, sex was only significantly associated with ACE inhibitor prescribing (men were 42% more likely [p=0.009] to be prescribed an ACE inhibitor than women, even after adjusting for age). The multivariable analyses revealed that, compared to patients younger than 65 years, older patients were less likely to be prescribed ACE inhibitors (odds ratios [OR] 0.60 for patients aged 75-84 years [p<0.001] and OR 0.39 for patients older than 85 years [p<0.001]) or the combination of ACE inhibitors plus beta-blockers (OR 0.60 for patients aged 75-84 years [p=0.03] and OR 0.32 for patients older than 85 years [p=0.001]).

Prescribing patterns did not vary by deprivation category on bivariate (Figure 7) or multivariable analyses. There were wide discrepancies in prescribing between general practitioners; however, these discrepancies disappeared after adjusting for differences in patient demographics. For example, the variables associated with ACE inhibitor prescribing on multivariable analysis were sex (Odds Ratio [OR] 1.42 for males compared to females, p=0.009) and age (OR 0.60 for patients aged 75-84 years [p=0.004] and OR 0.39 for patients older than 85 years [p<0.001] compared to patients younger than 65 years). Deprivation category (p=0.31) and general practitioner (p=0.79) were not independently associated with prescriptions for ACE inhibitor.

Table 34 Pharmacological treatment of men with heart failure in Scotland between April 1999-March 2000

Treatment	Age group						
	45-64	65-74	75-84	85+	<75 yrs	≥75 yrs	all ages
n=	64	132	164	74	201	238	439
Frusemide	36 (56.3)	80 (60.3)	114 (69.5)	49 (66.2)	119 (59.2)	163 (68.5)	282 (64.2)
Any diuretic	47 (73.4)	105 (79.6)	139 (84.8)	58 (78.4)	155 (77.1)	197 (82.8)	352 (80.2)
ACE Inhibitor	39 (60.9)	71 (53.8)	69 (42.1)	21 (28.4)	111 (55.2)	90 (37.8)	201 (45.8)
Angiotensin receptor blocker	4 (6.3)	5 (3.8)	8 (4.9)	1 (1.4)	9 (4.5)	9 (3.8)	18 (4.1)
β-Blocker	20 (31.3)	34 (25.8)	33 (20.1)	14 (18.9)	55 (27.4)	47 (19.8)	102 (23.2)
Spironolactone	12 (18.8)	16 (12.1)	16 (9.8)	4 (5.4)	28 (13.9)	20 (8.4)	48 (10.9)
Digoxin	17 (26.6)	30 (22.7)	43 (26.2)	15 (20.3)	47 (23.4)	58 (24.4)	105 (23.9)
Any HF treatment	57 (89.1)	114 (86.4)	149 (90.9)	61 (82.4)	175 (87.1)	210 (88.2)	385 (87.7)

HF = heart failure

Table 35 Pharmacological treatment of women with heart failure in Scotland between April 1999-March 2000

Treatment	Age group						
	45-64	65-74	75-84	>85	<75 yrs	≥75 yrs	All ages
n=	56	116	227	166	176	393	569
Frusemide	30 (53.6)	66 (56.9)	124 (54.6)	97 (58.4)	97 (55.1)	221 (56.2)	318 (55.9)
Any diuretic	42 (75.0)	95 (81.9)	190 (83.7)	132 (79.5)	138 (78.4)	322 (81.9)	460 (80.8)
ACE Inhibitor	24 (42.9)	53 (45.7)	76 (33.5)	41 (24.7)	77 (43.8)	117 (29.8)	194 (34.1)
Angiotensin receptor blocker	5 (8.9)	5 (4.3)	14 (6.2)	6 (3.6)	10 (5.7)	20 (5.1)	30 (5.3)
β-Blocker	14 (25.0)	27 (23.3)	51 (22.5)	22 (13.3)	41 (23.3)	73 (18.6)	114 (20.0)
Spironolactone	3 (5.4)	10 (8.6)	13 (5.7)	12 (7.2)	13 (7.4)	25 (6.4)	38 (6.7)
Digoxin	6 (10.7)	18 (15.5)	43 (18.9)	35 (21.1)	25 (14.2)	78 (19.8)	103 (18.1)
Any HF treatment	49 (87.5)	102 (87.9)	206 (90.7)	139 (83.7)	153 (86.9)	345 (87.8)	498 (87.5)

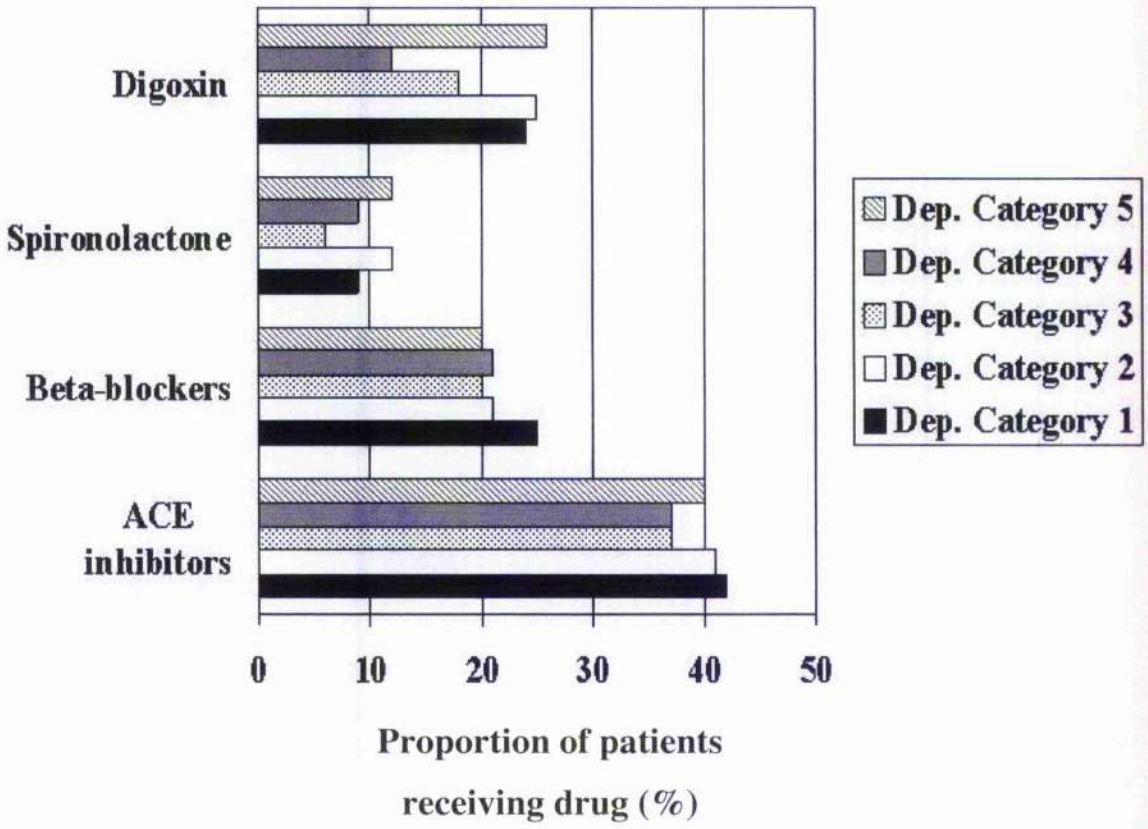
HF = heart failure

Table 36 Pharmacological treatment of heart failure in Scotland between April 1999-March 2000 (men and women combined)

Treatment	Age group						
	45-64	65-74	75-84	>85	<75 yrs	≥75 yrs	All ages
n=	120	248	391	240	377	631	1008
Frusemide	66 (55.0)	146 (58.9)	238 (60.9)	146 (60.8)	216 (57.3)	384 (60.9)	600 (59.5)
Any diuretic	89 (74.2)	200 (80.7)	329 (84.1)	190 (79.2)	293 (77.7)	519 (82.3)	812 (80.6)
ACE Inhibitor	63 (52.5)	124 (50.0)	145 (37.1)	62 (25.8)	188 (49.9)	207 (32.8)	395 (39.2)
Angiotensin receptor blocker	9 (7.5)	10 (4.0)	22 (5.6)	7 (2.9)	19 (5.0)	29 (4.6)	48 (4.8)
β-Blocker	34 (28.3)	61 (24.6)	84 (21.5)	36 (15.0)	96 (25.5)	120 (19.0)	216 (21.4)
Spironolactone	15 (12.5)	26 (10.5)	29 (7.4)	16 (6.9)	41 (10.9)	45 (7.1)	86 (8.5)
Digoxin	23 (19.2)	48 (19.4)	86 (22.0)	50 (20.8)	72 (19.1)	136 (21.6)	208 (20.6)
Any HF treatment	106 (88.3)	216 (87.1)	355 (90.8)	200 (83.3)	328 (87.0)	555 (87.9)	883 (87.6)

HF = heart failure

Figure 7 Prescribing patterns in patients with heart failure, stratified by socioeconomic status



5.4 Discussion

This study has a number of important strengths. Not only does it describe the prevalence and incidence of heart failure across a whole country but it also describes overall contact rates with general practitioners. Furthermore, comparative contact rates for other common cardiovascular (and non-cardiovascular) conditions are reported. Finally, the contemporary pharmacological treatment of heart failure in primary care is also described.

A number of recent prevalence studies in the United Kingdom have focused on the presence of echocardiographic left ventricular systolic dysfunction and not a clinical diagnosis of heart failure *per se*.[120-122] The first of these, from Glasgow, was limited in concentrating on a relatively young age group (1640 persons aged 45-74), when heart failure is known to be uncommon before the age of 70 years (as confirmed in the present study).[121] The second report from Poole in England examined 817 subjects aged 70-84 years.[122] Another more recent survey examined 3960 patients ≥ 45 years, but, like the former studies, was limited to a single urban area (the West Midlands of England).[120] Other studies in the United Kingdom have usually involved only a small number (one to three) of General Practices and/or relied on diuretic prescription as a surrogate for heart failure.[105-108] Recording of concomitant medical problems, concomitant drug therapy and the frequency and nature of contacts (surgery or office visits, home visits, out of hours visits) has been limited or absent.[105-108]

It is difficult to precisely compare my findings to prior studies as many of these did not include men and women and/or the whole population age range. Nevertheless, looking at men aged 0-74 years, the prevalence rate (0.32%) was very close to that found in the Rochester epidemiology project (0.33%).[103;104] The proportions for females were 0.28% in Scotland and 0.21% in Rochester. The National Health and Nutrition Examination Survey (NHANES) investigators reported a prevalence of 1.1% in men and 1.0% in women aged 25-74 years in the USA.[118] The prevalence in men aged 45-74 years in the current study was 0.92% and 0.78% in women. I also had reasonably close agreement with another north European study, the Rotterdam study, which reported a prevalence of 3.4% in persons aged 65-84 years [111] (compared to 3.6% in the same age group in my study). On the other hand, a study from Copenhagen reported the prevalence of heart failure signs and symptoms in 3 GP practices was 6.4% in patients over 50 years. This is much higher than

the prevalence in CMR (1.8% in patients over 45 years).[124] Another national primary care survey from southern Europe also reported discrepant findings. The Epidemiologia da Insuficiência Cardiaca a Aprendizagen (EPICA) investigators reported a prevalence of heart failure in men aged >25 years of 4.33%. The prevalence in women was 4.38%.[110]

The deficiencies in existing epidemiological investigations of heart failure are even more apparent when it comes to incidence studies with only one Finnish, two U.K. and one US study reported until recently.[125-127;129;350] The Finnish and American studies were confined to a limited geographical area (four rural communities in eastern Finland and Olmsted County in Minnesota).[127;129;350] Of the two UK studies, one was hospital based, was limited to part of London, and adopted an unusually broad definition of heart failure (including heart failure arising as a complication during hospitalisation with an acute coronary syndrome).[125] The second UK study used data from the UK General Practice Research Database to describe the incidence of newly diagnosed heart failure during 1996.[126] That study did not, however, describe pharmacological treatment. The incidence rate of heart failure in the Scottish population was 1.8/1000 in males and 2.2 per 1000 in females, and this figure is in keeping with the previous estimates from the UK (1.4 and 1.2/1000)[125], Finland (1.0 and 4.0/1000)[127] and the USA (3.4 and 2.4/1000)[129].

What appears to be different at first sight between this study and previous studies is the higher overall prevalence and incidence of heart failure in women compared to men. This, however, is likely to reflect the wider age range included in my study, compared to most others, and the predominance of women over men with heart failure in the very elderly segment of the population.[351;352]

The lack of information on contact rates in primary care has been a surprising gap in the literature on heart failure. [353] I found that the contact rate is 2-3 times the prevalence, that is, patients average 2-3 heart failure related contacts, per year, with their GP. This rate was remarkably consistent between men and women and across all age groups.

Not only are there few data on the rates of consultation with GPs but there is also little information on the reasons for consultation.[354;355] I found that lower respiratory tract infection was the single most common problem recorded by GPs in both men and women with heart failure. The potential importance of this is suggested by the knowledge that pulmonary infection is a commonly recorded precipitant of heart failure hospitalisation.[356;357] These two observations underscore the importance of influenza and

pneumococcal immunisations in patients with heart failure.[358;359] The other major co-morbidities reflect the most common causes of heart failure (coronary artery disease and hypertension), other smoking related illnesses (such as COPD) and degenerative diseases of ageing (back problems, osteoarthritis).

Another gap in our knowledge has been how the primary care burden of heart failure compares to that of other cardiovascular and non-cardiovascular conditions.[354;355] Consultation rates for heart failure were much lower than those for angina and, especially, hypertension in patients < 75 years. Thereafter heart failure consultation rates exceeded those for angina and by the age of 85 or above exceeded those for hypertension also. It is interesting to speculate that the falling prevalence and consultation rates for hypertension and angina, relative to heart failure, in the older age groups may reflect the natural history of coronary heart disease and hypertension progressing to heart failure over time.

Another important feature of this study is the description of the contemporary pharmacological management of heart failure in primary care across a whole country. Though, as expected, most patients had been prescribed a diuretic, there was a striking age differential in the prescription of evidenced-based therapies: older patients were significantly less likely to be prescribed ACE inhibitors, beta-blockers and/or spironolactone. There are a number of possible explanations for these observations. The above treatments are indicated when left ventricular systolic function is reduced and not when it is preserved. Heart failure in the elderly is more often associated with preserved left ventricular systolic function.[352] Digoxin, however, was used at least as commonly in the elderly, yet is also only indicated when left ventricular systolic function is reduced. Perhaps ACE inhibitors, beta blockers and spironolactone have a perceived or real contraindication more frequently in the elderly or are not as well tolerated by the elderly.[352] The other possibility is that these treatments are not offered to the elderly as often they are to younger patients, as has been reported in other conditions.[360] The concern that older patients with heart failure might be inappropriately denied treatments proven to reduce morbidity and mortality is worthy of further investigation. Women also received less evidence-based therapy and this was not wholly explained by the generally older average age of women. Preserved left ventricular systolic function is also more common in women and this could explain at least part of the sex difference in treatment.[351;352] Women may also tolerate these other treatments less well and there is some evidence that this is true for ACE inhibitors.[351;361] Curiously, however, the greatest sex difference in evidence based prescribing was for spironolactone which should be better tolerated by women than men.

This, again, raises the concern, as in other disease areas, that women are under-treated compared to men.[362]

In addition in this study socioeconomically deprived individuals were significantly more likely to develop heart failure, but were significantly less likely to see their general practitioner on an ongoing basis. Contrary to speculation, there was no relationship between general practitioner prescribing practices and socioeconomic status.
Although the finding of an increased incidence of heart failure in socioeconomically deprived individuals has not previously been reported, a study from the United States did demonstrate an inverse association between heart failure incidence and educational attainment.[363] However, my finding is not unexpected given data showing increased heart failure hospitalisations in deprived patients.[143;346]Furthermore, as the risk factors for heart failure (which are similar to those for coronary artery disease) are more prevalent in socioeconomically deprived groups,[113;364] it is entirely plausible that heart failure incidence would be higher in these groups. Despite the marked gradient in incidence, there was only a trend towards differences in prevalence across the deprivation categories. This is not unexpected given that deprived patients have higher case fatality rates and shorter survival times when they do develop heart failure as demonstrated in this study and another Scottish study which examined survival in 66 547 patients hospitalized with heart failure between 1986 and 1995.[143] The finding that socially deprived individuals with heart failure have less ongoing contact with their general practitioners is novel and worrying, particularly since the limited data in this field suggest that socially deprived patients with heart failure have a worse functional status.[365;366] The obvious questions raised by this novel example of Tudor Hart's inverse care relationship are twofold: (1) why does this occur, and (2) what consequences might ensue? There are several potential factors that may contribute to these lower consultation rates. Firstly, illness behaviour is substantially different in deprived groups, fatalism is more common, and individuals often consult non-professionals for health care advice.[348] Secondly, socially deprived patients may seek care in hospital emergency rooms rather than attend their primary care physicians - indeed, this pattern has been observed for other cardiovascular and respiratory illnesses characterized by intermittent acute exacerbations.[367;368] Thirdly, their general practitioners may fail to offer regular follow-up care. However, the comparable rates of prescribing across the social class spectrum argue against this. Although we do not know what consequences may ensue from less frequent follow-up with general practitioners for socioeconomically deprived heart failure patients, other studies suggest that this lack of contact may have important consequences for patients with chronic diseases. For example, patients with heart failure

or asthma who are not seen regularly after hospital discharge are more likely to be re-admitted.[347;369] Moreover, a retrospective analysis of administrative data from Canada found improved survival rates in heart failure patients who were regularly followed by a physician compared to those without ongoing contact (P. Kaul, personal communication). Finally, there is a wealth of evidence that closer follow-up of heart failure patients (either by physicians or by specially trained nurses) does lead to better outcomes.[370] It is thus intriguing to speculate whether disease management programs specifically targeting more deprived individuals with heart failure would improve their prognosis- this is an important hypothesis that needs to be tested. I did not find any evidence of socioeconomic bias in these general practitioners' prescribing patterns. Although there was no information on patient adherence, an earlier study in Scotland did not find any differences in diuretic compliance between deprived and affluent heart failure patients.[346]

As in any study of this type, there are limitations. One is the lack of information on cardiac structure and function, which did not allow differentiation between patients with reduced and preserved left ventricular systolic function. Nevertheless, I have been able to provide information on the community burden of the syndrome of heart failure, rather than left ventricular systolic dysfunction which has been the main focus of most other epidemiological studies. Second, the diagnosis of heart failure was not confirmed independently nor was there data on disease severity.

In summary, this study confirms that heart failure is predominantly a problem of the elderly. When the full age spectrum is accounted for, there are more women than men with heart failure in the population. In the elderly, heart failure is one of the commonest causes of consultation with a GP and is at least as common a cause of consultation as angina and hypertension. There is a marked age discrepancy in prescribing of evidence based treatment, with the elderly receiving less life saving therapy. There is also an independent sex effect with women also receiving less evidence based treatment. These discrepancies merit further investigation.

Although the incidence of heart failure diagnosed in General Practice is significantly higher in socioeconomically deprived individuals, the subsequent follow-up is significantly less frequent. My study has eliminated the prescribing bias hypotheses commonly cited as a potential explanation for the socioeconomic gradients in heart failure. Indeed, it raises another potentially important explanation, that socioeconomically deprived patients may have poorer outcomes because they have less ongoing contact with their general

practitioner. Further studies are required to determine why such patients are followed less closely. Once the mechanisms behind these socioeconomic gradients in heart failure are better understood, programs can then be devised to ensure that outcomes are optimized for all afflicted patients, irrespective of social class.

6 PREVALENCE, INCIDENCE, PRIMARY CARE BURDEN AND MEDICAL TREATMENT OF ATRIAL FIBRILLATION IN SCOTLAND: AGE, SEX AND SOCIOECONOMIC DISPARITIES

6.1 Introduction

Atrial fibrillation is the commonest chronic arrhythmia.[154] As outlined in the literature review the prevalence and incidence of atrial fibrillation are believed to be increasing[171] probably because population age is increasing[371] and survival from conditions predisposing to atrial fibrillation (e.g. coronary heart disease) is improving.[143;156] Atrial fibrillation is associated with significant morbidity and excess mortality, including heart failure and stroke, two of the most disabling and costly cardiovascular conditions known.[186;199] The risk of stroke can be substantially reduced with warfarin.[372] Two recent trials suggest that rate control and anticoagulation are at least as good as rhythm control and medical treatment is the preferred option for most patients with atrial fibrillation.[373;374]
As outlined in the literature review there are many studies examining the prevalence and incidence of atrial fibrillation however only recently have studies which have analysed the prevalence of atrial fibrillation using data from general practices in the UK been published.[158;159;161] In addition there is relatively little contemporary information about the primary care burden and treatment of atrial fibrillation in the community. CMR was analysed to accurately estimate the prevalence, incidence and consultation rates for atrial fibrillation in primary care and also to describe concomitant medical problems and drug therapy.

6.2 Methods

The CMR atrial fibrillation database was used as described in chapter 3.

6.3 Results

6.3.1 Atrial fibrillation Read codes used

The vast majority (99.3%) of contacts were coded as atrial fibrillation (84.6%), atrial fibrillation /atrial flutter (9.8%), paroxysmal atrial fibrillation (3.5%) or atrial flutter (1.4%).

6.3.2 Prevalence of atrial fibrillation

The prevalence of atrial fibrillation was 8.7/1000 and was higher in men (9.4/1000) than women (7.9/1000). Prevalence increased with age from 0.3/1000 in <45 to 30.5/1000 in 65-74 and more than doubling to 70.7/1000 in >85 years (Table 37). Age and sex standardised prevalence of atrial fibrillation decreased with increasing socioeconomic deprivation from 9.2 per 1,000 in the least deprived to 7.5 per 1,000 in the most deprived category (p for trend =0.02). Deprived individuals had an 18% lower prevalence than more affluent individuals (Table 38).

6.3.3 Incidence of atrial fibrillation

The incidence of atrial fibrillation was 0.9/1000 - 1.0/1000 in men and 0.8/1000 in women. Incidence in men increased with age from 0.1/1000 in <45, 3.8/1000 in 65-74 and 8.6/1000 in those >85 years. The corresponding rates for women were 0.0/1000, 2.7/1000 and 7.4/1000, respectively (Table 37). There was no difference in incidence of atrial fibrillation according to deprivation class (Table 38, p for trend =0.537), although the number of cases in each category was small.

Table 37Prevalence, incidence and contact rates per 1,000 population of atrial fibrillation by sex and age group for all CMR practices in Scotland; April 2001-March 2002

	Age group	Population	Number of patients with AF	Prevalence	Number of first diagnoses of AF	Incidence	Number of contacts for AF	Contact rate	No of contacts per patient	No of contacts per patient with first diagnosis of AF	No of contacts per patient with recurrent or persistent AF
Men	<45	110,080	42	0.4	6	0.1	39	0.4	0.93	4.17	0.39
	45 – 54	25,763	126	4.9	20	0.8	116	4.5	0.92	2.35	0.65
	55 – 64	19,929	305	15.3	34	1.7	350	17.6	1.15	2.47	0.98
	65 – 74	13,740	539	39.2	52	3.8	611	44.5	1.13	2.67	0.97
	75 – 84	7,256	532	73.3	54	7.4	545	75.1	1.02	2.85	0.82
	85+	1,628	137	84.2	14	8.6	102	62.7	0.74	2.36	0.56
	65+	22,624	1208	53.4	120	5.3	1258	55.6	1.04	2.72	0.86
	75+	8,884	669	75.3	68	7.7	647	72.8	0.97	2.75	0.77
	All ages	178,396	1681	9.4	180	1.0	1763	9.9	1.05	2.68	0.85
Women	<45	106,743	29	0.3	3	0.0	12	0.1	0.41	1.00	0.35
	45 – 54	25,185	34	1.4	4	0.2	63	2.5	1.85	7.75	1.07
	55 – 64	20,304	127	6.3	12	0.6	118	5.8	0.93	1.75	0.84
	65 - 74	15,959	368	23.1	43	2.7	398	24.9	1.08	2.81	0.85
	75 - 84	11,241	612	54.4	61	5.4	601	53.5	0.98	2.49	0.81
	85+	4,327	284	65.6	32	7.4	201	46.5	0.71	2.59	0.47
	65+	31,527	1264	40.1	136	4.3	1200	38.1	0.95	2.62	0.75
	75+	15,568	896	57.6	93	6.0	802	51.5	0.90	2.53	0.71
	All ages	183,759	1454	7.9	155	0.8	1393	7.6	0.96	2.65	0.76
Both sexes	<45	216,823	71	0.3	9	0.0	51	0.2	0.72	3.11	0.37
	45 – 54	50,948	160	3.1	24	0.5	179	3.5	1.12	3.25	0.74
	55 – 64	40,233	432	10.7	46	1.1	468	11.6	1.08	2.28	0.94
	65 - 74	29,699	907	30.5	95	3.2	1009	34.0	1.11	2.74	0.92
	75 – 84	18,497	1144	61.8	115	6.2	1146	62.0	1.00	2.66	0.82
	85+	5,955	421	70.7	46	7.7	303	50.9	0.72	2.52	0.50
	65+	54,151	2472	45.7	256	4.7	2458	45.4	0.99	2.66	0.80
	75+	24,452	1565	64.0	161	6.6	1449	59.3	0.93	2.62	0.73
	All ages	362,155	3135	8.7	335	0.9	3156	8.7	1.01	2.67	0.81

AF = atrial fibrillation

Table 38 Incidence, prevalence, and contact rates (per 1,000 population), stratified by socioeconomic status for the year April 2001-March 2002

Deprivation category	Population	Number of patients with AF	Prevalence	Age and sex standardised prevalence	Number of first diagnoses of AF	Incidence	Age and sex standardised incidence	Number of contacts for AF	Contact rate	Age and sex standardised contact rate	Number of contacts per patient
1 (least)	79,765	709	8.9	9.2	60	0.8	0.6	669	8.4	8.6	0.94
2	70,368	653	9.3	8.9	74	1.1	0.8	641	9.1	8.7	0.98
3	110,216	992	9.0	9.5	113	1.0	0.9	1010	9.2	9.6	1.02
4	68,835	549	8.0	7.5	59	0.9	0.8	644	9.4	8.8	1.17
5 (most)	31,520	229	7.3	7.5	29	0.9	0.8	191	6.1	6.1	0.83
Rate ratio (95% confidence interval) for deprivation category 5 versus 1			0.82 (0.70-0.95)	0.82 (0.72-0.92)		1.22 (0.79-1.91)	1.25 (0.74-1.76)		0.72 (0.67-0.76)	0.71 (0.66-0.76)	0.88 (0.82-0.94)
P value for trend			0.002	0.02		0.537	0.7		<0.001	0.02	0.01

AF = atrial fibrillation

6.3.4 Contact-rates for atrial fibrillation

The one-year contact-rate was higher in men (9.9/1000) than women (7.6/1000), Table 37. The contact-rate varied with age, initially increasing from 0.2/1000 in <45, to 62.0/1000 in 75-84 but fell to 50.9/1000 in >85 years. The average number of contacts per patient with newly diagnosed atrial fibrillation was highest in men <45 years (4.17) and women aged 45-54 years (7.75).

The proportions of women consulting >65 years and >75 years were 86.1% and 57.6%, respectively (the corresponding proportions in men were 71.4% and 36.7%, respectively). Age and sex standardised contact-rates fell from 8.6 per 1,000 in the most affluent group to 6.1 per 1,000 in the most deprived group (Table 38). Deprived individuals had a 29% lower contact-rate than more affluent individuals (p for trend =0.02).

Comparison with contact-rates for angina and heart failure.

The contact-rates for heart failure and angina in 2002 were 14.3/1000 and 17.0/1000, respectively, for men and 14.6/1000 and 13.5/1000, respectively, for women. Consultation rates for atrial fibrillation were lower than those for angina in younger individuals and similar to angina in those >75 years (Figure 8 and 9). Consultation rates for atrial fibrillation were considerably lower than those for heart failure in men and women >65 years.

Figure 8 Age stratified GP consultation rates per 1000 population for heart failure, angina and atrial fibrillation in men.

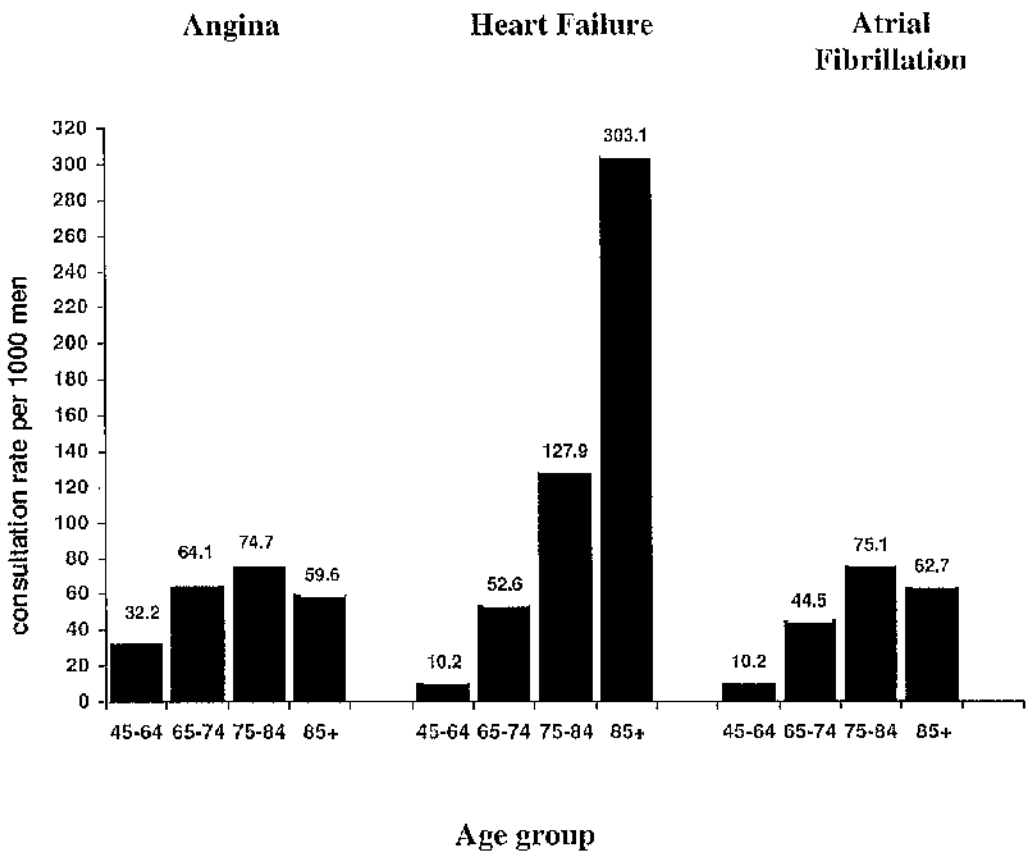
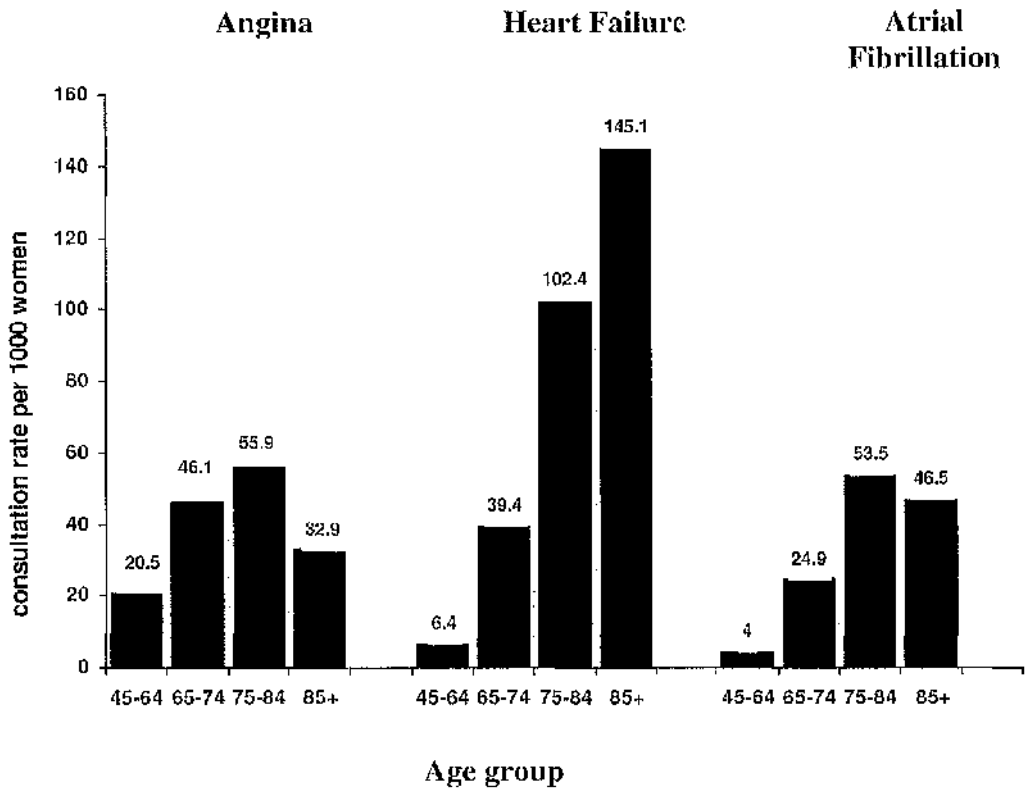


Figure 9 Age stratified GP consultation rates per 1000 population for heart failure, angina and atrial fibrillation in women



6.3.5 Top ten concomitant diagnoses in patients with atrial fibrillation

In both sexes, hypertension was the most common concomitant diagnostic coding (in 24.8% of men and 27.1% of women, Table 39). Respiratory, infection, coronary heart disease and heart failure were the next most commonly coded conditions. Stroke was only recorded in 4.7% of men and women. Atrial fibrillation was the nineteenth most common reason for consulting a GP in men 65-74 years and the 21st most common reason in those >85. In women 65-74 years atrial fibrillation was in position 49 while in women >85 it was in position 31.

Table 39 Proportion of atrial fibrillation patients seen with specified condition/illness; April 2001 March 2002

Condition/illness	Men	Women
Hypertension	24.8%	27.1%
Lower respiratory tract infection	16.5%	20.4%
Coronary heart disease – miscellaneous	16.2%	12.6%
Heart failure	15.3%	19.8%
Upper respiratory tract infection (excluding sore throat)	9.5%	11.1%
Chest pain	9.2%	9.1%
Miscellaneous	9.2%	9.4%
Breathlessness	9.2%	13.2%
Back problems	9.2%	-
Diabetes	8.2%	-
Urinary tract infection	-	11.9%
Stroke	4.7%	4.7%

6.3.6 Concomitant medication

71% of patients with atrial fibrillation received rate-controlling medication: beta-blocker 28%, rate limiting calcium channel blocker 42% and digoxin 43%. Of men, (Table 40) 31% received one rate-limiting agent and 38% >2 drugs. The respective proportions for women (Table 41) were 39% and 35%. 19% of patients received an antiarrhythmic drug. 42% of patients received warfarin, 44% aspirin and 78% ≥1 of these.

Sex, age and socioeconomic differences in prescribing

On multivariable modelling, after adjusting for deprivation, age and GP practice, women were 25% more likely to receive digoxin and 18% less likely to receive warfarin compared to men (Table 42). On multivariable modelling, men and women ≥75 years were more likely than those <75 years to receive digoxin (men OR 1.41 95%CI 1.14, 1.74; women OR 1.88, 95% CI 1.50, 2.37) and aspirin (2.04 (1.66, 2.51); 1.79 (1.42, 2.25)) and less likely to receive an antiarrhythmic drug (0.62 (0.48, 0.81); 0.52 (0.39, 0.70)) or warfarin (0.74 (0.60, 0.91); 0.58 (0.46, 0.73)). After adjusting for age, sex and GP, there was no socioeconomic gradient in prescribing.

Table 40 Pharmacological treatment of men with atrial fibrillation April 2001-March 2002

Treatment	Age group								
	<45	45-54	55-64	65-74	75-84	85+	<75 yrs	≥75 yrs	all ages
n=	42	126	305	539	532	137	1012	669	1681
	n (%)								
β-Blocker	12 (28.6)	46 (36.5)	107 (35.1)	181 (33.6)	139 (26.1)	13 (9.5)	346 (34.2)	152 (22.7)	498 (29.6)
Calcium channel blockers*	17 (40.5)	67 (53.2)	153 (50.2)	262 (48.6)	206 (38.7)	23 (16.8)	499 (49.3)	229 (34.2)	728 (43.3)
Digoxin	2 (11.1)	33 (26.2)	112 (36.7)	216 (40.1)	223 (41.9)	73 (53.5)	363 (35.9)	296 (44.2)	659 (39.2)
Class I antiarrhythmics †	2 (4.8)	6 (4.8)	16 (5.2)	15 (2.8)	9 (1.7)	0 (0)	39 (3.9)	9 (1.3)	48 (2.9)
Amiodarone	5 (11.9)	17 (13.5)	49 (16.1)	64 (11.9)	56 (10.5)	11 (8.0)	135 (13.3)	67 (10.0)	202 (12.0)
Sotalol	3 (7.1)	10 (7.9)	26 (8.5)	30 (5.6)	26 (4.9)	2 (1.5)	69 (6.8)	28 (4.2)	97 (5.8)
Warfarin	10 (23.8)	43 (34.1)	146 (47.9)	292 (54.2)	238 (44.7)	37 (27.0)	491 (48.5)	275 (41.1)	766 (45.6)
Aspirin	6 (14.3)	32 (25.4)	114 (37.4)	209 (38.8)	275 (51.7)	79 (57.7)	361 (35.7)	354 (52.9)	715 (42.5)
Clopidogrel	0 (0.0)	3 (2.4)	2 (0.7)	21 (3.9)	14 (2.6)	4 (2.9)	26 (2.6)	18 (2.7)	44 (2.6)
Any antithrombotic ‡	14 (33.3)	64 (50.8)	223 (73.1)	451 (83.7)	452 (85.0)	110 (80.3)	752 (74.3)	562 (84.0)	1314 (78.2)
Negative chronotropes ¶	18 (42.9)	82 (65.1)	213 (69.8)	389 (72.2)	365 (68.6)	86 (62.8)	702 (69.4)	451 (67.4)	1153 (68.6)
Any antiarrhythmic §	10 (23.8)	31 (24.6)	84 (27.5)	105 (19.5)	91 (17.1)	13 (9.5)	230 (22.7)	104 (15.5)	334 (19.9)

*** Excluding dihydropyridines**
† Includes quinidine, disopyramide, propafenone and flecainide
‡ Warfarin or aspirin or clopidogrel
¶ β-blocker or rate limiting calcium channel blocker or digoxin
§ Class 1 antiarrhythmic or amiodarone or sotalol

Table 41 Pharmacological treatment of women with atrial fibrillation April 2001-March 2002

Treatment	Age group								
	<45	45-54	55-64	65-74	75-84	85+	<75 yrs	≥75 yrs	all ages
n=	29	34	127	368	612	284	558	896	1454
	n (%)								
β-Blocker	1 (3.4)	6 (17.6)	43 (33.9)	96 (26.1)	178 (29.1)	45 (15.8)	146 (26.2)	223 (24.9)	369 (25.4)
Calcium channel blockers *	5 (17.2)	11 (32.4)	73 (57.5)	165 (44.8)	267 (43.6)	71 (25.0)	254 (45.5)	338 (37.7)	592 (40.7)
Digoxin	2 (6.9)	11 (32.4)	43 (33.9)	159 (43.2)	303 (49.5)	177 (62.3)	215 (38.5)	480 (53.6)	695 (47.8)
Class I antiarrhythmics †	3 (10.3)	4 (11.8)	8 (6.3)	13 (3.5)	8 (1.3)	1 (0.4)	28 (5.0)	9 (1.0)	37 (2.5)
Amiodarone	2 (6.9)	6 (17.6)	13 (10.2)	47 (12.8)	73 (11.9)	12 (4.2)	68 (12.2)	85 (9.5)	153 (10.5)
Sotalol	2 (6.9)	2 (5.9)	12 (9.4)	26 (7.1)	29 (4.7)	7 (2.5)	42 (7.5)	36 (4.0)	78 (5.4)
Warfarin	5 (17.2)	14 (41.2)	62 (48.8)	176 (47.8)	246 (40.2)	60 (21.1)	257 (46.1)	306 (34.2)	563 (38.7)
Aspirin	2 (6.9)	4 (11.8)	48 (37.8)	151 (41.0)	290 (47.4)	159 (56.0)	205 (36.7)	449 (50.1)	654 (45.0)
Clopidogrel	0 (0.0)	0 (0.0)	4 (3.1)	13 (3.5)	19 (3.1)	8 (2.8)	17 (3.0)	27 (3.0)	44 (3.0)
Any antithrombotic ‡	7 (24.1)	16 (47.1)	96 (75.6)	308 (83.7)	495 (80.9)	209 (73.6)	427 (76.5)	704 (78.6)	1131 (77.8)
Negative chronotropes ¶	7 (24.1)	16 (47.1)	91 (71.1)	279 (75.8)	466 (76.1)	216 (76.1)	393 (70.4)	682 (76.1)	1075 (73.9)
Any antiarrhythmic §	7 (24.1)	11 (32.4)	32 (25.2)	81 (22.0)	108 (17.6)	20 (7.0)	131 (23.5)	128 (14.3)	259 (17.8)

*** Excluding dihydropyridines**
† Includes quinidine, disopyramide, propafenone and flecainide
‡ Warfarin or aspirin or clopidogrel
¶ β-blocker or rate limiting calcium channel blocker or digoxin
§ Class 1 antiarrhythmic or amiodarone or sotalol

Table 42 Relative risk of being prescribed various medication for atrial fibrillation for women compared to men*, for men and women aged over 75 years compared to under 75 years† and for Carstairs deprivation category 5 compared to Carstairs deprivation category 1¶

	Women versus men	≥75 years versus < 75 years		Carstairs deprivation category 5 versus 1
		Men	Women	
	OR	OR	OR	OR
β-blockers	0.92 (0.78, 1.09)	0.55 (0.44, 0.70)	0.89 (0.69, 1.16)	0.72 (0.43, 1.21)
Calcium channel blockers §	1.05 (0.91, 1.24)	0.51 (0.42, 0.64)	0.69 (0.55, 0.87)	0.73 (0.45, 1.19)
Digoxin	1.25 (1.07, 1.46)	1.41 (1.14, 1.74)	1.88 (1.50, 2.37)	1.00 (0.62, 1.63)
Class I antiarrhythmics ‡	1.34 (0.84, 2.13)	0.32 (0.15, 0.67)	0.14 (0.06, 0.32)	0.62 (0.14, 2.82)
Amiodarone	0.94 (0.74, 1.19)	0.73 (0.53, 1.01)	0.77 (0.54, 1.03)	1.10 (0.49, 2.48)
Sotalol	1.11 (0.80, 1.54)	0.60 (0.38, 0.96)	0.48 (0.30, 0.79)	0.51 (0.18, 1.50)
Warfarin	0.82 (0.70, 0.96)	0.74 (0.60, 0.91)	0.58 (0.46, 0.73)	1.21 (0.75, 1.96)
Aspirin	0.93 (0.80, 1.08)	2.04 (1.66, 2.51)	1.79 (1.42, 2.25)	0.78 (0.48, 1.26)
Any antithrombotic **	0.85 (0.70, 1.03)	1.81 (1.40, 2.35)	1.11 (0.85, 1.45)	1.11 (0.61, 2.03)
Negative chronotropes ††	1.28 (1.08, 1.51)	0.90 (0.72, 1.12)	1.33 (1.03, 1.72)	0.97 (0.56, 1.70)
Any antiarrhythmic ¶¶	1.03 (0.85, 1.24)	0.62 (0.48, 0.81)	0.52 (0.39, 0.70)	0.80 (0.42, 1.50)

*** Adjusted for practice, age, and deprivation category**
† Adjusted for practice and deprivation category
¶ Adjusted for age, sex and practice
§ Excluding dihydropyridines
‡ Includes quinidine, disopyramide, propafenone and flecainide
**** Warfarin or aspirin or clopidogrel**
†† β-blocker or rate limiting calcium channel blocker or digoxin
¶¶ Class 1 antiarrhythmic or amiodarone or sotalol

6.4 Discussion

The overall prevalence of atrial fibrillation in Scotland in 2001-2002 was 8.7/1000, was higher in men than women (and in the less compared to the more socioeconomically deprived) and increased strikingly with age (to 64/1000 in those >75 years). Digoxin was used much less commonly, and rate-limiting CCBs and beta-blockers more commonly, when compared to results of older studies. Women and older individuals were, however, less likely to be prescribed warfarin and more likely to be prescribed digoxin than a beta-blocker or rate-limiting calcium channel blocker for rate control.

Prevalence

Other UK primary care studies have reported on the prevalence of atrial fibrillation. A study of the records of 4,522 patients ≥50 years in two GPs in West Birmingham taking drugs relevant to the treatment of atrial fibrillation, showed that 111 (2.4%) had the arrhythmia, indicating a similar prevalence to that in those in CMR ≥45 years (2.1%).[176] Electrocardiographic screening of 4,843 subjects in 26 GPs in Northumberland, England, revealed a 4.7% prevalence of atrial fibrillation in individuals > 65 years, comparable to the 4.6% prevalence in the same age group in CMR.[160] The prevalence of atrial fibrillation was estimated from the computer records of 211 GPs in England and Wales 1994-1998, using the GP Research Database (GPRD).[159] The prevalence of atrial fibrillation in 1994 was very similar to that in CMR but the prevalence in 1998 was considerably higher e.g. 9.5% in men and 7.2% in women 75-84 years, compared to 7.3% and 6.2%, respectively. The prevalence of Read-coded atrial fibrillation in 131 GPs included in the DIN-LINK database increased from 1994 to 2003 - from 0.84% to 1.49% in men and from 0.83% to 1.29% in women.[158] The overall prevalence in the DIN-LINK database, as well as the only age-specific prevalence reported (13.2% in men and 11.0% in women ≥85 years in 2003 compared to 8.4% and 6.6%, respectively, in my study), was considerably higher than in CMR, as well as the other UK studies. Even taking account of the increase in recorded prevalence that has occurred over time, the prevalence in CMR still seems lower than that found in the DIN-LINK database. One possible explanation is that my analysis only included patients consulting their GP (for any reason) during the year of study. Consequently, a patient with atrial fibrillation who did not have a GP contact for any reason in the period April 2001-March 2002 would not have been identified. On the other hand, the analyses of the epidemiology of heart failure and angina using CMR data as

discussed in earlier chapters have given estimates very consistent with those from other parts of the UK and elsewhere. [330;375] Geographical variation and, particularly, differences in socioeconomic status (see below) might also have accounted for some of the differences observed. The prevalence in Scotland was similar to that found in a primary care study in the Netherlands[162] and a report from the Kaiser Permanente system in Northern California[163].

I found that the prevalence of atrial fibrillation fell with increasing socioeconomic deprivation, which has not been reported before and which contrasts with other cardiovascular disorders. Possible reasons for the higher recorded prevalence of atrial fibrillation in more affluent patients may be higher rates of certain types of contact with GPs leading to diagnosis (e.g. greater uptake of "health screening" and more recording of electrocardiograms) and reduced survival in more deprived patients with atrial fibrillation.

Incidence

There are few studies reporting the incidence of atrial fibrillation. The incidence of atrial fibrillation in patients 40-89 years was estimated to be 1.7 per 1000 person-years in the GPRD in 1996.[181] This was comparable to the 2 per 1000 per year incidence in patients aged 45-84 years in CMR. However, the Framingham Heart[182], Cardiovascular Health (CHS)[183] and Olmsted County studies[180], all from the USA, reported much higher incidence rates than either CMR or the GPRD. This can be explained by methods of ascertainment. In the CMR study and in the GPRD analysis only patients who attend their GP with symptoms or who had an incidental finding of atrial fibrillation would have been identified. By contrast, in the studies from the USA, either regular examination (including recording of an ECG) of subjects or examination of hospital records and other physician records was conducted over a long period of follow-up.

Primary care burden

There is little information on the health care burden created by atrial fibrillation in general practice. Patients with atrial fibrillation have few contacts with their GP - approximately one per year – and atrial fibrillation was not one of the common reasons for a patient to contact their GP. The consultation rate for atrial fibrillation was less than that for angina in subjects < 75 years but greater than for angina above that age; the contact rate for atrial fibrillation was much less than that for heart failure. These data, however, underestimate the complete community burden related to atrial fibrillation as many patients in Scotland at the time of this survey had anticoagulation monitoring in hospital-based clinics.

Medication

The few prior reports on the pharmacological treatment of atrial fibrillation have focussed upon the use of antithrombotic therapy. Observations from this Scottish study confirm the finding of other recent studies from the UK that about 40% of patients receive warfarin,[158;176;181] a considerably higher proportion than reported in earlier studies.[160] Although we do not know what proportion of patients should have been treated with warfarin (because we did not know which of our patients had an indication or contraindication to warfarin), other investigators have estimated that between 40-60% of patients might benefit from anticoagulation. [160;376] Paradoxically, however, warfarin was less likely to be prescribed in women and in the elderly, both of which are at greater risk of stroke. This has been a consistent finding in both older and more recent studies and suggests that there is still an educational deficit in these respects.[377]

There is much less recent information on the use of other medications to treat atrial fibrillation in primary care. I found that 71% of patients were treated with an agent that controls ventricular rate: 43% digoxin, 42% a calcium channel blocker and 28% a beta-blocker. This is a quite different pattern than in older studies which showed that digoxin was the most common agent of this type used.[176] As recently as 1996, digoxin was used in approximately 70% of cases in the GPRD.[181] Recent recommendations preferring calcium channel blockers and beta-blockers for rate control may, therefore, have influenced clinical practice.[378] Older patients, however, were less likely to be treated with these more effective agents and were more likely to be treated with digoxin. Older individuals were also less likely to be prescribed antiarrhythmic agents. Duration of atrial fibrillation and differential referral to secondary care may explain some of the age related differences in prescribing.

It is interesting, however, to contrast prescribing in Scotland with the rest of Europe. A recent Euro Heart Survey, conducted 2003-2004, described the treatment of atrial fibrillation in secondary care in 35 countries. Twenty three per cent of patients with persistent and 50% of patients with permanent atrial fibrillation were prescribed digoxin.[379] A beta-blocker (excluding sotalol), was used as an anti-arrhythmic or rate-controlling agent in 30% of patients with persistent or permanent atrial fibrillation, (which is similar to Scotland) but only 10% of these patients were prescribed a rate-limiting calcium channel blocker, a much lower rate than in Scotland.

Also of interest was the finding that, although prevalence and contact rates differed according to socioeconomic status, treatment did not. This is in keeping with prior findings

in other disease areas and may relate to the greater use of secondary care by more deprived individuals.[330;375]

Limitations

Atrial fibrillation is frequently asymptomatic[380] and cases may be missed if the patient is not examined or an ECG recorded e.g. atrial fibrillation was an incidental finding on electrocardiography in 12% of cases in the CHS[183]. Also, many cases are paroxysmal. Consequently, the findings in this study almost certainly underestimate the prevalence and incidence of all types of atrial fibrillation.

Summary

I have confirmed the higher prevalence and incidence of atrial fibrillation with increasing age and in men. I have made the novel observation that the prevalence of atrial fibrillation fell with increasing socioeconomic deprivation. This unexpected finding deserves further investigation as it probably reflects poorer detection, prognosis or both in more deprived individuals. I have shown that the rate of prescription of warfarin was higher than in past studies and that calcium channel blockers and beta-blockers are now more commonly (and digoxin less commonly) used for rate control that previously reported. Women and older individuals, however, were less likely to be prescribed warfarin and older subjects less likely to be prescribed more effective rate-controlling treatment with a calcium channel blocker or a beta-blocker. This suggests that there is still a need for education regarding the risks and benefits of the pharmacological treatments of atrial fibrillation in women and the elderly.

7 TRENDS IN HOSPITAL DISCHARGE RATES FOR SUSPECTED ACUTE CORONARY SYNDROMES BETWEEN 1990 AND 2000: STEEP DECLINE IN ACUTE MYOCARDIAL INFARCTION AND MARKED INCREASES IN ANGINA AND OTHER CHEST PAIN

7.1 Introduction

As outlined in the literature review much has been written about the incidence of, and case-fatality related to, acute myocardial infarction (AMI), however there is little information on the clinical epidemiology of hospitalised angina and other types of chest pain.[62-64;66;70;72;77;80;81;94;381;382] This is surprising. Many recent clinical trials have focused on hospitalised angina yet the public health impact and cost of the resulting new treatments are impossible to assess without relevant epidemiological data.[383-389] Similarly, while it is widely perceived that chest pain has been an important contributor to the increase in emergency medical admissions documented in many "developed" countries over the past decade, hospital admissions rates for this problem, and associated resource utilisation, have not been documented.[367;390;391] Recent trends in the population discharge rates for AMI, angina and chest pain (collectively referred to as "suspected acute coronary syndromes") over the period 1990 to 2000 was examined.

7.2 Methods

A retrospective cohort study of all hospital discharges in Scotland (population 5.1 million) between the January 1990 and December 2000 was carried out. The SMR acute coronary syndrome database was used as described in chapter 3.

7.3 Results

7.3.1 Baseline characteristics

Table 43 shows the baseline characteristics of the 225,512 individuals hospitalised as an emergency with a *first* suspected acute coronary syndrome, between January 1990 and December 2000. The discharge diagnosis was AMI in 96,026 (43%) patients, angina in 37,403 (17%) and other chest pain in 92,083 (41%).

Patients with chest pain were younger than those with hospitalised angina or AMI. Patients with angina were an average of 11 years older ($p<0.001$), and those with AMI 13 years older, than patients with chest pain ($p<0.001$). A substantially higher proportion of patients with chest pain were aged less than 55 years (52%), compared to those hospitalised with angina (20%) or AMI (16%).

The proportions of men and women in the three diagnostic categories varied according to age. There were fewer women than men amongst those aged less than 55 years hospitalised with angina or with AMI. This sex imbalance was not as notable in patients hospitalised with chest pain. Conversely, there were proportionately more women aged over 75 years, across all three diagnostic categories.

Compared to patients with chest pain, patients with an AMI or angina were more likely to have a prior admission with diabetes, cerebrovascular disease, peripheral arterial disease, heart failure, hypertension, atrial fibrillation, renal failure or respiratory disease. For example patients with angina were nearly twice as likely to have a prior admission with stroke (OR 2.1; 95% CI 1.9-2.2) or heart failure (OR 1.9; 95% CI 1.7-2.0) and patients with AMI were 50% more likely to have a prior admission with diabetes (OR 1.5; 95% CI 1.5-1.6), than patients with chest pain.

Table 43 Baseline characteristics of 225,512 patients with suspected acute coronary syndrome

	All possible ACS (n=225,512)		Acute myocardial infarction (n=96,026)		Angina (n=37,403)		Chest pain (n=92,083)	
	Men	Women	Men	Women	Men	Women	Men	Women
Total 1990-2000	122618 (54%)	102831 (46%)	55999 (58%)	40027 (42%)	18880 (50%)	18523 (50%)	47802 (52%)	44281 (48%)
Mean (median) age (yrs)	60 (61)	64 (67)	65 (65)	72 (73)	64 (64)	68 (69)	53 (52)	56 (56)
Age group (%)								
< 55 years	43670 (36)	27360 (27)	12332 (22)	3121 (8)	4550 (24)	3026 (16)	26788 (56)	21213 (48)
55-64 years	29252 (24)	19287 (19)	14530 (26)	6475 (16)	5175 (27)	4101 (22)	9547 (20)	8710 (20)
65-74 years	28770 (24)	24470 (24)	16493 (30)	11992 (30)	5366 (28)	5318 (29)	6911 (15)	7160 (16)
75-84 years	17254 (14)	22556 (22)	10332 (18)	12782 (32)	3172 (17)	4596 (25)	3750 (8)	5179 (12)
≥85 years	3735 (3)	9158 (9)	2312 (4)	5657 (14)	617 (3)	1482 (8)	806 (2)	2019 (5)
Deprivation categories (%)								
I- least deprived	19531 (16)	15727 (15)	9517 (17)	6529 (16)	2852 (15)	2632 (14)	7162 (15)	6566 (15)
II	22688 (19)	18586 (18)	11084 (20)	7669 (19)	3471 (18)	3298 (18)	8133 (17)	7618 (17)
III	23746 (19)	20047 (20)	11028 (20)	7955 (20)	3690 (20)	3658 (20)	9028 (19)	8434 (19)
IV	24817 (20)	21258 (21)	11148 (20)	8288 (21)	3901 (21)	4008 (22)	9768 (20)	8962 (20)
V- most deprived	27848 (23)	25143 (25)	11405 (20)	8744 (22)	4202 (22)	4483 (24)	12241 (26)	11917 (27)
Unassigned	4051 (3.3)	2070 (2.0)	1817 (3.2)	842 (2.1)	764 (4.0)	44 (2.4)	1470 (3.1)	784 (1.8)
Prior admission (%)								
Diabetes	3071 (3)	3231 (3)	1487 (3)	1582 (4)	656 (4)	665 (4)	928 (2)	985 (2)
Malignancy	5285 (4)	5393 (5)	1951 (4)	1712 (4)	1027 (5)	1054 (6)	2307 (5)	2628 (6)
Respiratory disease	3650 (3)	3475 (3)	1842 (3)	1693 (4)	701 (4)	658 (4)	1107 (2)	1124 (3)
CVD	3718 (3)	2651 (3)	1921 (3)	1359 (3)	823 (4)	591 (3)	974 (2)	701 (2)
PAD	4943 (4)	3927 (4)	2345 (4)	1563 (4)	843 (5)	702 (4)	1755 (4)	1662 (4)
Hypertension	3240 (3)	3962 (4)	1368 (2)	1599 (4)	704 (4)	1002 (5)	1168 (2)	1361 (3)
Atrial fibrillation	2314 (2)	2506 (2)	823 (2)	897 (2)	549 (3)	658 (4)	942 (2)	951 (2)
Heart Failure	2825 (2)	3584 (4)	1245 (2)	1649 (4)	670 (4)	848 (5)	910 (2)	1087 (3)
Renal failure	990 (1)	908 (1)	403 (1)	415 (1)	199 (1)	216 (1)	388 (1)	277 (1)

PAD=peripheral arterial disease CVD=cerebrovascular disease

7.3.2 Trends in discharge rates, diagnostic mix and sex and age characteristics

Changes in discharge rates

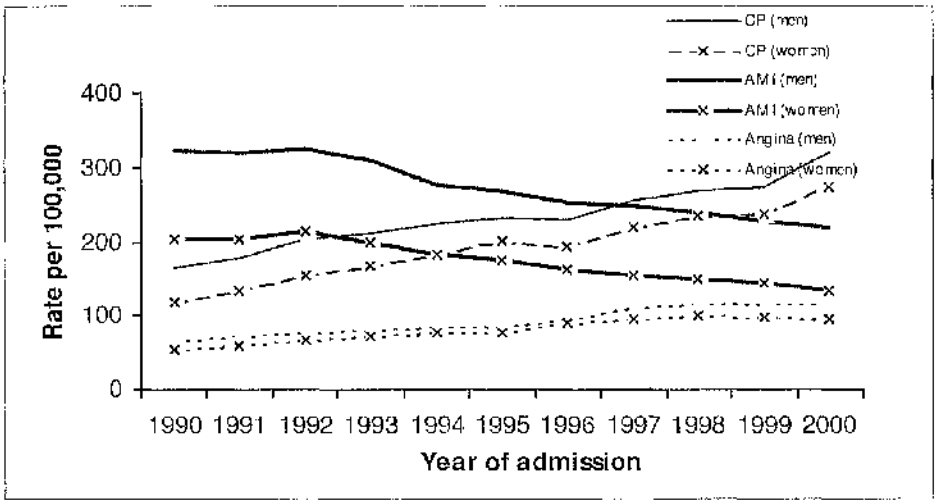
Table 44 and Figure 10 show population discharge rates for all suspected acute coronary syndromes (AMI, angina and chest pain) between 1990 and 2000. Though this increased only modestly, by 25%, the overall change conceals important differences in the diagnostic mix, between men and women and in younger compared to older patients.

Table 44 Number of cases per year and population rates per 100,000 per year, for men and women in each diagnostic group between 1990 and 2000.

	All suspected ACS				Acute myocardial infarction				Hospitalised angina				Chest pain			
	Number of cases		Population rates		Number of cases		Population rates		Number of cases		Population rates		Number of cases		Population rates	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
1990	10202	7861	550	379	5956	4245	322	205	1174	1128	63	54	3072	2488	165	119
1991	10580	8243	570	396	5947	4226	320	204	1327	1218	71	59	3306	2799	178	134
1992	11250	9030	605	434	6056	4426	326	213	1424	1384	77	67	3770	3221	203	154
1993	11222	9172	602	440	5776	4148	310	199	1480	1523	79	73	3966	3501	212	168
1994	10892	9261	583	443	5139	3804	275	182	1567	1641	84	79	4186	3816	223	182
1995	10972	9528	587	456	5032	3671	269	176	1586	1637	85	78	4354	4220	232	202
1996	10816	9275	580	444	4725	3378	254	162	1782	1867	96	90	4309	4030	231	193
1997	11403	9783	612	469	4596	3228	247	155	2063	1978	111	95	4744	4577	254	219
1998	11650	10139	625	485	4485	3111	241	149	2159	2115	116	101	5006	4913	268	234
1999	11466	10021	614	479	4211	3009	226	144	2143	2054	115	98	5112	4958	273	237
2000	12228	10518	655	502	4076	2781	219	133	2175	1978	117	95	5977	5758	319	274
Change %	+19.8	+33.7	+19.1	+32.5	-31.6	-34.5	-32.0	-35.1	+85.3	+75.4	+85.7	+75.9	+94.6	+131.4	+93.3	+130.3

ACS= Acute coronary syndrome

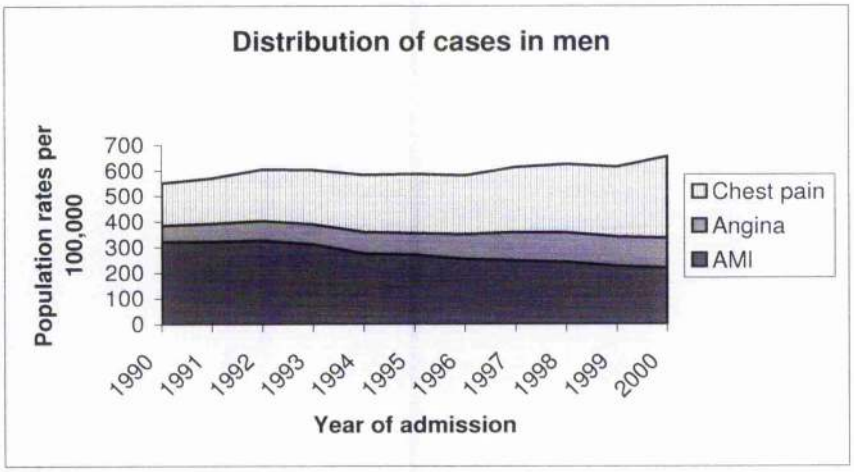
Figure 10 Population discharge rates per 100,000 per year for AMI, angina and chest pain in Scotland, 1990-2000.

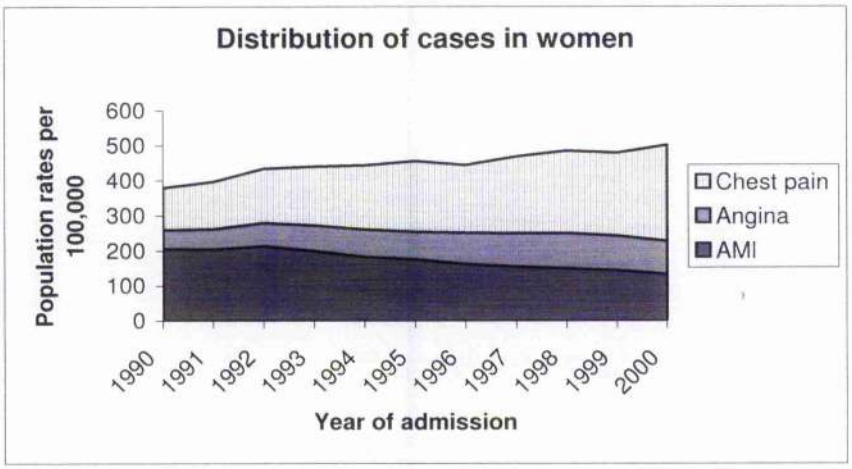


Changes in diagnostic mix

The population discharge rate for AMI fell by 33%, from 260 to 173 per 100,000 between 1990 and 2000 (Figure 11) ($p<0.001$). In contrast, the population discharge rates for angina increased by 79%, from 59 to105 per 100,000 ($p<0.001$), during the same period. The increase in the discharge rate for other chest pain was even more striking at 110% (from 114 to 296 per 100,000) ($p<0.001$).

Figure 11 Trends in population admission rates of different diagnostic groups in men and women between 1990 and 2000





Sex differences

There was a greater relative increase in the population discharge rate for all suspected acute coronary syndromes in women (+33%) than in men (+19%). This was explained, mainly, by a larger rise in the discharge rates for chest pain in women than in men. The relative change in discharge rates for AMI and angina were comparable in men and women overall (Table 44).

Age trends

The age of patients hospitalised with a possible acute coronary syndrome decreased from 1990 to 2000 (from a median of 61 to 59 years in men and from 68 to 65 years in women). This overall change again concealed important differences between diagnostic groups and between men and women. In patients with angina, the median age increased (from 62 to 65 years in men and 67 to 70 years in women). The median age with AMI also increased from 65 to 66 years in men and from 73 to 75 years in women. In contrast, the median age of patients with chest pain decreased (from 52 to 51 years in men and from 56 to 55 years in women).

Figure 12 andFigure 13 summarise how age, sex and diagnostic mix interacted to determine the overall temporal changes in discharge rates for suspected acute coronary syndromes. The greatest change, across all diagnostic sub-groups, occurred in the elderly. The absolute decline in AMI discharge rates was much greater in men than in women in both the younger and older age groups. The absolute increase in angina was slightly greater in men than in women in both the younger and older age groups. There was little difference in the absolute increase in discharge rates for chest pain between men and women in either age category.

Figure 12 Changes in population rates per 100,000 between 1990 and 2000 by age, sex and diagnostic group.

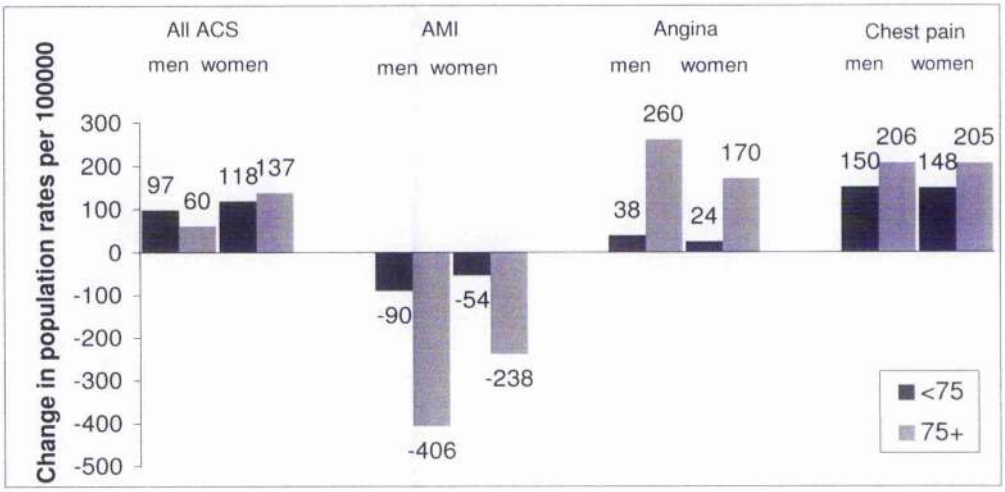
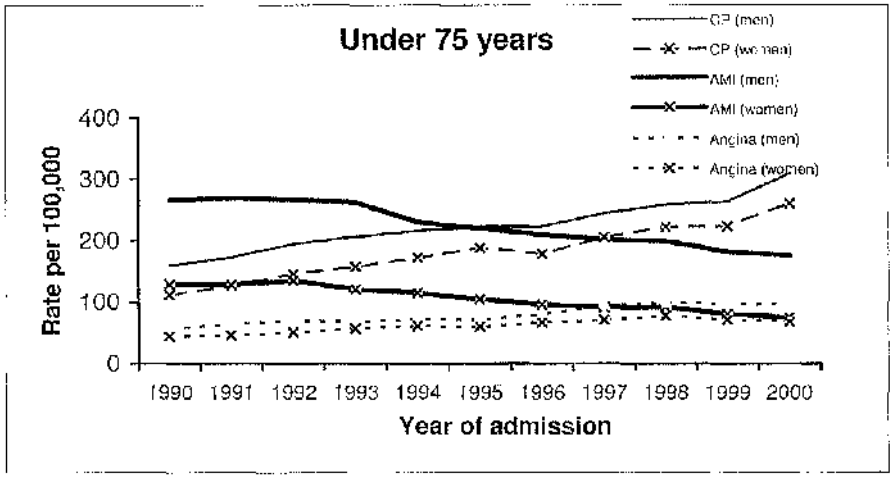
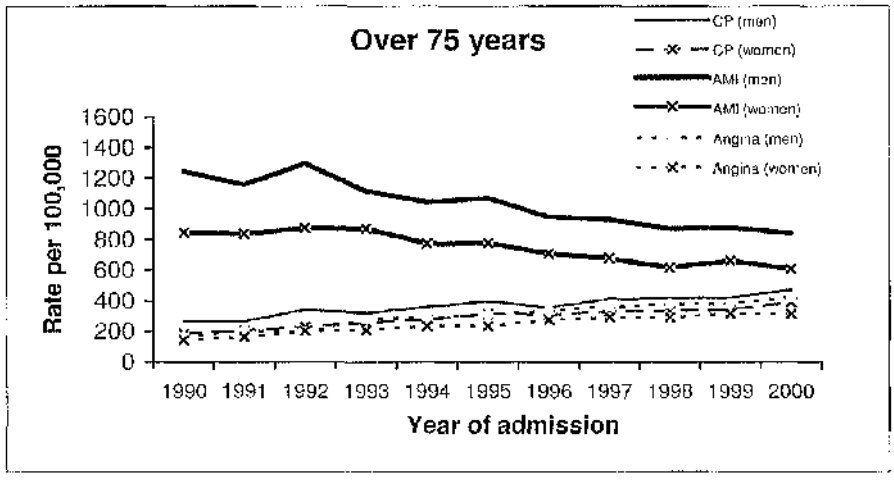


Figure 13 Population discharge rates per 100,000 per year for AMI, angina and chest pain in Scotland, 1990-2000 according to age group.





7.4 Discussion

This analysis of all discharges between 1990 and 2000 for suspected acute coronary syndromes reveals several interesting and important temporal trends.
Firstly, the overall number and rate of emergency hospitalisations has increased only modestly. There was, however, a very striking change in the proportion of patients in each of the diagnostic sub-categories.

The fall in rates of hospitalisation for AMI is in keeping with numerous other reports from many countries.[62;64;66;70;72;77;80;81;381;382] This contrasts markedly with hospitalisation rates for angina which increased by around 80%. There is only one other report of this latter change. The Minnesota Heart Survey reported a 56% increase in the discharge rate for angina in men and a 30% increase in women between 1985 and 1995 (with a 20% decline in the discharge rate for AMI in both men and women).[38] Though the Minnesota group looked at *all* and not just *first* hospitalisations, our findings are consistent.
What has caused this apparent shift from AMI to angina? Increased "survivorship" from previous acute coronary events, a possibility raised by the Minnesota investigators, seems unlikely given that only *first* admissions were included. Another possibility is that the natural history of coronary heart disease has changed. As the pathogenesis of "unstable" angina and AMI are both believed to involve coronary arterial plaque rupture, this hypothesis would require a change in the risk of progression to complete coronary occlusion. The more widespread use of aspirin and other anti-platelet agents could, in theory, account for this.[339] Increased use of early in-hospital anti-thrombotic therapy, aborting AMI, could also have played a role.[392-394]

Less likely is better diagnostic exclusion of infarction, with a "transfer" of patients from the AMI category to the angina category. No major changes in the use of enzymatic or other diagnostic criteria or approaches took place in Scotland during the period of study (and those that have occurred more recently have tended to increase rather than decrease diagnosis of AMI).[395] Similarly, there are no financial influences, relating to reimbursement, on coding in the NHS.

Alternatively, there may have been "threshold" changes for both admission and diagnosis over the period of study. Primary care practitioners may have become more aware of the

clinical importance of unstable angina and the newer treatments available which reduce the risk of infarction and death. They may also have become less happy about excluding the possibility of infarction without a hospital assessment. This may have reduced their threshold for hospital referral and admission. Similar recognition may also have increased in-patient efforts to diagnose and treat angina (resulting in more cases of "chest pain" becoming cases of angina).

The other major and new finding of this study was the striking increase in discharges for chest pain which doubled between 1990 and 2000. There are no similar reports of this change from elsewhere. What is the explanation for this change? Similar influences to those already discussed that may have increased discharges for angina, might also have led to an increase in discharges labelled "chest pain". In other words, the importance of identifying and treating acute coronary events may have resulted in an increase in referrals to hospital and intensified diagnostic effort, leading to more patients having definite angina or AMI excluded. That the overall number of cases of "possible acute coronary syndromes" did not increase much (and that the major change was in the diagnostic label applied at discharge), suggests that the latter change (better diagnosis) had to be the more important one, if this analysis is correct. Of course, this may not be the case and the success of diagnostic triage is best measured by the long-term prognosis of patients with a discharge diagnosis of chest pain.

Whatever the explanation, I have clearly shown two new findings with important clinical implications. The increase in hospitalisations for angina has enormous resource and financial implications, given the proven benefits of certain pharmacological treatments and percutaneous coronary intervention in these patients.[383-386] Conversely, the potential public health benefits are also substantial as these treatments reduce the risk of progression to infarction (with all its consequences), recurrence of angina (and hospital readmission) and improve quality of life.[383 386]

The large increase in hospitalisations for chest pain raises different issues. What exactly is wrong with these patients? Has coronary disease been properly excluded? What is their long-term prognosis? Clearly, if this is a benign syndrome, the need for hospital admission at all must be questioned. The substantial and increasing use of acute hospital beds certainly suggests that chest pain observation units are a potentially attractive alternative to the conventional approach to management of this growing problem.[396-398]

8 SHORT-TERM AND LONG-TERM OUTCOMES IN PATIENTS ADMITTED WITH UNSTABLE ANGINA OR MYOCARDIAL INFARCTION IN SCOTLAND 1990-2000

8.1 Introduction

Every year, hospitals admit large numbers of emergency patients with suspected acute coronary syndromes: about one million in the UK and two million in the US.[397;399-401] This places a massive burden on the health service and such suspected acute coronary syndromes represent a high priority group.[402] By time of discharge, most patients with acute coronary syndrome have a clear diagnosis of acute myocardial infarction or unstable angina. However, the subsequent management plan is crucially dependent on a sound assessment of the individual patient's prognosis.[401-403]

A few small population-based surveys in Australia, Iceland and the UK have suggested that, compared with myocardial infarction, long-term survival in middle aged men is apparently much better for angina, whether defined as ECG abnormalities or "Rose positive angina" on a Rose angina questionnaire with a normal ECG.[5;20;54;404] However, none of these studies specifically examined unstable angina. As discussed in the literature review long-term survival following acute myocardial infarction has been extensively studied, however much less is known about prognosis following emergency admission for unstable angina. In Canada, Chang et al[56] reported a five year case-fatality rate of 19.5% in men and 21.6% in women following unstable angina, compared with 26.8% and 38.8% and respectively following acute myocardial infarction in a large administrative database. Longer term prognosis also reflected associated conditions including age, ventricular function and co-morbidity.[312]

Cardiology has seen a therapeutic revolution since the 1980s. In addition to CABG surgery and angioplasty, a growing armamentarium of effective medical therapies now include thrombolysis, aspirin, beta blockers, glycoprotein receptor antagonists and statins.[388;401-403;405] But has this evidence-based therapy actually benefited ordinary

patients in the general population?[52;56] In spite of the increasingly widespread use of these therapies, there are almost no recent UK data describing survival in unselected patients in a population context. This highlights the practical difficulties of long-term follow-up in large unselected patient cohorts. However, such studies are now increasingly facilitated by the record linkage achieved in Britain and elsewhere.[94;306;406;407] In this present study, short and long-term outcome and prognostic factors have been analysed in this large population-based cohort of unselected patients with a first emergency hospitalisation for suspected acute coronary syndrome between 1990 and 2000 in Scotland.

8.2 Methods

The SMR acute coronary syndrome database was used as described in chapter 3.

8.3 Results

Between 1990 and 2000, 225,512 patients had a first emergency hospitalisation for suspected acute coronary syndrome: 96,026 with acute myocardial infarction (43%), 37,403 with angina (17%) and 92,083 with chest pain (41%). This chapter only considers the patients with an acute myocardial infarction and angina.

Angina patients were slightly younger than those with acute myocardial infarction. The median age of men with angina was 64 years compared to 65 years in men with acute myocardial infarction (women, 69 versus 73 years respectively).(Table 43)

8.3.1 Cause of death

Following a first hospitalisation with acute myocardial infarction 41.1% of patients died within five years. The principal causes of death were acute myocardial infarction (37.8%), other coronary disease (2.7%), other cardiovascular disease (40.6%), cancer (13.6%) and all other causes (5.3%). The proportions were similar in the 21.8% patients who died within five years of their first emergency admission with angina: acute myocardial infarction (28.4%), other coronary heart disease (4.3%), other cardiovascular disease (30.9%), cancer (17.7%) and all other causes (18.7%).

8.3.2 Univariable analysis

8.3.2.1 Short-term case fatality

Crude short-term case-fatality within one month was high in patients with acute myocardial infarction (15.7% in men and 25.7% in women), but low for emergency admissions with angina (2.0% in men and 1.8% in women).

8.3.2.2 Longer-term case fatality

After excluding deaths within 30 days, longer-term crude case-fatality at one, five and ten years in men with angina, was 6.5%, 23.9%, and 39.8%, respectively (6.4%, 23.5% and 41.5% in women). These are very similar to the 6.4%, 21.6% and 36.0% respectively seen in men after a first admission for acute myocardial infarction (and 8.9%, 26.0% and 40.6% respectively in women). Age-specific case-fatality rates were likewise very similar in patients following acute myocardial infarction or angina.

8.3.2.3 Death rates in acute myocardial infarction and angina groups compared with the general population

At five years 25.8% of men with angina and 37.3% with acute myocardial infarction had died. In comparison the five year case fatality rate for a 64 year old man in Scotland (mean age of angina group) was only 15.3%. Likewise in women the five year case fatality rate in the general population was lower (13.2% in a 68 year old and 17.9% in a 72 year old) than that of either angina (25.2%) or acute myocardial infarction (51.7%).

8.3.3 Multivariable analysis

8.3.3.1 Short-term case fatality: age, co-morbidity and sex effects

After adjustment for other factors using logistic regression, short-term case-fatality in both patient groups approximately doubled for each decade of increasing age, and increased by

up to two-fold with a wide range of co-morbidities including cancer, respiratory disease, renal disease and peripheral vascular disease. (Table 45) Adjusted short-term case-fatality following acute myocardial infarction was 22% higher in women than in men, (95% confidence intervals 18%, 27%), but 29% (18%, 40%) lower in women than in men following an angina hospitalisation.

8.3.3.2 Longer-term case fatality: age, co-morbidity and sex effects

As for short term case fatality adjusted case-fatality over five years also doubled for each decade of increasing age, and increased almost two-fold with a wide range of comorbidities. (Table 45) Compared with men, adjusted case-fatality in women was 29% (95% confidence intervals 24%, 33%) lower following angina, but only 7% (4%,10%) lower following acute myocardial infarction.

8.3.3.3 Socioeconomic effects

A modest 9% adverse socio-economic gradient was seen in short-term case-fatality following myocardial infarction but not angina (Table 45) The socioeconomic gradient increased over the longer-term rising to a 22% (16%, 29%) increase in the hazard of death in the most deprived quintile compared with the most affluent following myocardial infarction, and a 14% (4%, 25%) increase in angina patients.

8.3.3.4 Comparison of survival after acute myocardial infarction and angina

After adjustment for other factors, short-term case-fatality in patients with angina was 92% lower than that seen in patients with acute myocardial infarction. (Table 46) However after excluding deaths in the first 30 days, longer-term case-fatality in male angina patients was only 8% lower than that of acute myocardial infarction patients. In women, however, longer-term case-fatality in angina patients was 24-28% lower than that in acute myocardial infarction patients.

Table 45 Factors influencing short-term and long-term case-fatality in emergency admissions with acute myocardial infarction or angina: (Multivariable analyses)*

		Short-term case fatality		Long-term case fatality	
		Acute myocardial infarction	Angina	Acute myocardial infarction	Angina
		Odds ratio (95% confidence intervals)		Hazard ratio (95% confidence intervals)	
Sex	Men	1.00	1.00	1.00	1.00
	Women	1.22 (1.18,1.27)	0.71 (0.60,0.82)	0.93 (0.90,0.96)	0.71 (0.67,0.76)
Age (years)	<55	1.00	1.00	1.00	1.00
	55-64	2.31 (2.10,2.55)	2.52 (1.63,3.88)	2.01 (1.85,2.18)	2.48 (2.13,2.88)
	65-74	5.08 (4.64,5.55)	4.25 (2.82,6.39)	3.89 (3.61,4.20)	5.07 (4.40,5.83)
	75-84	9.79 (8.95,10.70)	9.77 (6.54,14.58)	7. 29 (6.76,7.87)	10.19 (8.86,11.73)
	>84	15.86 (14.39,17.48)	13.16 (8.52,20.33)	12.69 (11.66,13.82)	17.02 (14.54,19.92)
Deprivation	1 (most affluent)	1.00	1.00	1.00	1.00
	2	1.11 (1.05,1.17)	1.08 (0.85,1.38)	1.07 (1.02,1.13)	0.99 (0.89,1.09)
	3	1.11 (1.05,1.17)	0.91 (0.71,1.17)	1.08 (1.03,1.14)	1.05 (0.96,1.16)
	4	1.11 (1.05,1.17)	1.00 (0.78,1.28)	1.13 (1.07,1.19)	1.06 (0.97,1.17)
	5 (most deprived)	1.09 (1.03,1.15)	1.00 (0.78,1.28)	1.22 (1.16,1.29)	1.14 (1.04,1.25)
Comorbidity	Diabetes	1.17 (1.10,1.24)	1.24 (0.97,1.59)	1.53 (1.45,1.61)	1.59 (1.44,1.75)
	Cancer	1.67 (1.56,1.78)	1.50 (1.18,1.90)	1.79 (1.68,1.90)	1.70 (1.55,1.87)
	Respiratory	1.28 (1.21,1.35)	1.06 (0.85,1.33)	1.41 (1.34,1.48)	1.41 (1.29,1.53)
	Cardiovascular	1.72 (1.62,1.82)	1.69 (1.33,2.16)	1.72 (1.63,1.82)	1.61 (1.46,1.78)
	Peripheral vascular	1.25 (1.18,1.34)	1.26 (0.99,1.60)	1.43 (1.35,1.51)	1.46 (1.33,1.60)
	Hypertension	0.74 (0.69,0.78)	0.69 (0.54,0.88)	1.02 (0.96,1.08)	0.92 (0.84,1.01)
	Heart failure	1.26 (1.20,1.31)	1.95 (1.60,2.37)	1.83 (1.76,1.90)	1.75 (1.61,1.90)
	Atrial fibrillation	0.73 (0.68,0.78)	0.79 (0.61,1.03)	1.28 (1.21,1.35)	1.19 (1.08,1.31)
	Renal disease	2.80 (2.56,3.05)	2.19 (1.56,3.07)	1.87 (1.70,2.06)	2.35 (1.99,2.76)

*** All risk values reported come from multivariate analyses using logistic regression models and Cox models. The values are thus independent, being adjusted for all other variables.**

Table 46 Adjusted short-term and longer-term case fatality rates in patients with a first emergency admission for angina, compared with a first admission for acute myocardial infarction (AMI) 1990-2000. (Logistic regression and Cox multivariable analysis)*

		Men	Women	Both sexes
		Risk of death (95% confidence intervals)		
Case-fatality at 30 days (logistic regression)	**AMI**	1.00	1.00	1.00
	Angina	0.11 (0.10,0.12)	0.06 (0.05,0.07)	0.08 (0.07,0.09)
Case-fatality from 30 days to 5 years (Cox model)	**AMI**	1.00	1.00	1.00
	Angina	0.92 (0.88,0.97)	0.72 (0.69,0.75)	0.81 (0.79,0.84)
Case-fatality from 30 days to 10 years (Cox model)	**AMI**	1.00	1.00	1.00
	Angina	0.92 (0.86,0.98)	0.76 (0.70,0.81)	0.83 (0.79,0.88)

***all the hazard values reported come from multivariate analyses using Logistic Regression and Cox models. The values are thus independent, being adjusted for all other variables.**

8.3.4 Subsequent non-fatal events

8.3.4.1 Post AMI

Within five years of the first admission with acute myocardial infarction, 15,406 (16.1%) of the surviving men experienced one or more non-fatal cardiovascular events. These comprised 9.9% acute myocardial infarction, 1.9% stroke, 3.2% heart failure, 7.2% CABG, and 3.1% angioplasty (and in women: 6.3%, 4.1%, 2.7%, 3.0%, and 1.9% respectively). These events were not mutually exclusive, and some patients experienced multiple events.

8.3.4.2 Post angina

Within five years of the first emergency angina admission, 6,715 (18.0%) of the surviving men experienced a non-fatal cardiovascular event within five years of the first admission: 6.6% acute myocardial infarction, 4.7% stroke, 1.7% heart failure, 10.1% CABG, and 5.1% angioplasty (and in women 5.1%, 5.1%, 1.8%, 4.2%, and 3.0% respectively.

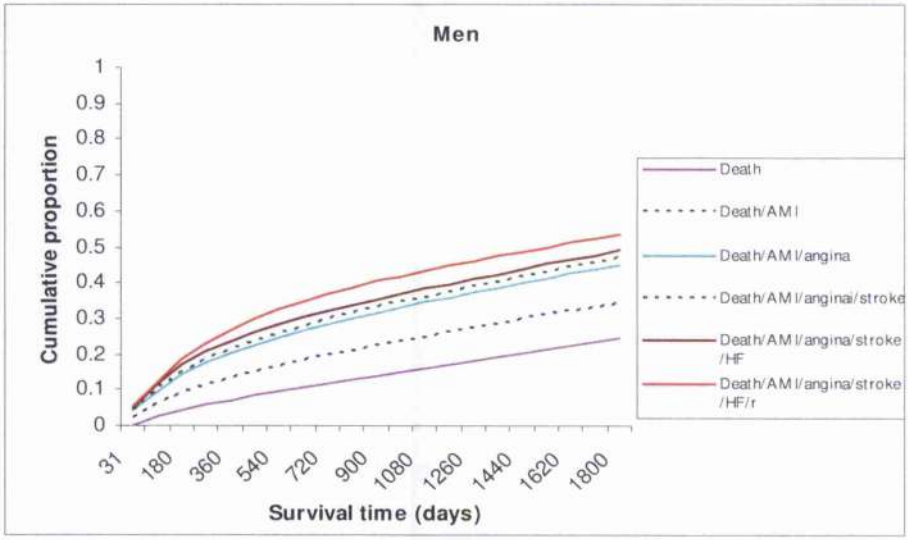
8.3.4.3 Subsequent revascularisation

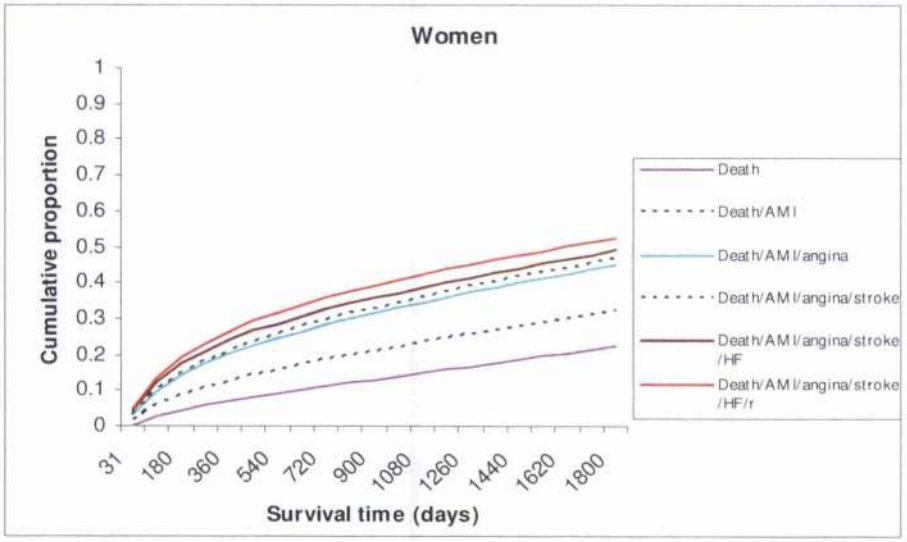
Men were approximately twice as likely as women to undergo a revascularisation procedure within 5 years of their index hospitalisation (3.6% in men versus 2.2% in women for CABG and 7.9% in men versus 3.4% in women for angioplasty). Revascularisation rates showed a substantial negative age gradient and a consistent sex inequality. Following an acute myocardial infarction, CABG surgery rates within five years decreased from 11.5% in men aged under 55 years, to 0.8% in those aged 75-84 years (8.5% versus 0.2% in women; corresponding rates after angina decreasing from 10.5% to 2.6% in men (3.5% to 0.9% respectively in women). A similar age gradient was seen for angioplasty within five years following acute myocardial infarction, decreasing from 7.0% in men aged less than 55 years, to 0.5% in men aged 75-84 years (8.1% to 0.3% respectively in women). Corresponding rates after angina decreased from 7.7% to 1.3% in men (5.0% to 0.6% respectively in women).

8.3.5 Subsequent fatal and non-fatal events

Within five years of the first admission, almost half of all men experienced a fatal or non-fatal event: death, acute myocardial infarction, angina admission, stroke, heart failure, angioplasty or CABG surgery. Following acute myocardial infarction, age-adjusted event rates in women were as high as in men (52.6% versus 53.6%, Figure 14), and almost as high following angina (48.8% v. 56.3%, Figure 15).

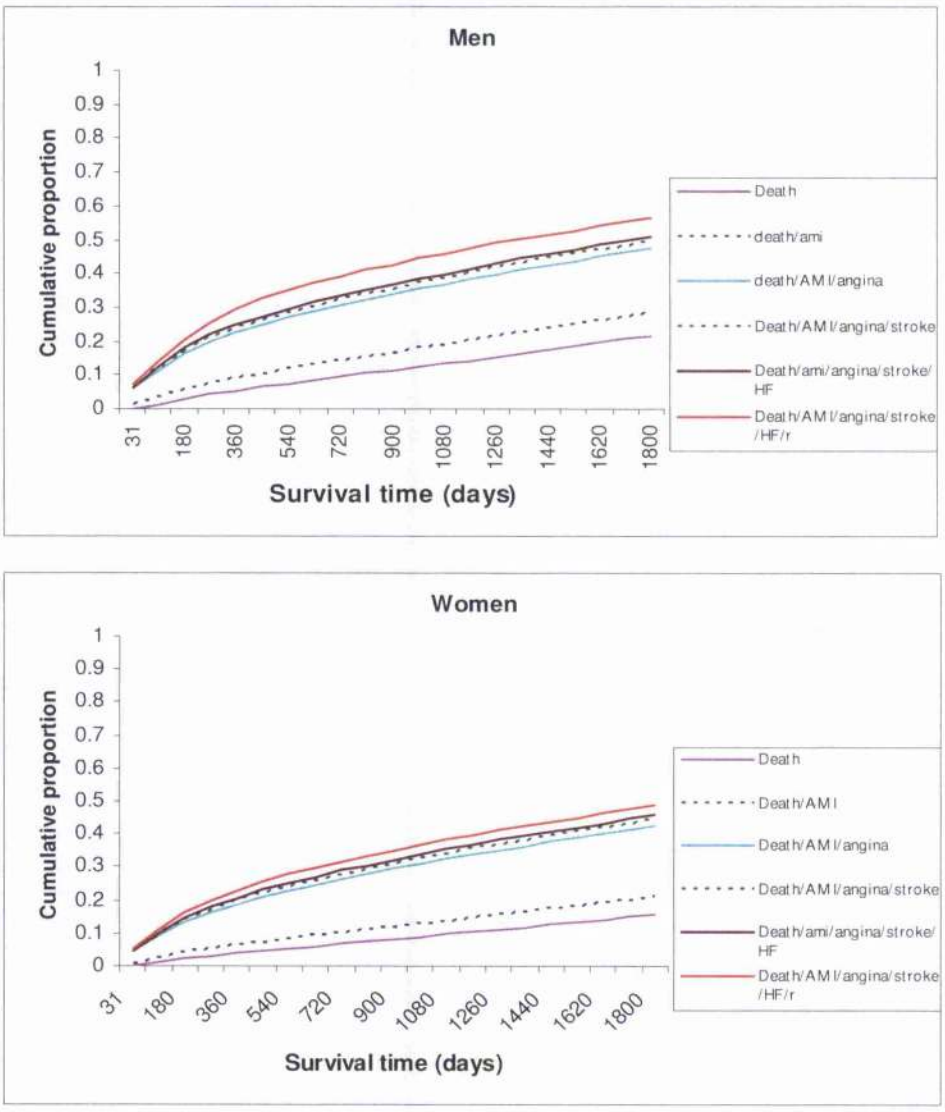
Figure 14 Probability of fatal or non-fatal event in men and women following a first admission for acute myocardial infarction in Scotland 1990- 2000 (adjusted for age, excludes deaths up to 30 days)





AMI= acute myocardial infarction; HF= heart failure; r= revascularisation

Figure 15 Probability of fatal or non-fatal event in men and women following a first admission for angina in Scotland 1990- 2000 (adjusted for age, excludes deaths up to 30 days)



AMI= acute myocardial infarction; HF= heart failure; r= revascularisation

8.3.5.1 Subsequent fatal and non-fatal events: multivariable analysis

After adjustment for age and other factors, the risk of fatal plus non-fatal event was 34% (95% CI 31%, 37%) lower in women compared with men following a first hospitalisation for angina, but only 11% (95% CI 8%, 13%) lower following an acute myocardial infarction hospitalisation (Table 47). After adjustment for other factors, the risk of fatal and non-fatal events were greatly increased by age, (three-fold following acute myocardial infarction and four-fold following angina, aged <55 versus aged 75-84 years). Risk was also increased up to 60% by different co-morbidities. However, socio-economic deprivation had an adverse effect of only 8% following angina and 15% following acute myocardial infarction.

Table 47 Factors influencing fatal plus non fatal event rates from 30 days to five years following a first emergency admission for acute myocardial infarction or angina (multivariable analyses, excludes deaths at 30/7)*

		Acute myocardial infarction	Angina
		Risk of fatal plus non fatal event (95% confidence intervals)	
Sex	Men	1.00	1.00
	Women	0.89 (0.87,0.92)	0.66 (0.63,0.69)
Age (years)	<55	1.00	1.00
	55-64	1.13 (1.08,1.18)	1.59 (1.47,1.72)
	65-74	1.37 (1.31,1.43)	1.99 (1.85,2.15)
	75-84	2.00 (1.91,2.09)	2.74 (2.54,2.96)
	>84	3.03 (2.86,3.21)	4.15 (3.74,4.60)
Deprivation	1 (most affluent)	1.00	1.00
	2	1.04 (0.99,1.08)	1.04 (0.96,1.12)
	3	1.04 (1.00,1.09)	1.05 (0.98,1.14)
	4	1.06 (1.01,1.10)	1.02 (0.95,1.10)
	5 (most deprived)	1.15 (1.10,1.20)	1.08 (1.00,1.16)
Comorbidity	Diabetes	1.32 (1.26,1.38)	1.41 (1.30,1.53)
	Cancer	1.48 (1.39,1.56)	1.35 (1.24,1.47)
	Respiratory	1.27 (1.21,1.32)	1.20 (1.12,1.29)
	Cardiovascular	1.52 (1.45,1.60)	1.44 (1.32,1.57)
	Peripheral vascular disease	1.27 (1.21,1.34)	1.21 (1.12,1.31)
	Hypertension	1.07 (1.02,1.12)	1.01 (0.94,1.08)
	Heart failure	1.51 (1.46,1.57)	1.42 (1.32,1.53)
	Atrial fibrillation	1.22 (1.16,1.29)	1.04 (0.95,1.13)
	Renal disease	1.62 (1.48,1.77)	1.68 (1.44,1.97)

***all the hazard values reported come from multivariate analyses using Logistic Regression and Cox models. The values are thus independent, being adjusted for all other variables.**

8.4 Discussion

This paper describes clinical outcomes in a large unselected cohort of patients after a first emergency admission with suspected acute coronary syndrome. Short-term case-fatality following a diagnosis of acute myocardial infarction was high, as reported elsewhere.[56;94;402] However, short-term case-fatality was only 2% following an emergency hospitalisation with angina (the proxy for unstable angina using this database). These data therefore support the current clinical priority of rapidly triaging such patients.[388;401;402;405] Following exclusion of initial deaths, longer-term case-fatality following a first emergency admission was almost as high for angina as for acute myocardial infarction, approximately 4%-5% per year. These novel and important findings suggest that long-term risk is substantial in all emergency admissions with coronary heart disease, not just acute myocardial infarction survivors. Non-fatal event rates were also high. This highlights the importance of secondary preventative strategies for all patients with acute coronary syndromes.

Short-term and long-term case-fatality in all groups with suspected acute coronary syndromes approximately doubled with each increasing decade of age, and was further increased by a range of comorbid diagnoses. These findings are consistent with earlier studies[52;56;408] and endorse the recommended prioritisation of older and sicker patients.[52;388;405]

As in the smaller Canadian series[56], socioeconomic deprivation consistently increased longer-term case-fatality in all patient groups with suspected acute coronary syndromes, with the risk of death increasing by approximately 20% from the most affluent to the most deprived quintiles. Although lower use of secondary prevention medications might partly explain this gradient, other factors may also be important, such as diet and smoking.[56;156;409] These modest deprivation gradients contrast with the consistently reported threefold variations in disease incidence.[156]

Risk of subsequent non-fatal events

Within five years of their first admission, approximately one quarter of the surviving patients experienced a non-fatal cardiovascular event: (principally acute myocardial infarction, but also stroke, angina, heart failure or revascularisation). This is consistent with the 10%-15% rates reported after just 12 months in trial and registry patients.[52;57;410]

Interestingly, while a further, non-fatal myocardial infarction was more common in myocardial infarction survivors than in angina survivors, the opposite was seen for stroke. This merits further research. After adjustment for other factors, cardiovascular event rates increased three-fold with age, increased by up to 60% with different co-morbidities, and by up to 15% with increasing socioeconomic deprivation. This finding strengthens the case for equally aggressive secondary prevention, irrespective of age and class.[156;401-403]

Inequalities in revascularisation after a first admission for acute coronary syndrome

Revascularisation rates were generally low, much as might be expected in the 1990s. Revascularisation was twice as likely in men as women of the same age. Clinical justification for this finding appears difficult. Revascularisation rates also showed a substantial age gradient. Following an acute myocardial infarction, CABG surgery within five years was approximately fifteen times less likely in men aged 75-84 years compared with men aged less than 55 years. Even larger age gradients were seen in women. These findings provide yet more evidence of the substantial age and sex biases reported in North America, Europe and elsewhere.[56;360;411] The probability of undergoing CABG surgery within five years of hospitalisation with AMI was approximately twice as high as for angioplasty between 1990 and 2000. However, this ratio is now close to unity.[399;400;412]

My study captured essentially all hospital and fatal events in the Scottish population of 5.1 million, and is thus cautiously generalisable to similar populations elsewhere. However, it has a number of potential limitations. While routine death certification of coronary heart disease in Britain appears reliable up to the age of 65, it may overestimate coronary heart disease in older age groups by up to 20%.[413] However, any such inflation is unlikely to have changed substantially between 1990 and 2000. The definition of a first admission, may have included some long-term survivors with a prior admission, albeit less than 5%.[94;156] The proxy for unstable angina, "emergency admission with angina" may have resulted in milder cases of angina being included in this analysis. This may have resulted in an underestimation of the case-fatality of patients admitted with angina. However, this may have been balanced by some over-estimation of case fatality, because these data come from the "pre-troponin era" and probably include some patients with actual myocardial infarction. There were no data on severity of cardiovascular disease, so it was not possible to take this into account when looking at the potential effects of age, sex and socio-economic status on variations in rates for deaths, events, or revascularisation. Furthermore, some mis-classification is possible, for instance, some angina patients dying in hospital may have been re-coded as myocardial infarction. However, my findings are

generally consistent with smaller series from clinical disease registers.[52;56;410;414] Furthermore, coding is essentially complete and accuracy exceeds 90%.[94;306] It was only possible to identify those non-fatal events actually admitted to hospital. However, this is likely to have included the great majority of significant events. Furthermore, if the true total was even higher, this further emphasises the substantial event rates in these patients.

In conclusion, following a first emergency hospitalisation for acute coronary syndrome, the long-term prognosis is almost as poor for angina as it is for acute myocardial infarction. Within five years, half of all patients will experience a future fatal or non-fatal event. These data may strengthen the case for aggressive secondary prevention in all patients hospitalised with acute coronary syndrome.

9 REDUCED BETWEEN-HOSPITAL VARIATION IN SHORT-TERM SURVIVAL FOLLOWING ACUTE MYOCARDIAL INFARCTION: THE RESULT OF IMPROVED CARDIAC CARE?

9.1 Introduction

In a study of the period 1988 to 1991, substantial variation in 30 day survival following admission with AMI was identified between hospitals in Scotland.[1] Since that study, at least one Cardiologist has been appointed in each Scottish hospital and acute medical care has been reorganised in most to ensure more rapid and appropriate care of patients suspected of this diagnosis. [2] I have re-examined variation in survival following admission with AMI, ten years after the initial study. The aim was to determine whether there has been a reduction in the variation in survival between Scottish hospitals in this more recent time period compared to the earlier one.

9.2 Methods

The SMR AMI database 1988-91 and 1998-2001 was used as described in chapter 3.

9.3 Results

9.3.1 Baseline characteristics

Table 48 shows the baseline characteristics of the 61,484 individuals discharged with a first AMI during the two time periods of study. 36,108 (58.7%) were admitted between 1988 and 1991 and 25,376 (41.3%) were admitted between 1998 and 2001. The mean age of men and women increased between these time periods ($p<0.001$). In the period 1988-

1991, 48.2% of men were aged 65 or over. This proportion rose to 50.5% in 1998-2001 ($p<0.001$). The corresponding figures for women were 72.1% and 75.4% ($p<0.001$). Between 1988 and 1991, 39.4% of men and 45.3% of women had one or more co-morbidities or prior admissions. This proportion rose to 46.9% in men and 52.9% in women in 1998-2001 ($p<0.001$).

Table 48 Baseline characteristics of patients discharged following a first acute myocardial infarction during the periods 1998-2001 and 1988-1991

	1988-1991 (n=36,108)		1998-2001 (n=25,376)	
	Men	Women	Men	Women
Total 1998-2001	20985 (58.1)	15123 (41.9)	14953 (58.9)	10423 (41.1)
Mean (median) age yrs	64.4 (65.0)	71.6 (73.0)	65.0 (66.0)	72.9 (74.0)
Age group				
< 55 years	4892 (23.3)	1378 (9.1)	3677 (24.6)	987 (9.5)
55 – 64 years	5997 (28.6)	2840 (18.8)	3713 (24.8)	1573 (15.1)
65-74 years	6036 (28.8)	4726 (31.3)	4132 (27.6)	3046 (29.2)
75-84 years	3518 (16.8)	4767 (31.5)	2768 (18.5)	3296 (31.6)
>85 years	542 (2.6)	1412 (9.3)	663 (4.4)	1521 (14.6)
Deprivation categories				
I- least deprived	3416 (16.3)	2325 (15.4)	2665 (17.8)	1837 (17.6)
II	3856 (18.4)	2715 (18.0)	2950 (19.7)	1935 (18.6)
III	3850 (18.3)	2784 (18.4)	3057 (20.4)	2108 (20.2)
IV	4156 (19.8)	3096 (20.5)	2927 (19.6)	2146 (20.6)
V- most deprived	4437 (21.1)	3409 (22.5)	2991 (20.0)	2261 (21.7)
Missing	1270 (6.1)	794 (5.3)	363 (2.4)	136 (1.3)
Prior admission or co-morbidity*				
CHD†	2187 (10.4)	1577 (10.4)	1297 (8.7)	857 (8.2)
Other heart disease	4048 (19.3)	3619 (23.9)	3901 (26.1)	3305 (31.7)
Stroke	743 (5.0)	604 (5.8)	909 (4.3)	962 (6.4)
Peripheral arterial disease	850 (5.7)	561 (5.4)	825 (3.9)	539 (3.6)
Respiratory disease‡	1154 (5.5)	799 (5.3)	1396 (9.3)	1149 (11.0)
Malignancy	823 (3.9)	559 (3.7)	1038 (6.9)	697 (6.7)
Diabetes mellitus	940 (4.5)	907 (6.0)	162 (1.1)	160 (1.5)
Any of above	8274 (39.4)	6851 (45.3)	7018 (46.9)	5510 (52.9)

*** Primary or secondary discharge diagnosis in the previous 5 years or secondary discharge coding at time of admission with index myocardial infarction.**

† Coronary heart disease

‡ Includes influenza, pneumonia and chronic lower respiratory diseases.

9.3.2 30 day survival following hospital admission

Improved crude and age and sex adjusted 30 day survival (Table 49)

Crude 30 day survival for first AMI increased from 77.7% in 1988-1991 to 80.9% in 1998-2001 in Scotland as a whole. The number of hospitals with a 30 day survival of less than 75% decreased from 5 to 0 (and those with a survival of less than 80% from 18 to 7) between these two time periods.

Decreased variation in crude and age and sex adjusted 30 day survival (Table 49 and Figure 16)

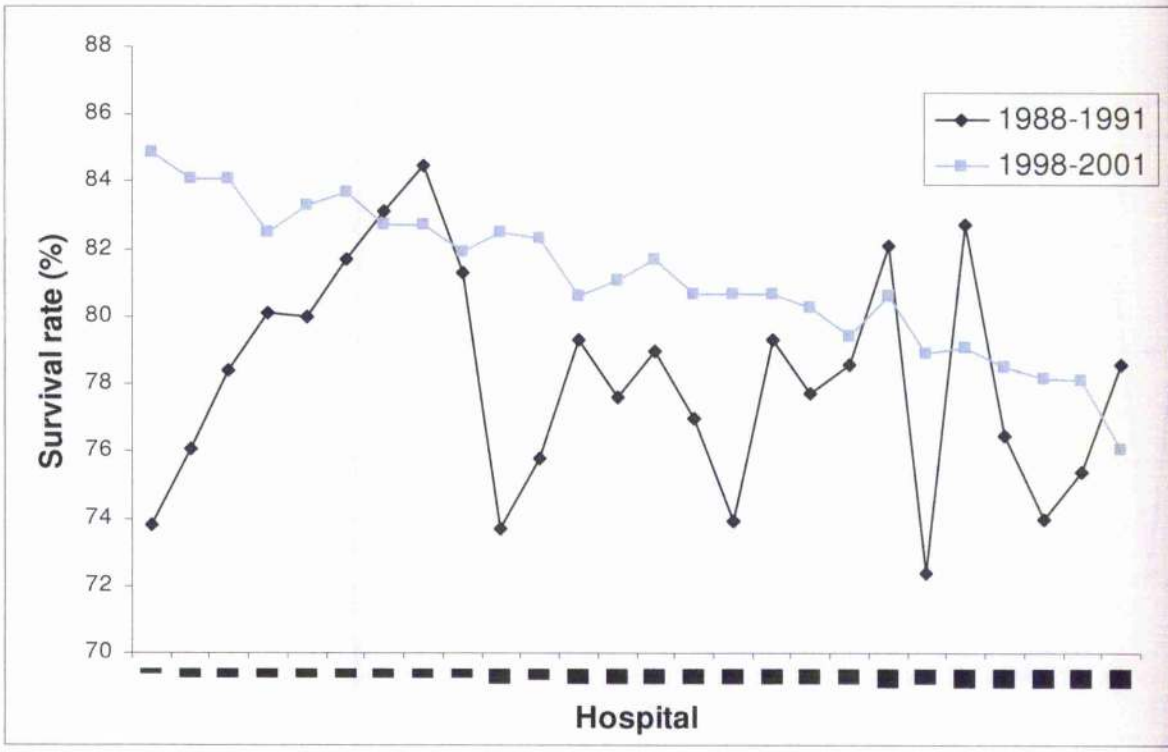
Between 1988 and 1991 the median crude 30 day survival rate was 79.2% with a range from 72.1% to 85.1% across hospitals, a difference of 13.0%. After standardising for age and sex, there was still a difference of 12.1% in 30 day survival between hospitals. Between 1998 and 2001 the median crude 30 day survival rate was 81.6% with a range from 78.0% to 85.6%. This difference of 7.6% increased slightly to 8.8% after standardising for age and sex. Therefore the inter-hospital variability decreased between these two time periods after adjusting for age and sex differences. The hospitals with the worst survival in 1988-1991 had the most marked improvement in 1998-2001.

Table 49 Crude and age and sex adjusted 30 day survival after admission with a first acute myocardial infarction in 1988-1991 and 1998-2001.

	Crude 30 day survival (%)					Age and sex adjusted 30 day survival (%)		
	1988-1991		1998-2001			1988-1991	1998-2001	
	number	%	number	%	difference	%	%	difference
Scotland	36108	77.7	25376	80.9	3.2			
1	1361	74.1	939	85.5	11.4	73.8	84.9	11.1
2	1209	76.8	1156	83.3	6.5	76.1	84.1	8
3	1095	78.2	685	84.7	6.5	78.4	84.1	5.7
4	2309	81.6	1651	83.4	1.8	80.1	82.5	2.4
5	2099	81.4	2000	83.1	1.7	80.0	83.3	3.3
6	919	82.8	714	85.6	2.8	81.7	83.7	2
7	922	83.8	730	81.4	-2.4	83.1	82.7	-0.4
8	1948	84.5	1365	82.8	-1.7	84.5	82.7	-1.8
9	601	80.5	504	81.0	0.5	81.3	81.9	0.6
10	957	72.9	586	81.4	8.5	73.7	82.5	8.8
11	912	76.9	605	82.5	5.6	75.8	82.3	6.5
12	1173	80.8	668	83.1	2.3	79.3	80.6	1.3
13	536	78.5	452	82.1	3.6	77.6	81.1	3.5
14	1314	82.0	1137	81.6	-0.4	79.0	81.7	2.7
15	706	78.5	861	81.7	3.2	77.0	80.7	3.7
16	664	73.6	688	81.1	7.5	73.9	80.7	6.8
17	1029	79.3	575	80.4	1.1	79.3	80.7	1.4
18	1013	77.7	582	81.6	3.9	77.7	80.3	2.6
19	1243	80.8	1093	80.1	-0.7	78.6	79.4	0.8
20	470	80.6	419	78.0	-2.6	82.1	80.6	-1.5
21	1188	72.1	837	80.1	8	72.4	78.9	6.5
22	598	85.1	761	82.4	-2.7	82.7	79.1	-3.6
23	839	79.0	815	80.5	1.5	76.5	78.5	2
24	1020	78.2	1106	81.0	2.8	74.0	78.2	4.2
25	1201	77.3	799	79.2	1.9	75.4	78.1	2.7
26	1455	80.8	805	78.5	-2.3	78.6	76.1	-2.5
*Total**	28781	79.2	22533	81.6	2.4	78.6	80.9	2.3

*** Total number and median survival for 26 hospitals**

Figure 16Age and sex standardised 30 day survival after admission with acute myocardial infarction between 1988-1991 and 1998-2001

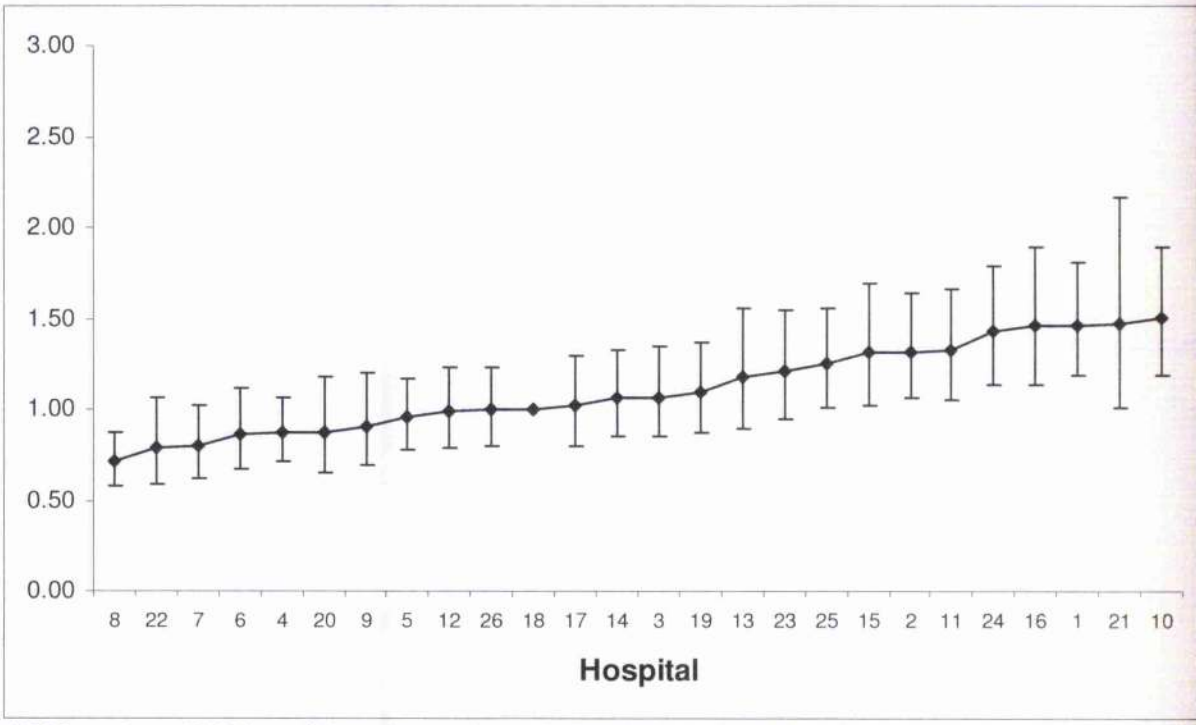


9.3.3 Multiple logistic regression

1988-1991: After adjusting for age, sex, deprivation category and prior (previous admissions) and co-morbidity (secondary discharge diagnoses), admission hospital was a highly significant predictor of outcome at 30 days ($p<0.001$). The odds ratio (OR) for death following admission with AMI, ranged from 0.71 (95% CI 0.58, 0.88) to 1.50 (1.19, 1.89) between hospitals. The index hospital was hospital 18 which had the same crude survival as Scotland as a whole (Figure 17). The adjusted risk of death within 30 days following an admission with AMI was significantly higher than average in 9 (and better in 1) of 26 hospitals.

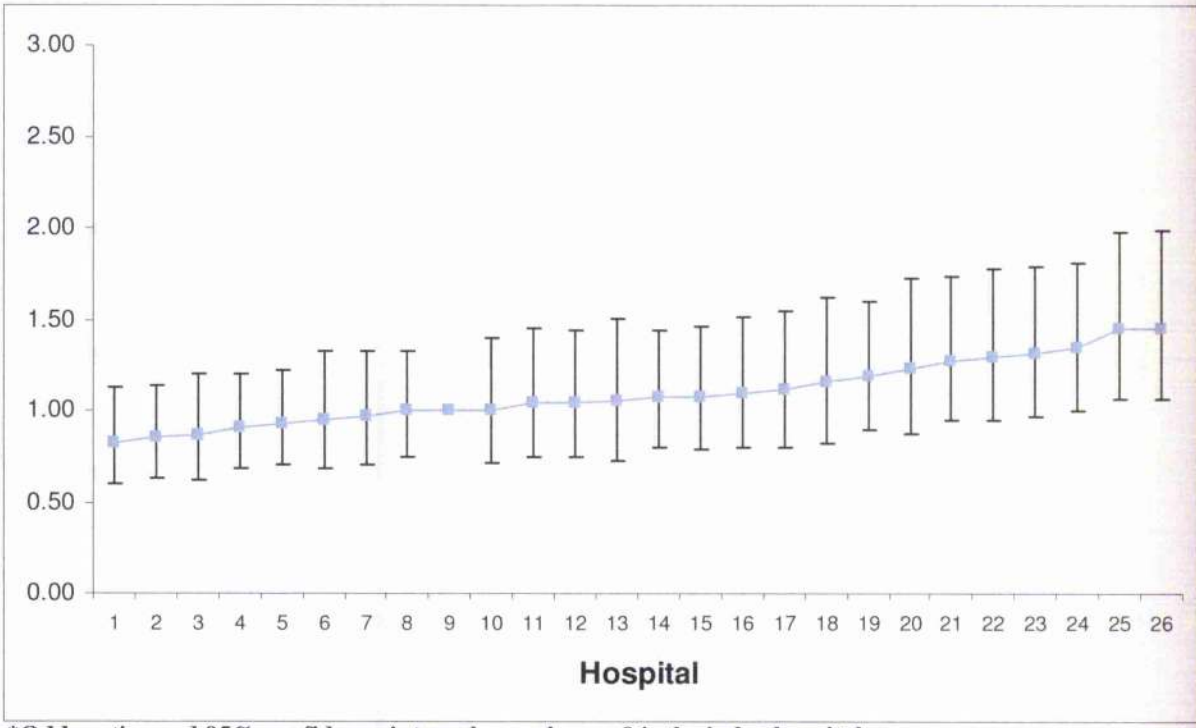
1998-2001: Admission hospital remained an independent predictor of outcome at 30 days ($p<0.001$). The OR for death ranged from 0.82 (0.60, 1.13) to 1.46 (1.07, 1.99) between hospitals, relative to hospital 9 which had a similar crude survival as Scotland as a whole (Figure 18). Inter-hospital variation was less and the adjusted risk of death was significantly higher than average in only 2 hospitals.

Figure 17 The adjusted probability of death* at 30 days post AMI between 1988-1991



*Odds ratios and 95% confidence intervals are shown. 18 is the index hospital.

Figure 18 The adjusted probability of death* at 30 days post AMI between 1998-2001



*Odds ratios and 95% confidence intervals are shown. 9 is the index hospital.

9.4 Discussion

There are two notable findings of this study. Firstly, despite an increase in age and documented co-morbidity, patients hospitalised with AMI had a higher 30 day survival in Scotland between 1998 and 2001 than in 1988 to 1991. Secondly, and most germane to the aims of this study, inter-hospital variation declined substantially between 1988-1991 and 1998-2001.

Though not the principal aim of this study, it was of interest to be able to confirm that there has been a fall in the incidence of AMI between the two study periods, a finding consistent with prior studies from Scotland and elsewhere. [9-18] This may be attributable to a variety of factors including better primary prevention, falling rates of smoking, a change in the natural history of coronary artery disease and better public and doctor awareness of the importance of potential cardiac symptoms. Similarly, the increase in 30 day survival following an AMI is also consistent with prior reports from Scotland and elsewhere. [10-19] Several factors, including those which may have contributed to the decline in incidence, may be important. [20] Others include changing thresholds for referral (whereby patients with chest pain are more likely to be referred to hospital by primary care practitioners) and admission (when referred more likely than previously to be admitted). Diagnostic thresholds may also have been lowered, with consequent changes in severity of infarction. New treatments may also have played an important part.

The second major finding of this study (and the one most pertinent to the aim of the study) is that inter-hospital variation declined substantially between 1988-1991 and 1998-2001. This is less easy to attribute to the factors mentioned above in connection with the decline in case fatality between these two periods. Indeed, the hypothesis was that greater input of Cardiology services and re-organisation of care should have led to reduced between hospital variation in 30 day survival and the findings are consistent with this (these may also, of course, have contributed to the improvement in survival). The reduction in variation between hospitals seemed to be due, largely, to a particularly notable improvement in survival in those hospitals which had the highest care fatality in the 1988-1991 study.

Though there was less variation between 1998 and 2001 than previously, inter-hospital variation persisted, with a 9% difference in adjusted survival. The reasons for this require

further study as identification of correctable factors (such as deficiencies in treatment) could lead to further improvements in outcome and reductions in variation. This highlights the major limitation of this study which is absence of information on treatment and on other factors such as measurement of ventricular function, which might allow better adjustment of case mix.

In summary, the appointment of Cardiologists and their involvement in the care of acute admissions to Scottish hospitals seems to be associated with an overall improvement (and less variation between hospitals) in survival following AMI.

10 A POPULATION STUDY OF THE LONG-TERM CONSEQUENCES OF ANGINA: 20 YEAR FOLLOW-UP OF THE RENFREW-PAISLEY STUDY.

10.1 Introduction

Although the incidence of myocardial infarction is decreasing, the prevalence of angina pectoris has changed little and remains high.[4;15] As such, angina remains the most common manifestation of coronary heart disease and the most common symptomatic cardiac condition. As evident from chapter 1, relatively little is known about the long-term natural history of angina at a population level, especially in women.[30;31;53;55] As discussed previously most existing population-based studies have mainly or exclusively reported outcomes in men.[13;22;50;54] Only a few described prognosis in women and those that did have not usually compared their outcome to men in the same population.[14;21] Furthermore, most existing studies which have reported clinical outcomes have focussed on death, myocardial infarction or both.[13;22;30;53-55] Patients with angina are likely to be at increased risk of other complications of coronary heart disease (e.g. heart failure) and non-cardiac vascular events (e.g. stroke).[50] Similarly, the true lifetime burden of angina is reflected not only in fatal but also in non-fatal events, especially those leading to hospital admission. Consequently, the aim of this study was to examine the long-term population risk of fatal and non-fatal cardiovascular events in both men and women with angina, during 20 year follow up of 15,402 initially middle-aged individuals (8,354 women) who were first screened between 1972 and 1976.

10.2 Methods

The Renfrew-Paisley study database was used as described in chapter 3.

10.3Results

10.3.1Prevalence of angina

At baseline screening, 669(9.5%) men and 799(9.6%) women had Rose-positive angina. Of these, 22.7% of men and 14.8% of women had an ischaemic ECG. Conversely, 697(9.9%) men and 712(8.5%) women had an ischaemic ECG. Of these, 21.8% of men and 16.6% of women had angina

10.3.2Baseline characteristics according to the presence or absence of angina at baseline

Compared to individuals with no angina and no ischaemic ECG changes, those with angina or an ischaemic ECG were older and more likely to have cardiovascular risk factors or prior cardiovascular disease (these findings were generally more marked for subjects with an abnormal ECG). (Table 50) This gradient was also seen for pulmonary disease. Compared to women, men with angina were significantly more likely to be current or ex-smokers ($p<0.001$) (and to have a lower FEV_1 ($p<0.001$) and more likely to have chronic bronchitis ($p=0.002$)). Men were also more likely to have a history of Rose-myocardial infarction ($p<0.001$). Conversely, women had a higher total cholesterol ($p<0.001$), systolic blood pressure ($p=0.005$) and cardiothoracic ratio ($p<0.001$).

Table 50 Baseline characteristics of the Renfrew-Paisley Cohort according to the presence or absence of angina and ischaemic ECG changes at baseline.

	Men				Women			
	No angina / no ischaemic ECG (n =5834)	No angina / ischaemic ECG (n=545)	Angina/ no ischaemic ECG (n =517)	Angina / ischaemic ECG (n=152)	No angina / no ischaemic ECG (n =6961)	No angina / ischaemic ECG (n=594)	Angina/ no ischaemic ECG (n=681)	Angina / ischaemic ECG (n=118)
	Mean ± SD or N (%)				Mean ± SD or N (%)			
Age (years)	54 ± 6	56 ± 6 ‡	56 ± 5 ‡	57 ± 5 ‡	54 ± 6	56 ± 5 ‡	55 ± 6 ‡	58 ± 5 ‡
Past history stroke	55 (0.9)	19 (3.5) ‡	13 (2.5) †	6 (4.0) †	53 (0.8)	30 (5.1) ‡	12 (1.8) †	9 (7.6) ‡
Rose myocardial infarction	380 (6.5)	98 (18.0) ‡	136 (26.3) ‡	74 (48.7) ‡	296 (4.3)	58 (9.8) ‡	121 (17.8) ‡	29 (24.6) ‡
Current or ex-smoker	4811 (82.5)	462 (84.8)	463 (89.6) ‡	131 (86.2)	3786 (54.4)	284 (47.8) †	387 (56.8)	69 (58.5)
Diabetes	67 (1.1)	10 (1.6)	9 (1.7)	4 (2.6)	70 (1.0)	17 (2.9) ‡	8 (1.2)	5 (4.2) †
Blood glucose (mmol/L)	5.1 ± 1.6	5.5 ± 2.1 ‡	5.1 ± 1.6	5.2 ± 1.3	5.0 ± 1.3	5.4 ± 2.2 †	5.1 ± 1.3	5.6 ± 2.3 *
Plasma cholesterol (mmol/L)	5.9 ± 1.0	5.9 ± 1.0 *	5.9 ± 1.0	6.0 ± 1.0 *	6.4 ± 1.1	6.5 ± 1.1	6.4 ± 1.1	6.6 ± 1.2 *
Body mass index (kg/m^2)	25.8 ± 3.4	26.5 ± 3.4 ‡	25.9 ± 3.6	26.3 ± 3.6	25.6 ± 4.4	26.7 ± 4.9 ‡	26.9 ± 4.9 ‡	27.0 ± 5.5 †
Systolic BP (mmHg)	147 ± 22	159 ± 26 ‡	150 ± 24 *	154 ± 25 †	149 ± 24	163 ± 29 ‡	153 ± 27 ‡	165 ± 31 ‡
Diastolic BP (mmHg)	85 ± 13	91 ± 15 ‡	86 ± 14	89 ± 16 †	84 ± 13	90 ± 15 ‡	87 ± 14 ‡	92 ± 17 ‡
Cardiothoracic ratio	0.46 ± 0.05	0.49 ± 0.05 ‡	0.47 ± 0.05 *	0.50 ± 0.05 ‡	0.48 ± 0.05	0.50 ± 0.06 ‡	0.49 ± 0.05 ‡	0.52 ± 0.06 ‡
Adjusted FEV_1 (%)	90.2 ± 21.6	85.4 ± 21.8 ‡	78.7 ± 25.7 ‡	79.9 ± 25.1 ‡	93.7 ± 22.7	88.8 ± 23.6 ‡	84.8 ± 25.6 ‡	83.5 ± 26.2 ‡
Chronic bronchitis	247 (4.2)	38 (7.0) †	100 (19.3) ‡	27 (17.8) ‡	207 (3.0)	32 (5.4) †	96 (14.1) ‡	9 (7.6) *
Atrial fibrillation on ECG	35 (0.6)	10 (1.8) †	5 (1.0)	3 (2.0)	20 (0.3)	14 (2.4) ‡	6 (0.9) *	7 (5.9) ‡

***p<0.05; †p<0.01;‡p<0.001 for each group compared to the no angina / no ischaemic ECG group**

10.3.3Survival over 20 years follow-up

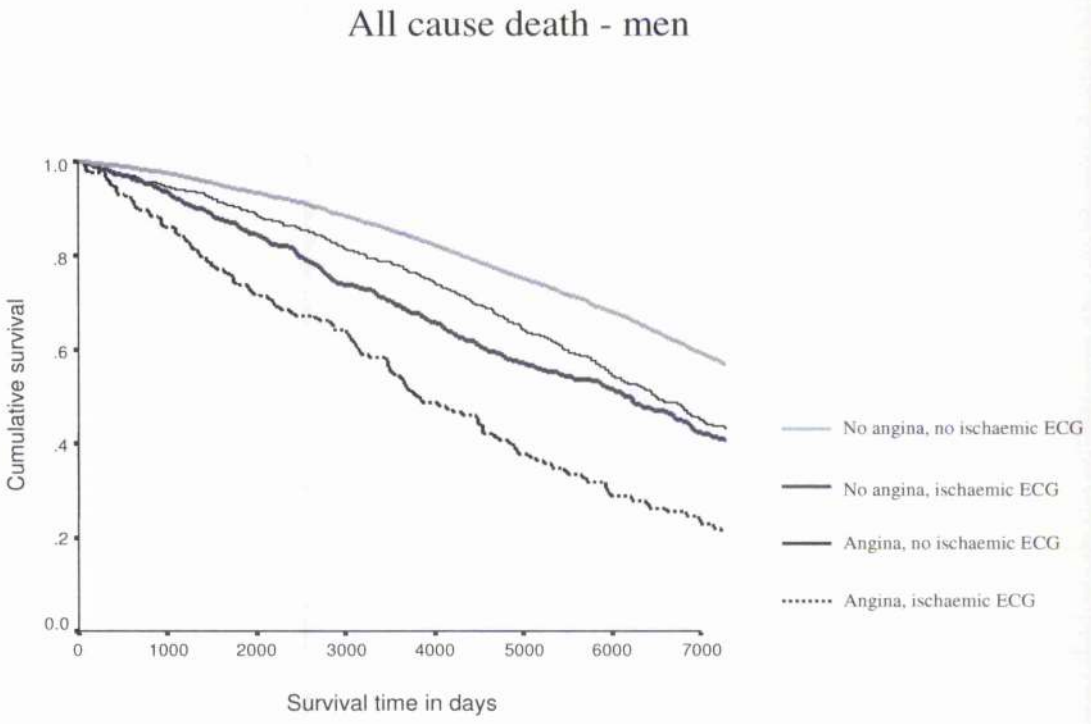
A larger proportion of men than women died over the 20 year follow-up period, irrespective of whether or not they had angina (Figure 19 and Table 51). Men and women with angina were more likely to die than those without angina. 67.7% of men with angina died over the 20 years of follow-up, compared to 45.4% of men without angina ($p<0.001$). The corresponding figures for women were 43.3% and 30.4% respectively ($p<0.001$). Both angina and ischaemic ECG changes were associated with an increased risk of death. An ischaemic ECG was associated with a somewhat greater risk than that seen with angina alone (i.e. where there were no ischaemic ECG changes).

Subjects with angina *and* an abnormal ECG had the highest risk of death. 84.2% of men and 66.1% of women with angina and an ischaemic ECG died by 20 years, compared to 62.9% and 39.4% of men and women with angina but without an abnormal ECG. Angina was associated with an increase in the *adjusted* relative risk of death from all causes, cardiovascular causes and, especially, coronary causes. The adjusted relative risk of death from any cause was 1.38 (95% confidence interval 1.25, 1.53) in men and 1.24 (95% confidence interval 1.11, 1.39) in women (compared to those without angina), whereas the relative risk of death from a coronary cause was 1.95 (1.68, 2.27) in men and 1.50 (1.23, 1.82) in women.

Both angina and an ischaemic ECG were separately associated with increased risk, though the risk associated with an abnormal ECG was greater. Men with angina, but no ECG changes, had a 71% increase in the adjusted risk of dying from coronary heart disease (compared to individuals with neither angina nor ECG changes) while women had a 33% increased risk. The corresponding increases in individuals with an abnormal ECG but no angina were 108% in men and 81% in women.

The increase in relative risk was greatest in individuals with angina *and* an abnormal ECG, where men had a more than 4-fold and women a more than 3-fold increased risk of death from coronary heart disease, compared to individuals without angina or an ischaemic ECG.

Figure 19 Age-adjusted Cox survival curves for all cause death according to the presence or absence of angina or ischaemic ECG changes in men and women



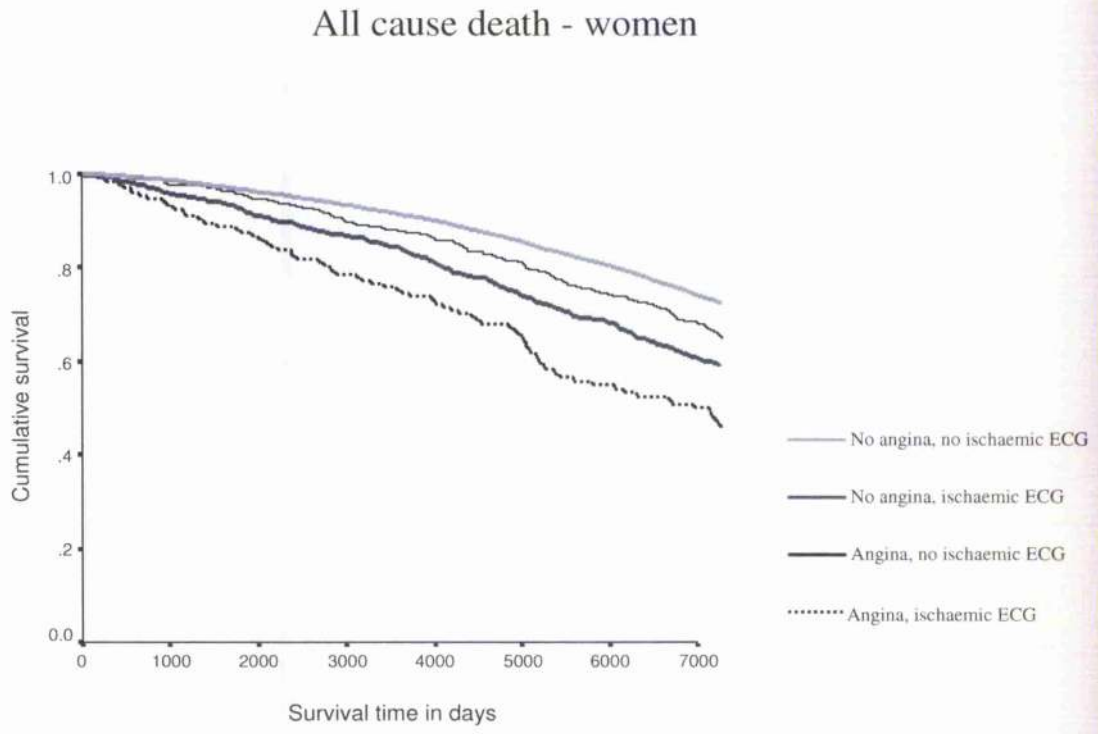


Table 51 Cause of death over 20 years according to the presence or absence of angina and ischaemic ECG changes at baseline. Adjusted risk of cardiovascular death over 20 years relative to those with no angina and no ischaemic ECG changes

	Men				Women			
	No angina, no ischaemic ECG (n=5834)	**No angina, ischaemic ECG (n =545)**	**Angina, no ischaemic ECG (n=517)**	**Angina, ischaemic ECG (n =152)**	**No angina, no ischaemic ECG (n=6961)**	**No angina, ischaemic ECG (n =594)**	**Angina, no ischaemic ECG (n=681)**	**Angina, ischaemic ECG (n =118)**
	N (%) *HR (95% CI)*				N (%) *HR (95% CI)*			
Any cause	2537 (43.5) *1.00*	358 (65.7) *1.57(1.40, 1.75)*	325 (62.9) *1.24(1.10, 1.40)*	128 (84.2) *2.66(2.22, 3.19)*	2012 (28.9) *1.00*	285 (48.0) *1.48(1.31, 1.69)*	268 (39.4) *1.18(1.03, 1.34)*	78 (66.1) *2.08(1.65, 2.61)*
Any cardiovascular cause	1249 (21.4) *1.00*	246 (45.1) *2.10(1.82, 2.41)*	179 (34.6) *1.46(1.25, 1.71)*	96 (63.2) *3.93(3.18, 4.87)*	916 (13.2) *1.00*	190 (32.0) *1.91(1.63, 2.25)*	141 (20.7) *1.31(1.10, 1.57)*	58 (49.2) *2.96(2.26, 3.89)*
Coronary heart disease	889 (15.2) *1.00*	170 (31.2) *2.08(1.76, 2.46)*	145 (28.0) *1.71(1.43, 2.04)*	77 (50.7) *4.50(3.54, 5.71)*	543 (7.8) *1.00*	104 (17.5) *1.81(1.45, 2.25)*	83 (12.2) *1.33(1.05, 1.68)*	38 (32.2) *3.34(2.39, 4.68)*
Myocardial infarction	730 (12.5) *1.00*	143 (26.2) *2.10(1.75, 2.52)*	112 (21.7) *1.60(1.31, 1.96)*	65 (42.8) *4.55(3.51, 5.91)*	462 (6.6) *1.00*	82 (13.8) *1.66(1.31, 2.12)*	73 (10.7) *1.37(1.07, 1.76)*	33 (28.0) *3.36(2.34, 4.83)*
Heart failure	34 (0.6) *1.00*	7 (1.3) *2.57(1.12, 5.91)*	5 (1.0) *1.68(0.64, 4.38)*	2 (1.3) *3.75(0.88, 15.9)*	26 (0.4) *1.00*	10 (1.7) *3.57(1.67, 7.62)*	6 (0.9) *1.87(0.67, 4.61)*	3 (2.5) *5.00(1.47, 17.0)*
Atrial fibrillation	1 (0.0) *1.00*	0 (0.0) -	0 (0.0) -	0 (0.0) -	0 (0.0) *1.00*	1 (0.2) -	3 (0.4) -	0 (0.0) -
Stroke	232 (4.0) *1.00*	48 (8.8) *2.00(1.45, 2.75)*	14 (2.5) *0.56(0.33, 0.97)*	8 (5.3) *1.61(0.79, 3.29)*	277 (4.0) *1.00*	58 (9.8) *1.87(1.39, 2.51)*	38 (5.6) *1.19(0.85, 1.68)*	14 (11.9) *2.36(1.37, 4.07)*
Aortic aneurysm	26 (0.4) *1.00*	5 (0.9) *1.88(0.71, 5.01)*	2 (0.4) *0.68(0.16, 2.94)*	1 (0.7) *2.10(0.28, 15.9)*	7 (0.1) *1.00*	0 (0.0) -	1 (0.1) *1.05(0.13, 8.89)*	0 (0.0) -
Venous thromboembolism	17 (0.3) *1.00*	2 (0.4) *1.46(0.33, 6.44)*	2 (0.4) *1.33(0.30, 5.88)*	1 (0.7) *3.44(0.44, 26.9)*	12 (0.2) *1.00*	4 (0.7) *2.58(0.79, 8.41)*	1 (0.1) -	0 (0.0) -

10.3.4 Hospitalisation from cardiovascular causes

Men and women with angina were more likely than those without angina to experience a subsequent cardiovascular hospitalisation. 43.5% of men with angina experienced such an event over the 20 years of follow-up, compared to 32.7% of those without angina ($p<0.001$). The corresponding figures for women were 37.4% and 24.6%, respectively ($p<0.001$). 47.4% of men and 52.5% of women, with *both* angina and an abnormal ECG, experienced a cardiovascular hospitalisation, compared to 42.4% of men and 34.8% of women with angina but a normal ECG ($p<0.001$). (Table 52)

The adjusted relative risk of admission to hospital for a cardiovascular reason was increased to a similar extent as the risk of death from a cardiovascular cause. As with death, the increased risk of a major *coronary* event was even greater.

As with death alone, the risk of hospital admission for a cardiovascular reason was increased by both angina and an ischaemic ECG, separately. *Unlike* death, the increase in risk was *not* substantially greater with an abnormal ECG than with angina. However, as with death, the greatest risk was seen in subjects with angina *and* an abnormal ECG. In these individuals, the relative risk of a cardiovascular hospitalisation was increased 2.7-fold in men and 2.8-fold in women (compared to individuals with neither angina nor an ischaemic ECG).

Angina, an ischaemic ECG and, especially, both, were associated with an increased risk of hospitalisation due to heart failure and stroke (angina alone did not increase this latter risk in men).

Table 52 Proportion of patients admitted to hospital for a cardiovascular cause* over 20 years according to the presence or absence of angina and ischaemic ECG changes at baseline. Adjusted risk of hospitalisation relative to those with no angina and no ischaemic ECG changes.

	Men				Women			
	No angina, no ischaemic ECG (n=5834)	**No angina, ischaemic ECG (n =545)**	**Angina, no ischaemic ECG (n=517)**	**Angina, ischaemic ECG (n =152)**	**No angina, no ischaemic ECG (n=6961)**	**No angina, ischaemic ECG (n =594)**	**Angina, no ischaemic ECG (n=681)**	**Angina, ischaemic ECG (n =118)**
	N (%) *HR (95% CI)*				N (%) *HR (95% CI)*			
Any cardiovascular cause	1859 (31.9) *1.00*	230 (42.2) *1.62(1.41, 1.86)*	219 (42.4) *1.49(1.29, 1.72)*	72 (47.4) *2.71(2.14, 3.45)*	1647 (23.7) *1.00*	211 (35.5) *1.48(1.28, 1.71)*	237 (34.8) *1.46(1.27, 1.68)*	62 (52.5) *2.78(2.15, 3.59)*
Coronary heart disease	821 (14.1) *1.00*	113 (20.7) *1.85(1.51, 2.26)*	117 (22.6) *1.88(1.54, 2.29)*	37 (24.3) *3.02(2.16, 4.23)*	557 (8.0) *1.00*	83 (14.0) *1.70(1.34, 2.15)*	110 (16.2) *1.99(1.62, 2.45)*	24 (20.3) *2.65(1.75, 4.02)*
Myocardial infarction	652 (11.2) *1.00*	79 (14.5) *1.54(1.21, 1.95)*	86 (16.6) *1.65(1.31, 2.08)*	32 (21.1) *3.11(2.16, 4.74)*	393 (5.6) *1.00*	61 (10.3) *1.68(1.27, 2.22)*	78 (11.5) *1.89(1.48, 2.42)*	18 (15.4) *2.60(1.61, 4.20)*
Heart failure	227 (3.9) *1.00*	40 (7.3) *2.06(1.46, 2.89)*	33 (6.4) *1.41(0.97, 2.04)*	15 (9.9) *3.72(2.18, 6.35)*	177 (2.5) *1.00*	51 (8.6) *2.82(2.04, 3.89)*	47 (6.9) *2.23(1.60, 3.10)*	13 (11.0) *4.12(2.33, 7.30)*
Atrial fibrillation	60 (1.0) *1.00*	7 (1.3) *1.59(0.72, 3.53)*	12 (2.3) *2.67(1.41, 5.06)*	0 (0.0) -	65 (0.9) *1.00*	11 (1.9) *1.95(1.01, 3.75)*	20 (2.9) *3.16(1.90, 5.27)*	1 (0.8) *1.14(0.16, 8.26)*
Stroke	371 (6.4) *1.00*	54 (9.9) *1.59(1.19, 2.13)*	35 (6.8) *0.97(0.68, 1.38)*	12 (7.9) *1.84(1.03, 3.29)*	423 (6.1) *1.00*	59 (9.9) *1.29(0.97, 1.71)*	61 (9.0) *1.28(0.97, 1.68)*	14 (11.9) *1.82(1.06, 3.11)*
Aortic aneurysm	54 (0.9) *1.00*	6 (1.1) *1.38(0.59, 3.25)*	4 (0.8) *0.87(0.31, 2.44)*	4 (2.6) *5.60(1.99, 15.8)*	13 (0.2) *1.00*	0 (0.0) -	1 (0.1) *0.62(0.08, 4.78)*	1 (0.8) *3.64(0.43, 30.8)*
Venous thromboembolism	102 (1.7) *1.00*	10 (1.8) *1.32(0.68, 2.54)*	9 (1.7) *1.05(0.53, 2.10)*	2 (1.3) *1.33(0.33, 5.64)*	72 (1.0) *1.00*	6 (1.0) *1.00(0.43, 2.33)*	10 (1.5) *1.26(0.65, 2.46)*	1 (0.8) *0.92(0.13, 6.66)*

*** Principal discharge diagnosis**

10.3.5 Total hospitalisations for cardiovascular reasons

Both angina and an ischaemic ECG were associated with more subjects requiring at least one admission for a cardiovascular reason and also more admissions per patient. (Table 53) The high rate of death in patients with both angina and an abnormal ECG reduced the overall numbers and rate of admission in this sub-group.

Table 53 Total number of hospital admissions (and number per patient) for cardiovascular reasons (coded as principal discharge diagnosis) according to the presence or absence of angina and ischaemic ECG changes at baseline

	Men				Women			
	No angina / no ischaemic ECG (n =5834)	No angina / ischaemic ECG (n=545)	Angina/ no ischaemic ECG (n =517)	Angina / ischaemic ECG (n=152)	No angina / no ischaemic ECG (n =6961)	No angina / ischaemic ECG (n=594)	Angina/ no ischaemic ECG (n=681)	Angina / ischaemic ECG (n=118)
	N (admissions per patient)				N (admissions per patient)			
Any cardiovascular cause	4750 (0.81)	639 (1.17)	573 (1.11)	185 (1.22)	3679 (0.53)	558 (0.94)	640 (0.94)	133 (1.13)
Coronary heart disease	2062 (0.35)	249 (0.46)	262 (0.51)	75 (0.49)	1147 (0.16)	189 (0.32)	238 (0.35)	44 (0.37)
Myocardial infarction	1322 (0.23)	150 (0.28)	159 (0.31)	54 (0.36)	686 (0.10)	110 (0.19)	143 (0.21)	32 (0.27)
Heart failure	399 (0.07)	68 (0.12)	55 (0.11)	22 (0.14)	300 (0.04)	79 (0.13)	80 (0.12)	18 (0.15)
Atrial fibrillation	88 (0.02)	8 (0.01)	14 (0.03)	0 (0.00)	88 (0.01)	15 (0.03)	31 (0.05)	1 (0.01)
Stroke	562 (0.10)	103 (0.19)	53 (0.10)	19 (0.13)	750 (0.11)	100 (0.17)	99 (0.15)	23 (0.19)
Aortic aneurysm	83 (0.01)	8 (0.01)	4 (0.01)	4 (0.03)	20 (0.00)	0 (0.00)	4 (0.01)	2 (0.02)
Venous thromboembolism	120 (0.02)	16 (0.03)	11 (0.02)	2 (0.01)	95 (0.01)	9 (0.02)	10 (0.01)	1 (0.01)

10.3.6Death or hospitalisation from cardiovascular causes

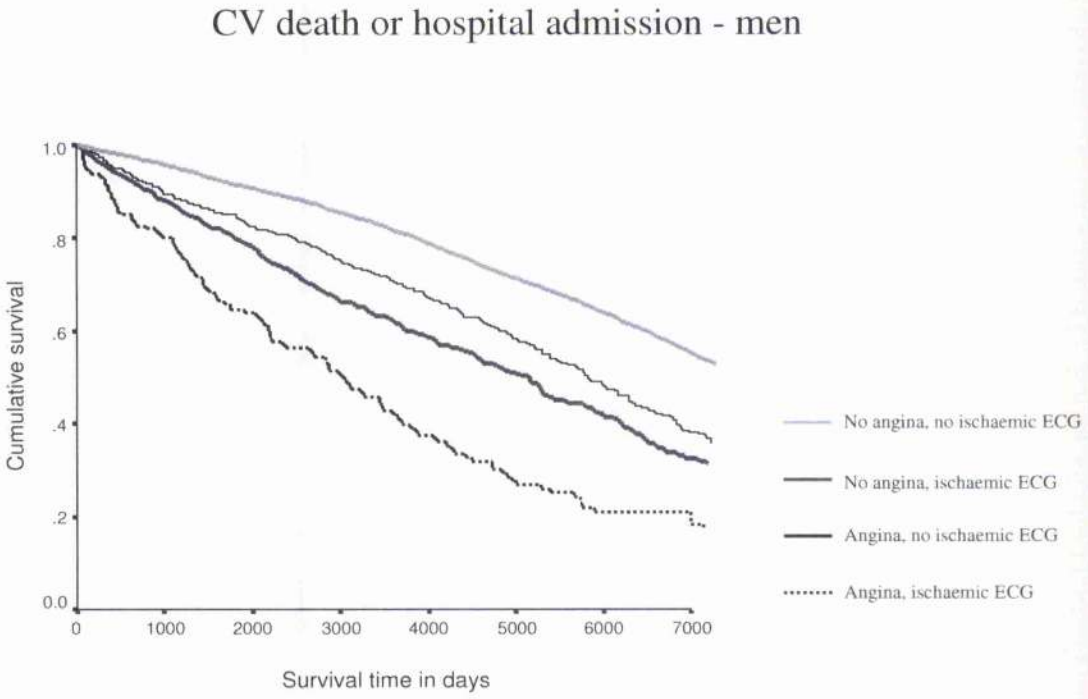
Men and women with angina were more likely than those without angina to experience a major non-fatal or fatal cardiovascular event. 61.6% of men with angina experienced such an event over the 20 years of follow-up, compared to 43.4% of those without angina ($p<0.001$). The corresponding figures for women were 45.9% and 30.9% respectively ($p<0.001$). 77.6% of men and 69.5% of women, with *both* angina and an abnormal ECG, experienced a major adverse cardiovascular event, compared to 56.9% of men and 41.9% of women with angina but a normal ECG ($p<0.001$). (Figure 20 and Table 54)

The adjusted relative risk of a major fatal or non-fatal cardiovascular event was increased to the same extent as the risk of death from a cardiovascular cause in individuals with angina. As with death, the increased risk of a major *coronary* event was even greater. Men with angina had an increased risk of cardiovascular death or hospitalisation (HR1.62 95%CI 1.46, 1.80), myocardial infarction (1.80 (1.56, 2.08)) and heart failure (1.62 (1.19, 2.19)) relative to men without angina. The corresponding hazard ratios for women were 1.48 (1.32, 1.65), 1.67 (1.41, 1.98) and 2.05 (1.55, 2.71).

As with death alone, the risk of either a major fatal or non-fatal event was increased by both angina and an ischaemic ECG, separately. The increase in risk was greater with an abnormal ECG. However, even those with angina, but without an abnormal ECG, had substantial and significant increases in risk of cardiovascular (40-50% increase) and coronary (70-80% increase) events, compared to individuals with neither angina nor an ischaemic ECG.

All of these risks were enhanced in subjects with angina *and* an abnormal ECG, in whom the relative risk of a major fatal or non-fatal coronary event was increased 4-fold in men and 3-fold in women (compared to individuals with neither angina nor an ischaemic ECG). Examination of composite fatal and non-fatal outcomes also showed that angina, an ischaemic ECG and, especially, both, were associated with an increased risk of death or hospitalisation due to heart failure and stroke (angina alone did not increase this latter risk in men).

Figure 20 Age-adjusted Cox survival curves for cardiovascular (CV) death or hospital admission according to the presence or absence of angina or ischaemic ECG changes in men and women



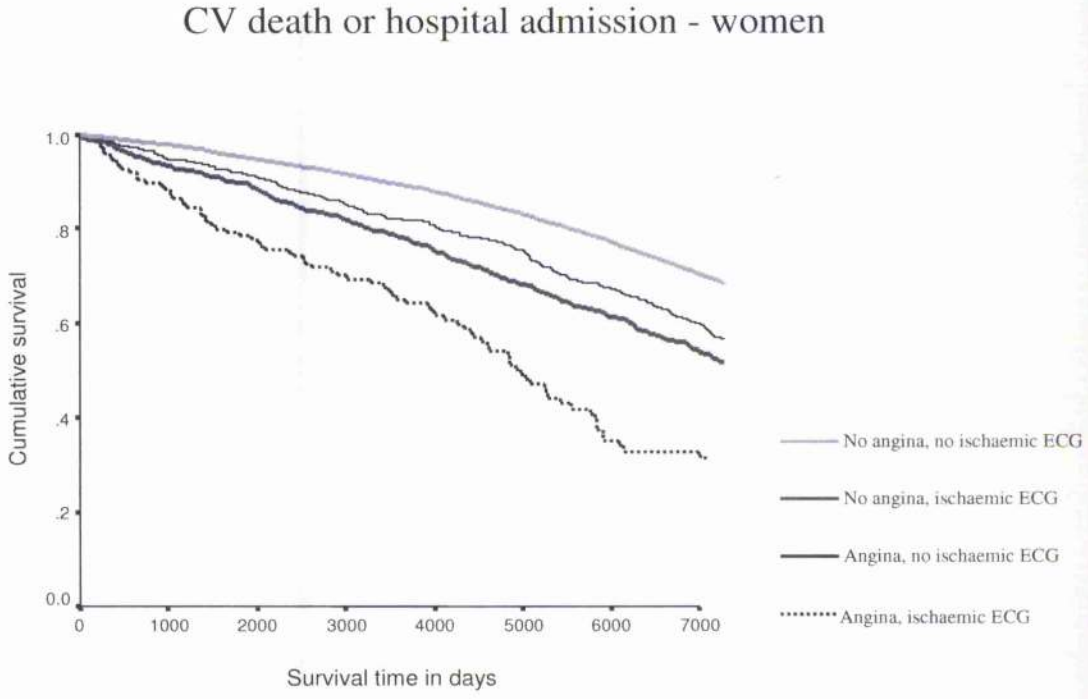


Table 54 Cardiovascular events* over 20 years according to the presence or absence of angina and ischaemic ECG changes at baseline. Adjusted risk of cardiovascular event over 20 years relative to those with no angina and no ischaemic changes

	Men				Women			
	No angina, no ischaemic ECG (n=5834)	**No angina, ischaemic ECG (n =545)**	**Angina, no ischaemic ECG (n=517)**	**Angina, ischaemic ECG (n =152)**	**No angina, no ischaemic ECG (n=6961)**	**No angina, ischaemic ECG (n =594)**	**Angina, no ischaemic ECG (n=681)**	**Angina, ischaemic ECG (n =118)**
	N (%) *HR (95% CI)*				N (%) *HR (95% CI)*			
Any cardiovascular cause	2421 (41.5) *1.00*	345 (63.3) *1.80(1.60, 2.01)*	294 (56.9) *1.46(1.29, 1.66)*	118 (77.6) *3.26(2.70, 3.93)*	2046 (29.4) *1.00*	292 (49.2) *1.59(1.40, 1.81)*	285 (41.9) *1.39(1.22, 1.57)*	82 (69.5) *2.82(2.26, 3.53)*
Coronary heart disease	1392 (23.9) *1.00*	224 (41.1) *1.97(1.71, 2.28)*	205 (39.7) *1.75(1.51, 2.03)*	91 (59.9) *3.96(3.19, 4.92)*	913 (13.1) *1.00*	155 (26.1) *1.83(1.54, 2.18)*	158 (23.2) *1.68(1.41, 1.99)*	48 (40.7) *2.96(2.20, 3.98)*
Myocardial infarction	1128 (19.3) *1.00*	186 (34.1) *1.92(1.64, 2.44)*	154 (29.8) *1.55(1.31, 1.84)*	80 (52.6) *4.10(3.25, 5.17)*	710 (10.2) *1.00*	117 (19.7) *1.70(1.39, 2.08)*	124 (18.2) *1.61(1.33, 1.95)*	39 (33.1) *2.85(2.05, 3.96)*
Heart failure	243 (4.2) *1.00*	42 (7.7) *2.02(1.45, 2.82)*	36 (7.0) *1.44(1.01, 2.07)*	16 (10.5) *3.71(2.21, 6.22)*	192 (2.8) *1.00*	57 (9.6) *2.92(2.15, 3.96)*	50 (7.2) *2.18(1.59, 3.00)*	15 (12.7) *4.30(2.52, 7.34)*
Atrial fibrillation	61 (1.0) *1.00*	7 (1.3) *1.57(0.71, 3.47)*	12 (2.3) *2.63(1.39, 4.98)*	0 (0.0) -	65 (0.9) *1.00*	12 (2.0) *2.07(1.10, 3.89)*	23 (3.4) *3.61(2.22, 5.87)*	1 (0.8) *1.10(0.15, 8.02)*
Stroke	473 (8.1) *1.00*	74 (13.6) *1.69(1.32, 2.17)*	40 (7.7) *0.85(0.61, 1.18)*	15 (9.9) *1.78(1.06, 2.99)*	523 (7.5) *1.00*	85 (14.3) *1.54(1.21, 1.95)*	75 (11.0) *1.28(1.00, 1.64)*	22 (18.6) *2.30(1.49, 3.55)*
Aortic aneurysm	67 (1.1) *1.00*	9 (1.7) *1.58(0.78, 3.21)*	5 (1.0) *0.82(0.33, 2.06)*	4 (2.6) *4.10(1.47, 11.5)*	19 (0.3) *1.00*	0 (0.0) -	2 (0.3) *0.85(0.20, 6.68)*	1 (0.8) *2.50(0.32, 19.9)*
Venous thromboembolism	115 (2.0) *1.00*	12 (2.2) *1.38(0.76, 2.54)*	10 (1.9) *1.03(0.54, 1.99)*	3 (2.0) *1.75(0.55, 5.57)*	77 (1.1) *1.00*	9 (1.5) *1.35(0.67, 2.73)*	11 (1.6) *1.15(0.59, 2.23)*	1 (0.8) *0.82(0.11, 5.96)*

***death or hospital admission**

10.3.7 Outcomes in men compared to women

The adjusted hazard for death from any cause in women with angina compared to men with angina was 0.51 (0.43, 0.60), p<0.001. Even after adjusting for the powerful effect of an ischaemic ECG (which was more commonly found in men), women had less than half the risk of men of any adverse cardiovascular outcome (Table 55). However, this difference was mainly explained by a lower risk of coronary events; the risk of stroke and heart failure was not lower in women.

Table 55 Adjusted risk* of fatal and non-fatal outcomes over 20 years in women compared to men with angina.

	Death	Hospital admission	Death or admission
	HR (95% confidence interval)		
Any cardiovascular cause	0.44 (0.35, 0.54)	0.60 (0.50, 0.73)	0.53 (0.45, 0.63)
Coronary heart disease	0.32 (0.25, 0.41)	0.49 (0.36, 0.64)	0.41 (0.33, 0.50)
Myocardial infarction	0.37 (0.28, 0.50)	0.49 (0.36, 0.67)	0.43 (0.34, 0.54)
Heart failure	1.05 (0.32, 3.44)	0.78 (0.50, 1.22)	0.80 (0.52, 1.22)
Atrial fibrillation	-	0.78 (0.35, 1.78)	0.86 (0.39, 1.92)
Cerebrovascular accident	1.49 (0.83, 2.69)	0.95 (0.61, 1.47)	1.11 (0.74, 1.65)
Aortic aneurysm	0.32 (0.02, 5.31)	0.18 (0.03, 0.98)	0.23 (0.05, 1.04)
Venous thromboembolism	-	0.54 (0.21, 1.41)	0.50 (0.20, 1.26)

*** Adjusted for age, ischaemic ECG, cholesterol, systolic blood pressure, adjusted FEV_1, smoking, social class, past history of diabetes.**

10.4Discussion

This population-based study describes, in a more complete way than previously, the mortality and morbidity burden associated with angina over a long period of follow-up. In particular, fatal and non-fatal outcomes are described in a large cohort of women who have, generally, been excluded from prior epidemiological studies of angina.

Although it has been suggested that angina is associated with a relatively good prognosis, the present analysis clearly shows otherwise.[416] Consideration of only fatal outcomes underestimates the adverse prognostic effect of an angina diagnosis.[50;417] While approximately 40% of men and 25% of women reporting this symptom in middle-age died from a cardiovascular cause, almost half of women and two thirds of men went on to experience a major fatal or non-fatal cardiovascular event over the next two decades. This study's findings in men closely support those of prior studies such as the Reykjavik Study, the Gothenburg Primary Prevention Study and the British Regional Heart Study.[50] I found that women had a better prognosis than men, as noted in the few prior studies to include both sexes.[31;53] This was especially true for coronary events (both fatal and non-fatal). Although men had a greater prevalence of certain adverse coronary prognostic factors (especially ECG evidence of ischaemia and infarction), women remained at lower risk after adjusting for these differences. Interestingly, however, women were less protected from non-coronary cardiovascular events including stroke, heart failure and atrial fibrillation. I do not know of any other reports of this discrepancy. Consequently, though women had only a 1 in 5 twenty-year risk of fatal or non-fatal myocardial infarction, compared to a 1 in 3 risk in men, the risks in women of stroke and heart failure were 1 in 8 and 1 in 12, respectively, compared to 1 in 12 and 1 in 13, respectively, in men. These differences may reflect the significantly greater systolic blood pressure (a powerful risk factor for stroke) and cardiothoracic ratio (a powerful risk factor for heart failure and atrial fibrillation) in women at baseline.

Why do women have a better survival than men? One explanation is that a higher proportion of women who are "Rose positive" for angina do not have cardiac disease.[6;327;418] Alternatively, women with definite angina and coronary heart disease have

better left ventricular systolic function than men (though they have as much heart failure).[419] Left ventricular systolic function is a very powerful predictor of death.

As described by others previously (and alluded to above), ischaemic changes on the ECG were found to be a powerful predictor of coronary death.[54;320] In addition, these changes were also strong predictors of non-fatal coronary events and of other non-fatal and fatal cardiovascular events such as heart failure and stroke. Indeed, an abnormal ECG was a more powerful predictor of all these adverse outcomes than the symptom of angina alone (i.e. in the absence of ischaemic changes on the ECG). Individuals with both an abnormal ECG *and* angina had the worst outcome, with a risk in men of 1 in 2 for myocardial infarction and 1 in 10 for stroke and heart failure. For women these risks were 1 in 3, 1 in 5 and 1 in 8, respectively. Indeed, more than three-quarters of men and more than two-thirds of women in this category experienced a major fatal or non-fatal cardiovascular event during follow-up.

It is, nevertheless, important to emphasise that angina without associated ECG changes (similar to "uncomplicated angina" in prior studies[13;22;30;54]) was still predictive of a poor outcome, even in women. However, as in the overall cohort, the risk of a coronary death in these subjects was increased to a greater extent in men (+71%) than women (+33%), whereas this difference was less for death from cardiovascular causes (+46% in men and +31% in women). There was also much less difference between men and women when combined fatal and non-fatal outcomes were considered, with an approximately 70-80% increase in risk of coronary events and 40-50% increase in risk of cardiovascular events in both sexes in this category (i.e. those with angina but without ECG changes).

This study has a number of limitations. Angina was documented at only one time point and spontaneous variation is well recognised.[417;420] The validity of the Rose questionnaire and which Rose categories should be included have been debated.[16;17;421] The study was conducted in an area with a high prevalence of coronary heart disease.[18] Morbidity (e.g. symptoms, functional limitation) not associated with hospital admission were not measured.[417] Records of coronary revascularisation either as an outcome or a treatment or information on medical treatment was not available. The prevalence of angina increases with increasing age[375] however by design our study looks at outcome in a group of middle-aged individuals. There is a possible lack of generalisability to other populations, as this is a cohort from Scotland and also because the inception of the cohort occurred thirty years ago. By necessity, this is a historical cohort, demographics and risk factor profiles have

changed in the time interval, and the cohort could not benefit from a number of recent treatments which are known to reduce morbidity and mortality in angina.[323;422-424] The mortality rate of individuals with angina in our study is higher than that reported in contemporary pharmaceutical trials. For example, the PEACE trial reported an 8.1% mortality rate at 5 years[425] and in the ACTION trial the mortality rate was 1.53 per 100 patient years[329] (Renfrew-Paisley angina cohort 5-year mortality rate 11.6% and 2.62 per 100 patient years). The mean age of patients was higher in both these studies (approx 63 years versus 56 years in our study). It is likely that contemporary pharmacological treatments and revascularisation options have improved outcome in patients with angina.

In summary, angina, as identified by the Rose questionnaire, is common and is associated with substantial long-term mortality and morbidity in both men and women. Consideration of only death (or death and myocardial infarction) greatly underestimates the public health burden related to angina. Of middle-aged subjects with angina, almost two thirds of men and half of women will die or require hospital admission for a cardiovascular reason over the subsequent 20 years. If these individuals have an ischaemic ECG, the proportions rise to more than three quarters of men and two thirds of women. Vigorous efforts to identify and treat subjects with angina (many of which, especially women,[426] are not known to the health care system[55;427]) could lead to substantial reductions in the direct and indirect burden of cardiovascular disease.[428;429]

11 LONG-TERM CARDIOVASCULAR CONSEQUENCES OF OBESITY: 20 YEAR FOLLOW-UP OF MORE THAN 15,000 MIDDLE AGED MEN AND WOMEN (THE RENFREW-PAISLEY STUDY).

11.1 Introduction

The prevalence of obesity has reached unprecedented proportions.[210] Nearly one third of Americans are obese.[211;212] It is estimated that there are up to 200 million obese citizens in the recently expanded European Union. The obesity epidemic is also affecting developing countries.[210] There is appropriate concern that this alarming trend will have major public health consequences globally, with evidence linking obesity to an increased risk of more than 30 medical conditions.[430]

One of the first medical consequences of obesity to be recognised was coronary heart disease.[224;235-237] Obesity, however, carries a broader cardiovascular risk though this has not been fully explored in any society. Neither the full range of cardiovascular problems related to obesity nor the complete burden, as measured by both fatal and non-fatal events, has been quantified in detail. In particular, the whole spectrum of cardiovascular problems related to obesity has not been evaluated in a single population-based cohort in order to compare the relative effect of obesity on different outcomes.

Between 1972 and 1976, the Renfrew-Paisley Study enrolled 7,048 men and 8,354 women, representing 80 per cent of individuals aged 45-64 years residing in these two towns in the west of Scotland.[8;185;313] Because of the large number of events over 20 years (3,028 cardiovascular deaths and 11,028 hospital admissions), this cohort provides the opportunity to quantify the entire cardiovascular burden of obesity in the long-term. Furthermore, when combined with monitored trends in body mass index in Scotland[321], this information enables projection of the future cardiovascular consequences likely to result from recent increases in the population prevalence of obesity.

11.2Methods

The Renfrew Paisley study database was used as described in chapter 3

11.3Results

11.3.1Baseline characteristics

The baseline characteristics of the Renfrew-Paisley cohort, divided into the different BMI categories, are shown in Table 56. Compared to individuals with a normal BMI, obese men and women had more risk factors for cardiovascular disease (with the notable exception of smoking), more clinical evidence of cardiovascular disease and more ECG abnormalities. Of particular note, the prevalence of diabetes was two-fold higher in obese subjects and systolic blood pressure was an average of more than 15 mmHg higher. Individuals who were "overweight" had a profile intermediate between that of those who were obese and men and women with a normal BMI.

Table 56 Characteristics of the Renfrew-Paisley cohort, by body mass index category at baseline

	Men (n = 6992)			Women (n = 8152)			Both sexes (n=15144)		
	Normal (n = 2811)	Overweight (n = 3428)	Obese (n = 753)	Normal (n = 3830)	Overweight (n = 3065)	Obese (n = 1257)	Normal (n=6641)	Overweight (n=6493)	Obese (n=2010)
	N (%)			N (%)			N (%)		
Age (years)	54 ± 6	54 ± 6	54 ± 6	54 ± 5	55 ± 6†	55 ± 6†	54 ± 6	54 ± 6†	55 ± 6†
Cardiovascular risk factors									
Past history stroke	33 (1.2)	47 (1.4)	13 (1.7)	43 (1.1)	38 (1.2)	17 (1.4)	76 (1.1)	85 (1.3)	30 (1.5)
Rose angina	258 (9.2)	325 (9.5)	79 (10.5)	289 (7.5)	301 (9.8)**	190 (15.1)†	547 (8.2)	626 (9.6)**	269 (13.4)†
Current or ex-smoker	2444 (86.9)	2786 (81.3)†	586 (77.8)†	2408 (62.9)	1445 (47.1)†	514 (40.9)†	4852(73.1)	4231 (65.2)†	110 (54.7)†
Plasma cholesterol (mmol/L)	5.7 ± 0.9	6.0 ± 1.0†	6.0 ± 1.0†	6.4 ± 1.1	6.5 ± 1.1†	6.4 ± 1.1	6.1± 1.1	6.2± 1.1†	6.3 ± 1.1†
Diabetes	32 (1.1)	43 (1.3)	15 (2.0)	30 (0.8)	40 (1.3)	28 (2.2)†	62 (0.9)	83 (1.3)	43 (2.1)†
Clinical profile									
Body mass index (kg/m^2)	22.8 ± 1.6	27.1 ± 1.3†	32.1 ± 2.2†	22.5 ± 1.6	27.1 ± 1.4†	33.6 ± 3.6†	22.6 ± 1.6	27.1 ± 1.4†	33.0 ± 3.2†
Systolic BP (mmHg)	145 ± 22	150 ± 23†	158 ± 24†	144 ± 23	153 ± 24†	164 ± 28†	145 ± 23	151 ± 24†	162± 27†
Diastolic BP (mmHg)	83 ± 13	87 ± 13†	94 ± 14†	81 ± 12	87 ± 12†	94 ± 15†	82 ± 12	87 ± 13†	94 ± 15†
Cardiothoracic ratio	0.45 ± 0.04	0.47 ± 0.04†	0.50 ± 0.05†	0.47 ± 0.05	0.49 ± 0.05†	0.51 ± 0.05†	0.46 ± 0.05	0.48 ± 0.05†	0.51 ± 0.05†
Blood glucose (mmol/L)	5.1 ± 1.3	5.2 ± 1.4*	5.5 ± 2.2†	5.0 ± 1.3	5.1 ± 1.5	5.3 ± 1.6†	5.0 ± 1.3	5.1 ± 1.4**	5.4 ± 1.9†
Adjusted FEV_1 (%)	86.0 ± 23.3	90.9 ± 21.4†	91.0 ± 19.9†	93.1 ± 23.1	93.4 ± 22.8	91.0 ± 23.6**	90.1 ± 23.5	92.1 ± 22.1†	91.0 ± 23.6
Chronic bronchitis	179 (6.4)	186 (5.4)	40 (5.3)	145 (3.8)	111 (3.6)	69 (5.5)**	324 (4.9)	297 (4.6)	109 (5.4)
Pathological Q waves on ECG	70 (2.5)	143 (4.2)†	27 (3.6)	56 (1.5)	69 (2.3)*	37 (2.9)**	126 (1.9)	212 (3.3)†	64 (3.2)**
ST segment changes on ECG	104 (3.7)	207 (6.0)†	45 (6.0)**	179 (4.7)	210 (6.9)†	115 (9.1)†	283 (4.3)	417 (6.4)†	160 (8.0)†
Left bundle branch block on ECG	15 (0.5)	19 (0.6)	3 (0.4)	15 (0.4)	14 (0.5)	12 (1.0)*	30 (0.5)	33 (0.5)	15 (0.7)
Atrial fibrillation on ECG	15 (0.5)	32 (0.9)	6 (0.8)	21 (0.5)	18 (0.6)	5 (0.4)	36 (0.5)	50 (0.8)	11 (0.5)

BMI= body mass index

Difference between overweight and obese category compared to the normal weight category: *p<0.05, **p<0.01, †p<0.001

11.3.2Death from any cause over 20-years of follow-up

51.2% of obese men died within 20 years of screening, compared to 48.9% of men with a normal BMI (p value for BMI as a continuous variable =0.285, Table 57). The corresponding figures for women were 39.2% and 29.8% respectively (p=0.015). The adjusted HR (95% CI) of death (compared to those with a normal BMI) was 1.16 (1.03, 1.30) in obese men and 1.23 (1.11, 1.37) in obese women. The proportion of "overweight" men who died was 45.5% (1.00 (0.93, 1.08)) and in women this proportion was 29.3% (0.95 (0.87, 1.04)). There was evidence of a quadratic trend for death in men (p value for BMI squared = 0.001) and women (p<0.001).

11.3.3Death from cardiovascular causes over 20 years of follow-up

Compared to individuals with a normal BMI, a significantly higher proportion of obese men and women died from a cardiovascular cause (men 35.6% compared to 23.2% p<0.001; women 25.5% compared to 15.6%, p<0.001) (Figure 21 and Table 57). The adjusted HR of cardiovascular death was 1.49 (1.28, 1.72) in obese men and 1.45 (1.25, 1.67) in obese women, compared to individuals with a normal BMI. The risk of death from a cardiovascular cause was increased in men in the overweight category (1.14 (1.03, 1.26)) but not in women (0.92 (0.81, 1.05)).

11.3.4Death from coronary heart disease over 20 years of follow-up

Obese men (HR 1.60 95% CI 1.35, 1.90) and women (1.44 (1.19, 1.74)) were more likely to die from coronary heart disease. Again the risk of death from coronary heart disease was increased in men in the overweight category (1.19 (1.06, 1.35)) but not in women (0.99 (0.83, 1.16)) (Table 57). Examination of deaths attributed to acute myocardial infarction showed similar findings.

11.3.5 Death from non-coronary cardiovascular causes over 20 years of follow-up

There were many fewer deaths from stroke than from coronary heart disease and only a small number of deaths from heart failure, venous thromboembolism and atrial fibrillation, making assessment of their risk related to obesity unreliable. Examination of combined fatal and non-fatal outcomes gives a more reliable estimate of risk (see below).

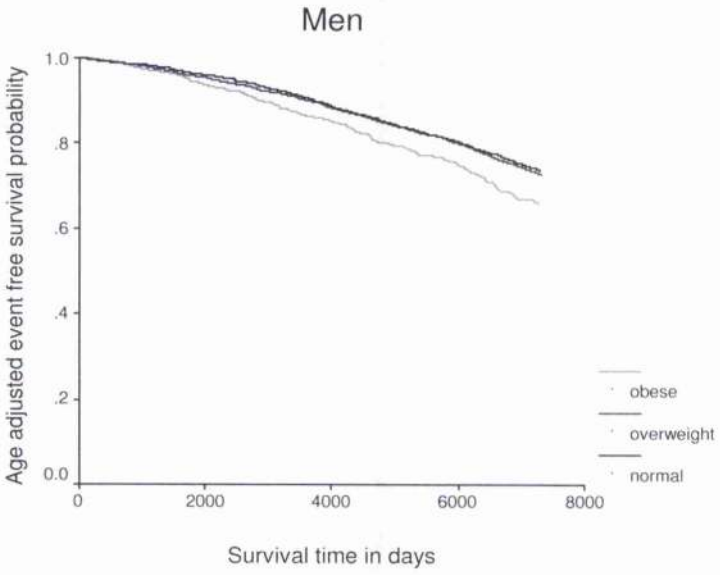
Table 57 Principal cause of death according to body mass index category

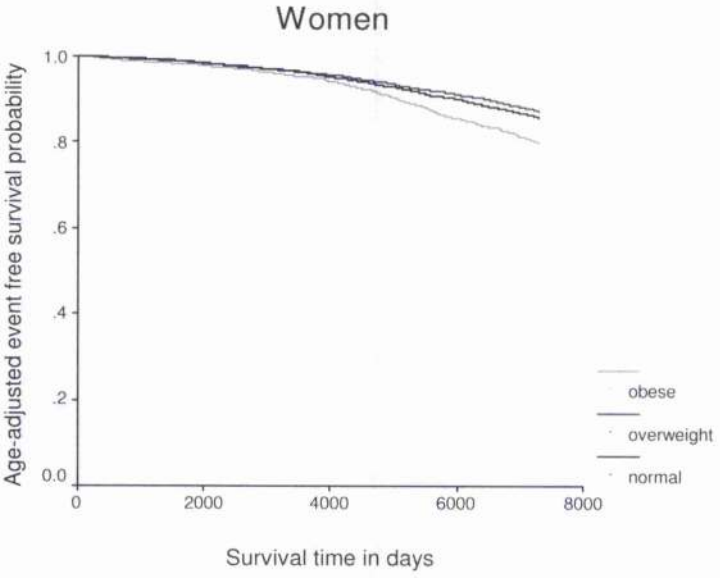
	Men			Women			Both		
	Normal (n=2811)	**Overweight (n=3428)**	**Obese (n=753)**	**Normal (n=3830)**	**Overweight (n=3065)**	**Obese (n=1257)**	**Normal (n=6641)**	**Overweight (n=6493)**	**Obese (n=2010)**
	N (%) *HR (95% CI)*			N (%) *HR (95% CI)*			N (%) *HR (95% CI)*		
Any cause	1373 (48.8) *1.00*	1556 (45.4)** *1.00 (0.93, 1.08)*	385 (51.1) *1.16 (1.03, 1.30)*	1141 (29.8) *1.00*	(29.6) *0.95 (0.87, 1.04)*	493 (39.2)† *1.23 (1.11, 1.37)*	2514 (37.9) *1.00*	2462 (37.8) *0.97 (0.92, 1.03)*	878 (43.7)† *1.18 (1.09, 1.28)*
Any CV cause	653 (23.2) *1.00*	866 (25.3) *1.14 (1.03, 1.26)*	242 (32.1)† *1.49 (1.28, 1.73)*	542 (14.2) *1.00*	435 (14.2) *0.93 (0.81, 1.05)*	290 (23.1)† *1.45 (1.25, 1.67)*	1195 (18.0) *1.00*	1301 (20.0)** *1.06 (0.98, 1.15)*	532 (26.5)† *1.49 (1.34, 1.65)*
CHD	453 (16.1) *1.00*	637 (18.6)* *1.19 (1.06, 1.35)*	183 (24.3)† *1.60 (1.35, 1.91)*	318 (8.3) *1.00*	264 (8.6) *0.99 (0.84, 1.16)*	164 (13.0)† *1.44 (1.19, 1.74)*	771 (11.6) *1.00*	901 (13.9)† *1.12 (1.02, 1.24)*	347 (17.3)† *1.54 (1.36, 1.75)*
AMI	366 (13.0) *1.00*	537 (15.7)** *1.24 (1.08, 1.41)*	142 (18.9)† *1.53 (1.26, 1.86)*	263 (6.9) *1.00*	223 (7.3) *1.01 (0.85, 1.22)*	144 (11.5)† *1.54 (1.25, 1.89)*	629 (9.5) *1.00*	760 (11.7)† *1.16 (1.04, 1.29)*	286 (14.2)† *1.55 (1.35, 1.79)*
Stroke	122 (4.3) *1.00*	145 (4.2) *1.04 (0.81, 1.32)*	34 (4.5) *1.14 (0.77, 1.69)*	169 (4.4) *1.00*	123 (4.0) *0.79 (0.63, 1.01)*	87 (6.9)† *1.33 (1.02, 1.73)*	291 (4.4) *1.00*	268 (4.1) *0.90 (0.76, 1.07)*	121 (6.0)** *1.27 (1.03, 1.57)*
Heart failure	13 (0.5) *1.00*	21 (0.6) *1.40 (0.70, 2.82)*	14 (1.9)† *4.33 (2.02, 9.30)*	18 (0.5) *1.00*	13 (0.4) *0.82 (0.40, 1.68)*	12 (1.0) *1.77 (0.84, 3.72)*	31 (0.5) *1.00*	34 (0.5) *1.05 (0.64, 1.72)*	26 (1.3)† *2.67 (1.57, 4.53)*
VTE	8 (0.3) *1.00*	12 (0.4) *1.15 (0.46, 2.85)*	2 (0.3) *0.86 (0.18, 4.10)*	2 (0.1) *1.00*	7 (0.2) *3.56 (0.73, 17.35)*	7 (0.6)** *7.85 (1.60, 38.65)*	10 (0.2) *1.00*	19 (0.3) *1.71 (0.79, 3.72)*	9 (0.4)* *2.69 (1.08, 6.68)*
AF	0 (0.0) *1.00*	1 (0.0) -	0 (0.0) -	1 (0.0) *1.00*	0 (0.0) -	3 (0.2)* *5.07 (0.49, 52.93)*	1(0.0) *1.00*	1 (0.0) *0.98 (0.06, 15.90)*	3 (0.1)* *7.54 (0.34, 79.90)*

Difference between overweight and obese category compared to the normal weight category: *p<0.05, **p<0.01, †p<0.001

BMI= body mass index; CV= cardiovascular; CHD= coronary heart disease; AMI= myocardial infarction; AF= atrial fibrillation; VTE= venous thromboembolism

Figure 21 Age adjusted event free survival in men and women for cardiovascular death





11.3.6 Hospitalisations for cardiovascular causes over 20 years of follow-up

The excess risk of cardiovascular hospitalisations associated with obesity was broadly similar to the increased risk of cardiovascular death (Table 58). Table 59 shows the total number of hospitalisations for different cardiovascular reasons over 20 years of follow-up. Obesity was associated not only with more subjects requiring at least one admission for a cardiovascular reason but also more admissions per patient. Overweight patients were at intermediate risk. Obesity accounted for an "extra" 600 (95%CI 530, 670) admissions (difference between the observed and expected number of admissions) for cardiovascular reasons (an increase of 47%) amongst the 2,010 individuals in this BMI category i.e. 30 per 100 extra admissions. Heart failure accounted for the greatest proportional increase (138%) in hospital episodes related to obesity (i.e. 139 (95%CI 119, 159) extra heart failure admissions).

This was because of a two fold increase in the rate of two admissions ($p=0.001$) and a four fold increase in the rate of three or more admissions ($p<0.001$) in obese compared to normal weight individuals.

The prevalence of "overweight" was much greater than that of obesity. Consequently, though the relative risk related to "overweight" was less, the absolute number of events attributable to overweight was greater. Overweight accounted for an additional 884 (95%CI 759, 1009) cardiovascular hospitalisations (an increase of 22%) amongst the 6,493 individuals in this BMI category i.e. 14 per 100 extra admissions.

Table 58 Patients with at least one hospital admission for a cardiovascular cause (coded as principal discharge diagnosis) according to body mass index category

	Men			Women			Both		
	Normal (n=2811)	**Overweight (n=3428)**	**Obese (n=753)**	**Normal (n=3830)**	**Overweight (n=3065)**	**Obese (n=1257)**	**Normal (n=6641)**	**Overweight (n=6493)**	**Obese (n=2010)**
	N (%) *HR (95% CI)*			N (%) *HR (95% CI)*			N (%) *HR (95% CI)*		
Any CV cause	875 (31.1) *1.00*	1201 (35.0)** *1.16 (1.06, 1.26)*	295 (39.2)† *1.38 (1.21, 1.58)*	904 (23.6) *1.00*	789 (25.7)* *1.09 (0.99, 1.20)*	408 (32.5)† *1.43 (1.27, 1.61)*	1779 (26.8) *1.00*	1990 (30.6)† *1.13 (1.06, 1.21)*	703 (35.0)† *1.41 (1.29, 1.54)*
CHD	366 (13.0) *1.00*	574 (16.7)† *1.28 (1.12, 1.46)*	145 (19.3)† *1.56 (1.28, 1.89)*	306 (8.0) *1.00*	289 (9.4)* *1.19(1.01, 1.40)*	165 (13.1)† *1.69 (1.39, 2.03)*	672 (10.1) *1.00*	863 (13.3)† *1.25 (1.13, 1.38)*	310 (15.4)† *1.64 (1.43, 1.87)*
AMI	293 (10.4) *1.00*	438 (12.8)** *1.20 (1.03, 1.39)*	115 (15.3)† *1.51 (1.22, 1.88)*	222 (5.8) *1.00*	205 (6.7) *1.18 (0.97, 1.43)*	114 (9.1)† *1.59 (1.26, 2.00)*	515 (7.8) *1.00*	643 (9.9)† *1.20 (1.07, 1.35)*	229 (11.4)† *1.57 (1.34, 1.83)*
Stroke	177 (6.3) *1.00*	231 (6.7) *1.14 (0.93, 1.39)*	64 (8.5)* *1.53 (1.14, 2.04)*	226 (5.9) *1.00*	197 (6.4) *1.01 (0.84, 1.23)*	119 (9.5)† *1.49 (1.19, 1.87)*	403 (6.1) *1.00*	428 (6.6) *1.07 (0.93, 1.23)*	183 (9.1)† *1.51 (1.26, 1.80)*
Heart failure	102 (3.6) *1.00*	149 (4.3) *1.32 (1.02, 1.70)*	64 (8.5)† *2.76 (2.01, 3.78)*	100 (2.6) *1.00*	112 (3.7)* *1.30 (0.99, 1.71)*	67 (5.3)† *1.83 (1.33, 1.50)*	202 (3.0) *1.00*	261 (4.0)** *1.31 (1.09, 1.58)*	131 (6.5)† *2.23 (1.78, 2.78)*
VTE	39 (1.4) *1.00*	64 (1.9) *1.32 (0.88, 1.98)*	20 (2.7)* *1.95 (1.13, 3.36)*	28 (0.7) *1.00*	38 (1.2)* *1.73 (1.05, 2.83)*	23 (1.8)** *2.59 (1.48, 4.54)*	67 (1.0) *1.00*	102 (1.6)** *1.44 (1.05, 1.97)*	31 (1.5)** *2.15 (1.46, 3.17)*
AF	29 (1.0) *1.00*	42 (1.2) *1.19 (0.74, 1.92)*	7 (0.9) *0.96 (0.42, 2.20)*	37 (1.0) *1.00*	32 (2.0)* *1.02 (0.63, 1.65)*	25 (32.5)† *2.04 (1.22, 3.43)*	66 (1.0) *1.00*	74 (1.1)† *1.13 (0.80, 1.57)*	32 (1.6)† *1.65 (1.07, 2.52)*

Difference between overweight and obese category compared to the normal weight category: *p<0.05, **p<0.01, †p<0.001

BMI= body mass index; CV= cardiovascular; CHD= coronary heart disease; AMI = myocardial infarction; AF= atrial fibrillation; VTE= venous thromboembolism

Table 59 Total number of hospital admissions (admissions per patient) for each cardiovascular event (coded as principal discharge diagnosis) according to body mass index category

	Men (n = 6992)			Women (n = 8152)			Both sexes (n=15144)				
	Normal (n = 2811)	Overweight (n = 3428)	Obese (n = 753)	Normal (n = 3830)	Overweight (n = 3065)	Obese (n = 1257)	Normal (n=6641)	Overweight (n=6493)		Obese (n=2010)	
								Observed	Expected	Observed	Expected
Any CV cause	2182 (0.78)	3091 (0.90)	859 (1.14)	2005 (0.52)	1884 (0.61)	1007 (0.80)	4187 (0.63)	4975 (0.77)	4091	1866 (0.93)	1266
CHD	892 (0.32)	1396 (0.41)	357 (0.47)	659 (0.17)	597 (0.19)	346 (0.28)	1551 (0.23)	1993 (0.31)	1493	703 (0.35)	462
AMI	605 (0.22)	865 (0.25)	212 (0.28)	399 (0.10)	367 (0.12)	195 (0.16)	1004 (0.15)	1232 (0.19)	974	407 (0.20)	302
Stroke	262 (0.09)	360 (0.11)	115 (0.15)	369 (0.10)	347 (0.11)	219 (0.17)	631 (0.10)	707 (0.11)	649	334 (0.17)	201
Heart failure	161 (0.06)	255 (0.07)	128 (0.17)	144 (0.04)	211 (0.07)	112 (0.09)	305 (0.05)	466 (0.07)	325	240 (0.12)	101
VTE	45 (0.02)	74 (0.02)	30 (0.04)	37 (0.01)	49 (0.02)	29 (0.02)	82 (0.01)	123 (0.02)	65	59 (0.03)	20
AF	44 (0.02)	55 (0.02)	8 (0.01)	51 (0.01)	44 (0.01)	37 (0.03)	95 (0.01)	99 (0.02)	65	45 (0.02)	20

BMI= body mass index; CV= cardiovascular; CHD = coronary heart disease; AMI = myocardial infarction; AF= atrial fibrillation; VTE = venous thromboembolism

11.3.7Death or hospitalisation for cardiovascular causes over 20 years of follow-up

58.6% of obese men died from, or were admitted to hospital for a cardiovascular reason compared to 47.9% of men in the normal BMI category (p<0.001) (Table 60 and Figure 23). The risk for overweight men (50.6%) was intermediate. The adjusted HR was 1.44 (1.29, 1.61) for obese men and 1.15 (1.06, 1.24) for overweight men. The picture for women was similar; 45.6% of obese women died or were admitted to hospital (HR 1.44, (1.30, 1.60)) compared to 34.0% of overweight women (HR 1.06 (0.97, 1.15)) and 32.0% of women with a normal BMI. The pattern for deaths and admissions related to coronary heart disease were similar.

Examination of the composite of hospital admission or death doubled the number of individuals experiencing a stroke (n=1288). The proportion of men and women admitted to hospital with a stroke was increased in obese subjects. The adjusted HR was 1.33 (1.03, 1.73) for obese men and 1.47 (1.20, 1.80) for obese women.

The addition of hospital admissions to deaths increased the total number of patients experiencing a heart failure related event seven-fold (n=641). Obesity increased the adjusted risk of heart failure in men (2.61 (1.92, 3.56)) and women (1.70 (1.26, 2.30)). Obesity also increased the risk of fatal and non-fatal episodes of venous thromboembolism in men (1.89 (1.13, 3.17)) and women (2.91 (1.72, 4.94)). Patients in the overweight category had an intermediate risk. There was no increase in the adjusted risk of atrial fibrillation in men though this risk was increased in obese women (2.18 (1.31, 3.56)) (Table 60).

For every 1 kg/m^2 increase in BMI there was a 4% increased risk of myocardial infarction (1.04 (1.03, 1.05)), a 3% increased risk of stroke (1.03 (1.01, 1.04)), a 6% increased risk of heart failure (1.06 (1.04, 1.08)), a 8% increased risk of venous thromboembolism (1.08 (1.05, 1.11)) and a 5% increased risk of atrial fibrillation (1.05 (1.01, 1.08)).

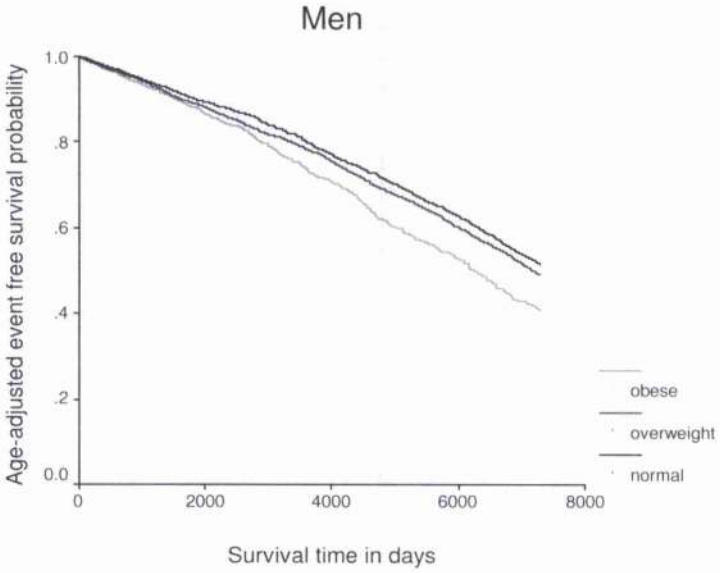
Table 60 Fatal or non-fatal cardiovascular events (death or hospital admission) according to body mass index category

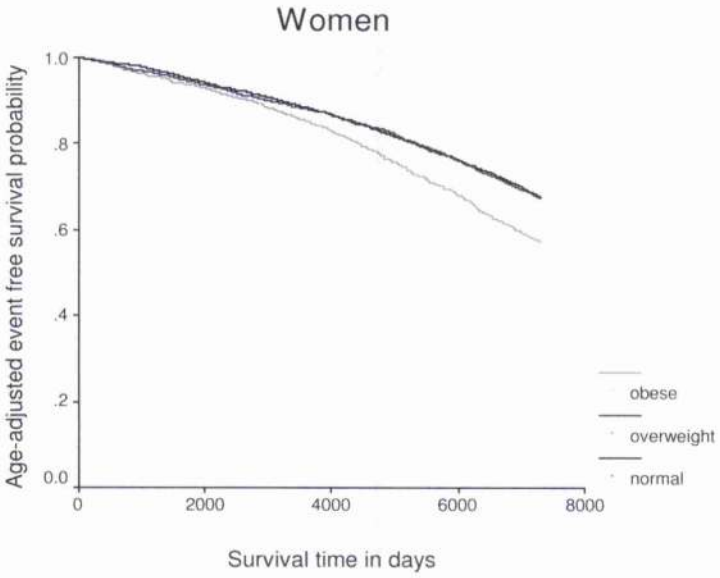
	Men			Women			Both		
	Normal (n=2811)	**Overweight (n=3428)**	**Obese (n=753)**	**Normal (n=3830)**	**Overweight (n=3065)**	**Obese (n=1257)**	**Normal (n=6641)**	**Overweight (n=6493)**	**Obese (n=2010)**
	N (%) *HR (95% CI)*			N (%) *HR (95% CI)*			N (%) *HR (95% CI)*		
Any CV cause	1174 (41.8) *1.00*	1580 (46.1)** *1.15 (1.06, 1.24)*	408 (54.2)† *1.44(1.29, 1.61)*	1131 (29.5) *1.00*	968 (31.6) *1.06 (0.97, 1.16)*	529 (42.1)† *1.44 (1.30, 1.60)*	2305 (34.7) *1.00*	2548 (39.2)† *1.11 (1.05, 1.18)*	937 (46.6)† *1.45 (1.34, 1.57)*
CHD	660 (23.5) *1.00*	977 (28.5)† *1.24 (1.12, 1.37)*	264 (35.1)† *1.60 (1.38, 1.85)*	518 (13.5) *1.00*	452 (14.7) *1.07 (0.94, 1.22)*	271 (21.6)† *1.56 (1.34, 1.81)*	1178 (17.1) *1.00*	1429 (22.0)† *1.18 (1.09, 1.28)*	535 (26.6)† *1.60 (1.45, 1.78)*
AMI	541 (19.2) *1.00*	787 (23.0)† *1.21 (1.08, 1.35)*	212 (28.2)† *1.54 (1.31, 1.81)*	398 (10.4) *1.00*	354 (11.5) *1.10 (0.95, 1.27)*	212 (16.9)† *1.57 (1.33, 1.86)*	939 (14.1) *1.00*	1141 (17.6)† *1.17 (1.07, 1.28)*	424 (21.1)† *1.57 (1.40, 1.77)*
Stroke	241 (8.6) *1.00*	283 (8.3) *1.02 (0.86, 1.21)*	77 (10.2) *1.33 (1.03, 1.73)*	292 (7.6) *1.00*	243 (7.9) *0.97 (0.81, 1.15)*	152 (12.1)† *1.47 (1.20, 1.79)*	533 (8.0) *1.00*	526 (8.1) *0.99 (0.88, 1.12)*	229 (11.4)† *1.41 (1.21, 1.65)*
Heart failure	111 (3.9) *1.00*	160 (4.7) *1.30 (1.02, 1.67)*	66 (8.8)† *2.61 (1.92, 3.56)*	114 (3.0) *1.00*	119 (3.9)* *1.22 (0.94, 1.58)*	71 (5.6)† *1.70 (1.26, 2.30)*	225 (3.4) *1.00*	279 (4.3)** *1.26 (1.05, 1.50)*	137 (6.8)† *2.08 (1.68, 2.58)*
VTE	44 (1.6) *1.00*	74 (2.2) *1.35 (0.92, 1.97)*	22 (2.9)* *1.89 (1.13, 3.17)*	29 (0.8) *1.00*	40 (1.3)* *1.71 (1.05, 2.77)*	28 (2.2)† *2.91 (1.72, 4.94)*	73 (1.1) *1.00*	114 (1.8)** *1.47 (1.09, 1.98)*	50 (2.5)† *2.29 (1.60, 3.30)*
AF	29 (1.0) *1.00*	43 (1.3) *1.22 (0.76, 1.96)*	7 (0.9) *0.97 (0.42, 2.22)*	38 (1.0) *1.00*	32 (1.0) *0.99 (0.61, 1.59)*	28 (2.2)** *2.18 (1.33, 3.60)*	67 (1.0) *1.00*	73 (1.2) *1.12 (0.81, 1.57)*	35 (1.7)* *1.76 (1.17, 2.66)*

Difference between overweight and obese category compared to the normal weight category: *p<0.05, **p<0.01, †p<0.001
CV= cardiovascular; CHD= coronary heart disease; AMI= myocardial infarction; AF= atrial fibrillation; VTE= venous thromboembolism

Figure 22 Age adjusted event free survival in men and women for cardiovascular death or hospital admissionMI= myocardial infarction; AF= atrial fibrillation; VTE= venous thromboembolism

Figure 23 Age adjusted event free survival in men and women for cardiovascular death or hospital admission





11.3.8Fully adjusted risk of death or hospitalisation for cardiovascular causes over 20 years of follow-up

When we included diabetes, cholesterol and hypertension in the multivariable analysis obesity remained an independent risk factor for any cardiovascular hospitalisation or death in men (HR 1.21 (95% CI 1.08, 1.36)) and women (1.22 (1.10, 1.36)) and for a coronary heart disease event in men (1.32 (1.14, 1.53)) and women (1.30 (1.11, 1.51)). Obesity also increased the risk of heart failure (men 2.16 (1.57, 2.97); women 1.37 (1.00, 1.88)), venous thromboembolism (men 1.92 (1.13, 3.26); women 2.90 (1.67, 5.01)) and atrial fibrillation in women (1.76 (1.04, 2.98)) although it was no longer an independent risk factor for stroke (men 1.04 (0.79, 1.35); women 1.17 (0.95, 1.44)).

11.3.9Potential consequences of increase in obesity

Using the above data it is possible to estimate the cardiovascular consequences of the increase in prevalence of obesity from the time of the initial Renfrew-Paisley study screening (1972-1976) and the present day. A recent survey showed that the prevalence of obesity in Scotland has risen to 28.8% in men and 26.0% in women aged 45-54 years and 23% in men and 31.5% in women aged 55-64 years in 1998. We applied the rate of cardiovascular events seen in the Renfrew-Paisley cohort to the Scottish obese population in 1972 and 1998. The number of obese Scots aged 45-64 years in 1972 and 1998 was calculated using age specific population estimates and the obesity prevalence for each year. The difference between the numbers of obese men and women experiencing a cardiovascular event in both years was expressed per 100 men and women in Scotland in 1998. Assuming the cardiovascular risk profile and outcomes associated with obesity have remained unchanged, the increase in prevalence of obesity between 1976 and 1998 is expected to lead to an additional 9 (95% CI 8.7, 9.9) per 100 men and an additional 5 (5.5, 6.2) per 100 women experiencing a cardiovascular event (death or hospital admission) between 1998 and 2018. The increase in obesity is also projected to lead to an extra 18 (17.7, 18.6) hospital admissions for cardiovascular disease per 100 men and 10 (10.0, 10.6) per 100 women over this period.

The increased prevalence of men and women in the overweight category is expected to result in an additional 1 (1.0, 1.1) per 100 cardiovascular events and an additional 1.9 (1.9, 1.9) per 100 cardiovascular hospital episodes in men (the corresponding figures for women would be 0.04 (0.04, 0.04) per 100 and 0.07 (0.07, 0.07) per 100).

11.4Discussion

I have been able to examine the association between obesity and a broad spectrum of cardiovascular events in a single, large, population-based cohort followed for 20 years and examine the rates and rankings of these outcomes. The principal finding of this study is that the harmful cardiovascular effects of obesity extend beyond coronary heart disease though, numerically, coronary events account for the greatest proportion of all cardiovascular events.

In the Renfrew-Paisley cohort, obesity was also associated with an increased, long-term, risk of fatal and non-fatal (and recurrent) heart failure, venous thromboembolism, atrial fibrillation (in women) and, probably, stroke. Consideration of only coronary events, only fatal events and only first events, therefore, greatly underestimates the cardiovascular burden of obesity.

Stroke and heart failure were, numerically, the two next most frequent adverse cardiovascular outcomes after coronary heart disease. The comparative risk of these two outcomes differed between men and women across the range of body mass index.

Heart failure was relatively more common in men but there was a clear association between obesity and an increased risk of heart failure in both sexes. Indeed, the relative risk of a heart failure event was greater than that for any other type of cardiovascular event, including coronary events, with the exception of the much less common problem of venous thromboembolism (see below). Obesity was also particularly associated with multiple hospital admissions for heart failure which is important given the huge symptom burden and cost related to heart failure.

Another equally dreaded and expensive cardiovascular complication is stroke. This was relatively more common in women but, unlike heart failure, the fully adjusted relative risk

of this outcome was not statistically significantly increased, in relation to obesity. This finding is consistent with other studies which have also demonstrated no consistent relationship between obesity and stroke in prior studies.[237;245-248;251-253] There seem to be a number of explanations for this. The risk of stroke related to obesity may be different in men and women and for ischaemic compared to haemorrhagic stroke.[245;247] More contentious is the completeness of adjustment for baseline co-variables. Two separate multivariable analyses are reported, one excluding and one including blood pressure, cholesterol and diabetes. There has been much debate as to whether these obesity related variables should be adjusted for when examining the independent effect of obesity on cardiovascular outcomes. Clearly, doing so attenuates the strength of the relationship between obesity and stroke (and other cardiovascular outcomes).

Venous thromboembolic events were infrequent compared to heart failure or stroke. However, the adjusted risk for thromboembolism was increased *relatively* more than for any other adverse cardiovascular outcome. Increased risk of thromboembolism has been reported before but no comparison with the rate and risk of other cardiovascular events has been provided.[260-262]

Lastly, I also looked at the relationship between obesity and atrial fibrillation which was also infrequent and relatively more common in women. The adjusted relative risk for the composite of death or hospital admission was increased, significantly, in women but not in men though this apparent difference may not be real and may simply reflect low power due to small numbers. The few prior reports on the relation between obesity and atrial fibrillation have given inconsistent results.[164;174;259]

Overall, obesity was associated with 9 additional cardiovascular deaths and 36 additional cardiovascular hospital admissions for every 100 affected middle-aged men over the subsequent 20 years; for women these numbers were 9 and 28, respectively. Clearly, the rise in the prevalence of obesity may result in a rise in cardiovascular events although the calculated number of these events given in the "Results" section may be excessive, as newer preventive treatments such as blood-pressure and cholesterol lowering, as well as a fall in smoking prevalence, are likely to have reduced the risk related to obesity in more recent times.

This study has several limitations. A small proportion of individuals had heart disease at initial screening and this wasn't adjusted for in the analysis. The main analysis did not adjust for cholesterol, diabetes and hypertension as it is impossible to disentangle the effect of these different factors from each other and they are important mediators in the risk between obesity and cardiovascular disease; these factors were however, included in a separate analysis to determine the independent effects of obesity. These figures have, of course, only quantified the cardiovascular burden of obesity as reflected by death and hospital admission. Clearly there was also a potentially huge additional symptom burden related to cardiovascular disease which may not have led to admission or death e.g. angina, peripheral arterial disease, atrial fibrillation and heart failure. Hypertension was another cardiovascular consequence of obesity not directly measured in this study. The analysis may also have underestimated the true risk of obesity as body mass index was only measured at baseline and may increase beyond middle-age i.e. some of our "normal" body mass index group may have become obese during the follow-up period. There is also the possibility of unmeasured confounding factors contributing to the findings. There is a possible lack of generalisability to other populations, as this is a cohort from Scotland and because the inception of the cohort occurred thirty years ago. By design, the non-cardiovascular effects of obesity were not quantified.

In summary, obesity is associated with an increased long-term risk of cardiovascular death and hospital admission from a wide range of cardiovascular problems in addition to coronary heart disease. There are 3 to 4 times as many admissions as deaths related to obesity. The rising prevalence of obesity will have a potentially huge impact not only on individual health but on the population and hospital sector.

12 OVERALL DISCUSSION AND CONCLUSION

12.1 Findings from current studies

I have reported on the epidemiology of important cardiovascular conditions in Scotland using data from primary care (Continuous Morbidity Recording in General Practice Scheme), secondary care (Linked Scottish Morbidity Recording Scheme) and from a prospective cohort study (Renfrew-Paisley Study).

I used CMR data to examine the primary care burden of angina in Scotland. Most existing studies of angina were conducted over a decade ago, used selected cohorts or identified angina patients by either questionnaire or prescription data. In my study a GP reported diagnosis of angina was used. The prevalence of angina in Scotland was 28 per 1000 in men and 25 per 1000 in women ($p<0.05$) and increased with age. The incidence of angina was also higher in men (1.8 per 1,000) than in women (1.4 per 1000) ($p=0.004$) and also increased with increasing age. I also analysed current prescribing patterns for angina which is relevant given the emergence of new evidence-based treatments and the publication of guidelines. In men, 52% were prescribed β-blockers, 44% a calcium channel blockers, 72% aspirin, 54% statins and 36% ACE inhibitors or angiotensin receptor blockers. The corresponding prescription rates for women were 46% ($p<0.001$), 41% ($p=0.02$), 69% ($p<0.001$), 45% ($p<0.001$) and 30% ($p<0.001$). In patients under 75 years 52% were prescribed a β-blocker and 58% a statin. The corresponding figures for patients over 75 years were 42% ($p<0.001$) and 31% ($p<0.001$). These prescription rates were better than prior studies, however there is still scope for improvement. Guideline recommended treatments for angina were underused in women and the elderly and these discrepancies warrant further investigation. Deprived individuals were more likely to have angina but were less likely to consult their general practitioner. Despite this lower contact rate, deprived patients were less obviously under-treated than women or older individuals. In fact deprived patients were more likely to be treated with ACE inhibitors. These sub-optimal practice patterns show the potential value of this sort of analysis in raising questions about under treatment and inequalities in health care.

I have also examined the outcome of individuals with angina using the Renfrew-Paisley Study. Relatively little is known about the long-term natural history of angina at a population level, especially in women. Furthermore, most existing studies have focused on death or AMI however patients with angina are likely to be at increased risk of other complications of coronary heart disease (e.g. heart failure) and other non-cardiac vascular events (e.g. stroke). I have shown that angina in middle-age substantially increases the risk of death, myocardial infarction, heart failure and other cardiovascular events. All-cause mortality for those with angina on the Rose angina questionnaire was 67.7% in men and 43.3% in women at 20 years compared to 45.4% and 30.4% in those without angina ($p<0.001$). In a multivariable analysis, men with Rose angina had an increased risk of cardiovascular death or hospitalisation (HR 1.49 95%CI 1.33-1.66), myocardial infarction (1.63 (1.41-1.85)) and heart failure (1.54 (1.13-2.10)) relative to men without angina. The corresponding hazard ratios for women were 1.38 (1.23-1.55), 1.56 (1.31-1.85) and 1.92 (1.44-2.56). An abnormal ECG increased risk further and both angina and an abnormal ECG were associated with the highest risk of adverse events when compared to those with neither angina nor an ischaemic ECG. Relative to men with no angina and no ischaemic ECG changes, men with both angina and an abnormal ECG had a four fold increased risk of AMI and heart failure and a three fold increased risk of stroke (three fold, four fold and two fold for women respectively). Compared to men, women with Rose angina were less likely to have a cardiovascular event (HR 0.54 (0.46-0.64)), or myocardial infarction (0.44 (0.35-0.56)), though there was no sex difference in the risk of stroke (1.11 (0.75-1.65)), atrial fibrillation (0.84 (0.38-1.87)) or heart failure (0.79 (0.51-1.21)) which is a novel finding. These findings shed new light on the prognosis of angina, particularly in women, and have obvious public health implications. They strongly reinforce the need for vigorous attempts to identify and treat patients with angina to reduce the burden of cardiovascular disease.

I examined trends in hospitalisation rates for suspected acute coronary syndrome and the prognosis following a hospitalisation with suspected acute coronary syndrome in Scotland using the Scottish Morbidity Record Database between 1990 and 2000. There have been many studies looking at the incidence and case-fatality related to AMI, however, there is little information on the clinical epidemiology of hospitalised angina and other types of chest pain.

I have shown that the pattern of emergency admissions with heart disease to Scottish hospitals has changed dramatically over recent years. Between 1990 and 2000 the population hospitalisation rate for AMI declined by 33% while the population

hospitalisation rate for angina increased by 79% and for chest pain by 110%. Population hospitalisation rates for all suspected acute coronary syndromes (AMI, angina and chest pain) increased by 25% over the time period. These overall trends conceal striking age and sex differences e.g. the change in AMI and angina admissions has been greater in men than in women and the change in all groups has been greatest in the elderly. There are a number of potential explanations for this changing pattern of hospitalisations for acute coronary events, including an alteration in the natural history of coronary heart disease, changes in threshold for both admission and diagnosis over the period of study or more widespread use of anti-platelet or anti-thrombotic therapy. A new clinical challenge is the substantial increase in emergency admissions with chest pain. Regarding prognosis following a hospitalisation for suspected acute coronary syndrome, I have shown that emergency admissions with angina have a low risk of death in the short-term, but have a poor long-term prognosis. After excluding deaths within 30 days, crude five year case-fatality was 23.9% for men with angina versus 21.6% in men with acute myocardial infarction (23.5% versus 26.0% in women respectively). Furthermore, the longer-term risk of a subsequent fatal or non-fatal event within five years was high after both acute myocardial infarction (54% in men and 53% in women) and angina (56% and 49% respectively). Event rates after a hospitalisation for AMI or angina increased with increasing age and with different co-morbidities, but were lower in women than in men. These novel findings strengthen the case for aggressive secondary prevention in all patients presenting with an acute coronary syndrome.

In a study of the period 1988 to 1991, substantial variation in 30 day survival following admission with AMI was identified between hospitals in Scotland. Using the SMR scheme I re-examined inter-hospital variation in 30-day survival after AMI 10 years on (1998-2001) to see if the appointment of new Cardiologists and their involvement in emergency care has improved outcome after AMI. The average 30 day case-fatality rate following admission with an AMI has fallen substantially over the past 10 years. Between-hospital variation is also considerably less marked due to better survival in the previously poorly performing hospitals. Between 1988 and 1991, median 30 day survival was 79.2% (inter-hospital range 72.1-85.1%). The difference between highest and lowest hospital was 13.0% (age and sex adjusted 12.1%). Between 1998 and 2001, median survival rose to 81.6% (and range decreased to 78.0-85.6); difference 7.6% (8.8%). Admission hospital was an independent predictor of outcome at 30 days during the 2 time periods ($p<0.001$). Over the period 1988-1991, the odds ratio for death ranged between hospitals, from 0.71 (95% CI 0.58-0.88) to 1.51 (1.19-1.89) and, for the period 1998-2001 from 0.82 (0.60-1.13) to 1.46

(1.07-1.19). The adjusted risk of death was significantly higher than average in 9 of 26 hospitals between 1988 and 1991 but in only 2 hospitals between 1998 and 2001. It seems likely that the greater involvement of Cardiologists in the management of AMI has contributed to this reduction in between-hospital variation in short term case fatality. This study highlights the usefulness of this type of epidemiological research in revisiting such questions.

I also examined the epidemiology, primary care burden and treatment of heart failure using CMR. I have shown that heart failure is a common condition especially with advancing age. The prevalence of heart failure was 7.1 per 1000, increasing with age to 90.1 per 1000 in those >85 years and the incidence of heart failure was 2.0 per 1000, increasing with age to 22.4 per 1000 in those >85 years. There is few data on contact rates for heart failure in primary care, the reason for consultation or how the primary care burden of heart failure compares to that of other cardiovascular conditions. I have shown that patients average 2-3 heart failure related contacts per year. There was a high rate of concomitant respiratory tract infection which emphasises the need for strategies to immunise patients with heart failure against influenza and pneumococcal infection. In the elderly, the community burden of heart failure was at least as great as that of angina or hypertension. Another important feature of my study is the description of the contemporary pharmacological management of heart failure in primary care across a whole country. Drugs proven to improve survival in heart failure were used less frequently in elderly patients and in women. This again highlights the benefit of this type of research in highlighting discrepancies in treatment and also the potential of this type of analysis to examine the impact of the new GP contract on better treatment of coronary heart disease and heart failure. It has been shown previously that socioeconomic deprivation is associated with more frequent admissions to hospital and higher case fatality in patients with heart failure. These excess risks are independent of age, sex, comorbidities, disease severity and treatment adherence. I therefore examined whether there were socioeconomic gradients in the treatment and GP follow-up of patients with heart failure. Compared with affluent patients, socioeconomically deprived individuals were 44% more likely to develop heart failure, but 23% less likely to see their general practitioner on an ongoing basis. Contrary to speculation prescribed therapy did not differ between affluent and socioeconomically deprived individuals. This research highlights how routine datasets can be used to identify key modifiable factors in an attempt to properly direct efforts to reduce socioeconomic gradients. Further research is needed to determine why socioeconomically deprived individuals with heart failure are followed less closely. Once we understand the mechanisms behind this, programs can be devised to

ensure that outcomes are optimised for all patients with heart failure irrespective of social class.

Again using primary care data, I examined the epidemiology of atrial fibrillation. The prevalence and incidence of atrial fibrillation are believed to be increasing probably because of the ageing population and improving survival from conditions predisposing to atrial fibrillation. In my study the prevalence of atrial fibrillation in Scotland was 9.4/1000 in men and 7.9/1000 in women ($p<0.0001$) and increased with age (to 71/1000 in individuals >85 years). There is little information on the health care burden that atrial fibrillation exerts on general practice. Atrial fibrillation was not a common reason for a patient to contact their GP however the complete community burden related to atrial fibrillation is likely underestimated as anticoagulation monitoring in hospital based clinics was not included in this analysis.

There is relatively little contemporary information about the treatment of atrial fibrillation in the community. I have shown that digoxin was used much less commonly and rate limiting calcium channel blockers and beta-blockers more commonly when compared to the results of older studies. Prior studies have demonstrated that the risk of stroke in patients with atrial fibrillation can be substantially reduced with warfarin. I found that recommended treatments for atrial fibrillation including warfarin were underused in women and the elderly. This is of particular concern given current trends in population demographics and the evidence that both groups are at higher risk of stroke. The results from this study and from my analysis of angina and heart failure in primary care suggest that there is still a need for education regarding the risks and benefits of the pharmacological treatments of cardiovascular disease in women and the elderly. Deprived individuals were less likely to have atrial fibrillation, a finding raising concerns about socioeconomic gradients in detection and prognosis. This has not been reported before and contrasts to heart failure and angina where the incidence of these diseases increased with increasing socioeconomic deprivation. A possible explanation is that atrial fibrillation is often asymptomatic and picked up incidentally whereas heart failure and angina are symptomatic. Affluent individuals have more contact with GPs which increases the likely hood of detection of atrial fibrillation (e.g. greater uptake of "health screening" and more recording of electrocardiograms). Treatment did not vary according to socioeconomic status which is in keeping with my findings for angina and heart failure and may relate to the greater use of secondary care by more deprived individuals.

The prevalence of obesity has reached unprecedented proportions in Europe and elsewhere, with huge implications for Cardiologists. While it is known that obesity is a recognised risk factor for coronary heart disease its effect on the risk of other cardiovascular events is much less clear. I examined the long-term cardiovascular consequences of obesity in middle aged men and women using the Renfrew-Paisley study. Compared with normal weight individuals (BMI 18.5-24.9), obesity (BMI ≥30) was associated with an increased adjusted risk of coronary heart disease (hazard ratio for death or hospital admission: 1.60, 95%CI 1.45-1.78), heart failure (2.09, 1.68-2.59), stroke (1.41, 1.21-1.65), venous thromboembolism (2.29, 1.60-3.30) and atrial fibrillation (1.75, 1.17-2.65). The impact of obesity on cardiovascular health in a single population like this has not been quantified before. I also projected the cardiovascular consequences of the recent increase in prevalence of obesity. Obesity was associated with 9 additional cardiovascular deaths and 36 additional cardiovascular hospital admissions for every 100 affected middle-aged men over the subsequent 20 years (7 deaths and 28 admissions in women). Assuming no change in cardiovascular risk profile and outcomes related to obesity, the increase in prevalence in 1998, compared to 1972, is projected to lead to an additional 4 cardiovascular deaths and 14 admissions per 100 middle-aged men and women over the next 20 years. My findings strongly highlight the importance of public health strategies to combat obesity and primary preventive approaches to cardiovascular disease in obese individuals.

12.2How the datasets could be improved

12.2.1Continuous Morbidity Recording in General Practice Scheme

As discussed previously the two main issues with CMR are whether it is a representative sample of general practitioners in Scotland and the completeness of information collected. By addressing these two issues the data collected from CMR could be further improved.

The age and sex characteristics of the populations registered with CMR practices are broadly representative of Scotland as a whole. The practices that participate in the CMR scheme differ in some respects from practices nationally.[431] The practice populations are

more likely to be from rural areas and less likely to be from deprived areas. The CMR practices tend to be larger partnerships and are more likely to be training practices. While improving the representation of practices would improve the data, there is evidence to suggest that the socio-economic deprivation discrepancies discussed in these studies are representative of the affluent and deprived groups in the population as a whole. Differences in contact rates between affluent and deprived population groups in CMR are not significantly different to that found in the Scottish Health Survey. Also the difference in prescribing costs between affluent and deprived CMR practices is comparable to the difference found between all affluent and all deprived Scottish practices.

The CMR scheme used in these studies collected data on GP contacts only and therefore did not capture all the workload such as duration of consultations, telephone contacts and nurse contacts. Any patient therefore who has a consultation with another member of the practice team other than the GP would be missed and therefore this may underestimate the prevalence of disease. The new general medical services (GMS) contract was introduced in 2004 and has specific performance indicators to attempt to improve the management of patients with cardiovascular disease. This provides incentives for better identification and recording of cases and prescribing and therefore should result in improvements of the completeness and accuracy of primary care data. Since April 2003 the scheme was extended to include face-to-face consultations (in a surgery or the patient's home) between patients and any member of the Practice Team (general practitioners, practice nurses, district nurses and health visitors). The name of the scheme has been changed from CMR to Practice Team Information (PTI). Currently 44 practices are involved in PTI, covering around 5 per cent of the Scottish population.
The data available for the studies was for one calendar year. At least 44 general practices have participated in CMR since 1998 and therefore it would be useful to have data available for each year from 1998-2005 to enable analysis of temporal trends.

The data would be further improved by including diagnostic data such as the results of biochemical, haematological, radiological and other diagnostic tests. This would improve the validity of the conditions studied and also may partly explain the reasons why patients are on different medications. For example for the heart failure studies it would be useful to have information on cardiomegaly or pulmonary oedema on CXR and left ventricular systolic function on echocardiogram. Cardiovascular risk factor profile would also be interesting for the angina study.

Record linkage of CMR to SMR and to the Registrar General's death certificate data would greatly improve the scope of analysis possible with CMR data. It would allow the analysis of both fatal and non-fatal outcomes of diseases recorded in primary care. It would allow the true burden of diseases in Scotland to be estimated in terms of primary care and secondary care burden. It would also mean that the studies using SMR data would have risk factor profiles and the potential for prescription data on admission to hospital. The Community Health Index (CHI) number is normally available for GPASS patients and has been linked previously to SMR. A pilot study is currently underway in ISD which involves linkage of Practice Team Information (PTI) data to SMR data in order to examine issues around emergency medical admissions in Scotland. It is hoped that this pilot study will address some of the technical and indeed ethical problems surrounding this potential linkage and lead to future linkages. The Scottish Health Survey is already record linked to SMR and the Scottish Longitudinal Study is in the progress of being linked to SMR.

12.2.2 Linked Scottish Morbidity Recording Scheme

The Linked Scottish Morbidity Recording scheme provides large population-based robust databases. As discussed previously the quality of routine data is generally considered to be good, but there are some areas where the data are incomplete or lack accuracy. In addition there may be important pieces of information that are not collected routinely.

More accurate and more detailed secondary coding on hospital discharge forms would allow better identification of co-morbidities. It would also be useful to expand the coding of secondary diagnoses to include information on risk factors including smoking, obesity and cholesterol. It would also be beneficial if the there was information as to whether these co-morbid conditions were new or longstanding, as is available in CMR.

The Linked Scottish Morbidity Recording would be further improved by inclusion of pharmacological treatment and the results of diagnostic tests. For example for the suspected acute coronary syndrome analysis information on thrombolysis, results of biomarkers such as troponin and results of coronary angiography would be very useful and would further strengthen these studies. National datasets for cardiology are currently being developed. These would contain detailed clinical and therapeutic information related to

each episode of care. Cardiology is at the forefront of these developments although it is likely to be sometime before such systems are fully integrated into routine data recording.

Linkage of SMR data to primary care data would be very useful as discussed previously. It would provide information on pharmacological treatment prior to admission. This would allow us to see whether the benefits seen in clinical trials translate into the general population. It would also provide information on concomitant conditions. This would enable a greater understanding of the predictors of diseases and better identification of high risk groups.

The SMR dataset would also be markedly improved if it was linked to Scottish census data. This would allow researchers to explore the complex relationships between employment, social class, educational attainment and different diseases. In addition, it would allow the examination of the pattern of various diseases in different ethnic groups. Ethnicity is poorly completed in SMR. A linkage between SMR and census data has been achieved but has proved technically and ethically difficult.

12.2.3 Renfrew-Paisley Study

Follow-up of mortality was established at the time of the Renfrew-Paisley study with the Registrar General for Scotland and the Renfrew-Paisley study receives information on deaths of the study participants on a three monthly basis. Information on subsequent hospitalisations is obtained by record linkage to SMR and was only available up to 1996 at the time of my research. It was therefore necessary to censor all deaths and hospitalisations at exactly 20 years following the date of initial screening. The follow-up has recently been extended to 25 years however these data were not available at the time of my research. The database could be further improved if an extraction of hospitalisation data could be received at annual intervals from ISD. Inclusion of treatment and clinical data in SMR as discussed would also improve follow-up of the Renfrew-Paisley study.

The Renfrew-Paisley cohort was initially screened between 1972 and 1976 and approximately 60% of the cohort re-attended for repeat screening between 1977 and 1979. However, unlike the Framingham study, the cohort did not have any further follow-up visits and subsequent follow-up is available through linkage with hospitalisation and death

certification data. Further follow-up visits would provide knowledge about changes in risk factors and development of non-hospitalised diseases such as diabetes.

12.3Further research

Following on from the work I have done showing the adverse effect of socioeconomic deprivation on cardiovascular health I helped prepare a successful grant application to use the Renfrew-Paisley study to examine the long-term cardiovascular effect of socioeconomic deprivation. The Renfrew-Paisley cohort is a mixed urban and rural one with a high proportion of socially deprived individuals. Baseline data includes Carstairs' deprivation class and social class. The aim of this study is to look at the independent effect of socioeconomic deprivation on the risk of developing myocardial infarction, angina, heart failure, stroke, atrial fibrillation, aortic aneurysm or pulmonary embolism and the strength of the association between social deprivation and these conditions. In addition we will investigate the effect of socioeconomic deprivation not only on mortality from these individual conditions but also on first and recurrent non-fatal events and cumulative cardiovascular events of all types.

Subsequent to the studies I did on the primary care burden of angina, atrial fibrillation and heart failure it would be interesting to examine the primary care burden and prescribing practices for hypertension and look at age, sex and socioeconomic disparities. It would also be interesting to use the new Practice Team Information (CMR was superseded by PTI in 2003) to examine trends in the incidence and prescribing practices of these conditions over time.

As a follow-up to the work I have done using the SMR Scheme to examine hospitalisations for acute coronary syndromes I helped prepare a successful grant application to do similar analyses for stroke. As a major priority research area, cerebrovascular disease and, in particular, stroke exerts a significant burden on the Scottish population and its health care system. There is a general paucity of related studies that have systematically examined the epidemiologic profile and impact of stroke within a whole population. Trends in hospital admissions for stroke between 1986 and 2002 and short to long-term case fatality rates could be examined as I have done for acute coronary syndromes. Between-hospital

variations in morbidity and mortality could also be described. The economic burden of stroke and impact of stroke units/specialist services could also be investigated. It would also be interesting to project the future burden of stroke (2005 – 2025). Similar analyses could also be done for peripheral arterial disease.

I have shown a reduction in hospitalisations for AMI and an improvement in case fatality following a hospitalisation for AMI between 1990 and 2000. This study was performed prior to the application of widespread troponin testing and the new definition of AMI. The advent of sensitive and specific serologic biomarkers and precise imaging techniques necessitated the re-evaluation of the definition of AMI. In 2000 the European Cardiac Society and the American College of Cardiology published a consensus report for the redefinition of AMI.[432] The new definition requires documentation of a rise and fall in troponin or CK-MB as well as ischaemic symptoms or ischaemic ECG changes or coronary intervention. The previous WHO definition allowed a diagnosis to be made on the basis of serial ECG changes alone, or a combination of symptoms and 'probable' ECG changes and /or abnormal plasma enzymes. It would now be interesting to re-examine trends in hospitalisations and case fatality following the adoption of the new definition of AMI and the more widespread use of troponin. It is likely that hospitalisation rates for AMI will increase and case fatality rates for AMI will improve as a result individuals with a mild troponin leak being labelled as AMI that would previously been labelled as unstable angina.

It has previously been suggested that an improvement in survival following a hospitalisation for heart failure between 1986 and 1995 might have been due to increased use of ACE inhibitors.[143] It would be interesting to use SMR data to re-look at trends in survival of patients hospitalised with heart failure following the introduction of beta-blockers.

I know that national linked record databases are also available in Sweden, Denmark and New Zealand and provincial/ regional linked datasets are available in Canada, Leicestershire in England and Lombardy in Italy (and possibly in other countries/ regions). It would be interesting to compare and contrast trends in hospitalisation rates and short to longer term case fatality rates for different cardiovascular conditions between Scotland and other countries. A similar analysis to the one I have done in Scotland for acute coronary syndromes could be done for each country. This could then be repeated for other cardiovascular conditions such as atrial fibrillation, heart failure and stoke. This would

require using common definitions to extract comparable data. This would allow inter country comparison of differences in hospitalisation rates, practices (e.g. length of hospital stay), outcomes (short to longer term case fatality rates) and trends in each of these.

12.4Conclusion

I have reported on the epidemiology of important cardiovascular diseases (including angina, AMI, acute coronary syndromes, heart failure, atrial fibrillation and obesity) in Scotland using data from primary care (CMR Scheme), secondary care (Linked SMR Scheme) and from a prospective cohort study (Renfrew-Paisley Study).

Using primary care data from a representative sample of all General Practices in Scotland, I examined the epidemiology, primary care burden and prescribing practices of angina, heart failure and atrial fibrillation. I have shown that guideline recommended treatments for these conditions were underused in women and the elderly. I have also shown deprived individuals were more likely to develop angina or heart failure but were less likely to follow-up with their GP. This is in contrast with atrial fibrillation where deprived individuals had a lower prevalence of AF. There were no socioeconomic biases in prescribing.

Using secondary care data (SMR) I examined temporal trends in hospitalisation rates and short and longer-term case-fatality in all patients admitted with a suspected acute coronary syndromes in Scotland between 1990 and 2000. I have shown a decline in hospitalisation rates for acute myocardial infarction between 1990 and 2000 but marked rises in hospital admission rates for angina and chest pain. The long-term prognosis, following an admission for AMI and angina are similar, when short-term deaths are excluded. In addition, I re-examined inter-hospital variation in short-term survival following a hospitalisation with AMI in Scotland. Between-hospital variation in 30-day survival following an AMI has declined between two time periods (1988-1991 and 1999-2001).

Using the Renfrew-Paisley study I examined 20 year follow-up data for 15,406 middle aged men and women who underwent comprehensive cardiovascular screening between 1972 and 1976. I analysed all deaths and hospitalisations for cardiovascular reasons

occurring over the subsequent 20 years according to baseline BMI category. Compared with normal weight individuals, obesity was associated with an increased adjusted risk of coronary heart disease, heart failure, stroke, venous thromboembolism and atrial fibrillation. Again using the Renfrew-Paisley study I analysed morbidity and mortality data over the 20 year follow-up period according to baseline Rose angina score. Individuals with Rose angina had an increased risk of cardiovascular death or hospitalisation, myocardial infarction and heart failure relative to individuals without angina. Compared to men, women with Rose angina were less likely to have a cardiovascular event, or myocardial infarction, though there was no sex difference in the risk of stroke, atrial fibrillation or heart failure.

Subsequent to this research, the long-term cardiovascular effect of socioeconomic deprivation in the Renfrew-Paisley cohort, the epidemiology of stroke in Scotland using SMR data, and the primary care burden of hypertension using the CMR scheme could be examined. Routine data could also be used to re-examine trends in AMI hospitalisations and case fatality, following the adoption of the new definition of AMI and to re-look at trends in survival of heart failure patients following the introduction of beta-blockers. Finally comparison of hospitalisation rates and case fatality rates for different cardiovascular conditions between different countries with similar national linked record databases would be of value.

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