Outcomes in Heart Failure

Study of Contemporary Trends in a Multi-Ethnic Population

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Science is what you know. Philosophy is what you don't know.

- Bertrand Russell

To my Parents

Abstract

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Heart failure is a growing cause of morbidity in an ageing population. Despite increasing use of clinically proven therapies its overall prognosis remains poor, and our knowledge of outcomes in some patient groups is still very limited. Most of existing evidence is based on clinical trial populations, which often exclude ethnic minorities, women or sicker elderly patients. UK's South Asian population has been shown to suffer from particularly high rates of cardiovascular disease but data on their clinical outcomes have been lacking.

This study aimed to evaluate heart failure outcomes in an unselected population and to test a hypothesis of poorer prognosis among South Asians.

Using population-based historical cohort design, this thesis evaluates the long-term survival in a large unselected cohort of 5,789 patients with an initial heart failure admission between 1998 and 2001, on a background of the overall trends in heart failure hospitalisation and fatality between 1993 and 2001. The relative risks linked to main patient groups are estimated using logistic regression and survival modelling and a prognostic model is proposed.

The results show a plateau in the rates of hospitalisation in the late 1990s. Despite a 50% improvement in survival between 1993 and 2001, outcomes remain poor with a 40% one year fatality. South Asian patients tend to be younger at first admission (by 8 years) and with higher rates of comorbidity, however, their survival appears to be similar to other groups. The developed models indicate high prognostic value of concomitant conditions, such as stroke and renal failure, but only a moderate effect of diabetes.

This is the first large study to describe heart failure outcomes in a multi-ethnic contemporary population with an almost complete follow-up of patients. On a background of higher cardiovascular risk, younger age at first admission and higher rate of hospitalisation among South Asians, their clinical outcomes appear to be similar to white patients.

Despite the clear limitations inherent in routine data sources, this study shows clear benefits in developing routine risk assessment models for public health research and health care evaluation.

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List of Publications

Principal results presented in this thesis have been published the following original papers:

1. Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12 220 index admissions in Leicestershire 1993-2001. Heart. 2003 Jun; 89(6):615-20.
URL: http://www.ncbi.nlm.nih.gov/pubmed/12748214

2. Blackledge HM, Newton J, Squire IB. Prognosis for South Asian and white patients newly admitted to hospital with heart failure in the United Kingdom: historical cohort study. British Medical Journal. 2003 Sep 6;327(7414):526-31.
URL: http://www.ncbi.nlm.nih.gov/pubmed/12958110

3. Newton JD, Blackledge HM, Squire IB. Ethnicity and variation in prognosis for patients newly hospitalised for heart failure: a matched historical cohort study. Heart. 2005 Dec; 91(12):1545-50.
URL: http://www.ncbi.nlm.nih.gov/pubmed/15797930

4. Blackledge HM, Squire IB. Improving long-term outcomes following coronary artery bypass graft or percutaneous coronary revascularisation: results from a large, population-based cohort with first intervention 1995-2004. Heart. 2009 Feb ;95(4):304-311.
URL: http://www.ncbi.nlm.nih.gov/pubmed/19001000

Abbreviations

ACE – angiotensin converting enzyme

ACEI – angiotensin converting enzyme inhibitor

ADHF – acute decompensated heart failure

AHFS – acute heart failure syndrome

BME – black and minority ethnic

BNP – brain natriuretic peptide

BUN – blood urea nitrogen

CHD – coronary heart disease

CHF – chronic/congestive heart failure

CI – confidence interval

CRT – cardiac resynchronisation therapy

DBP – diastolic blood pressure

EF – ejection fraction

ESC – European Society of Cardiology

HF – heart failure

HR – hazard ratio

ICD – International Classification of Diseases

IHD – ischaemic heart disease

IMD – index of multiple deprivation

LLR – Leicester, Leicestershire and Rutland

LV – left ventricular

LVSD – left ventricular systolic dysfunction

LVEF – left ventricular ejection fraction

LSOA – lower super output area

MI – myocardial infarction

MONICA – monitoring trends and determinants in cardiovascular disease

NHANES – US National Health and Nutrition Examination Survey

NHS – National Health Service

NICE – National Institute for Clinical Excellence

NSTEMI – Non-ST-elevation myocardial infarction

OPT – optimal pharmacological therapy

OR – odds ratio

PAD – peripheral arterial disease

PVD – peripheral vascular disease

PH – proportional hazards

RAAS – renin-angiotensin-aldosterone system

RR – relative risk

SBP – systolic blood pressure

SCD – sudden cardiac death

SE – standard error

SES – socioeconomic status

SMR – standardised mortality ratio

SSHF – symptoms and signs of heart failure

STEMI – ST-elevation myocardial infarction

SVT – supraventricular tachycardia

TIA – transient ischaemic attack

T2DM – type 2 diabetes mellitus

VT – ventricular tachycardia

Chapter 1: Introduction

Heart failure is associated with significant morbidity and mortality among the elderly and accounts for at least 5% of total healthcare costs in the UK. In the developed world, it is most commonly a sequel of ischaemic heart disease (IHD) and while IHD mortality is generally falling, the burden of heart failure appears to be rising. Interest in heart failure was particularly high in the late 1990s, following several reports from many developed countries of rising levels of hospitalisation and increasing morbidity.

Management of heart failure is complex. It includes non-pharmacological measures, such as appropriate self-care and patient education, and optimal pharmacological therapy based on a combination of ACE inhibitors, diuretics, beta-blockers, aldosterone antagonists, angiotensin receptor blockers, cardiac glycosides, vasodilators, positive inotropic agents, antiarrhythmic and anticoagulation (1). In some cases resistant to pharmacotherapy, surgery or devices are sometimes effective, such as revascularisation for patients with underlying IHD, valvular surgery, cardiac resynchronisation therapy (CRT), implantable cardioverter defibrillation (ICD) or heart transplantation (1).

Despite increasingly effective pharmacological treatment options, once established, heart failure is progressive with episodes of decompensation requiring hospital admission and specialist management in the community. In most studied populations, its annual case fatality exceeds 40%, on par with most common cancers. Clearly, heart failure is a significant clinical and public health problem in an ageing population, with both economic and equity implications. Despite the increasing evidence of higher burden of cardiovascular disease among UK ethnic minority populations, particularly those of South Asian descent, little is known about the epidemiology and prognosis of heart failure in these groups.

AIMS AND OBJECTIVES

The principal hypothesis underlying this work was that, as a result of higher levels of CHD and diabetes, the South Asian population suffered from higher than average heart failure morbidity and mortality. The specific objectives were as follows:

- To investigate the recent trends in heart failure incidence, prevalence and case-fatality.
- To investigate ethnic differentials in morbidity and prognosis following a first admission for heart failure.
- To evaluate the effect of risk factors and coronary surgery on prognosis.
- To develop a prognostic model for patients with a first heart failure admission.

Chapter 2: Literature Survey

Despite a substantial volume of literature on heart failure emerging in the past two decades, the knowledge about its epidemiology is rather fragmented. Most of existing evidence is derived either from randomised clinical trials (RCTs) or from population cohort studies. There is a relative scarcity of prospectively designed cohort studies in heart failure, and population studies often rely on administrative health care data or community disease registers. There are inherent problems in assessing the applicability to routine populations of the results of RCTs of interventions in heart failure, in that selected RCT populations tend to be young, male, Caucasian, and healthier than most of the heart failure patients in the community. Furthermore, reports from RCTs are often a result of secondary analysis of data, which had not been collected with a prospective epidemiological objective. Particularly where absolute measures of disease burden are required, RCT evidence should be treated with extreme caution. Although population based studies are more representative, they too have some serious limitations. Because of their observational nature, causal inferences are generally problematic and potential for confounding and bias is significant. Problems can result from poor diagnostic criteria, inadequate sampling or inherent errors, particularly when using routine or administrative data. This review aims to highlight the methodological issues as well as present the existing evidence on heart failure epidemiology.

EPIDEMIOLOGY

There have been significant advances in the understanding of clinical and public health aspects of heart failure syndrome in the last couple of decades (2) (3) (4), leading to the development of guidelines both in Europe and in the US (1) (5), addressing many aspects of diagnosis, classification and management of this complex syndrome. Heart failure is common, particularly among the elderly, with a lifetime risk at the age of 55 estimated at 30% (6). In a recent Scottish national survey (7) its prevalence was 9% in those over the age of 85 and nearly 1% across all ages. About 2% of those over 85 were diagnosed each year, often with a myriad of comorbidities and with a substantial proportion of elderly patients and women still receiving suboptimal treatment.

Heart failure is a complex, progressive and often fatal syndrome, characterised by a full spectrum of severity and presenting in variety of clinical pathways (Figure 1, page 19). It is most commonly defined by the presence of symptoms of breathlessness, tiredness, fatigue and ankle swelling together with signs of fluid retention and, according to the current consensus, objective evidence of an abnormality of the structure or function of the heart (1). Lack of unambiguous definition of the syndrome is one of the main reasons for broad variation in measured incidence and prevalence of heart failure in the community.

Acute Heart Failure

Acute HF is likely to contribute a large proportion of hospitalised cases. The current definition of acute heart failure syndrome (AHFS) includes all circumstances where there is change, whether rapid or gradual, in heart failure symptoms and signs warranting urgent therapy (8) (1). As a result, AHFS includes both new onset and decompensated chronic heart failure, both presenting with severe pulmonary congestion due to high LV filling pressures. Population based data on acute heart failure are relatively recent, and include the Euro-HF survey (9), ADHERE and OPTIMISE-HF in the US (10) (11). *New-onset acute HF* is often a complicating feature of a myocardial infarction, acute coronary syndrome, heart valve disease, hypertension, post-partum cardiomyopathy, septicaemia and other acute conditions. Most commonly though (65-87% of all AHFS) it is *decompensated* chronic, rather than de-novo heart failure, resulting from a variety of aetiologies, including non-compliance with treatment, fluid overload, infections, surgery, renal dysfunction, cerebrovascular event or even dietary indiscretion. The third important group classified as AHFS includes all patients with advanced condition which is *refractory* to usual therapy. Until recently, there was no consensus on definition or appropriate management of the syndrome (8). It is now recognised that treatment should be guided by patient's risk profile, including vital signs, low SBP, high BUN or serum creatinine, as all these are independent predictors of mortality (12). Outcomes in AHFS are very poor with about 4% of patients dying in hospital, 10% within 90-days post-discharge (five times more than following an acute MI) (8) and 30-40% within 12-months (13) (14). In recent reports, patients with new-onset AHFS appear to have better outcomes than those with decompensated CHF (13).

Aetiology

In principle, any pathological process leading to a significant deterioration in the heart's ability to fill in diastole or expel blood in systole can cause heart failure. However, the two most common factors, both in the aetiology and as concomitant conditions, are ischaemic heart disease (IHD) and hypertension. Their relative contribution to the overall burden of HF is still a subject of debate (15), but the role of IHD seems to be increasing (16). The most common aetiology in the Hillingdon study was IHD (36%), and in over a third of cases no aetiology could be assigned (17). The Framingham study results suggest that the population attributable risk (PAR) for IHD is higher for men than for women (39% vs. 18%), while the reverse is true for hypertension (39% vs. 59%) (18). Both IHD and hypertension are involved in a common set of biological pathways, mainly involving RAAS activation. Ischaemic heart disease, whether clinically silent or overt, can lead to lasting damage to the heart muscle and contribute to the onset of heart failure *de novo* or cause its decompensation. Several mechanisms of such damage have been postulated, commonly leading to scarring and remodelling of ventricular wall, mitral regurgitation and/or chronic inflammation and fibrosis. The most common pathology underlying IHD is atherosclerosis of coronary arteries, although in 10% other disease processes can be implicated (19). Less common causes of heart failure include genetic cardiomyopathies, drugs, toxins, infections, infiltrative conditions, endocrine and nutritional disorders, such as diabetes mellitus (1).

Incidence

Incidence can be expressed as *incidence rate*, which is a measure of the instantaneous force of disease frequency, or as *cumulative incidence*, which is a proportion of people who convert to illness (from a non-diseased state) during an identified period of time (20). For practical purposes, the former is most commonly expressed as the number of new cases in a given population within a specified time, usually one year, and used to describe disease frequency in a population. The concept of cumulative incidence was developed to approximate individual risk to a person in the given population and is less widely used outside of epidemiological research.

A serious bias in assessing incidence often arises from changing or inconsistent diagnostic practice, particularly affecting conditions with presenting with unspe-

cific symptoms or signs, such as heart failure. As a result, estimates of incidence vary substantially. However, most studies estimate heart failure incidence at minimum of 1/1000 of total population (3), often higher. Based on the UK general practice data, Johansson et al (21) estimated heart failure incidence at 4.4 per 1000 person-years in men and 3.9 per 1000 person-years in women. In the Hillingdon survey (17), the incidence was measured by clinical assessment (non-invasive techniques plus expert panel assessment) of all suspected HF cases referred by the general practitioners to a rapid access clinic, thus needs to be treated as an underestimate. It was estimated at 1/1000 population. Although based on a relatively small number of cases (220 in a population of 150,000), this is perhaps the most relevant source of age-specific estimate of incidence in the UK. The median age at the time of the first referral was 76 years.

A constant epidemiological finding across all population studies is that of a steep increase in incidence with age, although sex differentials are not reported consistently. In the Hillingdon study (22) the incidence proved to be relatively higher (by about 75% across all age groups) in men than women and rising steeply with age – from 0.02/1000 in 24-35 year olds to 12/1000 in those aged over 85. In the Rotterdam study (6), the incidence rate for men was significantly higher (by 40%), with a lifetime risk of heart failure of 33% for men and 28.5% for women at the age of 55.

Prevalence

Prevalence is defined as the proportion of the population with the disease at a specified point in time (20) and is relatively seldom used in etiologic inferential epidemiology. However, it is a very important measure of disease burden for health care research. The more recent estimates of prevalence of symptomatic heart failure in the industrialized countries vary at between 1% and 2% (4), with three times higher rate of asymptomatic left ventricular dysfunction - 3% to 6% (23). Although very uncommon before the age of 45, heart failure prevalence rises steeply with age. The Rotterdam study (6), revealed a prevalence of 1% in the 55-64 age group and 4%, 10% and 17.4% in the 65-74, 75-84 and 85 and above, respectively, with an overall estimate of 7% (all 55 and above). In the earlier prevalence studies, the methodology varied substantially and only rarely were any objective data on cardiac dysfunction used (3). Not surprisingly, older studies demonstrate a wide variation in prevalence estimates - from 0.3% - 2% overall all-age prevalence. Even

large population-based studies can suffer from age, gender or ethnic bias. For example the Framingham study (24) included only subjects under the age of 63. More contemporary studies tend to investigate prevalence of systolic and diastolic dysfunction rather than, or in addition to, overt heart failure, primarily in order to assess the scope for screening. Based on the initial results of the ECHOES study, Davies et al (22) reported 2.3% prevalence of definite HF in people aged 45 and above. In a further 1% of patients in that study there was symptomless but prognostically significant cardiac dysfunction. In a subsequent analysis, Davis and colleagues found that a large proportion of patients with IHD, particularly following an MI, have a systolic dysfunction (42% had EF <50%) detectable on echocardiographic screening (25). In a population over 45, 2% are likely to have moderate to severe LSVD and 6% LSVD of any kind (EF<50%) (26).

However, the relationship between heart failure diagnosis and systolic or diastolic dysfunction is complex. Many cases of overt HF have preserved systolic function (EF > 50%), perhaps in as much as 44% of patients (26). On the other hand, less than a half of patients with moderate or severe dysfunction of any type have heart failure recognized clinically. Ventricular dysfunction, regardless of its type, is highly predictive of mortality – in the Rochester study (26) the HR for all-cause mortality in mild diastolic dysfunction was 8.31, rising to 10.17 in moderate or severe cases. Based on a large survey of general practice population in Denmark, Nielsen et al (27) found a 6.4% prevalence of symptoms and signs of heart failure (SSHF) in patients over the age of 50 and a 2.9% prevalence of LVSD (defined as EF ≤ 45%). Half of all SSHF patients were treated in secondary care and a third of all LVSD patients were asymptomatic. Furthermore, half of all patients in primary care with a heart failure diagnosis had no LVSD on echocardiography. In a relatively small Swedish cohort (N=433) of 75 year old patients from a general population, 7% had LVSD, of which just over a half had clinical HF. The total prevalence of symptoms and signs of HF in that cohort was 6.7%, with more than a half of patients showing evidence of systolic dysfunction (28).

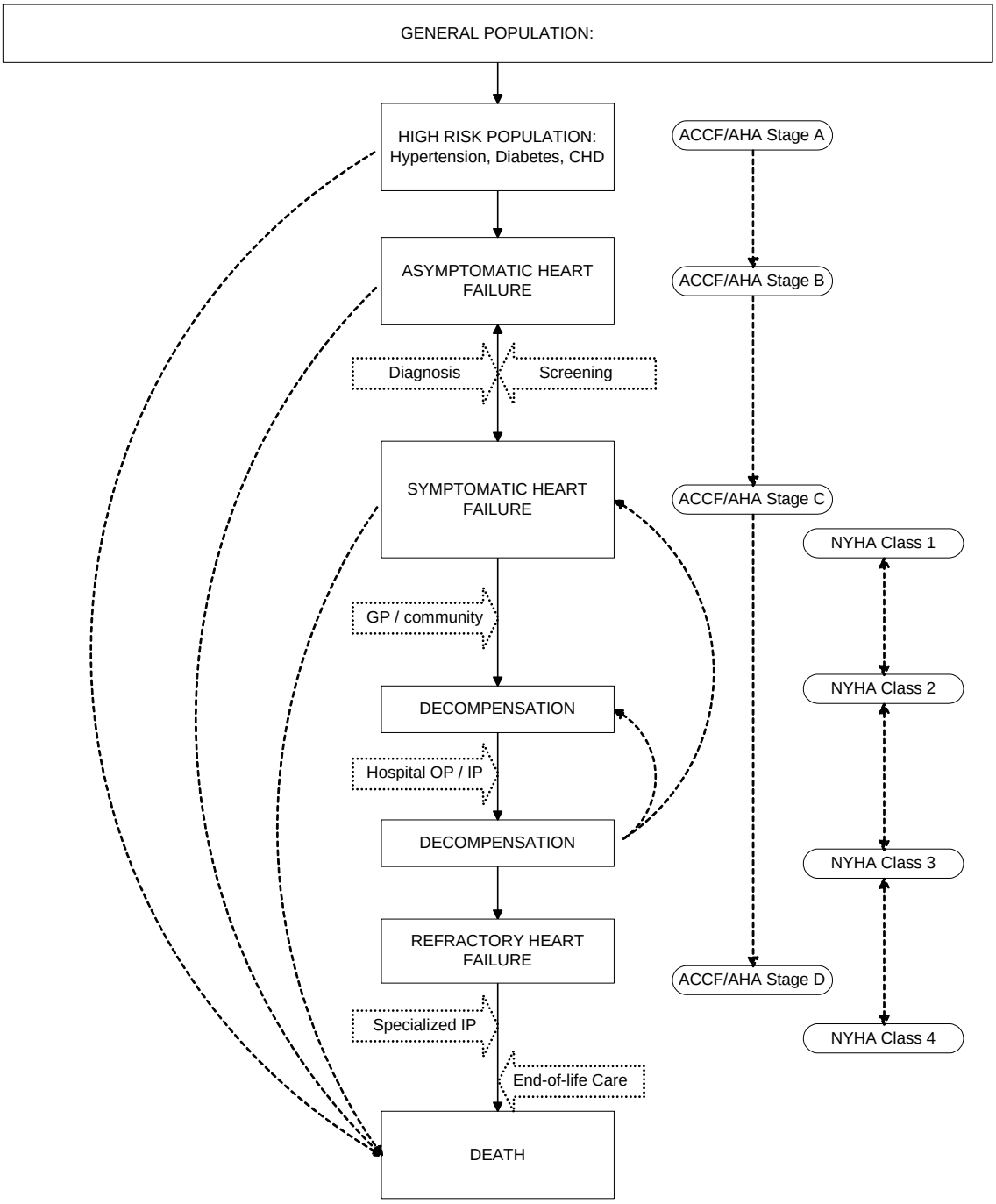
In summary, contemporary studies highlight high prevalence of overt heart failure and prognostically significant cardiac dysfunction among elderly patients in the community. As many patients with significant dysfunction are likely to be undiagnosed; equally many patients with a diagnosis of heart failure have no objective evidence of systolic dysfunction.

Outcomes

Heart failure is usually progressive, often rapidly so. The precise mechanism of worsening myocardial function is still disputed, but progressive myocardial remodelling, particularly following episodes of ischaemia, has been widely postulated. Cardiac arrhythmias have also been shown to play a significant role in disease progression (29). Figure 1 highlights the complexity of patients' pathways through a number of possible critical events expected with disease progression. Many of these events are recorded routinely in general practice or hospital data, as emergency readmissions for heart failure or other cardiovascular events, other episodes of in-patient or out-patient care, end-of-life care and ultimately death, whether from a cardiovascular or non-cardiovascular cause.

A note on terminology

Throughout this thesis, the term *mortality rate* is defined as the number of deaths with a specified underlying cause in the given population, in a period of time and *case-fatality,* or simply *fatality,* is reserved for death rate among cases with diagnosed heart failure. In many other reports these terms are used interchangeably. The rate of *readmission* is defined as a proportion of cases rehospitalised on an emergency basis with specified period of time from discharge and treated as a proxy, with caveats, of decompensation in established heart failure.



ACCF/AHA: American College of Cardiology Foundation / American Heart Association (Hunt 2009)
NYHA: The Criteria Committee of the New York Heart Association. Diseases of the heart and blood vessels: nomenclature and criteria for diagnosis. 6th edition. Boston: Little, Brown, 1964.
OP: Out-patient; IP: In-patient

Figure 1 Disease progression and patient pathway in heart failure

Mortality

Analyses reporting population-level heart failure mortality rates are generally of very limited value. As a clinical syndrome, heart failure is rarely reported as underlying cause of death. More commonly, an underlying or an immediate cause of death takes preference, such as myocardial infarction, chronic IHD or even a respiratory cause, such as bronchopneumonia. A number of studies were published based on death certification reports, reporting trends in adjusted heart failure mortality rates over time or a proportionate contribution of heart failure to the overall CVS mortality. Perhaps most useful is an analysis of underlying cause of death in the 1980s, showing increasing recognition of this syndrome over time (30).

Case-fatality

Case-fatality is the preferred outcome indicator in heart failure. It requires follow-up data at individual level, but it represents the additional risk robustly, whether in comparative or absolute terms. It is also suitable for evaluating individual-level predictors. However, a substantial proportion of community studies report on prevalent, rather than incident cohorts and, as a result, case-fatality estimates show wide variation. Another common approach is looking at deaths occurring in hospital, *in-hospital case fatality*; such data are much more readily available and rely on date of admission as start of follow-up. Generally, heart failure diagnosis doubles the risk of death, particularly sudden (HR 4.8), in the general population (31). Estimates of early, under 30 days, fatality following a hospital diagnosis of heart failure vary according to the source between 10 and 20% (32) (12) (33). Later into the follow-up, estimates at 12 months are between 27 and 38% (13) (34) and at five years can reach 40-55% (33) (35) (36). The Rotterdam study (6) showed a 41% fatality in prevalent heart failure cases at 5 years, compared with 15% in non-HF patients. Comparative risk of heart failure was also highlighted by Stewart et al (37), who contrasted 5-year survival in HF (25%) with four most common types of cancer in Scottish population in 1991. They found that only lung cancer, with 5-year survival of 5%, and female ovarian cancer, with 15% survival, was worse prognostically than heart failure. A large cohort of patients with first hospitalisation for heart failure in Ontario, Canada (38) has shown poor prognosis in unselected population with 12% case fatality at one month and 33% after one year from admission, with age, male sex and comorbidity as independent predictors of mortality. A recent Finnish study has shown that, despite a recent decrease, in-

hospital case fatality remains high with 15%, 20% and 27% of patients dying within 3, 6 and 12 months, respectively (13).

Heart failure patients often die as result of other conditions, although in many such cases heart failure is a predominant contributory cause. Henkel et al (36) recently reported a 5-year mortality of 55%, with 57% of deaths from cardiovascular causes. In the remaining 43% of deaths, more than half were pulmonary or cancer, followed by central nervous system, gastrointestinal or GU causes. Although the relative contribution of CVS mortality has changed over time from 74% in the early 1980s to 51% in late 1990s, mortality from non-cardiovascular causes did not decrease. Even in patients with preserved LVEF ischaemic heart disease was a common cause of death (29%), although preserved LVEF provided significant protection in CVS outcome (HR 0.71) (36). In the ATLAS trial (29), nearly half of all cardiovascular deaths in heart failure were considered sudden and most were out of hospital, and only in 7% was heart failure regarded as the underlying cause. Using a prevalent, rather than incident cohort, Hobbs et al (35) found in the follow-up to the population-based ECHOES study that HF fatality in the general population remains poor, reaching 47% at 5 years in those with HF and LSVD (EF under 40%), compared to 7% mortality in the general population. They found a clear correlation between ejection fraction and outcome, even patients with borderline EF (40-50%) exhibiting increased risk of death. Risk was also higher in patients with multiple aetiology and higher NYHA class. Even patients misdiagnosed in general practice (misdiagnosis rate of 50%) had significantly worse outcomes than healthy population, pointing at a significance of the symptoms, however non-specific.

Hospital readmissions

Emergency hospital readmissions in heart failure are often treated as a proxy of acute decompensation in established heart failure. In 1992 in Scotland (39), nearly a third of all patients with a first-time hospital admission for heart failure had a readmission within six months. Renal failure and respiratory infection were relatively common diagnoses on readmission, while patients readmitted for an acute MI had a 40% hospital fatality rate. This rate of readmission was similar among patients in the ATLAS trial of lisinopril (29), a population predominantly male (79%) and relatively young (69% under the age of 70) (40).

Trends

Study of trends in heart failure outcome, hospitalisation and risk factors can add to the understanding of current and future disease burden. The methods of assessing such trends in a cross-sectional setting usually involve some kind of standardisation, for example for age and sex of the population under study. A degree of caution is necessary in interpreting changes in such rates over time. In populations which are ageing over time, an apparent improvement in adverse outcomes in a condition prevalent among the elderly may be over exaggerated. As an example, in Canada in the decade between 1994 and 2004 the numbers of deaths, crude rates and standardised rates of mortality reduced by 7.4%, 19% and 30%, respectively (41). The 11% differential between crude and adjusted rate is solely due to changing characteristics of the population denominator and deaths occurring at increasingly older age. By comparison, studies which examine historical or prospective cohorts of patients show much less impressive survival improvement over time. Trends are thus best assessed through absolute counts, crude and standardised rates, although such data are not always presented in literature.

Time trends in hospitalisation and fatality in heart failure have been described by many authors, although the results are not always comparable. Reports from many countries of significant increases in volume of hospitalisation throughout the 1990s (42) (43) (44) initiated a wide discussion of an epidemic of heart failure, although it has not been made clear whether this was underpinned by genuine rise in incidence, increasing awareness of the condition or better survival, all possibly resulting in higher prevalence of heart failure in the community (3). Stewart et al estimated that the absolute numbers of men and women with heart failure could rise by as much as 31% and 17%, respectively, by year 2020 (45). A rise in the developing countries is also expected (46).

Throughout the 1980s in Scotland hospital discharge rates had increased by almost 60% (43) with a concomitant fall in hospital case-fatality. Trends in hospitalisation in Spain (1980 to 1993) had shown a significant 71% increase (42), particularly in the elderly population. In the Netherlands, hospital admission rates for HF increased by 40 and 48% for women and men, respectively, between 1980 and 1993 (44). There was a corresponding increase in readmissions and reduction in the length of stay in hospital and a reduction in in-hospital mortality from 19% to 15%. In England, the rates of hospitalisation for HF peaked in the mid-1990s (47) and

fell in late 1990s by 14%. There was also a significant drop in in-hospital case fatality in that period, by 40% in men and 60% in women. Similar findings were reported in Scotland (48), showing a peak in admissions around 1993-4 followed by a fall, with some corresponding drop in hospital mortality. However, a more recent Canadian review for period 1994-2004 has shown that both hospitalisation and in-hospital fatality from heart failure have improved by 28% and 8%, respectively (41). There has also been an improvement in the overall mortality (by 24%). Trends in heart failure paralleled those for stroke, but not for IHD, which showed much higher differentials. An important component of rise in hospitalisation was the rate of readmission, most common in the first few months following the initial admission (49). Many reports looked at possible risk factors for decompensation in heart failure in order to stem the tide of increasing hospitalisation - these are summarised in the section on prognostic models (page 37).

Trends in heart failure prognosis were also researched in many hospital cohorts. One-month case-fatality in Scotland (between 1986 and 1995) showed a decline of 17% and 26%, for women and men respectively, and a 15% and 18% longer-term (33). On a background of a 30% increase in hospitalisation between 1984 and 1992, Cleland et al (50) observed a risk reduction in 3-year mortality of 12% in patients aged under 65 and 5% reduction in those over 65. Senni et al (51) found no change in either the incidence (2.8 per 1000) or fatality in HF when comparing 1981 with the 1991 cohort from Rochester Epidemiology Project (Olmstead County, Minnesota). A recent study of a large, representative historical cohort of Medicare patients in the US (nearly 2.5 million, between 1992 and 1998) has shown no appreciable improvement (3% reduction, borderline significance) in the overall survival in heart failure and no reduction in hospital readmissions, despite of widespread introduction of ACEI and beta blocker use in the same period (52). Throughout the 1990s in Spain (53) patients with depressed LVEF appeared to have improving prognosis, but in those with preserved LVEF no such improvement was observed. Patients with preserved LVEF contribute as much as 50% in some series; 40% in this Spanish cohort. There was no trend to improved survival in the preserved LVEF group overall (54).

It has been hypothesised that, in addition to the overall ageing of the population in Europe and America, the increasing numbers of patients surviving acute MI is the main reason for increasing prevalence of heart failure, as measured by hospital admission rates (55), which are likely to increase even further into the 21st cen-

tury. IHD mortality among men fell by 70% between 1968 and 2000 in the US and by 50% in the UK (56). In the Netherlands, between 1975 and 1995 (57), IHD mortality reduced by 61% and was accompanied by 55% increase in hospital admission rate for IHD and 44% for HF. The Minnesota Heart Survey (58) also reported a significant reduction in case fatality after acute MI (by 41% for men and 31% for women; 1985-1997). However, a larger cohort of AMI patients (N=9827) of all ages from Worcester, US, experienced only a moderate and non-significant improvement in adjusted case-fatality (OR 1.23, 95% CI: 0.97-1.55, for patients discharged in 2001 when compared to 1975-1978 cohort). Crude fatality actually rose in that cohort by 6%, albeit on a background of increasing age and complexity of cases (59). Data from the US National Health and Nutrition Examination Survey (NHANES) suggest that numbers of survivors of acute MI and stroke have increased significantly in the decade between 1988-94 (NHANES III) and 1999-2002, by 7.3% and 28.8%, respectively (60). Rates of prevalence of angina symptoms and acute events, such as MI, were shown to decrease among British men between 1978 and 1996 (61).

DETERMINANTS OF OUTCOME

Many factors have been shown to affect the outcome in heart failure, including demographic, such age, sex and ethnicity, as well as a variety of social or environmental variables.

Age and Gender

Both incidence and prevalence of heart failure increase steeply with age, but the effect of age could be underestimated in clinical trials which tend to include relatively young patients. As a result, evidence of effectiveness of some of the treatment options in the majority of elderly patients is still inadequate. Independently, age can be a barrier to effective treatment. In a large US sample of elderly patients surviving a hospital admission for HF, ACE inhibitors were widely underprescribed, without any specific contraindications (62). Not only the response to treatment, but the clinical characteristics of the elderly with heart failure can be different. It was shown in the US that a large proportion (55%) of elderly with prevalent HF can have normal LVF or only mildly reduced systolic function (25%)

(63). This is more common among women (only 10% moderate or severe LVSD compared to 29% in men).

There are well recognised sex differentials and epidemiology and management of heart failure, including in women higher importance of hypertension, valve disease and diabetes in aetiology, higher comorbidity, less likely diagnosis, more HF with preserved LV function, less optimal treatment in both primary and secondary care (64). Because of the age structure of the population in the developed countries there is actually more prevalent HF among women than men in older age groups. However, it has been shown that men have significantly more LVSD than women – in a general practice survey (70-84 age group) the odds ratio for men was 5.1 (95% CI: 2.6 to 10.1) (65).

Women have been underrepresented in clinical trials. In a review of 31 heart failure trials (66) women constituted less than 20% of patients in almost a half of such studies (N=14) and all studies included less than a third of women. Exclusion of women is also age-related - women tend to be older and present in later stages of heart failure, often with comorbidities. As a result, trials are a poor source of information on gender epidemiology of heart failure.

The Rotterdam study (6) reported a lower incidence in women (12.5/1000 vs. 17.6/1000 in men) and a lower lifetime risk of heart failure at 55 years of age (29% vs. 33% for men). However, in older age the lifetime risk is the same for both genders. The Framingham study suggested that the lifetime risk of developing heart failure is independent of age and similar in both sexes at about 20% (16). Furthermore, for a given age, incidence measured by new hospital admissions is comparable for men and women (67). When standardised for age, rates of hospital admissions overall are also comparable (41). Thus, there is no indication that the overall burden of disease in women is any less than in men, indeed it has been shown that the more recent increases in hospitalisation for heart failure in the US were due primarily to increase in disease prevalence and its severity in women (68). A degree of gender bias in cardiovascular risk management in general practice in the UK had been reported, in which men were more likely to have their risk factors measured and reported, as well as having more lipid lowering treatment prescribed than women, relative to the rate of hypercholesterolaemia in both sexes (69). The Framingham Study first reported better survival for women in HF, when compared to men (24), although the nature of this survival advantage is disputed. In advanced HF, women appear to have significantly better survival after adjustment

for many baseline factors, principally in non-ischaemic HF (RR=3.1, p=0012), while in ischaemic HF there is some, albeit statistically non-significant advantage for women (RR=1.64, p=0.127) (70).

In a recent survey of hospitalisation for HF across England, Wales and Ireland Nicol et al (71) found that women were less likely to have echocardiographic assessment before admission (52% vs. 60 in men), receive ACE inhibitors (58% vs. 67%), and were less likely to be prescribed medication in hospital and on discharge. All patients still had a high in-hospital mortality rate (15%), and only 20% had planned specialist follow-up on discharge from acute care. Women were generally older on admission (80 vs. 75) and more likely to have preserved LF function.

The nature of gender differentials in heart failure and heart disease in general is largely unexplained. The trends in IHD mortality among men in many European countries in the 1960s and 1970s were of truly epidemic proportions and only since 1980 there was a significant reduction in rates. Patterns of mortality for women, although similar, were much less pronounced, raising a theory of the protective effect of oestrogen. However, more recent evidence points at a combination of modifiable environmental factors (72).

Ethnicity

Despite increasing focus on research and policy in cardiovascular health, comprehensive evaluation of the influence of ethnicity on heart failure epidemiology is largely missing. Many studies undertaken in specific populations cannot be translated or generalised and data on ethnicity are not collected routinely. Importantly from the heart failure perspective, ethnic minority populations are largely underrepresented in clinical trials. Based primarily on US findings, Hussai-Gambles et al (73) reviewed socio-political and cultural barriers to ethnic minority participation, from cultural and language needs to mistrust in health care system, underlining the paucity of relevant research in the UK.

South Asians

A picture of high cardiovascular risk in South Asian population is consistent, but reasons for this excess are not always clear. In the UK, age-adjusted premature mortality from IHD has been consistently higher among South Asians when compared to white population, by at least 50% (74) (75). The classical risk factor preva-

lence, including smoking, obesity and cholesterol, cannot easily explain this difference, as individual South Asian subgroups tend to vary substantially in this respect; wide differences have also been observed in the level of socio-economic deprivation among those groups (76). In many South Asian groups these factors are often, although not uniformly, lower than in Europeans and subsequently traditional risk calculations may be misleading (77). It has been estimated that for South Asian patients a factor of 1.79 should be applied to any Framingham-based CVD risk score and that South Asian patients should be treated at lower than 20% 10-year risk score (78). So far there have been no studies in the UK large enough to evaluate excess risk in individual subgroups of South Asian population, although evidence is emerging that there are substantial significant differences in access to care. For example, the rates of revascularisation in South Asians were reported to be lower, although not as result of physician bias and not resulting in different outcomes in ethnic cohorts comparable in terms of indications (79). In this UK cohort, there was a relative excess angioplasty for Indians (HR 1.22), with deficit for Bangladeshis (0.25) and Pakistanis (0.34).

Despite the complex risk factor patterns, evidence on increased cardiovascular morbidity for South Asians is clear. Diabetes is more common in this group, occurring at an earlier age, with higher risk both of early and late complications, particularly vascular (80). Teoh et al (81) found that Asian patients were younger by about 8 years when presenting with an acute coronary syndrome (ACS), more than twice as likely to have diabetes, and presenting with angina, rather than MI. Among the hypertensive patients in the UK, South Asians had significantly higher cardiovascular event rates than whites or Afro-Caribbeans, despite a similar, with exception of higher diabetes prevalence, risk factor profile (82). Audits of emergency hospitalisation for heart failure discovered excess of IHD and diabetes in South Asians (83). In a London hospital study (1988-92, N=313), the risk of hospitalisation and 6-month case fatality following an acute MI was higher among South Asian patients, when compared with their white counterparts (84). However, this was largely due their higher diabetic comorbidity, according to the authors of the report.

Among the recognised risk factors, only insulin resistance markers show significant excess in all South Asians. It is disputed whether this alone can account for an increase in risk of IHD. Genetically determined levels of lipoprotein Lp(a) and dietary habits (ghee consumption) were also postulated in the past (85), as

were the anatomy of cardiac vessels or observed angiographic patterns, not always related to concomitant diabetes. Bhopal (86) questions the validity of many assumptions about higher risk of IHD among UK South Asians. He postulates that, despite unequivocal evidence on excess mortality, particularly in younger South Asians, it could have explanations other than higher incidence. South Asians tend to have consistently lower mortality rates from cancer, which could explain higher proportional mortality ratios for IHD, for example. Numerator and denominator errors, definitional inconsistencies within South Asian groups and heterogeneity within the 'South Asian' population, could easily undermine the widely held belief of high incidence of IHD despite the low prevalence of classical risk factors. In fact, only smoking is lower and only in some subgroups, and most of other risk factors tend to be higher (87). In a recent study Joshi et al (88) suggested that increased risk for IHD in South Asians can indeed be explained by traditional, potentially modifiable, risk factors. Whincup et al (89) postulate the early onset insulin resistance as the principal cardiovascular risk among South Asians. In a study in Singapore, Indians had substantially higher HF prevalence rates than other Asian ethnic groups, but with comparatively lower mortality. Risk factors included abdominal obesity and diabetes (90). In a long-term follow-up study of heart failure hospital discharges (91), non-Europeans had better survival until six years of follow-up, after which survival was similar across all ethnic groups.

Ethnic differences were studied more extensively in the US, often showing white patients having higher post-hospitalization mortality rates than other ethnic groups, but lower hospitalization and readmission rates than African-Americans. Although Asian patients in the US were shown to have lowest admission rates and best outcomes (92), such results are generally not transferable to European populations.

African-Caribbeans

By contrast, in the UK both African-Caribbean and South Asian minorities show similar excess in cardiovascular mortality (75) when compared to white patients. Importantly the excess in circulatory disease mortality in African-Caribbean population is mainly attributed to stroke, not IHD, and has been shown to be related to the length of residence. This suggests that environmental influence, such as high-calorie and sodium diet and level of urbanisation and affluence, is at play rather than a genetic predisposition (93). Except for impaired glucose tolerance,

cardiovascular risk factors in African-Caribbeans are different than in South Asian groups in the UK (93).

Most results from the US show excess cardiovascular risk among black population (94), faster progression of heart failure, with a higher risk of hospital readmission and less effective pharmacological intervention, including ACEI (95) and beta-blockers, except for carvedilol (96). In the SOLVD study, African Americans with mild to moderate HF had shown faster progression and mortality than similarly treated white patients (97), with a relative risk of all-cause mortality 1.36 in the prevention trial and 1.25 in treatment arm, after adjustment for the relevant co-variates. Differentials in CVS mortality were even higher (1.57 and 1.32, respectively), but this is not a consistent finding, despite higher comorbidity from diabetes and hypertension (98). Access to care is not always equitable for US black population (98), particularly in the use of revascularisation in the US (99). The risk of HF among black population is similar to white, but higher than both Asian and Latino groups. No ethnic differences in macrovascular complications of diabetes were shown in the US (100), although hypertension and stroke seem to be commoner among African-Americans (101). Mortality following revascularisation appears to be higher in black patients in the US, although this is dependent more on suboptimal postoperative care than on patient characteristics (102). Although T2DM is also more prevalent in black patients, mechanisms of increased cardiovascular risks are likely to be different (103). In the UK, African-Caribbeans have LV structural impairment mainly associated with obesity and hypertension and across the whole spectrum of glucose intolerance (most likely unrelated to severity of diabetes) (104).

Socio-economic factors

Socio-economic deprivation is an established risk factor for adverse health outcome, although its effect is easily confounded by other influences and often difficult to explain. Cross-sectional data suggesting an independent effect of deprivation have been available for some years. Perhaps the best known is a 15% differential in mortality between the north and south of England, largely corresponding to increasing deprivation (105). Ischaemic heart disease contributes 50% to this excess in mortality, followed by stroke (15%) and COPD (13%). It has been estimated that the highest risk factor contribution is smoking (85% of excess mortality) followed by alcohol (6%), thus excess mortality could be largely due to the difference in indi-

vidual risk factors, with deprivation accounting for only 12%. The nature of these effects is not completely understood, but many psycho-social explanations have been proposed in the past. More disadvantaged populations do not benefit from positive trends in CVS risk factor prevalence to the same degree as population as a whole and as a result, the socioeconomic gap increases, rather than decreases over time (106). The first robust report of strong link between socio-economic gradient and IHD mortality was published in the UK using the Whitehall study data (107). Men in the lowest professional grade had 3-6 times higher mortality than men in the highest grade, having also adverse risk profiles, including higher prevalence of hypertension, obesity and smoking. Since that first report, a substantial volume of research has been published, suggesting a number of causal hypotheses, including prevalence of risk factors, inequitable access to care and others. Barakat et al (108) found in a study of 1417 AMI admissions at CCU, that deprivation predicted the early (under 30 days), but not later (30 days to 1 year) case fatality. Under a universal health care system in Canada in the late 1990s, an increase of $10,000 average income in an area was linked to 10% reduction in 1-year case fatality from acute MI (109). In the FINMONICA study, both the incidence and 28-day mortality following an acute MI was significantly higher in men with lower levels of education and/or income (110). The lowest income category had over 3-fold higher risk of early mortality, although authors adjusted only for age and geographical area so the risk estimate is probably an overestimate in this study. In the Glasgow MONICA study, there was no socioeconomic gradients for hospital case fatality following AMI, but there were indications of increased risk of death in the community (OR of 1.12 and 1.18 for men and women, respectively) and of lesser likelihood of being admitted to hospital (111). In this community based coronary event register, only 66% of patients were treated by secondary care overall. In a 478-strong cohort of HF patients in Scotland (112), hospital readmissions were much more common among patients from the more deprived areas, independently of disease severity or level of non-compliance with treatment. There is also evidence that deprivation is linked to access to health care. In Scotland between 1986 and 1996, patients from most deprived areas were younger, more likely to be female and had a three week longer waiting time for cardiac surgery (113), and had their operation half as likely to be classified as urgent.

In a study of 53 Scottish general practices (114), incidence of HF increased with social deprivation, with OR of 1.44, with less access to consultation in more de-

prived areas. In a heart failure review published in 2002 (115), only 8 papers, mostly clinical trials, adjusted for deprivation adequately, commonly finding higher hospital admission rates, lower access to surgery and heart transplantation. There was strong interaction with age and ethnicity. The outcome of this review is that evidence of independent link between SES and heart failure is as yet unproven, with individual risk factors playing perhaps a more significant part. However, it has also been postulated that most of the observed socio-economic gradient in health outcomes can be explained by differentials in individual lifestyle factors. The influence of social class on incidence of major IHD events and mortality was studied prospectively in a large cohort of middle-aged men in the UK (116). After full adjustment for individual coronary risk factors, population etiologic fraction was just 10% for major events and 16% for all-cause mortality, thus the contribution was relatively modest.

The independent link between socio-economic deprivation and outcome, whether area-based or individual, can be attenuated by age and other risk factors. Weizman at al (117) have shown it to be less clear in older age groups, with relative risk of CVS mortality for poverty-area residence 1.90 (1.24-2.90) for ages 25-54 but only 0.83 (0.66-1.03) for those aged 55-74. In the UK Renfrew and Paisley study, Davey-Smith et al (118) found significant correlation between area-based deprivation and CVS mortality, after adjusting for social class and age, but this relationship was attenuated by addition of known risk factors for CVD. White et al (119), examined individual measures from three UK population Censuses (1971, 1981 and 1991) in nearly 50,000 men against their mortality in 1995-2001. They found that the deprivation effect was affected strongly by social mobility. A substantial proportion of risk linked to deprivation is accounted for by increased prevalence of risk factors, in particular the extremes of BMI (high as well as low), diabetes, hypertension and smoking. In a large unselected study of mortality in patients undergoing cardiac surgery, diabetes increased mortality risk by 30%, smoking by 20%, but there was still a significant contribution of deprivation (120).Despite a well-researched IHD area, data linking heart failure and deprivation are reported much less often.

The choice of deprivation measure in any analysis has a bearing on the outcome. Individual socioeconomic status or position (SEP) and area-based measures, such as Townsend or Carstairs scores, can give dissimilar results. The lifecourse of an individual should be taken into account, such as their social and economic mo-

bility. Incidence and mortality from IHD are strongly related to SEP measures (121). Assigning residential area deprivation to individuals and treating them as proxy of SEP has been criticised as a source of significant bias through 'ecological fallacy'. However, such measures can also be regarded as a proxy of area effect. It has been shown that area-level deprivation, an expression of quality of residential environment, is an important, if not decisive factor in CHD morbidity, at least among women. In the British Women's Heart Study for example, the risk from living in areas with deprivation above the national median was shown to be 27% greater, after adjusting for individual SEP measures (122). In the British Regional Heart Study, the north-south gradient in IHD could not be fully explained by individual-level risk factors, such as smoking, blood pressure or social class (123).

Comorbidity

Heart failure patients, particularly those hospitalised, are commonly elderly with multiple comorbidities, which can contribute to the development and later to progression of heart dysfunction in an often dramatic way. An analysis of comorbidity in patients admitted for HF in Scotland in the 1990s (124) noted complex comorbidity patterns in admitted patients, most commonly presenting atrial fibrillation (15%), acute MI (13%), chronic airway disease (12%) and diabetes (11%). To aid analysis single indices have been developed, such as the Charlson index (125). Although such indices are useful for most basic risk adjustment, it is preferable to assess the effect of individual conditions separately.

Hypertension

Hypertension is not only a major cause of HF, but also one of the most important comorbidities, often acting synergistically with IHD. Increased blood pressure results in compensatory hypertrophy of cardiac muscle, particularly of the left ventricle, in response to afterload generated by peripheral vasculature, then diastolic dysfunction which often directly precedes the onset of overt HF. Hypertensive crises, or indeed any acute increase in blood pressure, can decompensate chronic HF (15). The results from NHANES data show, despite earlier reports, that the prevalence of hypertension in the US had risen throughout the 1990s by 4% (from 25% to 29%) and that its management remained suboptimal. The majority of increase could be accounted for by BMI increase (from average 26 in 1988-92 to 28 in 1999-2000) (126).

Ischaemic heart disease (IHD)

Myocardial function can be affected by both overt and silent IHD, whether acutely or chronically. Both forms of IHD commonly induce and subsequently complicate the course of heart failure, causing decompensation and death in already compromised patients. The relationship between HF and myocardial ischaemia is complex – in chronic compensated HF an acute cardiovascular event can precipitate a decompensation, leading to hospitalisation or even death. Patients in stabilised ACS, have a significantly increased risk of death (90-days) if developing HF (HR 2.6) (127). It is estimated that about a half of first ever admissions for heart failure are due to acute coronary events (128) and the Framingham results have shown that that since 1950s the contribution of MI to HF aetiology has increased substantially (16) (129) when compared to hypertension and other causes. Transient or persistent heart failure in the wake of an MI is likely to be more common than is apparent from surveys of hospital records or clinical trial reports, often being omitted from hospital discharge records. It is most commonly a result of LSVD, valve insufficiency or arrhythmia, but in a proportion of cases the causal pathway is unclear (130). Whatever the mechanism or timing of HF, its development is a grave prognostic factor, contributing to almost 85% of all MI case fatality (128). Given that acute MI is common (annual incidence of 4/1000) and its case fatality is still significant, the early recognition and management of HF is of paramount importance (130) (128). In a population register of acute MI in the UK, there was no change in in-hospital case fatality in the 1980s (1982-1992), despite major changes towards evidence-based treatment occurring in this period (131). In an unselected cohort of AMI patients from the early 1990s in Ireland, there was a high (18%) in hospital case fatality, contrasting with 6-10% hospital fatality recorded in trials (132). When compared to clinical trials AMI case fatality in this unselected population was almost double that from relevant clinical trials. Left ventricular failure was the most significant clinical predictor of mortality in that cohort. In the more recent years, patients with larger MI are more likely to survive and develop HF, leading to further increase in HF prevalence (128).

In the 25 years between 1975 and 2000, the risk of heart failure as pre-existing condition or complicating acute MI has increased by about 37%; currently as much as 40% of all AMI is complicated by HF (133). Other studies variably quote 24%, 28% or 48% depending on study design, population and setting, with an overall estimate of a third of all cases and more common after STEMI (134). Thus, HF in

acute MI is common and presents a clinical challenge, as outcomes are generally worse in these patients. HF is less common in unstable angina but a group particularly prone is that with undetermined ECG pattern. Nearly half of those patients may develop HF, although this finding is not consistent across studies. Risk factors for developing HF also include older age, female sex, diabetes, hypertension, renal insufficiency and other comorbidities. HF after ACS can be transient, although it is often missed and not treated optimally. HF increases the adjusted risk of in-hospital or 30-day case fatality between two and four-fold. HF on admission is regarded as the stronger predictor of mortality, with adjusted OR of around 1.70. There are less data on LVSD complicating MI, epidemiologically difficult to assess because many older patients are not treated by cardiologists and objective assessment of LV function by echocardiography or radionuclide study is not performed.

Anaemia

Anaemia is common in patients with HF, but estimates of its prevalence vary between 4% and 60% (135). It is more common among the elderly, women, those with low BMI or with chronic kidney disease, but precise mechanisms are still poorly understood. In patients with HF, even mild anaemia can cause significant reduction in aerobic capacity. Anaemia is an independent predictor of all-cause mortality and readmission, increasing the risk of mortality by approximately 5%-40% for every 1g/dL reduction in haemoglobin concentration (135). The wide variation in these estimates is of note, and reflects the paucity of reliable studies and different studied populations. The mechanisms of influence of anaemia on cardiac function are still poorly understood, it may well be that anaemia is a reflection of more severe myocardial status. Treatment of anaemia in heart failure remains of unproven value (1), although erythropoietin had been used in patients with moderate to severe anaemia with concomitant kidney disease. Recently, Anker et al (136) have shown benefit of treatment with intravenous ferric carboxymaltose in patients with chronic heart failure and iron deficiency, with acceptable profile of side-effects, but the results of the trial of the log-acting erythropoietin-stimulating agent (ESA) darbepoetin alfa in type 2 diabetes and chronic kidney disease have not been promising (137). The ongoing RED-HF trial (138) aims to evaluate the effect of darbepoetin alfa on mortality and morbidity in patients with heart failure and anaemia.

Diabetes

The burden of morbidity due to type 2 diabetes is rising across the industrialised countries. The national health surveys in the US have shown a significant increase in the prevalence of diagnosed diabetes (from 1.8% in 1960 to 5.8% in 2000), due primarily to increased detection (139), although there could also be further increase in undiagnosed disease; the total prevalence could reach nearly 15% among all people aged 20 years or more within the next three decades (140). Diabetes is a common comorbidity, diagnosed in up to 30% of patients with overt heart failure and an independent risk factor for mortality in asymptomatic cases. It increases the likelihood of developing heart failure by approximately 2-3 times when compared to non-diabetic patients (141). In a representative sample of US diabetics aged 65 and above (142), there was a 50% prevalence of cardiovascular disease. From the point of view of prevention and risk assessment, type 2 diabetes is regarded as part of cardiovascular disease spectrum, alongside IHD, stroke/TIA, peripheral arterial disease (PAD) and chronic kidney disease (CKD). All these conditions share many risk factors and respond to similar public health interventions. Importantly, it is possible to assess the risk for any of these conditions through a common screening process (143).

In many diabetic patients, heart failure is a sequel of IHD. In the Framingham study the relative risk of IHD among diabetic was 1.66 for men and 2.03 for women (144); these estimates were confirmed by the more contemporary studies (145). Coronary intervention is more likely to be ineffective in diabetic patients, with restenosis occurring more commonly (146). IHD mortality among diabetics is higher than in non-diabetics. In the US, diabetics treated with insulin had the highest 1-year case fatality following an acute MI (OR 1.90, adjusted for demographic characteristics), followed by those on diet alone (OR 1.52) and oral hypoglycaemic agents (OR 1.38) (147). In the UK, diabetes was also shown to be strongly associated with mortality, particularly from cardiovascular causes (148), correlated to deprivation and most pronounced in young people with NIDDM (149). Overall there is a two-fold increase in risk of cardiovascular mortality in diabetes, with women at a higher risk than men. The long latent development of T2DM is most likely the starting point for cardiovascular damage, even before overt hyperglycaemia (150). Squire et al (151) showed that following STEMI, even moderate elevation blood glucose concentration, rather than antecedent diabetes diagnosis, was associated with adverse impact on survival. Diabetes can predispose to heart

failure independently of IHD, albeit much less commonly (152). The pathological process is referred to as 'diabetic cardiomyopathy', resulting from unrecognised, silent ischaemia or coronary microvascular changes, often coinciding with hypertension (153).

Fatality is higher in heart failure patients with diabetes both in community-based studies (HR variable between 1.1 and 3.2) and in selected clinical trial populations (HR between 1.1 and 1.8) and there are substantial differences between ischaemic and non-ischaemic HF complicated by diabetes (141). In most of these cases the immediate cause of death is decompensated heart failure; effectively their prognosis (40% annual case fatality) is that of heart failure, rather than diabetes (3% case fatality).

Early diagnosis and treatment of IHD and HF in diabetes is of paramount importance in preventing cardiovascular complications and mortality (154). However, data from the British Regional Heart Study have shown that, despite their very high risk of developing heart disease, only a small proportion of patients with diabetes receive preventive medication for IHD (155).

Chronic obstructive airway disease (COPD)

Heart failure diagnosis is often overlooked in patients with COPD, despite, or perhaps because of the similarities in symptoms, such as breathlessness and fatigue. The two conditions frequently coexist. Among hospitalised heart failure patients 10% are likely to have COPD and almost a third of ambulatory stable COPD patients also have HF; many of these cases can be undiagnosed and untreated (156). Depending on the design of study and its population, estimates of prevalence of LVSD among COPD patients can vary substantially, between 10% and 46% (157). The odds ratio for prevalence of HF among COPD patients when compared to controls has been estimated at 3.8 (CI: 3.5-4.1) (158). The prevalence of COPD among HF patients is less well studied, although in a recent small cohort of stable HF patients from Portugal it was found to be as much as 39%, and giving a higher risk of mortality, when of significant enough severity (HR 1.40) (159).

Renal impairment

Poor kidney function has been consistently shown to predict mortality in heart failure, being associated with at least 50% greater short and long-term mortality (12) and is directly correlated to pathological processes in other risk factors, such as hypertension and diabetes. Mortality in heart failure is directly related to

creatinine levels, particularly among the elderly patients (160). Serum creatinine and renal dysfunction are common predictive variables of outcome in acute or ambulatory heart failure (13) (97).

Prognostic models

As highlighted above, the risk of dying in the immediate period following an admission for heart failure remains very high and long-term outcomes are poor. Such findings led to limited attempts at designing prognostic models based on clinical and demographic characteristics. Prognostic models which could be used in clinical practice should be relatively simple and rely on variables collected routinely in clinical care.

Several methods of assessing prognosis in patients with acute coronary events have been described, but few exist for acute or decompensated HF. Congestion-hypoperfusion classification, used for patients with an acute MI, was adapted for HF patients, showing that congestion ('wet-warm') doubles the risk of 1-year mortality, while hypoperfusion in the absence congestion ('dry-cold') has a four-fold increase in the risk of death (HR 2.10 and 3.66, respectively) (161). For ambulatory patients with chronic heart failure the existing risk scoring systems are based on exercise capacity (162) or NYHA classification (163), both of which can be subjective. The Minnesota score (164) is based on markers of renal dysfunction and diabetes, although it was developed using a relatively small cohort (N=152) and is not representative of the general heart failure population. The determinants of outcomes in acute decompensated HF were assessed using data from ADHERE registry in the US, showing that high BUN (≥15.35 mmol/L) and low SBP (<115) alone can stratify patients into low, moderate and high mortality risk groups. A model derived from Medicare admissions data in the USA for 30-day fatality following an admission for heart failure in the late 1990s (32) revealed significant excess risk with age and male sex (OR: 1.28), previous history of HF (1.57), acute MI (1.24), renal failure (1.53), dementia (1.47), liver disease (1.50) and cancer (2.2), with a protective effect of hypertension (0.71), unstable angina (0.90) and history of revascularisation (0.60). A model developed by the same authors from contemporaneous Medicare claims for acute MI (165) proves to be very similar, with exception of additional protective effect of chronic IHD or history of previous MI and less risk connected to male sex (1.07). Heart failure cohorts were slightly younger than the MI ones (about 10% under 65 years, compared with about 7-8%). These two studies

were the largest (all US Medicare records 1995-2001) looking at hospital admissions for these conditions. HF and AMI cohorts were broadly similar; with average age of 80 and 78 years (patients under the age of 65 were excluded). Fatality in HF was only slightly lower at 12%, compared to 18% after myocardial infarction. It seems that few, if any, of the routinely available variables can be regarded as disease-specific but can serve as a good proxy of the overall morbidity of elderly cardiac patients. Lee et al (12) derived a simple risk stratification model for patients admitted for HF, using a representative cohort from the late 1990s. In this analysis, the factors predicting early (30-day) and late (1-year) fatality were broadly similar. The highest risks were associated with liver disease (OR for liver cirrhosis 3.22 and 5.80, respectively), dementia (2.54, 2.50), cancer (1.86, 1.85), age (1.70, 1.61 for each decade of life) and COPD (1.66, 1.41). Additional risks were conferred by abnormal kidney function (BUN – 1.55, 1.49), hyponatraemia (1.53, 1.46) and increase in respiratory rate. Interestingly, diabetes was not associated with mortality in this cohort. This study also reported a 30-day fatality rate of around 11% (including 9% in-hospital) and 1-year fatality of 33%. LVD, defined as LVEF below 30%, was associated with five times greater risk of death in the MONICA risk factor survey in a relatively young (<75 years) population in Glasgow, UK, in 1992-1993 (166). Higher BNP (brain natriuretic peptide) concentration (≥17.9 pg/ml) was also associated with higher mortality (unadjusted HR 5.10) in that population-based cohort.

Ross et al (167) searched for predictive models for HF readmissions through a comprehensive review. They found that, despite a number of papers describing the characteristics of patients linked to hospital readmission, only five attempted to derive a risk model, and in only two of those discriminatory power of the model was assessed and proved to be relatively modest. Across all studies most commonly studied variables were age, sex, diabetes, hypertension, NYHA classification and SCr, but none of these factors showed a consistent association with the risk of readmission. Comparatively, mortality models, often including similar variables have more predictive power. Cowie at al (49) found that only age was associated with increased risk of hospitalisation, but that age, NYHA class and serum creatinine were all predictive of mortality. Socio-economic deprivation was not related either to readmissions or mortality in that cohort. Risk of readmission is highest in the first few months following an index admission.

PUBLIC HEALTH AND HEALTH SERVICE ISSUES

Heart failure has significant implications for health services. The cost of its management has been estimated at 1.9% of total NHS budget in 1995, hospitalisation being the main cost component (69%), followed by drug prescription (18%) (168). Prevention, from targeted health promotion to effective management of established disease to avert decompensation and premature death, is very important, although in most cases not cost neutral. There is increasing evidence of a growing inequality in the uptake of health promoting and preventative measures by the poorer groups in western societies.

Prevention

The primary prevention of heart failure includes targeted intervention on common cardiovascular risk factors, such as smoking or obesity, and promotion of healthy lifestyles. Secondary prevention includes tackling already existing disease processes commonly leading to CVD in general, such diabetes or hyperlipidaemia. There have been some positive trends in the prevalence of risk factors internationally. The national health surveys in the US showed that between 1960 and 2000 main CVD risk factors, except for diabetes and obesity, have fallen in adult population and that this reduction occurred independently of the level of obesity (169). However, the benefit of reduction was different across socio-economic groups, with widening gaps in smoking and diabetes prevalence and a more equitable reduction in cholesterol and blood pressure; only blood pressure improved more among the poorer quartiles of society (170). The relative contribution of smoking to the development of CHD is well established, with relative risk estimates between 1.50 and 3. A systematic review estimated that all-cause mortality in CHD patients who smoke can be reduced by a 36% through smoking cessation, exceeding the effect of many secondary prevention measures (171). Despite the overall reduction in smoking rates in Western Europe, the socio-economic gradient in many CVS risk factors has actually increased, as indicated by data for 1982-1992 from Danish MONICA study (106). In cross-sectional studies, overweight and obesity are strongly related to chronic diseases such as type 2 diabetes and hypertension, these relationships are even stronger in the younger (<55 years) age groups (172). There are inherent problems with quantifying this risk precisely, with increasing evidence that risk of cardiovascular morbidity may be higher than in general population even at BMI

levels regarded as 'healthy' (BMI between 22 and 25) (173). The Framingham Heart Study has shown that the independent risk of obesity is enhanced by inadequate level of control of other risk factors in obese patients (174). Both systolic and diastolic pressure show a continuous and independent relationship with risk of cardiovascular events or stroke, with wide pulse pressure particularly important as predictor in individuals aver the age of 55 (175). Management of hypertension depends on the grade and the overall risk profile with an aim to reduce end-organ damage, and thus reduce morbidity and mortality. In addition to hypertension, disturbed glucose metabolism even before the onset of diabetes, dyslipidaemia, abdominal obesity or overweight, are closely associated with development of cardiovascular disease and diabetes (176)(177). In the Finnish IHD Risk Factor Study (178), asymptomatic patients with obesity, pre-diabetes, dyslipidaemia and hypertension had a 2-3 times greater cardiovascular mortality. Tertiary measures include appropriate management of acute coronary syndromes to prevent the onset of heart failure and effective management of ambulatory cases to prevent acute decompensation in chronic heart failure. Trials of early administration of ACE inhibition after AMI show a reduction in CHF events (NNT=1000/6= 167), in addition to a significant reduction in fatality (179), providing early administration. Many precipitating factors for acute heart failure decompensation have been identified, such as non-compliance with medication or non-pharmacological treatment, i.e. dietary measures. Social or environmental factors can play a significant role (180). In practice, concurrent disease, whether preventable or not, is commonly involved including cardiovascular causes such as arrhythmia, hypertension, stroke or CHD, and other such as renal insufficiency, diabetes or lung disease (5).

Diagnosis

Diagnosis of heart failure remains difficult, particularly in older patients in the community, those with much comorbidity, or in acute setting following coronary events, for example. Up to a half of patients diagnosed in primary care may have no left ventricular dysfunction on echocardiography, although many of these patients still have poor prognosis. In the general practice, older patients are particularly difficult to diagnose due to their general level of morbidity, often atypical manifestation. Objective assessment may not be practical and in its absence even well designed clinical criteria fail. A study of Italian 533 patients aimed to compare different sets of diagnostic criteria in the elderly (181), including the Framingham,

Boston, Gothenburg and ESC (1995 version), and found those to be of variable usefulness. The value of clinical history, symptoms and signs in the diagnosis of HF in a representative sample of Portuguese population was found to be poor (182). Despite high specificity and negative predictive value (NPV), clinical findings have a poor positive predictive value (PPV), generally below 60%. The NPV of ECG in the same study was found to be about 75% and of CXR 83% (183). Fuat et al (184) identified possible barriers to effective diagnosis in primary care using general practitioner focus groups. They found that the prevailing reasons were lack of access to diagnostic services, uncertainty about best clinical practice and applicability of research to general practice and poor interaction between primary and secondary care. Open access to echocardiography is necessary for timely diagnosis of heart failure in primary care, although a proportion of cases will only have subtle systolic changes, not detected by conventional echocardiography (185). In an acute setting, elderly patients presenting with breathlessness rather than chest pain may be labelled as 'heart failure' rather than 'cardiac ischaemia' and denied beneficial treatment, if heart muscle damage is reversible (186). Many cases of transient heart failure following an MI or other acute coronary syndrome remain undiagnosed. These uncertainties about diagnosis of the syndrome have significant implications for conclusions drawn from follow-up studies in heart failure, and may explain the observed variation in epidemiological estimates of incidence and case fatality.

Clinical management of established heart failure

Pharmacological therapy

The evidence base for the effectiveness of ACEI was established in the early 1990s, followed in the late 1990 by evidence for beta-blockers (BB). Concerns have been raised about the quality and effectiveness of treatment as well as diagnosis of heart failure in general practice. A survey of a random sample of practitioners across Europe, the Euro-HF study (187), revealed a reliance of symptoms in the diagnosis of heart failure and underutilisation of ACE inhibitors. The EPICA study in Portugal has shown the management of HF in the late 1990s in general practice to be suboptimal, with only about a half of patients with clinical HF or those with LVSD receiving ACE inhibitors (188). These results were similar to other European series, particularly the Euro-HF (187).

Non-pharmacological and interventional management

Non-pharmacological aspects of heart failure management include self-care, diet and nutrition, psycho-social aspects, devices and surgery, and palliative care. Interventional options for patients with ischaemic cardiomyopathy include coronary intervention and revascularisation. Depending on the amount of viable myocardium, either CABG or PCI could restore blood flow to previously ischemic myocardium and lead to a reversal of its dysfunction ('hibernating myocardium'). Although there is sound theoretical basis for considering revascularisation in patients with IHD and clinical guidelines generally recommend such consideration (1), there are no contemporary randomized trials to provide level A evidence, or show superiority of either PCI or CABG (189). However, some observational studies did show some benefit in survival, albeit at variable level. The APPROACH (190) investigators found in large cohort (N=2,538) that the hazard of all-cause mortality was halved in patients undergoing revascularisation (HR 0.50; 95% CI: 0.44-0.57). Other observational series involving smaller groups of patients, focussed on clinical predictors of fatality, such as extent of viable myocardium, and showing more modest improvement of 5% or 13% (191) (192). Other reports were even less encouraging. Small observational studies can suffer from substantial bias. Furthermore, in the earlier series, the effect of surgery was likely to be substantially overestimated as a result of suboptimal medical therapy in comparison groups (189). One arm of the ongoing trial of Surgical Treatment for IsChaemic Heart failure (STICH) aims to provide more robust evidence on the effectiveness of CABG and intensive medical therapy in prolonging patients' survival (193), but these results are yet to be published.

In comparison, evidence on cardiac resynchronisation therapy (CRT) is now well established for moderate to severe heart failure, where it is a treatment for worsening symptoms and to prevent death. The relative reduction of all-cause fatality following could be as much as 29%, as shown in a meta-analysis of previous controlled trials (194), such as COMPANION (195) or CARE-HF (196). Currently CRT is recommended for patients in NYHA class III or IV and prolonged QRS interval, and who are symptomatic despite optimal therapy (1). However, there is increasing evidence of its effectiveness in mild cases (NYHA I and II), based on the recent results from REVERSE (197) and MADIT CRT (198), which indicate significant reverse left-ventricular remodelling and reduction in HF events, sustained over time.

Relative contribution of prevention

A number of studies highlighted the contribution of prevention and medical management to ischaemic heart disease mortality; no specific estimates for heart failure are available. It has been postulated that improved survival in IHD is linked to increasing use of thrombolysis, primary angioplasty in acute MI, stenting and CABG (58). However, the relative contribution of modern treatment, although significant, seems to be outweighed by primary and secondary prevention. Modelling of the UK data for period 1980-2000 (56), showed that as much as 58% of the reduction in mortality could be attributed to primary prevention through reduction of risk factors, mainly smoking, blood pressure and cholesterol reduction. The remaining 42% is the total treatment effect, including management of heart failure (13%), combined effect of secondary prevention measures (pharmacological and non-pharmacological, 11%), management of acute MI (8%), and of angina or hypertension (combined 10%). The total impact of revascularisation, whether for acute coronary syndromes or chronic IHD, has been estimated in that study at just 4%. Similar results were borne out from an earlier study in the UK (199), showing a 40% contribution of therapies and secondary prevention for mortality reduction occurring between 1975 and 1994. In New Zealand, IHD mortality fell by 24% between 1982 and 1993 (200). Half of this reduction has been attributed to medical treatment and half to reduction in major risk factors.

Chapter 3: Methods

KEY ELEMENTS

The following methods were used to fulfil the objectives of the study:

- Trends (1993-2001) in heart failure incidence, hospitalisation and survival were assessed using indirect standardisation, crude and adjusted (Cox proportional hazards) survival modelling.
- Ethnic differentials in survival were assessed in a sub-cohort of patients (1998-2001, N=5789), using crude and adjusted survival modelling (parametric and non-parametric) and logistic regression.
- Impact of revascularisation in patients with heart failure (1998-2001, N=5789) was assessed using time-dependent Cox proportional modelling.
- Prognostic model of long-term survival was developed using Cox proportional hazards method.

STUDY SETTING, POPULATION AND DATA SOURCES

The study included the population of Leicester, Leicestershire and Rutland (LLR), with a combined population of 924,000 in 2001 Census. This health community has contrasting socio-economic and ethnic characteristics, including highly disadvantaged urban centres as well as prosperous rural areas. The city of Leicester has one of the highest South Asian minority concentration in the UK (28% of total population in 2001) (201). In contrast, the counties of Leicestershire and Rutland have predominantly white population (95% in 2001). Across LLR, the largest BME population is of Indian descent (10%). Bangladeshi or Pakistani communities constitute a total of 1.5% and the black minority just over 2% of the total population (201).

Population and exclusion criteria

The study included all LLR residents above the age of 40, admitted for the first time in 5 years with a heart failure diagnosis between 1st of April 1993 and 31st of March 2001 (nine years). An admission was defined as the first hospital episode with a heart failure (ICD9: 428*; ICD10: I50*) as primary or a secondary diagnosis. From this initial cohort, all patients with either no record linkage or those who

were resident in Leicestershire for less than 5 years prior to the index event were excluded. Robust ethnicity coding (>97% of episodes) was available from April 1998 (Table A4, Appendix). A sub-cohort was chosen consisting of patients admitted for the first time between 1st of April 1998 and 31st of March 2001 to evaluate long-term outcomes in ethnic groups and assess other risk factors in more detail. The choice of this sub-cohort was motivated not only by tested completeness of ethnicity coding in hospital discharge data, but also by two other factors, namely the relative stability of the rate of first admission in that period and the availability of relatively robust contemporary ethnic population data from Census 2001

Data and Event Record Linkage

Data were obtained from the local NHS Health Information System (HIS), which includes all episodes of hospital care, whether inpatient, outpatient or accident and emergency, for all LLR residents. These records are record-linked to mortality records provided monthly by the Office for National Statistics (ONS) and other health data sets (Figure2). The local patient register (Exeter system) provides current ('live') and historical information on patients registered with all LLR GPs, including details of their residence, demographics, dates of registration and removal from local register. The linkage on the unique patient number allows for accurate assessment of patient pathway through secondary care and health outcomes, such as mortality or hospital readmissions. The proportion of patients with no record linkage was higher for years 1993/4 and 1994/5 (15%) compared with the more recent years (less than 5% of cases). A brief descriptive comparison of the demographic (age, sex and deprivation) and comorbidity characteristics of the cohort and the excluded group was undertaken, to ensure no significant bias would result from exclusion process in assessing clinical outcomes in earlier years. However, an adjustment for the two initial years in the incidence rate needed to be made.

In-patient care provided by the NHS hospitals is recorded as consultant episodes, defined as the 'period during which an admitted patient is under care of particular medical consultant within a Hospital Provider' (202). For commissioning purposes, episodes are often combined into 'spells' of care, including all episodes from the date of admission to discharge from acute care.

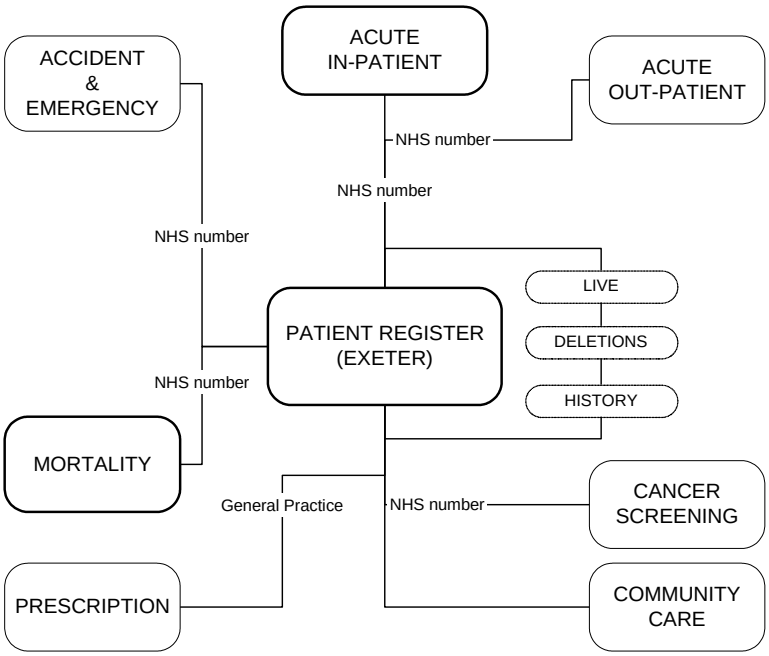


Figure 2 Record linkage schema

OUTCOMES AND EXPLANATORY VARIABLES

Mortality and survival

The primary outcome was mortality identified through record linkage on Public Health Mortality File (ONS). The analysis included mortality from any cause and cause specific mortality. In the latter case the underlying cause of death had to be recorded as either heart failure or any cardiovascular condition listed in the inclusion criteria (Table A1, Appendix). The length of survival was measured from the date of admission to the date of death, or for the censored cases to the end of the follow-up period. Record linkage to the FHS Register also identified patients who were lost to follow-up before the end of the follow-up (i.e. those who moved away from the area). In those cases the date of deletion from the Register was taken as the end of follow-up. Mortality records also provided information on the place of death, which was classified into in and out-of-hospital and the underlying cause of death.

Explanatory variables

Variables included patient's age, measured from the date of birth to the date of diagnosis, sex as recorded in the hospital records and verified through record linkage to the FHS Register, length of stay on the first admission and primary hospital diagnosis. In addition, a proxy of social deprivation (Index of Multiple Deprivation 2000) was obtained using patient's postcode at both ward and electoral district level. It was considered appropriate to retain this version of IMD, rather than using more recent (updates were published in 2004 and 2007) as it was more likely to represent socio-economic characteristics of patients admitted for the first time in the late 1990s. Different area-based SES measures were initially considered; each has its benefits and limitations (203). Index of Multiple Deprivation (IMD) is calculated from a variety of administrative data, which are updated regularly, making the index potentially more up to date than those based solely on population Census. However, it has a health component (e.g. years of potential life lost), which may cause over-estimation of some health risks; IMD is not a truly independent covariate. Less complex indices, such as those by Townsend or Carstairs, are derived solely from population Census variables, including unemployment, overcrowding, car ownership and low social class. Age and sex of patients were defined by hospital record at the time of the index hospital admission and validated using the Exeter patient register. Ethnicity was identified on hospital records, using all available admission data, giving most weight to the ethnicity recorded at the time of index admission (give details in the appendix). Data on comorbidities were derived from hospital discharge records. As a proxy measure of overall morbidity, hospital discharge data were record linked to give average annual hospital stay in the period of 3 years before the first heart failure admission. By definition this was hospitalisation for causes other than heart failure. Patients were classified according to concomitant or prior discharge record, i.e. at least one hospital admission with a given diagnosis (in any position) in the five years prior to index heart failure admission. These included any form of IHD, acute MI and other forms, atrial fibrillation or flutter, other heart disease, hypertension, valve disease, diabetes, stroke and renal failure.

STATISTICAL ANALYSIS

In brief, the analysis included initial data description with group comparisons, univariate Kaplan-Meier estimation of survival, Cox proportional hazards modelling of all potential explanatory variables. Stratified Cox procedure was used to investigate a) the changes in survival over the years of study, b) differences between the sites (hospitals) of first admission and c) the effects of variables not satisfying proportional hazards assumption (namely the length of stay on admission and diagnostic group). In a small proportion of cases (N=38) where deprivation measure was missing, it was imputed using the EM (expectation-maximisation) logarithm included in the MVA (missing value analysis) module within SPSS.

Descriptive methods

The distributions of patient group characteristics were tested using the chi-square test for categorical variables, Fisher exact test, and the t-test for continuous variables (204). Either direct or indirect standardisation method was used to adjust for age-sex differentials between ethnic groups (205). In the former case, the estimated population of England in 2001 was used as standard. To represent admission and incidence rates in South Asian compared to white population, indirectly standardised rate ratios were calculated, with their 95% confidence intervals. These are defined as SARR – standardised admission rate ratio:

$$SARR = \frac{O_{SA} / E_{SA}}{O_w / E_w} \quad (1)$$

where O_{SA} represents the number of observed events in South Asians and E_W the number of expected events in white cohort. SIRR (standardised incidence rate ratio) was constructed in the same way.

Statistical Modelling

The overall aim of statistical modelling is to derive a real and true interpretation of the effect of random explanatory variables on the outcome variable. There are significant trade-offs between the completeness and accuracy of the model and its realism or convenience of use in the interpretation of the results. The objective is to derive a model which is parsimonious rather than a comprehensive, but one

which truly reflects the impact of all clinically and statistically important variables.

The general modelling approach applied in this study included the following steps:

- a null model with no explanatory variables
- a saturated or maximal model, including all explanatory variables or interactions considered clinically important
- step-wise deletion process, assessing significance of excluding individual variables on the fit of the model at each step with significance level of 10%
- choice of the minimal adequate model, following the principle of parsimony
- final model diagnostics

In general, this strategy follows that that published by Collett (206) (207). Where the methodology deviates from these general principles, the adaptations are described in the appropriate results section.

Logistic regression - Generalized Linear Model (GLM)

GLM (208) provides a useful general framework for answering all questions on the relationship between explanatory and outcome (response) variables, using a regression model. A GLM model for a continuous response variable *y* with a normal distribution and constant variance, or linear regression, can be represented as

$$y \sim N(\mu, \sigma^2) \tag{2}$$

where

$$\mu = \beta_0 + \beta_1 x_1 + \cdots + \beta_q x_q \ .$$

Most commonly, clinical outcomes are binary or categorical and a transformation of dependent variable is necessary, in order to estimate the effect of predictors. Appropriate transformation is employed by the *link function g*, leading to a model:

$$\eta = g(\mu) = \beta_0 + \beta_1 x_1 + \cdots + \beta_q x_q \tag{3}$$

To obtain a predicted value of *y*, the linear predictor η needs to be transformed back by the inverse link function. In logistic regression, characterised by binary response variable with a binomial distribution, this is a logistic (logit) function of *p*, or probability of outcome

$$\text{logit}\,[p] = \log\frac{p}{1-p} = \beta_0 + \beta_1 x_1 + \cdots + \beta_q x_q \tag{4}$$

This transformation allows the dependent variable to be treated as a continuous variable in a multivariate regression with linear predictors. Estimation of the parameters in GLM is achieved using the maximum likelihood method. In this study, logistic regression was carried out primarily to evaluate the impact of measured risk factors, whether categorical or continuous, on all-cause and cardiovascular mortality. Outcomes were constructed as binary status (dead or alive), at defined periods in the follow-up, namely under 1 month, 1-6, 6-12 months, 1-2, 2-3 and between 3 and 5 years after index heart failure admission. Fitting the logistic regression models, their evaluation and choice were based on strategies summaries by Collett (207) and Gelman (209) and included optional model selection, checks for interactions and checks of model fit using residuals.

Survival analysis

The two fundamental functions used in describing the survival experience are the survivor function and the hazard function. Both are briefly described below. In general, the *survivor function* is defined as the probability that the survival time of an individual is greater than or equal to a time t:

$$S(t) = P(T \geq t) = 1 - F(t) \tag{5}$$

where

$$F(t) = P(T < t) = \int_0^t f(u)\mathrm{d}u \tag{6}$$

is the distribution function of T.

The *hazard function* is the probability of death at time *t*, equivalent to the instantaneous death rate at time *t* and is most generally expressed as:

$$h(t) = \lim_{\delta t \to 0} \left\{ \frac{P(t \leq T < t + \delta t | T \geq t}{\delta t} \right\} \tag{7}$$

The relationship between the survivor *S(t)* and the hazard *H(t)* functions is as follows:

$$S(t) = \exp\{-H(t)\} \tag{8}$$

and

$$H(t) = -\log S(t) \tag{9}$$

Kaplan-Meier (K-M) estimate of survival

To summarise the overall survival, the K-M estimator was used (210). The log-rank test (211) was used to examine the differences in survival between groups. Estimates produced by K-M analysis refer to population, thus are not a good predictor at individual level.

Cox proportional hazards model (Cox PH)

Cox proportional hazards, or Cox regression, modelling (212) was used to evaluate the effect of all fixed variables on outcome. This is a semi-parametric method of estimating survivorship, given a number of covariates (or explanatory variables) for an individual in a cohort. It assumes that hazard of death at a given time in one group is the same as for individuals in other groups (proportional hazards) but does not rely on any given distribution of survival times. Model diagnostics were carried out using graphical assessment of residuals, including Cox-Snell for overall fit, deviance for outliers, and Shoenfeld and Martingale residuals for proportional hazards (206).

Parametric and frailty models

Although Cox PH is the most routinely used survival analysis in a medical setting, parametric models need to be considered when suitable for the given data, i.e. when survival time distribution can be shown to follow a given pattern. If appropriate, parametric models have a distinct advantage over Cox PH in giving more precise estimates of risk. Several distribution-dependent models have been proposed, but in a medical setting the ones where hazard increases with time are most appropriate. This is because the risk of death in human subjects tends to rise exponentially after the age of 60. Most commonly used is the Weibull model and this is the one considered in this study as an alternative to Cox PH models for fixed covariates (206). Random effects (frailty) models (213) were also considered as part of modelling process. Such models take into account that some of the observed survival times may not be completely independent from one another, which is an inherent assumption in Cox PH method. It is unlikely that in case of such comprehensive data there would be substantial departures from this assumption, however, relationships between individuals within groups, affecting their survival, cannot be excluded.

Survival with time-dependent covariates

The effect on survival of revascularisation in the follow-up period was assessed using a time-dependent model, which included surgery as the time-dependent explanatory variable. Such models are an extension of Cox PH (206), using split observation times for each individual. The analysis included both modelling with revascularisation included with other covariates and with a common baseline hazard and stratified modelling, with different baseline hazard for survival without or pre-revascularisation and post-revascularisation.

Relative survival

The relative survival was examined comparing the KM estimates at given time-points, from one month to 10 years following the first admission, to estimated survival based the general mortality patterns in the UK between 1998 and 2001. The latter was calculated from the annual age and sex specific hazard rates published by the Human Mortality Database (214). For the purpose of comparison, an average survival was calculated for a hypothetical cohort, constructed with one-to-one matching by age (in years), sex and calendar year of index admission. The relative survival at a time t can be expressed as:

$$r(t) = \frac{S_O(t)}{S_P(t)} \tag{10}$$

where $S_O(t)$ is the observed survival and $S_P(t)$ stands for survival expected from population mortality actuarial tables. For conditions which commonly contribute to overall mortality, are thus a large component of $S_p(t)$, $r(t)$ will be an underestimate. Relative survival methodology is most useful when specific causes of death are not available for evaluation. Despite detailed information on causes of death, when examining heart failure mortality it is necessary to have a measure of relative survival. Survival can be shortened in heart failure for all kind of reasons, including concomitant pulmonary or renal pathology, for example.

Software

Analyses presented in this thesis were carried out using the R statistical and graphical environment (215). Contributed packages used in the analysis included *survival* (216), *cprsk* (217) and *arm* (218). As indicated, the missing values for a minority of deprivation indices were estimated using the MVA algorithm in SPSS software (219).

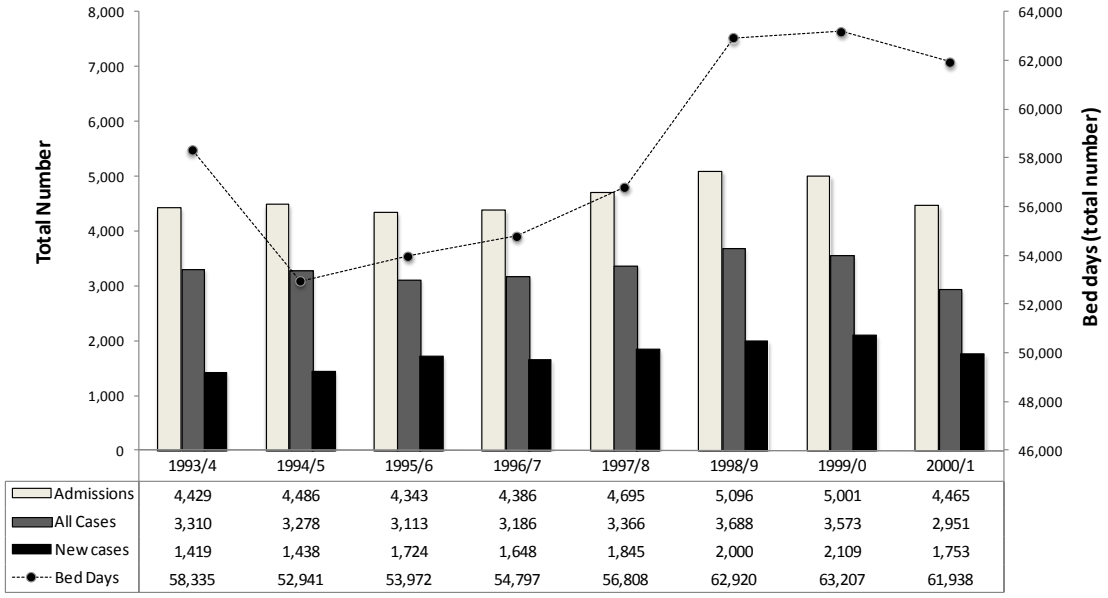
Chapter 4: Results

The results chapter presents the overall trends in heart failure in the eight years between 1993 and 2001, describes the primary selected study cohort from years 1998-2001 and presents detailed results of modelling of their survival experience, including a model of relative survival.

TRENDS IN HEART FAILURE BETWEEN 1993 AND 2001

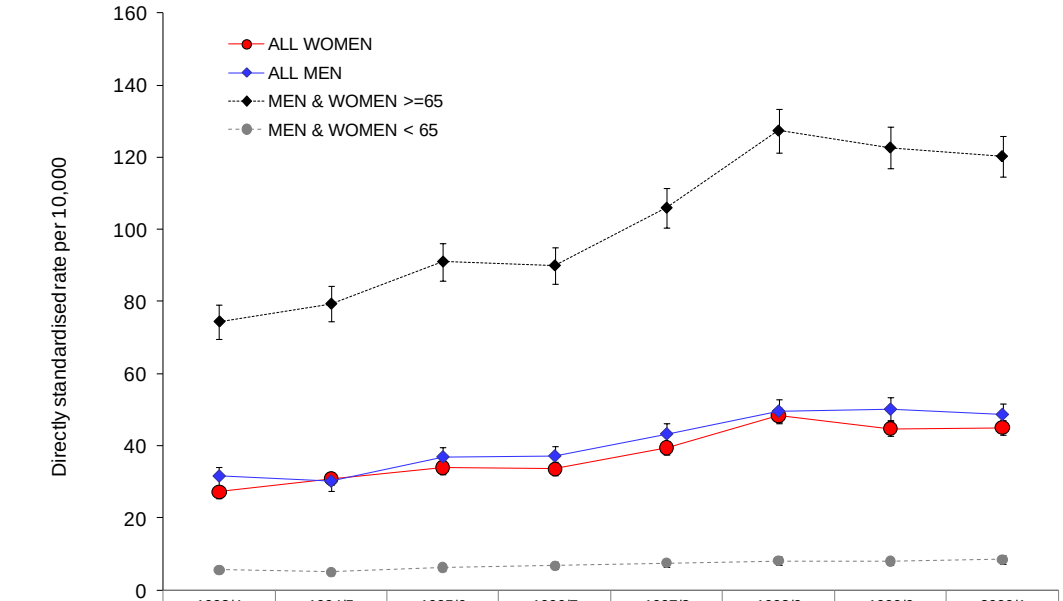
The number of patients treated in hospital for heart failure between 1st of April 1993 and 31st of March 2001 remained relatively stable (Figure 3). However, the number of incident cases and the overall hospital stay, defined as the sum of all bed-days attributed to heart failure, increased, peaking in 1998/9 and 1999/0. When standardised for age, hospital incidence rates had shown a much steeper increase for older patients, those over 65 years of age (Figure 4).

A total of 12,220 patients had their first (index) admission for heart failure in the eight years. In just over a third (36%) of patients their first admission had heart failure diagnosis in the primary position, but in the remainder of cases this diagnosis was secondary. There were approximately as many women as men in this cohort (51% and 49%, respectively) and the majority of patients were elderly (63% over 75 years of age). There was a significant excess (42%) of patients from the most disadvantaged fifth of population (the most disadvantaged IMD quintile, N=5,124/12,220). Nearly 20% of patients had a prior hospital diagnosis of IHD, whether acute or chronic, 15% hypertension and 2% valve disease, but more than half of patients had no hospitalisation in the five years prior to their index heart failure admission, so these figures are not a good proxy of aetiology of heart failure. The average length of the first admission was 8-9 days and did not show any temporal variation.



	1993/4	1994/5	1995/6	1996/7	1997/8	1998/9	1999/0	2000/1
Admissions	4,429	4,486	4,343	4,386	4,695	5,096	5,001	4,465
All Cases	3,310	3,278	3,113	3,186	3,366	3,688	3,573	2,951
New cases	1,419	1,438	1,724	1,648	1,845	2,000	2,109	1,753
Bed Days	58,335	52,941	53,972	54,797	56,808	62,920	63,207	61,938

Figure 3 Trends in heart failure hospitalisation between 1st April 1993 and 31st March 2001. Numbers of new cases are estimated, taking into account varying sensitivity of record linkage. New cases defined as first in 5 years hospital admission with a heart failure diagnosis in any position.



	1993/4	1994/5	1995/6	1996/7	1997/8	1998/9	1999/0	2000/1
ALL WOMEN	27.21	30.86	33.97	33.60	39.46	48.38	44.78	45.05
ALL MEN	31.54	30.12	36.89	37.16	43.32	49.64	50.19	48.73
MEN & WOMEN >=65	74.50	79.42	91.08	90.02	106.00	127.37	122.69	120.28
MEN & WOMEN < 65	5.65	5.01	6.27	6.72	7.51	8.09	8.02	8.45

Figure 4 Trends in the rate of first hospital admission for heart failure between 1993/4 and 2000/1, by age and sex.

There was a significant reduction in the hazard of all-cause and cardiovascular mortality over time (Table 1), both as crude estimate and after adjustment for age, sex, deprivation and gross comorbidity. The hazard of cardiovascular fatality in particular has reduced by 48% over the seven years of the study.

Table 1 Survival in patients admitted for the first time between 1st April 1993 and 31st March 2001 – Cox proportional hazards model

		ALL-CAUSE MORTALITY		CARDIOVASCULAR MORTALITY	
		univariate	**multivariate¶**	**univariate**	**multivariate¶**
Sex	male**				
	female	1.03(0.98-1.08)	0.86(0.82-0.90)	1.00(0.90-1.05)	0.83(0.78-0.88)
Age	10-year	1.43(1.39-1.46)	1.44(1.40-1.48)	1.43(1.38-1.47)	1.45(1.41-1.50)
Deprivation*	Q1**				
	Q2	1.01(0.91-1.11)	1.03(0.93-1.12)	0.99(0.88-1.11)	1.01(0.90-1.13)
	Q3	0.95(0.87-1.04)	0.98(0.89-1.07)	0.94(0.85-1.05)	0.97(0.87-1.08)
	Q4	0.96(0.95-1.04)	1.00(0.91-1.08)	0.96(0.87-1.06)	1.00(0.90-1.11)
	Q5	0.87(0.86-0.94)	0.94(0.87-1.01)	0.87(0.79-0.95)	0.94(0.85-1.03)
Comorbidity§	none**				
	<7 days	0.97(0.92-1.02)	1.06(1.00-1.12)	0.90(0.85-0.96)	1.00(0.93-1.07)
	7 - 29 d	1.52(1.40-1.64)	1.56(1.43-1.67)	1.35(1.22-1.48)	1.43(1.28-1.58)
	30+ d	1.76(1.39-2.22)	1.87(1.47-1.36)	1.44(1.06-1.94)	1.58(1.17-2.15)
Year	1993/4**				
of diagnosis	1994/5	0.81(0.73-0.89)	0.79(0.71-0.87)	0.80(0.71-0.89)	0.78(0.69-0.87)
	1995/6	0.80(0.73-0.88)	0.75(0.68-0.82)	0.77(0.68-0.86)	0.73(0.65-0.81)
	1996/7	0.81(0.73-0.89)	0.74(0.66-0.81)	0.83(0.74-0.92)	0.78(0.69-0.87)
	1997/8	0.80(0.73-0.88)	0.70(0.63-0.77)	0.79(0.70-0.88)	0.72(0.63-0.80)
	1998/9	0.86(0.78-0.94)	0.75(0.68-0.83)	0.82(0.73-0.91)	0.74(0.66-0.83)
	1999/0	0.77(0.69-0.84)	0.65(0.59-0.72)	0.70(0.62-0.78)	0.63(0.55-0.71)
	2000/1	0.77(0.70-0.85)	0.65(0.59-0.72)	0.59(0.52-0.67)	0.52(0.45-0.59)

* Index of Multiple Deprivation (DETR 2000) score by patient's ward of residence, in quintiles (Q1–least, Q5– most deprived)

** Reference categories

§ Defined as average annual stay in hospital in five years preceding the index heart failure admission

¶ Adjusted for age, sex, social deprivation and comorbidity

LONG TERM OUTCOMES IN PATIENTS ADMITTED BETWEEN 1998 AND 2001

Comparative rates of hospitalisation 1998-2001

The overall rates of heart failure hospitalisation were first compared. Although crude rates of hospitalisation and incidence of heart failure were similar or even lower among South Asian, the standardised rate ratios were significantly higher. This is to be expected, as South Asian patients are generally younger at presentation. After age adjustment, the incidence rates had a moderate 50% and 60% excess in South Asian males and females, and admission rates showed a higher two to three-fold ethnic differential.

Table 2 Rates of hospital admission and incidence of heart failure for period between 1st of April 1998 and 31st of March 2001

	Males		Females	
	South Asian	White	South Asian	White
All admissions				
Number	549	5659	488	5888
Crude rate per 1,000	1.09	1.04	9.3	9.8
Standardised admission ratio (SAR)	1.85 (1.70-2.08)	0.96 (0.93-0.98)	2.26 (2.06-2.47)	0.96 (0.93-0.98)
SAR ratio (SARR)*	1.93 (1.63-2.11)		2.36(2.00-2.59)	
Admissions with primary HF diagnosis				
Number	242	1859	193	1873
Crude rate per 1,000	4.8	3.4	3.7	3.1
Standardised admission ratio (SAR)	2.38(2.09-2.70)	0.93(0.89-0.97)	2.69 (2.33-3.10)	0.94 (0.90-0.98)
SAR ratio (SARR)*	2.56 (2.06-2.92)		2.87 (2.26-3.33)	
Incidence				
Number	190	2493	146	2564
Crude rate per 1,000	3.8	4.6	2.8	4.3
Standardised incidence ratio (SIR)	1.47 (1.26-1.69)	0.98 (0.94-1.02)	1.57 (1.32-1.84)	0.98 (0.94-1.02)
SIR ratio (SIRR)*	1.50 (1.21-1.74)		1.60 (1.28-1.89)	

* ratio South Asian:white

Characteristics of the study cohort

Between April 1st 1998 and March 31st 2001, 5,789 individuals had a first hospital admission with a diagnosis of heart failure (Table 3). Median follow-up was 21 months with a maximum of 134 months (11 years). The cohort was 87% white, 6% South Asian and less than 1% other ethnic groups. In 347 cases (6%) ethnicity was recorded as 'not given'. The demographic profile and the observed in-hospital mortality of 43% in this latter group suggest it to be predominantly white and comprising a high proportion of the most acutely unwell patients. The majority of South Asian patients (85%) came from areas with highest levels of social deprivation, in keeping with local patterns of residence. South Asian patients were on average younger by eight years with relatively more men when compared to white (57% c.f. 49%). Less than 10% (N=519) of cases were treated within a cardiological setting (any of the cardiological specialties) at the time of their first admission for heart failure. There was no difference between South Asian and white cohorts in this respect. Given the 924,000 population estimate at the time of Census 2001, the number of first hospitalisations of 5,789 can be expressed as a crude incidence rate of 209 per 100,000 population of all ages.

Comorbidity

As a surrogate measure of co-morbidity, the average annual hospital stay in previous 5 years was similar for the main ethnic groups, but there were distinct patterns of disease-specific hospital comorbidity (Table 3). Acute myocardial infarction, both prior to and concomitant, was nearly twice as prevalent in the South Asian cohort (10% vs. 6% and 19% vs. 10%, respectively, $p<0.001$). Overall, 27% of South Asian patients had had an MI, compared with 15% of whites. Similarly, a diagnosis of diabetes mellitus was recorded for 45% of South Asian patients, three times the prevalence in the white cohort. Hypertension was also recorded more frequently (44% vs. 29%).

Table 3 Demographic and clinical characteristics of 5789 patients admitted for the first time for heart failure between 1 April 1998 and 30th of March 2001.

Variable	White patients (n=5057)	South Asian patients (n=336)	Other BME groups (n=49)	Ethnicity not known (n=347)	P value*
Mean age in years (SD)	78 (9.8)	70 (10.4)	75 (11.6)	78 (11.0)	
Age range (years)	42-107	42-97	41-96	42-99	
Men (%)	2494 (49.3)	190 (56.5)	23 (46.9)	169 (48.7)	0.076
Women (%)	2563 (50.7)	146 (43.5)	26 (53.1)	178 (51.3)	
Deprivation quintile†					
Q1	603(11.0)	8(2.4)	2(4.1)	38(11.0)	<0.001
Q2	640(12.7)	11(3.3)	2(4.1)	51(14.7)	
Q3	808(16.0)	9(2.7)	5(10.2)	59(17.0)	
Q4	1063(21.0)	23(6.8)	8(16.3)	70(20.2)	
Q5	1943(38.4)	285(84.8)	32(65.3)	129(37.2)	
Comorbidity‡					
None	1501(29.7)	98(29.2)	24(49.0)	227(65.4)	
< 7 days	2714(53.7)	186(55.4)	23(46.9)	113(32.6)	
7-29 days	766(15.1)	49(14.6)	2(4.1)	7(2.0)	
30+ days	76(1.5)	3(0.9)			
Median/maximum follow-up (mo)	21 / 134	42 / 134	38 / 128	4 / 134	
Number (%) of deaths	4275 (84.5)	248 (73.8)	38 (77.6)	297 (85.6)	
Cardiological admission	474(9.4)	34(10.1)	6(12.2)	5(1.4)	
Comorbidity: number (%)					
Acute myocardial infarction	769 (15.2)	91 (27.1)	10 (20.4)	73 (21.0)	<0.001
before admission for heart failure	278 (5.5)	34 (10.1)	1 (2.0)	9 (2.6)	<0.01
concomitant	539 (10.7)	63 (18.8)	9 (18.4)	67 (19.3)	<0.001
Other IHD (excl. AMI)	1264 (25.0)	98 (29.2)	8 (16.3)	69 (19.9)	0.02
Other heart disease (excluding IHD)	3024 (59.8)	147 (43.8)	31 (63.3)	204 (58.8)	<0.001
Hypertension	1484 (29.3)	147 (43.8)	20 (40.8)	72 (20.7)	<0.001
Valve disease	250 (4.9)	6 (1.8)	2 (4.1)	7 (2.0)	<0.01
Diabetes	817 (16.2)	154 (45.8)	15 (30.6)	44 (12.7)	<0.001
Stroke	393 (7.8)	26 (7.7)	8 (16.3)	8 (2.3)	<0.001
Renal failure	646 (12.8)	48 (14.3)	8 (16.3)	41 (11.8)	0.637
Atrial fibrillation or flutter:	1744 (34.5)	46 (13.7)	15 (30.6)	97 (28.0)	<0.001
before admission for heart failure	646 (12.8)	15 (4.5)	4 (8.2)	6 (1.7)	<0.001
concomitant	1487 (29.4)	37 (11.0)	14 (28.6)	94 (27.1)	<0.001

* P value - Fisher's exact test or chi-square test, as appropriate

† Index of Multiple Deprivation (IMD2000); Q1=least deprived, Q5=most deprived

‡ Length of stay in five years prior to the index heart failure admission

OUTCOMES

By the end of the follow-up period (31/03/2009), a total of 4,858 (83.9%) patients died. The most common reported underlying cause of death was chronic IHD or acute MI (21% and 11%, respectively - Table 4). Heart failure was considered as underlying cause in less than 6% of cases. Only 53% of all deaths had a cardiovascular cause of death (acute MI, chronic IHD, heart failure or other form of cardiovascular disease). Cardiovascular mortality alone is likely to be an underestimate of total contribution of heart failure to reduced survival.

Table 4 The underlying cause of death of 4858 cases who died by the end of the study

Cause of death	Number	% of Total
Chronic IHD	1,029	21.2%
Pulmonary	966	19.9%
Non-IHD CVS	728	15.0%
Cancer	555	11.4%
Acute MI	553	11.4%
Heart failure	276	5.7%
Gastrointestinal	202	4.2%
CNS and senility	180	3.7%
Metabolic/endocrine	94	1.9%
Other	275	5.7%
Total	**4,858**	**100.0%**

Unadjusted survival

Figure 5 shows the survivorship estimate for the total cohort (N=5,789), by all-cause mortality (number of events 4,858, 83.9%) and cardiovascular causes (number of events 2,559, 44.2%). In the latter case all deaths due to other than cardiovascular causes were censored. The median survival (Table 5) was just under 2 years (23 months; 95% CI: 21-25), but cardiovascular average was nearly 6 years (69 months; 95% CI: 65-74). Patients of South Asian origin had the longest average survival of nearly 4 years, while those with unknown ethnicity survived on average

for only 4 months. These comparisons are presented here only for descriptive purposes – such crude results are clearly biased by age and other risk factors.

The overall crude survival estimate (Kaplan-Meier) for this unselected cohort of patients was 79% at one month (95%CI: 77-80%), 58% at one year (95%CI: 57-60%), 30% at 5 years (95%CI: 28-31%) and 13% at 10 years (95%CI: 12-14%). Estimates for the ethnic groups (Figure 6), were significantly different (log-rank test p-value<0.0001), although overall tests did not indicate differences between men and women for either all-cause or cardiovascular mortality (p=0.10 and p=0.76, respectively). The probability of survival at specific follow-up points for men and women in ethnic groups is presented in more detail in Table 6. These results indicate better all-cause, but not cardiovascular, survival among South Asian patients, except for women at 1-3 years of follow-up.

Table 5. Average survival for the main patient groups

	Median (months)	95% CI
All-cause survival	23	21-25
Men	24	21-26
Women	22	20-25
Ethnicity:		
white	22	20-24
South Asian	43	36-59
other	38	23-61
not known	4	1-15
Cardiovascular survival	69	65-74
Men	70	64-77
Women	68	62-75
Ethnicity:		
white	69	64-73
South Asian	102	79-0
other	83	46-0
not known	56	37-79

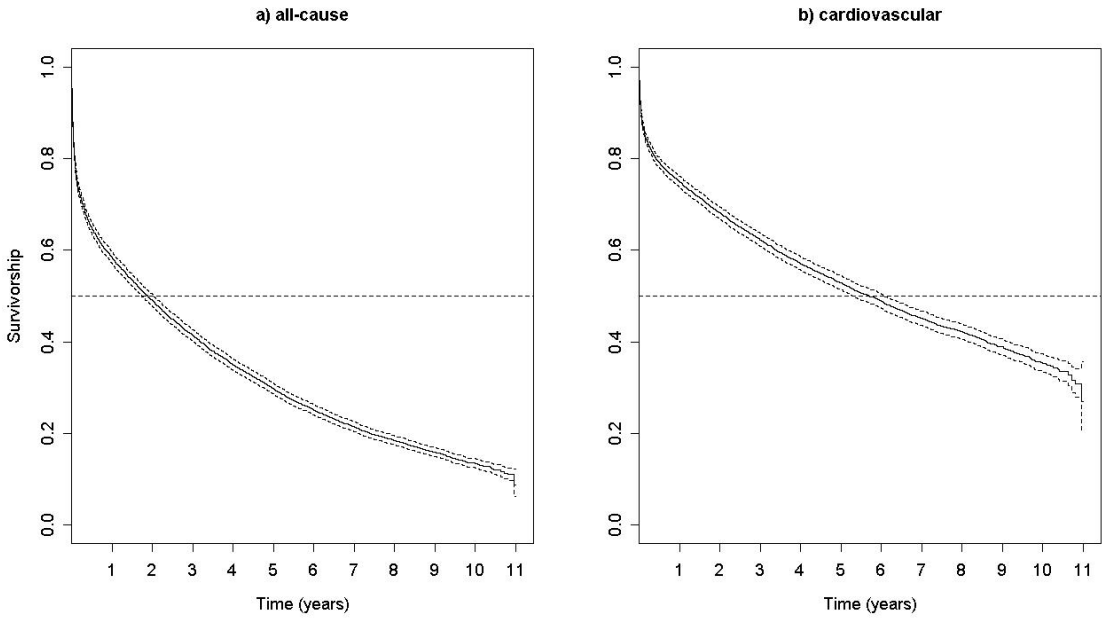


Figure 5 Overall Kaplan-Meier estimate of survival

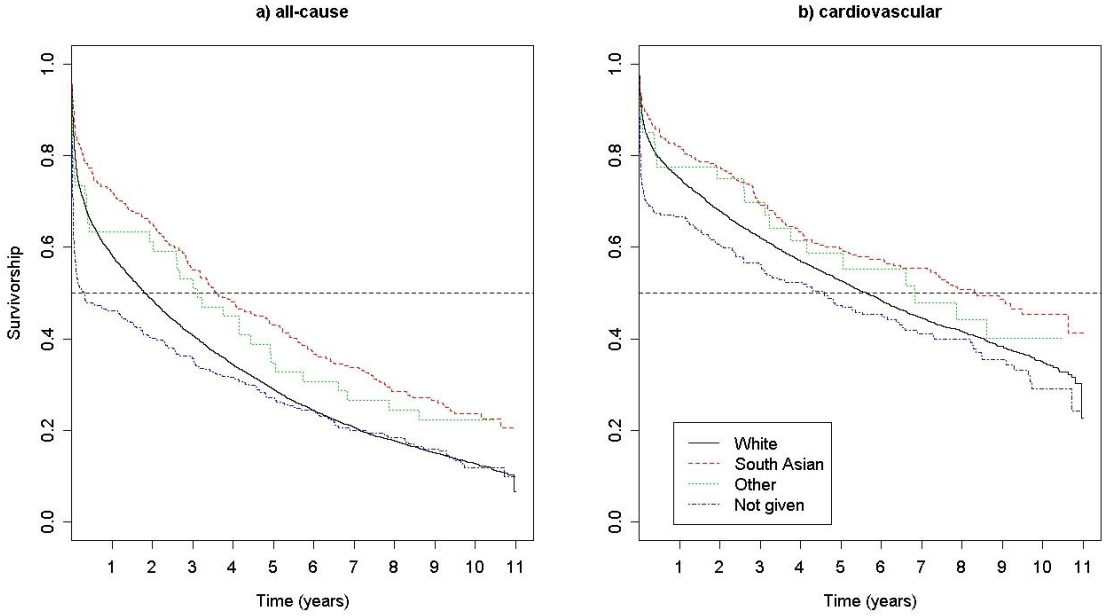


Figure 6 Estimated all-cause and cardiovascular KM survival by ethnic group

Table 6. Kaplan-Meier survival estimates for patients admitted for heart failure between 1/4/1998 and 31/3/2001 (N=5789); significant differences highlighted in bold.

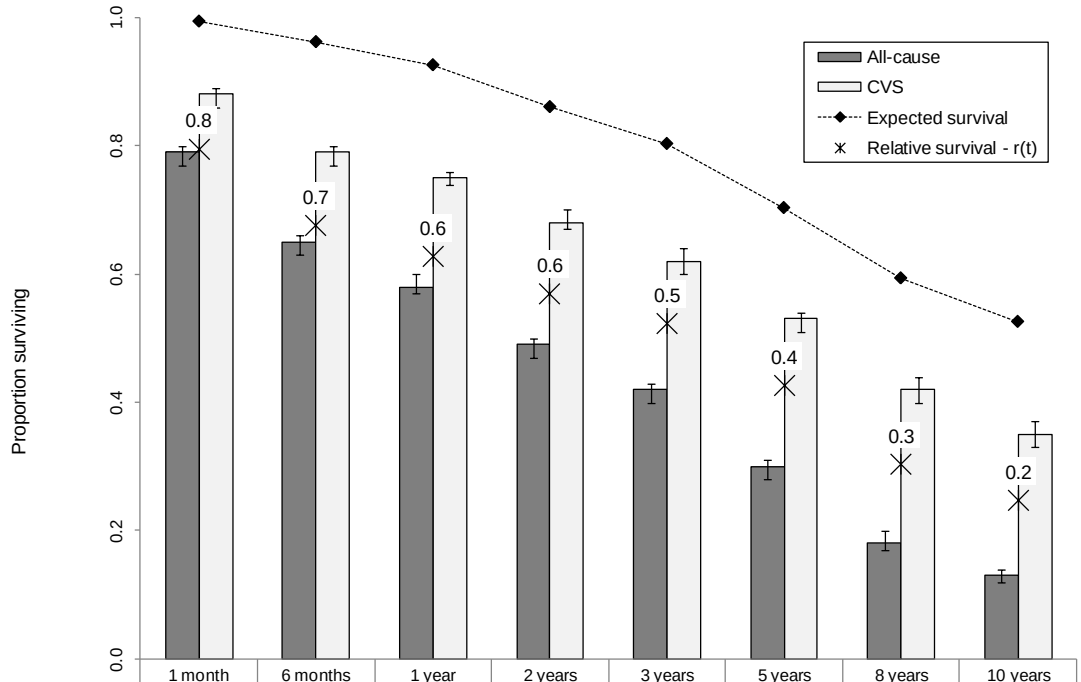
	Men				Women			
	White	South Asian	Other	Not known	White patients	South Asian	Other	Not known
Survival	(N=2494)	(N=190)	(N=23)	(N=169)	(N=2563)	(N=146)	(N=26)	(N=178)
All-cause:								
30 days	80 (78 to 81)	83 (78 to 89)	74 (57 to 94)	59 (51 to 67)	81 (79 to 82)	**90 (84 to 95)**	74 (57 to 94)	58 (51 to 66)
6 months	65 (63 to 67)	**75 (68 to 81)**	57 (39 to 81)	52 (44 to 60)	66 (63 to 67)	**78 (71 to 85)**	57 (39 to 81)	44 (37 to 52)
1 year	58 (56 to 60)	**70 (64 to 77)**	54 (37 to 79)	49 (42 to 56)	58 (56 to 60)	**74 (67 to 81)**	54 (37 to 79)	42 (36 to 50)
2 years	49 (46 to 51)	**62 (55 to 69)**	52 (35 to 77)	43 (36 to 51)	48 (46 to 50)	**68 (61 to 76)**	52 (35 to 77)	37 (31 to 45)
3 years	41 (38 to 43)	**53 (46 to 60)**	48 (31 to 73)	38 (31 to 46)	41 (38 to 43)	**58 (50 to 67)**	48 (31 to 73)	33 (26 to 41)
5 years	30 (28 to 32)	**41 (34 to 49)**	30 (16 to 56)	31 (24 to 39)	28 (26 to 30)	**45 (38 to 54)**	30 (16 to 57)	22 (16 to 29)
8 years	19 (16 to 20)	**31 (24 to 38)**	26 (13 to 52)	22 (16 to 30)	17 (15 to 19)	26 (19 to 34)	26 (12 to 52)	14 (9 to 20)
10 years	14 (12 to 15)	n/a	29 (9 to 47)	16 (10 to 23)	12 (10 to 14)	**23 (16 to 32)**	21 (9 to 47)	8 (4 to 14)
Cardiovascular:								
30 days	88 (87 to 90)	88 (83 to 93)	91 (80 to 100)	71 (63 to 78)	89 (87 to 90)	94 (89 to 98)	80 (65 to 97)	75 (68 to 82)
6 months	79 (77 to 81)	83 (77 to 89)	79 (62 to 100)	65 (58 to 74)	80 (78 to 82)	88 (82 to 93)	76 (60 to 95)	68 (61 to 76)
1 year	75 (73 to 77)	79 (73 to 86)	75 (57 to 98)	65 (57 to 73)	75 (73 to 77)	**85 (79 to 92)**	72 (56 to 91)	68 (60 to 76)
2 years	68 (66 to 70)	73 (67 to 80)	73 (54 to 97)	58 (50 to 67)	68 (65 to 70)	**83 (76 to 90)**	68 (52 to 88)	62 (54 to 71)
3 years	61 (59 to 64)	65 (58 to 73)	67 (48 to 93)	54 (46 to 63)	63 (60 to 65)	**74 (67 to 82)**	62 (44 to 85)	57 (49 to 66)
5 years	53 (50 to 56)	56 (48 to 64)	53 (33 to 84)	48 (40 to 58)	52 (50 to 55)	64 (55 to 73)	57 (39 to 82)	44 (36 to 55)
8 years	41 (38 to 44)	48 (40 to 57)	46 (26 to 79)	42 (34 to 52)	42 (39 to 45)	54 (45 to 65)	42 (24 to 73)	36 (27 to 46)
10 years	35 (32 to 38)	41 (32 to 51)	36 (18 to 74)	31 (22 to 43)	35 (31 to 38)	52 (43 to 63)	n/a	27 (18 to 40)

Relative survival

Estimated survival in the study cohort was compared to the expected survivorship in a hypothetical UK cohort matched for age, sex and year of first hospital admission through relative survival, *r(t)* defined on page 52. The relative survival at separate times in the follow-up and both all-cause and cardiovascular K-M estimates of survival in the study cohort are presented on Figure 7. At 30 days relative survival was 0.8 and fell steadily to 0.2 by 10 years after the first heart failure admission. It is also clear that at later follow-up times, non-cardiovascular causes predominate.

Approaching this from absolute numbers perspective, in a population of one million residents, one can expect about 2000 newly admitted heart failure cases per year. While in the general population a cohort of similar age could expect just 20 deaths in a month and at most 140 in one year, heart failure patients will experience 420 and 840 deaths, respectively. This gives a ball-park estimate of 700 excess deaths attributable to heart failure in a population of one million per year.

Because heart failure is such a common cause of mortality among the elderly, it contributes substantially to the background survivorship expectation and, as a result, the presented figures have to be regarded as an underestimate.



	1 month	6 months	1 year	2 years	3 years	5 years	8 years	10 years
All-cause	0.79	0.65	0.58	0.49	0.42	0.30	0.18	0.13
CVS	0.88	0.79	0.75	0.68	0.62	0.53	0.42	0.35
Expected survival	0.99	0.96	0.93	0.86	0.80	0.70	0.59	0.53
Relative survival - r(t)	0.8	0.7	0.6	0.6	0.5	0.4	0.3	0.2

Figure 7. Estimated survivorship at different times following an index heart failure hospitalisation, compared to expected survival in an age, sex and year matched reference population.

Modelling the impact of fixed covariates

The objective of modelling was to evaluate the impact of routinely available variables, such as ethnicity, age, sex, deprivation and comorbidity indicators derived from hospital discharge data, whether concurrent with the index admissions or from patients' admission history in the preceding five years. This section presents the results of modelling of the effect of fixed covariates using logistic regression, non-parametric (Cox proportional hazards), parametric (Weibull) and frailty methods. The prognostic effect revascularisation in the follow-up was assessed through a time-dependent Cox proportional hazards model – this model is presented separately.

Logistic regression

Separate logistic models were developed for mortality under 1 month, 1 and 5 years to assess the risk of all-cause and cardiovascular mortality. The results are presented in Table 7. The most consistent finding is that of at least 4% increase in risk of mortality for each year of age at the time of diagnosis (OR 1.03-1.06). This risk increases at longer follow-up times for all-cause, but not for cardiovascular mortality. For patients without recorded ethnicity the risk of mortality is generally significantly higher. This group is most likely composed of patients with acute, severe disease. The effect of deprivation is unclear, with an apparently protective effect of highest level (quintile 5) of deprivation in the earliest period of follow-up. Previous hospitalisation (gross comorbidity) appears to be a good predictor of all-cause mortality for up to one year, but appears to be completely unrelated to the cardiovascular outcome. There is an increased risk of all-cause fatality related to cancer, highest up to 3 years; after 3 years cancer diagnosis becomes protective as it is generally for cardiovascular outcome, a pattern characteristic for a competing cause of mortality. Chronic ischaemic heart disease seems to confer a protective effect if prior to heart failure admission but increases the risk if recorded concomitantly. Of the recorded comorbidities, stroke and renal failure, particularly when recorded at the time of admission, are both the strongest predictors of fatality. For diabetes, findings are largely non-significant, but indicating a moderate increase in risk in later stages of follow-up. Concomitant hypertension shows a protective effect, particularly for all-cause fatality. Valve disease was risk factor primarily for cardiovascular outcome.

These logistic regression models describe risk patterns for the incident cohort in terms of odds ratios, without allowing for censoring. Because of high all-cause mortality, this study has relatively small proportion of censored cases (N=5789, 16%) and logistic regression estimates can be expected to be relatively robust. However, for cardiovascular outcomes, because many cases (N=2299, 39.7%) had a competing cause of death and were thus censored, survival modelling is more appropriate.

Logistic regression modelling for the same data sets tend to give similar results for shorter observation periods, but for longer follow-up the two methods can give disparate results, as more information becomes available on the effect of time on outcome (220).

Table 7 Logistic regression estimates of relative risk of mortality at 1 month, 1 year and five years

		All-cause			Cardiovascular		
		< 30 days (N=1198)	**< 1 year** (N=2404)	**< 5 years** (N=4025)	**< 30 days** (N=675)	**< 1 year** (N=1298)	**< 5 years** (N=2146)
Ethnicity:	White	1.00	1.00	-	1.00	1.00	-
	South Asian	0.92 (0.66-1.29)	**0.74 (0.57-0.96)**	0.93 (0.72-1.20)	1.07 (0.71-1.62)	0.84 (0.62-1.15)	-
	Other	1.48 (0.74-2.93)	0.89 (0.47-1.66)	0.79 (0.42-1.49)	1.03 (0.41-2.59)	0.85 (0.40-1.79)	-
	Not known	**3.29 (2.60-4.16)**	**1.93 (1.53-2.45)**	**1.55 (1.20-2.00)**	**2.72 (2.07-3.58)**	**1.48 (1.14-1.91)**	-
Age (year)		**1.03 (1.03-1.03)**	**1.04 (1.04-1.04)**	**1.06 (1.06-1.06)**	**1.04 (1.04-1.04)**	**1.04 (1.04-1.04)**	**1.04 (1.04-1.04)**
Deprivation†:	Q1 (least)	1.00	-	-	1.00	-	-
	Q2	0.81 (0.63-1.05)	-	-	0.79 (0.57-1.11)	-	-
	Q3	**0.76 (0.59-0.98)**	-	-	0.74 (0.54-1.01)	-	-
	Q4	**0.74 (0.59-0.94)**	-	-	0.81 (0.60-1.09)	-	-
	Q5	**0.68 (0.55-0.84)**	-	-	**0.66 (0.50-0.87)**	-	-
Comorbidity‡:	none	1.00	1.00	1.00	-	-	-
	< 7 days	**1.26 (1.08-1.47)**	**1.15 (1.00-1.32)**	**1.28 (1.12-1.47)**	-	-	-
	7-29 days	**1.75 (1.41-2.17)**	**1.99 (1.67-2.38)**	**2.20 (1.78-2.73)**	-	-	-
	30+ days	**2.05 (1.21-3.49)**	**2.44 (1.49-3.97)**	**2.80 (1.53-5.14)**	-	-	-
Year:	1998/9	-	1.00	1.00	-	-	-
	1999/0	-	**0.86 (0.75-0.99)**	**0.84 (0.73-0.96)**	-	0.85 (0.73-1.00)	0.89 (0.77-1.02)
	2000/1	-	**0.83 (0.72-0.95)**	**0.78 (0.68-0.89)**	-	**0.84 (0.72-0.99)**	**0.82 (0.71-0.94)**
Cardiological admission		0.81 (0.62-1.07)	-	**0.66 (0.54-0.80)**	-	-	0.73 (0.48-1.13)
Cancer		**1.34 (1.04-1.72)**	**2.23 (1.79-2.76)**	**0.33 (0.16-0.67)**	**0.55 (0.36-0.84)**	**0.52 (0.38-0.71)**	**0.47 (0.37-0.61)**
Acute MI:	prior	**0.59 (0.42-0.85)**	**-**	-	0.74 (0.49-1.12)	-	**1.34 (1.04-1.72)**
	concomitant	**1.52 (1.20-1.93)**	**1.38 (1.13-1.68)**	1.17 (0.96-1.43)	**2.48 (1.85-3.33)**	**1.93 (1.53-2.45)**	**1.63 (1.32-2.03)**
IHD (non-AMI):	prior	**0.69 (0.55-0.87)**	-	-	**0.63 (0.48-0.83)**	-	-
	concomitant	-	-	-	**1.43 (1.07-1.92)**	**1.31 (1.06-1.63)**	1.21 (0.99-1.47)
Other heart disease		0.83 (0.68-1.01)	**1.26 (1.10-1.44)**	**1.26 (1.10-1.44)**	**0.61 (0.44-0.85)**	**0.78 (0.63-0.97)**	**0.81 (0.67-0.99)**
Stroke:	prior	**1.38 (1.03-1.85)**	-	**1.34 (0.98-1.83)**	**1.72 (1.21-2.44)**	**1.36 (1.04-1.79)**	**1.55 (1.20-2.00)**
	concomitant	**2.94 (2.15-4.03)**	**3.00 (2.15-4.19)**	**2.64 (1.75-3.98)**	**4.35 (3.12-6.07)**	**3.67 (2.68-5.02)**	**2.69 (1.97-3.68)**
Renal failure:	prior	-	**1.40 (1.05-1.89)**	**2.29 (1.55-3.39)**	1.36 (0.90-2.06)	**1.46 (1.07-2.00)**	**1.35 (1.03-1.78)**
	concomitant	**2.69 (2.21-3.27)**	**3.03 (2.49-3.69)**	**2.59 (2.04-3.27)**	**2.10 (1.66-2.65)**	**2.12 (1.74-2.58)**	**1.51 (1.26-1.80)**
Atrial fibrillation/flutter:	prior	-	-	1.36 (0.98-1.90)	-	-	1.17 (0.98-1.40)
Diabetes		-	-	1.16 (0.99-1.36)	-	-	**1.16 (1.01-1.33)**
Hypertension:	prior	-	-		-	-	
	concomitant	**0.53 (0.44-0.65)**	**0.65 (0.56-0.76)**	**0.68 (0.60-0.78)**	**0.68 (0.54-0.87)**	**0.80 (0.67-0.96)**	-
Valve disease		-	-	**1.38 (1.05-1.81)**	**1.55 (1.07-2.25)**	**1.68 (1.25-2.26)**	**1.93 (1.47-2.55)**

Cox proportional hazards models with fixed covariates

When unadjusted for other covariates, South Asian ethnicity appears to confer a 31% protection from all cause, and 24% from cardiovascular, mortality (Table 8). Not surprisingly, comorbidities such as cancer, stroke or renal failure increase the risk. Table 9 presents the results of modelling using AIC stepwise method. Variables which were excluded from the initial full models as statistically non-significant are shown, for comparison.

All-cause survival

The protective effect of South Asian ethnicity on all-cause fatality was attenuated by other factors, largely the lower age at admission, observed in this group of patients. Neither sex nor socioeconomic deprivation proved significant predictors of mortality in this cohort of heart failure patients. Of patients' socio-demographic characteristics only age was a significant predictor with a 4% increase in the risk of mortality for every year of life, after adjustment for other measured factors. However, clinical factors proved significant. In multivariate analysis, the gradient in mortality across the levels of gross comorbidity index remained, with 66% excess hazard in patients with more than 30 days hospitalisation per year prior to the index heart failure admission. None of the heart diagnoses were significant in predicting mortality when adjusted for other factors, except for concomitant chronic IHD which was moderately protective. This perhaps is an influence of patients admitted on an elective basis with established, less severe heart failure. These results stand in contrast to the findings from logistic regression, which showed a significantly higher mortality linked to a concomitant acute MI. Logistic regression is clearly a better model for a changing hazard of death in acute forms of IHD. Also, in patients with heart disease other than IHD, whether acute or chronic, logistic regression shows a moderate, about 20%, increase in risk after the early 6 months period. The risk of mortality in patients with concomitant stroke or renal failure was 70%-80% higher when estimated in the survival model, but again odds ratios obtained through logistic regression were much more striking (three-fold for 1-year mortality for both stroke and renal failure). There was a slight increase in risk due to diabetes after adjustment for other factors, but the result was of borderline significance and the results of logistic regression were similarly inconclusive. There

was also a 19% reduction in risk with concomitant hypertension; again, the protective effect of this variable is much more evident in logistic models.

The hazard function for the *i*'th patient thus takes the following form:

$$\begin{aligned}\hat{h}_i(t) = \exp\{&-0.068A1 - 0.082A2 + 0.298A3 + 0.0425AGE + 0.125C1 + 0.4073C2 + 0.5056C3 \\ &- 0.105Y1 - 0.117Y2 + 0.4295CA - 0.221CR - 0.091IHD + 0.137S1 + 0.5431S2 \\ &+ 0.225RF1 + 0.558RF2 + 0.094D \\ &- 0.207HT\}\,\hat{h}_0(t)\end{aligned} \quad (11)$$

where *A1, A2* and *A3* are South Asian, other and not known ethnicity; *AGE* is age in years, *C1-C3* are gross comorbidity groups; *Y1-Y2* years of first admission (1999/0 and 2000/1, respectively; *CA* represents cancer diagnosis; *CR* cardiological admission; *IHD* concomitant diagnosis of IHD; *S1* prior stroke diagnosis, *S2* concomitant stroke diagnosis; *R1* prior renal failure diagnosis; *R2* concomitant renal failure diagnosis; *D* any diagnosis of diabetes (prior or concomitant) and *HT* is any diagnosis of hypertension.

Cardiovascular survival

The results of survival analysis for cardiovascular causes were similar, with some notable exceptions. Not surprisingly, cancer diagnosis was linked to a lower hazard of cardiovascular death, while concomitant MI conferred a 28% excess hazard. Risks related to renal failure, diabetes, and understandably to stroke are higher for cardiovascular than for all-cause mortality, but not as high as those estimated in logistic regression. Valve disease diagnosis is linked to a 51% excess hazard.

Table 8 Unadjusted estimates of hazard for patients in risk groups (Cox PH – hazard ratios and their 95% confidence intervals).

Variable		All-cause	Cardiovascular
Ethnicity:	White	1.00	1.00
	South Asian	0.69 (0.61-0.78)	0.76 (0.64-0.90)
	Other	0.80 (0.58-1.09)	0.89 (0.58-1.35)
	Not known	1.19 (1.06-1.34)	1.31 (1.12-1.53)
Sex		1.05 (0.99-1.11)	0.99 (0.91-1.07)
Age (year)		1.05 (1.04-1.05)	1.04 (1.04-1.05)
Deprivation:	Q5 - least deprived	1.00	1.00
	Q4	0.89 (0.79-1.00)	0.89 (0.76-1.04)
	Q3	0.87 (0.77-0.97)	0.83 (0.71-0.97)
	Q2	0.91 (0.82-1.00)	0.90 (0.78-1.04)
	Q1 - most deprived	0.86 (0.79-0.95)	0.83 (0.73-0.94)
Gross comorbidity:	None	1.00	1.00
	< 7 days	1.14 (1.07-1.21)	1.10 (1.01-1.21)
	7-29 days	1.80 (1.65-1.97)	1.58 (1.40-1.79)
	30+ days	1.85 (1.46-2.33)	1.53 (1.09-2.16)
Year:	1998/9	1.00	1.00
	1999/0	0.90 (0.84-0.97)	0.89 (0.81-0.97)
	2000/1	0.90 (0.84-0.97)	0.84 (0.77-0.93)
Cardiological admission		0.62 (0.56-0.69)	0.73 (0.64-0.69)
Comorbidities:			
Cancer		1.70 (1.53-1.90)	0.83 (0.67-1.01)
Acute MI	Prior	0.87 (0.77-0.99)	1.08 (0.93-1.26)
	concomitant	0.81 (0.74-0.88)	1.17 (0.86-1.30)
IHD (non-AMI)	Prior	0.92 (0.85-0.99)	1.03 (0.97-1.14)
	concomitant	0.84 (0.79-0.90)	1.10 (0.91-1.20)
Other heart disease		1.19 (1.13-1.26)	0.87 (1.13-1.26)
Stroke	Prior	1.39 (1.23-1.58)	1.61 (1.37-1.89)
	concomitant	1.82 (1.56-2.13)	2.52 (2.10-3.03)
Renal failure	Prior	1.66 (1.45-1.90)	1.67 (1.39-2.01)
	concomitant	1.82 (1.67-1.99)	1.87 (1.66-2.10)
Atrial fibrillation/flutter	Prior	1.14 (1.05-1.25)	1.28 (1.14-1.44)
	concomitant		
Diabetes		0.94 (0.87-1.01)	1.02 (0.92-1.12)
Hypertension	Prior	0.99 (0.92-1.07)	1.09 (0.99-1.21)
	concomitant	0.75 (0.70-0.81)	0.87 (0.79-0.96)
Valve disease		0.87 (0.76-1.00)	1.17 (0.99-1.38)

Table 9 Adjusted hazard estimates for all-cause and cardiovascular mortality obtained through stepwise deletion (Cox PH AIC model)

Variable		All-cause	Cardiovascular
Ethnicity:	White	1.00	1.00
	South Asian	0.93 (0.82-1.07)	0.97 (0.81-1.15)
	Other	0.92 (0.67-1.27)	0.99 (0.65-1.50)
	Not known	1.35 (1.20-1.52)	1.42 (1.21-1.67)
Sex			
Age (year)		1.04 (1.04-1.05)	1.04 (1.04-1.05)
Deprivation:	Q5 - least deprived		
	Q4		
	Q3		
	Q2		
	Q1 - most deprived		
Gross comorbidity:	none	1.00	1.00
	< 7 days	1.13 (1.06-1.21)	1.08 (0.99-1.19)
	7-29 days	1.50 (1.37-1.65)	1.31 (1.14-1.50)
	30+ days	1.66 (1.31-2.10)	1.35 (0.95-1.91)
Year:	1998/9	1.00	1.00
	1999/0	0.90 (0.84-0.96)	0.87 (0.79-0.95)
	2000/1	0.89 (0.83-0.95)	0.80 (0.73-0.89)
Cardiological admission		0.80 (0.72-0.89)	0.82 (0.71-0.95)
Comorbidities:			
Cancer		1.54 (1.38-1.71)	0.76 (0.62-0.94)
Acute MI	prior		
	concomitant		1.28 (1.13-1.45)
IHD (non-AMI)	prior		
	concomitant	0.91 (0.85-0.98)	
Other heart disease			0.85 (0.77-0.93)
Stroke	prior	1.15 (1.01-1.31)	1.34 (1.13-1.58)
	concomitant	1.72 (1.47-2.01)	2.38 (1.98-2.86)
Renal failure	prior	1.25 (1.09-1.44)	1.29 (1.06-1.57)
	concomitant	1.75 (1.59-1.91)	1.83 (1.62-2.08)
Atrial fibrillation/flutter	prior		1.10 (0.98-1.24)
	concomitant		
Diabetes		1.10 (1.02-1.19)	1.16 (1.04-1.28)
Hypertension	prior		
	concomitant	0.81 (0.75-0.88)	0.92 (0.83-1.02)
Valve disease			1.51 (1.27-1.80)

Ethnicity – the stratified model

Finally, a number of stratified models were fitted in order to check the assumption of hazards proportionality and to examine changing patterns in groups. The focal point of this research was to test whether survival in BME minorities, specifically South Asian patients, is significantly different from that in white population. The final models presented are Cox PH-AIC for all-cause and cardiovascular mortality stratified by ethnic group (Figure 8). For all-cause mortality it seems to confirm the patterns of risk observed in logistic regression, with a relatively better survival among South Asians between 6 months and 2 years into the follow-up. The group classified as 'not given' is most likely composed of acutely sick patients with especially poor outcomes in the early period, about half of them dying within the first 30 days, mostly from non-cardiovascular causes.

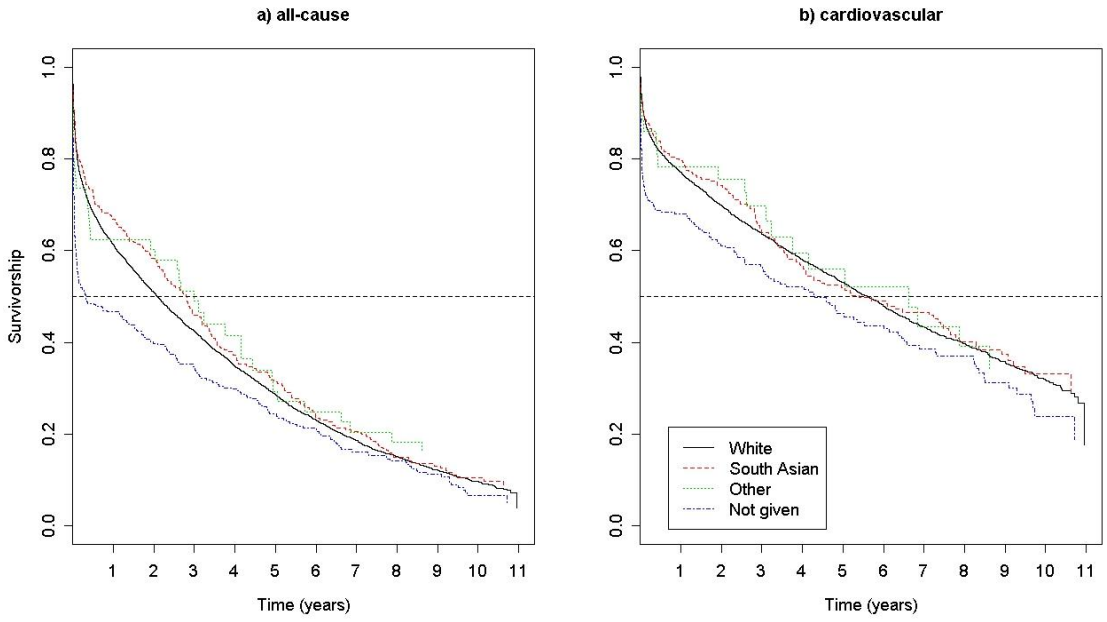


Figure 8 Stratified Cox PH-AIC model of all-cause and cardiovascular survival (strata - ethnic group)

Considering interaction terms

The size of the cohort precluded an automatic assessment of all possible interaction terms between the fixed variables, so the decision whether to include any in the model was based on careful inspection of plots of stratified models (Figures A1 and A6, Appendix). Any between-group differential in survival plot lines, particu-

larly crossing of lines would suggest that an interaction term needs to be at least considered. There were no substantial departures from proportionality, however for cancer, concomitant stroke and renal failure the survival curves were different for those with and without diagnosis and these variables were tested for interactions. None were found to substantially affect the estimates derived from the Cox PH model with fixed variables and as a result no interaction terms are included in the final Cox PH model.

Considering parametric (Weibull) and frailty models

Both parametric Weibull and frailty models for selective variables were considered in order to establish whether they would give a better fit survival data for this cohort. Based model parameters, Cox proportional hazards model, including only fixed variables selected through the AIC process (Cox PH-AIC) proved to be the most robust for this data set.

Revascularisation – time-dependent model

A total of 184 patients (3% of the cohort) had undergone a PCI or CABG procedure in the follow-up period. Timing of the procedure varied from 2 days to 10 years (median 9 months) into the follow-up, with 4 (2%) undertaken within the index admission, 35 (19%) within a month and the majority (70%) within 18 months after the index admission.

Table 10 presents the non-parametric models of all-cause and cardiovascular outcome where revascularisation after the index heart failure admission (in the follow-up period) was considered as a time-dependent variable. This model estimates the effect of revascularisation on outcome and confirms whether hazard estimates for other variables remain the same after an inclusion of a time-dependent covariate, with a potentially significant impact on survival.

It shows that revascularisation was associated with about a third reduction in risk (33% and 31%) of all-cause and cardiovascular mortality, respectively. There were no significant differences in hazard ratios for the fixed variables, when compared with the previously described Cox PH-AIC model.

Table 10. Cox proportional hazards model with a time-dependent variable (revascularisation in the follow-up).

	All-cause	**Cardiovascular**
Revascularisation*	0.67 (0.53-0.83)	0.69 (0.52-0.92)
Ethnicity:		
White	1.00	1.00
South Asian	0.94 (0.82-1.07)	0.97 (0.81-1.16)
Other	0.91 (0.66-1.26)	0.98 (0.64-1.49)
Not known	1.34 (1.19-1.51)	1.41 (1.20-1.66)
Age (year)	1.04 (1.04-1.05)	1.04 (1.04-1.05)
Gross comorbidity:		
none	1.00	1.00
< 7 days	1.13 (1.06-1.21)	1.08 (0.99-1.19)
7-29 days	1.50 (1.36-1.65)	1.30 (1.14-1.50)
30+ days	1.65 (1.30-2.09)	1.34 (0.94-1.90)
Year:		
1998/9	1.00	1.00
1999/0	0.90 (0.84-0.96)	0.86 (0.79-0.95)
2000/1	0.89 (0.83-0.95)	0.80 (0.73-0.89)
Cardiological admission	0.82 (0.73-0.91)	0.84 (0.73-0.97)
Comorbidities:		
Cancer	1.53 (1.37-1.71)	0.76 (0.62-0.93)
Acute MI		
prior		
concomitant		1.29 (1.14-1.46)
IHD (non-AMI)		
prior		
concomitant	0.92 (0.86-0.99)	
Other heart disease		0.84 (0.77-0.92)
Stroke		
prior	1.14 (1.00-1.30)	1.33 (1.12-1.58)
concomitant	1.72 (1.47-2.01)	2.38 (1.98-2.86)
Renal failure		
prior	1.25 (1.08-1.44)	1.29 (1.06-1.57)
concomitant	1.74 (1.59-1.90)	1.82 (1.61-2.06)
Atrial fibrillation/flutter		
prior		1.10 (0.98-1.24)
concomitant		
Diabetes	1.10 (1.02-1.19)	1.16 (1.05-1.29)
Hypertension		
prior		
concomitant	0.81 (0.75-0.87)	0.92 (0.83-1.01)
Valve disease		1.51 (1.27-1.80)

* time-dependent covariate

Model diagnostics

Proportional hazards assumption

The initial checks of proportional hazards assumption for Cox PH models using the stratified models for all categorical variables have shown no major causes for concern, i.e. hazards for groups of interest changing direction over time. This was considered acceptable for modelling purposes, but it is important to highlight the main departures and propose some explanations. Firstly, concomitant acute MI and stroke understandably increase hazard of cardiovascular death in the early period (Figure A6-f/i, Appendix). The same is true for renal failure both for all-cause and cardiovascular mortality (Figure A1-j and Figure A6-k, Appendix). When recorded only prior to heart failure admission, these conditions tend to increase the risk of death at later period, two to three years into the follow-up. Patients treated in a cardiological ward appear to have a similar risk of all cause mortality up to about a year and improved outcome later in the follow up. The somewhat worse cardiovascular outcome in those patients initially (Figure A6-e, Appendix) is perhaps a reflection of higher morbidity in this cohort; similarly, it is also likely to reflect cardiovascular mortality associated with the index admission, such as AMI, or revascularisation and other interventional procedures. Due to the routine nature of the data, it would be difficult to validate this assumption. Generally patterns of cardiovascular risk are a little more complex than for all-cause mortality, and competing risk caveats have to be taken into account here. Results of stratified analysis by ethnic group are presented in more detail on page 71. A more formal assessment of proportional hazards assumption included plots of *Schoenfeld residuals* (Figure A4 and A9, Appendix), which had shown symmetrical patterns, except for a couple of variables at very long follow-up times. The same was true for plots of *beta(t) residuals* (Figure A5 and A10, Appendix).

Overall model fit

The overall fit of models for all-cause and cardiovascular mortality was checked using Cox-Snell residuals and considered acceptable showing no substantial departures from straight line, which for both models was close to unity and a zero intercept. Martingale residual plots for variables of interest confirmed the linear fit of both models (Figure A2 and A7, Appendix).

Outliers

Deviance residuals (Figure A3 and A8, Appendix) show no significant outliers, although they tend to be more positive at early follow-up times and more negative at longer time. This is generally more pronounced for all-cause mortality and caused by underestimate of long-term survival normally observed in such analyses. From around 10 years of follow-up estimates of survival cannot be regarded as reliable.

Chapter 5: Discussion

This study assessed the impact of heart failure in a large, unselected population cohort in the modern era, with a focus on detecting ethnic or socio-economic inequalities. It also evaluated whether outcomes can be monitored routinely, using available health care information.

PRINCIPAL FINDINGS

1. Although improving over time, case fatality in patients hospitalised for heart failure remains high.
2. The morbidity burden of heart failure among South Asians is higher when compared to white population, although there are no significant ethnic differentials in survival following the first admission, whether short or long-term.
3. Although the majority of hospitalised patients are from areas of socio-economic disadvantage, implicating much higher burden of morbidity, the size and direction of the effect of deprivation on survival remains unclear.
4. In keeping with other studies, many measured comorbidities, particularly acute, are strongly predictive of poor outcome. The effect of diabetes is moderate in comparison.
5. Both the initial hospitalisation in specialist cardiological setting and revascularisation in the follow-up seem to have a positive impact on survival, although the frequency of revascularisation is relatively low in patients with established heart failure.

IMPLICATIONS OF STUDY RESULTS

Burden of heart failure

This study has shown that, in modern routine practice, only 13% of patients with heart failure are likely to survive for more than 10 years, against an expectation of 53% for patients of the same age and sex in the general population. This corresponds to an excess of 700 deaths each year in every million population. The recorded underlying cause of death is very rarely that of heart failure (6%), and in

only half of cases cardiovascular (53%). A quarter of all observed fatality in this study cohort was assigned to pulmonary or gastrointestinal causes, and in 11% to cancer; of those only cancer can be regarded as a true competing cause, a condition with potentially higher fatality than heart failure. It is evident that published heart failure mortality statistics are a gross underestimate and that the cardiovascular end-point cannot be regarded as cause-specific.

However, HF is likely to be a significant factor in lowering patients' life expectation, whatever the recorded cause of death. Complex comorbidity patterns in the elderly are generally difficult to unravel, but the current analysis indicates a striking impact of heart failure, reflected in relative survival estimated at just 20% after 10 years from first hospitalisation. Although relative survival methodology has been used widely in cancer research, it is largely unknown in other areas. However, its application in all clinical areas where disease-specific mortality is difficult to establish is clear (221) (222).

The characteristics of study population make it justifiable to generalise findings from this study to other developed countries, and to estimate that in every million population one would expect around 2000 new cases per year and at least 700 deaths attributable to heart failure. Such estimates of the absolute burden of disease morbidity and mortality could be used to evaluate potential impact of public health strategies for many chronic conditions, if follow up data are available.

This study suggests an improvement in the all-cause HF fatality when compared to earlier years, with a hazard ratio of 0.65 (95% CI: 0.59-0.72) in 2000/1 against a 1993/4 baseline. The reduction in cardiovascular fatality was even more pronounced (HR 0.52, 95%CI: 0.45-0.59). Contemporaneous trends presented in other reports, although relating mostly to hospital mortality, were generally more conservative (42)(44)(47)(52). In all these reports the positive trends in fatality, even where quite moderate, were accompanied by rising admission rates in the late 1990s.

Although no formal analysis of pharmacological therapy patterns was undertaken in this study, the improvement in survival coincided with increasing use of evidence-based treatments in the UK and locally and is likely to be an important contributory factor in improving life expectancy in HF.

Predictive modelling

Beyond population level statistics, age and sex matched life expectation can be usefully related to survival estimate for individual patients, as adjunct to predictive risk modelling, in order to present patients prognosis in a context of a general population outcome. A sample application of this concept is presented in Figure A11 in the Appendix. The model implemented in this predictive tool is the final CoxPH-AIC (formula on page 68), including all relevant demographic and morbidity covariates, described in the results section.

Several analytical steps would be required before recommending this model for wider use, including confirmation of its statistical efficacy, through model training and tuning, and its validity in other population settings, using different population data.

Ethnic differentials

The principal focus of this study was on the differential in outcome between South Asians and white population. The proportion of other ethnic groups was too small to allow for a meaningful analysis. This study was also underpowered to detect difference between Indian and other South Asian subgroups, which are generally underrepresented in Leicestershire.

Although the overall pattern of hospitalisation and incidence has shown a 50-60% excess in South Asian patients, there was no excess in fatality in this group, even at long follow-up after the first admission for heart failure. The higher cardiovascular comorbidity in the South Asian cohort was expressed in relative excess of acute coronary disease (up to 90% more than in white patients), hypertension and diabetes, which was nearly three times more common. The gross comorbidity index, based on the average number of days spent in hospital in the previous five years, was similar for white and South Asian patients and worse than in other ethnic groups. This is of note, as in this cohort South Asians were younger by as much as 8 years at the time of first admission and could be expected to have less, rather than more, comorbidity. Thus it seems highly unlikely for unmeasured disease severity to be a significant confounder. In fact, our subsequent study of clinical factors in a matched subset of patients (224), showed improved survival among South

Asian when compared to white patients (HR 0.71, 95% CI: 0.53-0.96), after adjustment for relevant clinical factors. In conclusion, the current data suggest that there is no inequality of outcome following a heart failure admission in South Asians.

It needs to be acknowledged that cardiovascular risk varies substantially across South Asian groups, with Pakistani and Bangladeshi communities at higher risk and generally lower access to care, when compared to Indian patients (79) (76). Thus these results will not be applicable to the BME communities which are predominantly Pakistani or Bangladeshi.

Socio-economic factors

Inequality in the distribution of IHD mortality, as measured by rates of death with IHD as cause, has been well documented in literature (225). This study indicates that the burden of heart failure is indeed higher in deprived areas, with most of incident cases from the two most deprived quintiles (38% from the highest quintile). One could argue that the geographic distribution of deprivation in LLR is a likely source of bias, as socio-economic disadvantage tends to correlate in urban with high rates of hospital referral. Even with this caveat in mind, the interpretation of a significant excess in hospitalised heart failure in more disadvantaged areas seems justified. On a background of such relative excess of hospital morbidity, it is perhaps surprising to find no statistically significant detrimental effect of deprivation on survival; on the contrary, the 30-day survival showed a positive trend with increasing deprivation, while at longer follow-up there was no effect. It is important to mention that in the same population (Leicester, Leicestershire and Rutland), similarly to HF, case-fatality in cancer, IHD or stroke were not linked to deprivation in previous routine assessment (226). If true, these findings are very encouraging from health equity perspective.

However, there are some very important methodological caveats. Firstly, referral patterns favouring earlier hospitalisation in more deprived areas could result in lead time bias. One could expect such patients to be generally younger and with less advanced disease. Although derived only from routine sources, both gross and specific comorbidity indicators should adjust efficiently, albeit indirectly, for disease severity. To investigate this hypothesis, our later study examined in detail clinical factors, physical, biochemical and echocardiographic, in a matched subset of patients (224). In this matched cohort of patients, the socio-economic deprivation was similarly unrelated to fatality. Thus, it seems highly unlikely that the influ-

ence of deprivation in the initial cohort was confounded by unmeasured severity of the disease. Secondly, one should consider the appropriateness of area-based measures as proxy of individual socio-economic status, or ecologic bias (227). A wider discussion of this well documented issue is beyond the scope of this thesis, but it needs to be acknowledged that area-based measures do not always reflect an individual's lifetime socio-economic deprivation. This is of particular importance in elderly cohorts of patients, and for those living in rural areas, where such measures correlate particularly poorly to individual disadvantage (228) and has serious implications for health equity assessment for many other long terms conditions.

In light of quite clear evidence regarding deprivation gradient in fatality following acute coronary events, hospitalisation, incidence, prevalence and mortality in IHD and in heart failure, the current results are surprising and require further investigation. Consistently negative findings in that regard from this population (224)(226)(228) are a call for the development of more robust methodologies for monitoring of socio-economic determinants in cardiovascular and other chronic diseases.

Comorbidity

In contrast, the risk related to a number of hospitalisation-related, particularly acute comorbidities and their demographic patterns are not surprising and correlate well with many previous reports.

Ischaemic heart disease could be the underlying cause in at least a half of all heart failure (1). In this study, 40% of patients had prior or concomitant IHD, whether acute or chronic, and IHD was significantly more common among South Asians (56%). The overall 40% may appear low compared with the estimates from other studies, but this is likely due to the routine nature of the current data. Acute MI was twice as common in South Asians whether before or at the time of heart failure admission, while the rate of chronic IHD was only 4% higher than in other groups. In contrast, the prevalence of atrial fibrillation or flutter was much lower in this group (14% vs. 35% among whites). Although the risk of early fatality in heart failure complicating or underlying acute MI is estimated to be significant (128), only acute MI coinciding with index heart failure admission was moderately predictive of cardiovascular, but not all-cause, fatality (HR 1.28, 95% CI:1.14-1.46). This finding could be linked to either better outcomes in acute MI or improving management of complicating heart failure (130). Heart disease other than IHD was

diagnosed more commonly in white than in South Asian patients (60% vs. 44%) and its slightly protective effect on cardiovascular mortality is most likely a reflection of less acute case-mix of these patients. Both stroke and renal failure, when recorded concomitantly with heart failure, were the strongest predictors of outcome (HR between 1.72 and 2.38), which is a manifestation of the overall morbidity in these patients.

This study strongly suggests an ethnic differential in diabetes prevalence in heart failure, with nearly half of South Asian patients with prior or concomitant diabetes (46% diagnosed vs. 16% among whites). These findings have to be interpreted against an average population estimate of 30% of concomitant diabetes in heart failure (141). However, despite the strong link to cardiovascular mortality documented in many previous reports (147) (149), in the current study hospital record of diabetes conferred a relatively small hazard for all-cause (HR 1.10, 95% CI: 1.02-1.19) or cardiovascular fatality (HR 1.16, 95% CI: 1.04-1.28). The protective effect of concomitant hypertension has been reported before (32) (HR=0.71), although the estimate from the current study is a little more conservative (HR 0.81, 95% CI: 0.75-0.88). As a competing cause, cancer was a risk for all-cause (HR 1.54, 95% CI: 1.38-1.71) but not for cardiovascular outcome. Although COPD is an important comorbidity in heart failure, the diagnostic overlap is likely to be substantial and it was not measured as a variable in this study. Any hospital discharge diagnosis of anaemia would be even less reliable, although, again, as a clinical indicator anaemia is a strong predictor of outcome in heart failure (135).

It needs to be stressed that many of the measured comorbidities have to be treated as general measures of disease severity, rather than precise clinical diagnoses. However, they provide a good indication of patient case-mix and an efficient method of adjustment in survival analysis. Their effect size, or relative risk estimate, tends to vary substantially depending on the methodology (logistic regression or survival); this issue is discussed in more detail on page 87. It is of some importance, as risk estimates from different studies are not always directly comparable.

Impact of revascularisation

Coronary revascularisation, PCI or CABG, was carried out in a relatively small number of cases (N=184/5789, 3%). In the majority (N=129, 70%) it was carried out within 18 months after the first heart failure admission. The reported results suggest that survival in these patients was significantly better (HR=0.67, 0.53-0.83), although this estimate could be biased by lack of information on disease severity or its aetiology. Thus patients undergoing revascularisation could be in less advanced stages, overestimating the protective effect of surgery. The second caveat is that the baseline survival in this study includes patients with non-ischemic aetiology, and current results cannot be directly compared to most published results. Both issues mean that this relative risk estimate is likely to be an overestimate of the true effectiveness of revascularisation in ischemic heart failure and has to be regarded purely as an observational finding. However, it is reasonable to surmise that revascularisation in this routine unselected cohort had some positive effect on survival, after adjustment for main demographic and comorbidity factors. These results underscore the necessity of confirmatory randomised trials in this area. So far, observational results on CABG in heart failure were inconclusive and trial results are awaited (1).

Heart failure as a risk factor for patients undergoing revascularisation in general

In our later study investigating the long-term outcomes following coronary revascularisation between 1995 and 2004 (228), a previous or concomitant heart failure hospitalisation was found in just 6.1% and 4.1% of patients, respectively. This proportion increased over the study period for concomitant, but not for prior heart failure (Table 11), reflecting the overall increase in age and comorbidity among patients undergoing first revascularisation, observed for CABG and PCI.

Table 11 Temporal trend in prior and concomitant discharge diagnosis of heart failure in patients with first revascularisation procedure undertaken between 1994 and 2004 (N=6068)

Date of first revascularisation	History (%)*		Concomitant (%)**		Average age	Total
April 1995 - March 1998	98	(6.0)	50	(3.1)	62.8	1,637
April 1998 - March 2001	124	(6.3)	81	(4.1)	63.3	1,954
April 2001 - March 2004	150	(6.1)	117	(4.7)	63.8	2,477
Total	372	(6.1)	248	(4.1)	63.4	6,068

* p Value = 0.97 (test for trend)
** p Value = 0.009

In this cohort of patients with first revascularisation (Figure 9), heart failure was one of the principal risk factors for all-cause fatality and cardiovascular outcome.

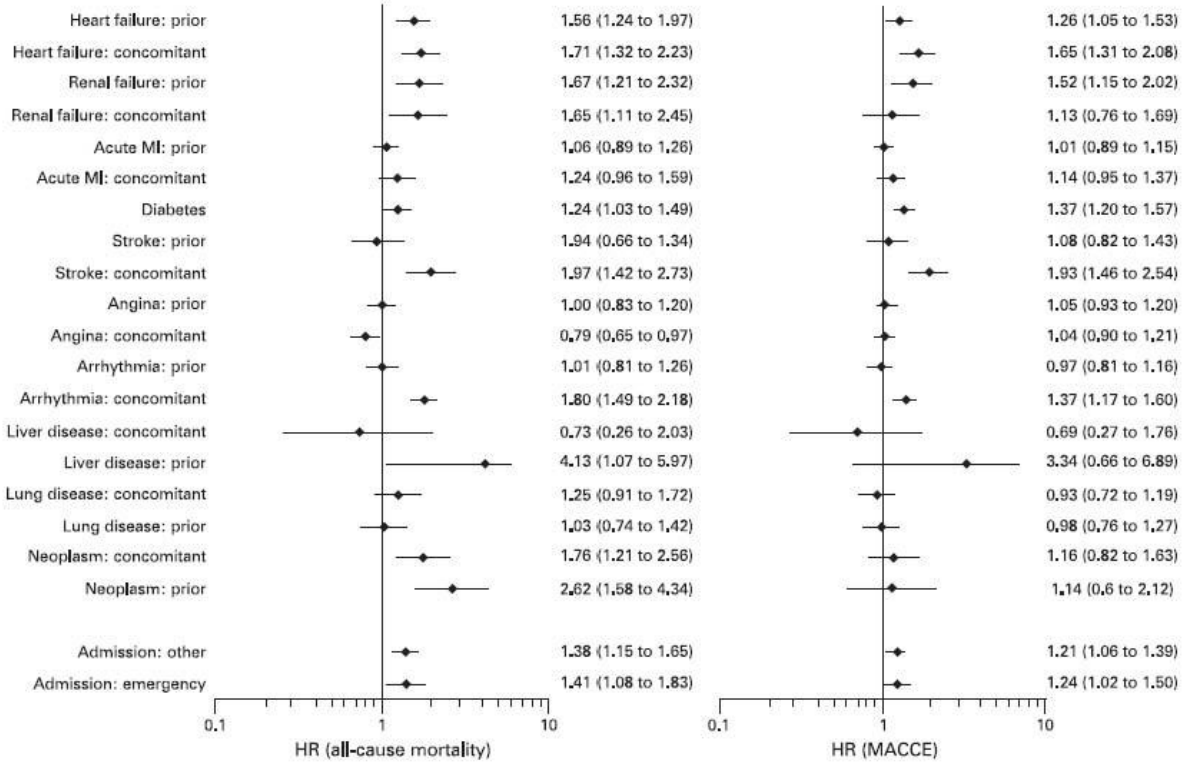


Figure 9 Hazard ratios for comorbidities from multivariate models for all-cause fatality and combined cardiovascular outcome (MACCE*) in 6,068 patients with first revascularisation between 1995 and 2004, Leicestershire

* MACCE – cardiovascular fatality, non-fatal MI, stroke or repeat revascularisation procedure

As a predictor of all-cause fatality, concomitant heart failure (HR=1.71) was comparable to a diagnosis of cancer (HR=1.76), renal failure (HR=1.65), but somewhat lower than that of stroke (HR=1.97) or arrhythmia (HR=1.80). However the risk linked to prior heart failure (HR=1.56), albeit significant, was substantially lower than for other previously diagnosed conditions, such as prior liver disease (HR=4.13, 95% CI: 1.07-5.97) or cancer (HR=2.62).

These results underscore that, although apparently effective, revascularisation is performed rarely in heart failure patients. However, once diagnosed, heart failure represents a significant risk of a poor surgical outcome for patients undergoing these procedures, for any cause. These findings, reflecting a contemporary unselected patient population, have clear clinical implications for prompt diagnosis and treatment of heart failure.

STRENGTHS AND LIMITATIONS OF THE STUDY

Design and setting

The observational nature of this historical follow-up study calls for a relatively cautious interpretation; particularly any causal inferences must be qualified in light of the routine character of the data used. However, these caveats have to be weighed against a number of undoubted benefits, such as a very long-term, robust follow-up of the whole population in a defined area, a representative setting in terms of general population health and a contrasting internal mix of socio-economic and demographic characteristics of study population. These are significant factors in an area of research where evidence is based primarily on clinical trials, whose external validity has often been called into question (229). Even larger trials include no more than 10% of eligible patients and, where baseline data are reported, the participants usually have significantly better outcomes than the general population (230). In their majority, surrogate outcomes which are often used in trials, biological or imaging markers, or combined outcomes may be difficult to interpret from a population health perspective. The problems in extrapolating trial results to the general population were well illustrated by Steg et al (231) who compared the participants, eligible patients and those not eligible for RCTs in myocardial infarction in terms of their risk of death. Fatality among the non-eligible patients was almost three-fold higher than in the participating group and even the eligible non-participants had a two-fold increase. These results underscore the importance of measuring cardiovascular outcomes in the general population, preferably using robust population registers.

Utility of hospital diagnosis of heart failure and comorbid conditions

It has been shown repeatedly that reliance of hospital records provides an underestimate of overall burden of heart failure in a hospital setting. For example, a study in the US using data from a population survey on CHD (232), has shown that as much as a third of patients presenting with acute HF in hospital could be missed using routinely recorded ICD diagnosis of heart failure. These authors also found only a third of all hospital admissions with HF are coded in the first diagnostic position. Sensitivity of patient discharge for recording heart failure has been regarded as poor, when compared with a full clinical assessment. Although based on a relatively small, multi-ethnic, inner-city cohort of patients (N=260), a Birmingham hospital audit (83) reported only 65% concordance with clinically defined heart failure. Similar limitations apply to any chronic condition recorded on hospital discharge which could be quite legitimately omitted from discharge record when patients are hospitalised for another reason. However, the inaccuracy of discharge diagnosis of heart failure has to be interpreted on a background level of diagnostic disagreement in a primary care setting, which is still substantial (1) (5).

To verify the diagnosis in the study cohort, we reviewed clinical records for a large randomly selected subset of patients (N=629) (224) and found no evidence sufficient for a new heart failure diagnosis in 16% (N=101) of patients. This suggests 84% accuracy of hospital data, which was higher than was previously reported (83). Furthermore, ours were new cases with an arbitrarily set five-year 'washout' period prior to the index admission, and in this light accuracy of 84% is relatively high.

With regards to between-group comparisons, any inaccuracy or misclassification of hospital baseline data would be likely to affect all patient groups equally, resulting in lower risk estimates (attenuation towards the null), rather than any significant bias.

Determination of life status

Unlike the baseline hospitalisation data, life status information for the study cohort has to be regarded as generally complete, based on the full reporting of mortality and census dates for patients who moved away before the end of the study. Although, as discussed above (page 76), death certification is a poor source of information on cause of death in heart failure, it is generally an accurate source of data on the follow-up time and at least some specific conditions, for example IHD.

In the US, the validity of death certificates for out-of-hospital IHD was evaluated and shown to have a high positive predictive value (96%, sensitivity 91%) indicating that no more than 5% of all IHD deaths could be misclassified as another cause (233).

Demographic variables

Recording of such factors as age and sex have to be regarded as relatively complete in the routine sources. The appropriateness of area deprivation as proxy of socio-economic status was discussed above (page 80). This was determined by patients' postcode of domicile at the time of the first hospital admission for heart failure and should be relatively constant in this, predominantly elderly, cohort, even with long follow-up. It has also been argued that for many health outcomes there is a distinct area effect, which could even be of greater interest than individual SES (234), one best assessed using hierarchical or multilevel modelling approach.

Significant limitations of racial and ethnic classification were highlighted in the past (235). These concepts are inherently imprecise and ethnic and racial identities are not always fixed or defined. Self reported, or 'self assigned', ethnicity is usually regarded the most appropriate, but even its validity has been called to question (236). It has been recommended that, when reporting results of studies on ethnicity, firstly the reasons for choosing a particular ethnic classification system are specified, secondly that the categories used are described and justified and, thirdly, that all relevant classes and variables are considered (236). This study used the classification currently used by the Office for National Statistics and the National Health Service in the UK (237) to derive broad categories for white, South Asian and other ethnic groups (Table A3, Appendix). A substantial group of patients (N=347, 6.9%) was reported as 'ethnicity not known', including most commonly, those in acute setting who could not report their ethnicity on admission (coded as 'ethnicity not given'). This is a group of acutely ill patients, with particularly poor outcomes in the early follow-up period, so it is perhaps not surprising that self-reported ethnicity was not recorded in such cases.

Statistical modelling

Comparing alternative survival models in such a large cohort using statistical criteria alone can be difficult. More complex models tend to fit the data better, but

their interpretation is difficult, particularly when interaction terms are included. In analysing the current data, more parsimonious models were generally chosen, over more complex one, providing the effect size was similar for variables of clinical interest.

Relative risk estimate from survival when compared to logistic models

Both hazard ratios derived from survival analysis and odds ratios from logistic regression are generally interpreted as measures of risk; both approximate relative risk. However, in studies with long follow-up and high proportion of events (e.g. high mortality) the resulting estimates can be of quite different magnitude. The odds ratios are confounded by follow-up time, as survival is often exponentially distributed, with an initial sharp fall followed by a plateau. In this study, the odds ratio estimates from logistic regression were generally much higher for short-term outcomes, when compared to the average hazard estimated from survival analysis, which is largely explained by the survival time distribution. Logistic regression is a useful technique for assessing relative risk for early outcomes (e.g. early post-operative fatality). However, for longer follow-up times and high event rates, survival modelling gives more unbiased estimates of relative risk (220).

CONCLUSIONS AND FUTURE PERSPECTIVES

The UK elderly population is set to rise by over 50% in absolute terms by 2030. Under this assumption, severe chronic conditions such as heart failure will have a significant impact on health and health care resources in the not so distant future. It is thus imperative to undertake an ongoing robust assessment of current disease burden, clinical outcomes and key risk factors, and particularly to evaluate the scope for effective prevention.

In all clinical areas characterised by rapidly changing practice, carefully conducted prospective research or randomised trials are rarely feasible and could even be unethical. And because of their strict selection criteria they are usually quite difficult to translate into general practice. Thus, the role of observational research should increase in the future, particularly with the growth of clinical and administrative data and improving access to skills and methodologies required for assessment. The increasing drive to raise quality and robustness of such studies is a welcome recent development (238).

This study highlights the considerable impact of heart failure diagnosis on individual patient's prognosis as well as on the overall health of the population, particularly when expressed in terms of relative survival. This methodology should find wider application in public health, as it would allow for more informative assessment of relative impact of chronic morbidity, disease prevention and clinical intervention on life expectancy.

The work presented in this thesis raises a number of clinical and public health questions, which could only be explored further through a more focussed research. Clearly, factors affecting cardiovascular morbidity in South Asian minority populations are complex, with high morbidity but with outcomes comparable to population as a whole. Much larger follow-up studies would be needed to unravel outcome variation between individual BME subgroups and further methodological work is necessary to robustly evaluate the effect of socio-economic deprivation, both in heart failure and other conditions with high case-fatality. Further research in both these areas is necessary, if the health service is to deliver on its promise to reduce health inequity.

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Appendix

Table A1. International Classification of Disease (ICD) codes used to classify causes of hospital admission

Disease	ICD-9 codes*	ICD-10 codes†
Cancer	140-208	C00-C97
Cardiovascular disease	390–459	I00–I99
Hypertension	401-405	I10-I15
Acute myocardial infarction	410	I21–I22
Atrial fibrillation or flutter	427.3	I48
Heart failure	428	I50
Valve disease	394-397, 424	I05-I08,I34-I39
Stroke	430–438	I60–I69
Renal failure	584-586	N17-N19
Diabetes mellitus	250	E11-E14

*International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM); available on: www.cdc.gov/nchs/about/otheract/icd9/abticd9.htm.
†International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10-CM), 2009 update; available: www.cdc.gov/nchs/about/otheract/icd9/icd10cm.htm.

Table A2. NHS/ONS Ethnicity groups and classification used in the study

Category	Group	Study classification
White	British	White
	Irish	White
	Any other White background	White
Mixed	White and Black Caribbean	Other BME
	White and Black African	Other BME
	White and Asian	Other BME
	Any other Mixed background	Other BME
Asian or Asian British	Indian	South Asian
	Pakistani	South Asian
	Bangladeshi	South Asian
	Any other Asian background	Other BME
Black or Black British	Caribbean	Other BME
	African	Other BME
	Any other Black background	Other BME
Chinese or Other	Chinese or other ethnic group	Other BME
	Chinese	Other BME
	Any other ethnic group	Other BME

Table A3. Demographic and clinical covariates used in the study

Variable Name	Description	Coding
Age	In years	
Sex	Sex as recorded on hospital discharge records	0: male; 1:female
Date of (index) admission	Date of first ever admission with a heart failure diagnosis in any position	
Deprivation (quintile)	Socioeconomic deprivation measured by area Index of Multiple of Deprivation 2000. As factor: quintiles	Q1 to Q5: most to least disadvantaged
Ethnicity	Self-declared ethnicity as recorded on hospital discharge records	0: white 1: South Asian 2: other BME* 3: not known
Gross Comorbidity	Gross measure of hospitalisation as total length of sty in five years prior to index admission for heart failure	0: none 1: less than 7 days 2: 7-29 days 3: 30+ days
Comorbidity a. prior b. concomitant	Classified according to discharge diagnosis in any position for a given condition during the index admission spell (concomitant) or in previous 5 years (prior)	0: no 1: yes
Year	Year (April-March) of index hospitalisation for heart failure	0: 1998/9 1: 1999/0 2: 2000/1

* Black and Minority Ethnic

Table A4. Completeness of ethnicity coding on hospital discharge records in LLR between 1st April 1995 and 31st March 2001

Year	Episodes with a valid ethnicity code	Total episodes	% valid	% 'Not given'*
1995**	90,413	154,664	58%	3%
1996	155,429	214,481	72%	5%
1997	162,359	217,186	75%	5%
1998	223,621	240,408	93%	23%
1999	250,629	254,478	98%	27%
2000	254,387	257,383	99%	22%
2001	267,976	270,656	99%	21%

* ethnicity no given by the patient

** April to December

Figure A1. Stratified Cox PH-AIC model for all-cause mortality

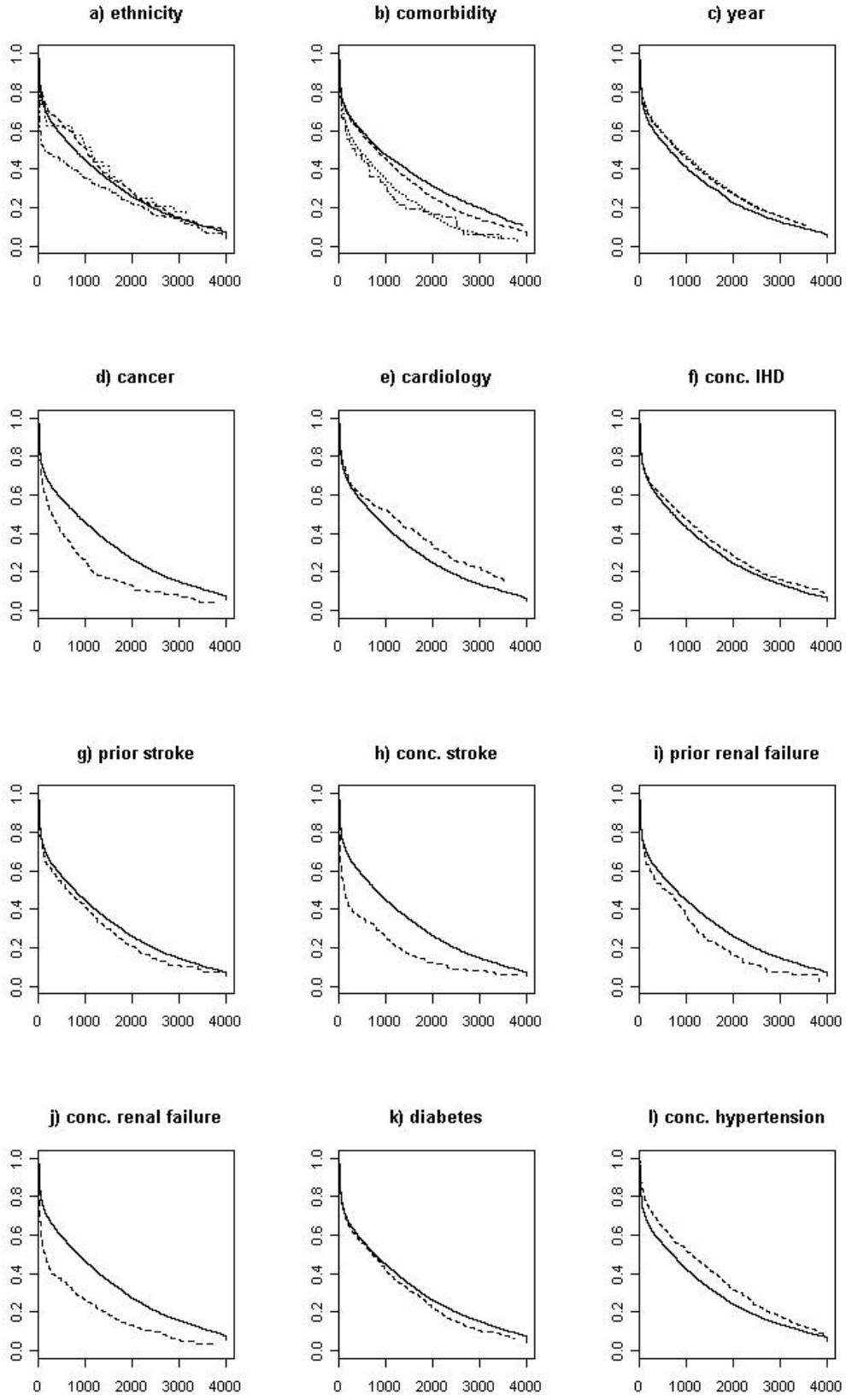


Figure A2 Diagnostics for Cox PH-AIC model for all-cause mortality – Cox-Snell and Martingale residuals

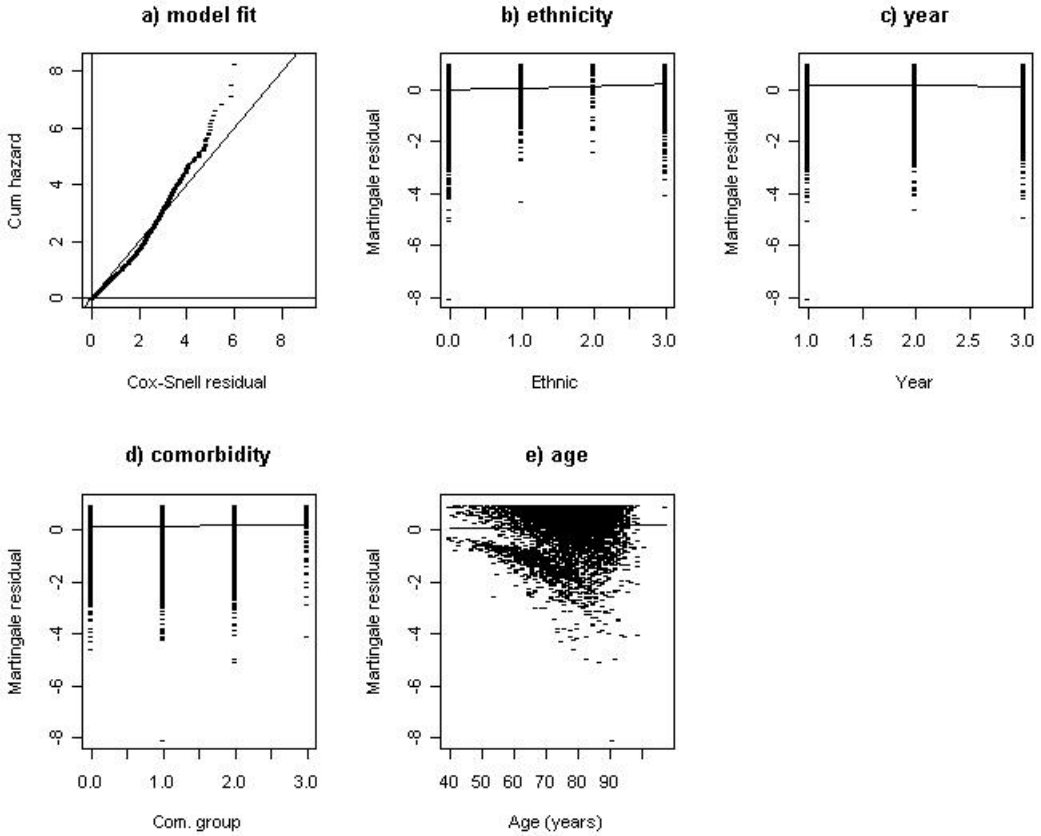


Figure A3 Diagnostics for Cox PH-AIC model for all-cause mortality – deviance residuals

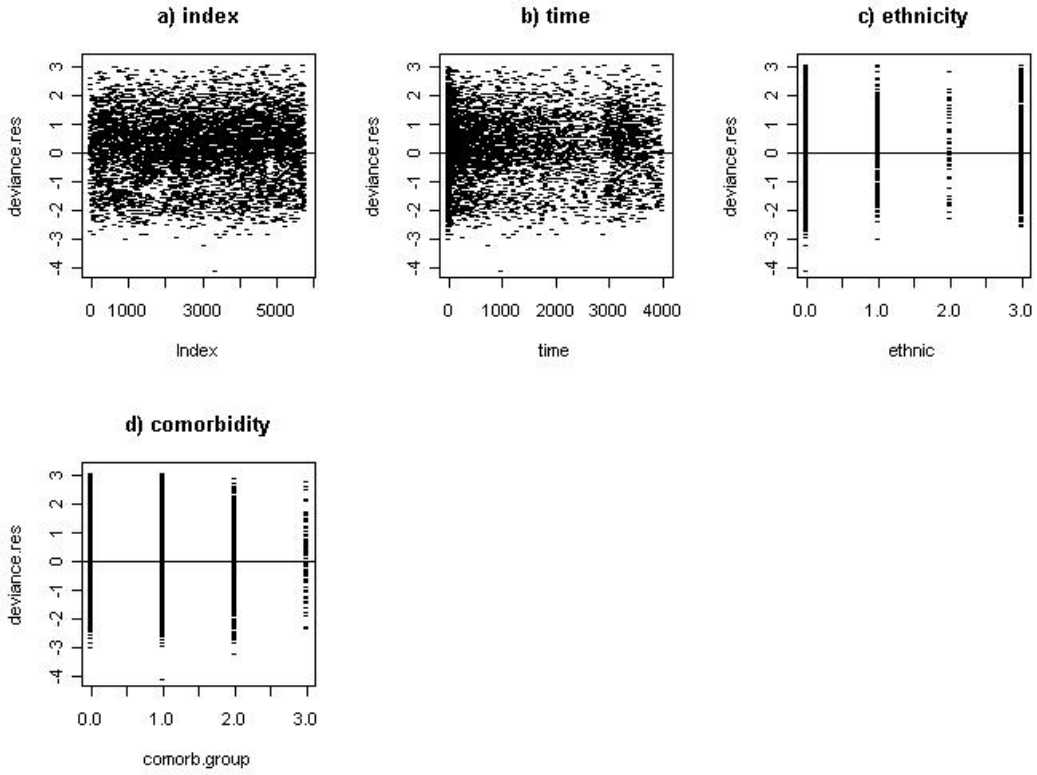


Figure A4 Diagnostics for Cox PH-AIC model for all-cause mortality –Shoenfeld residuals

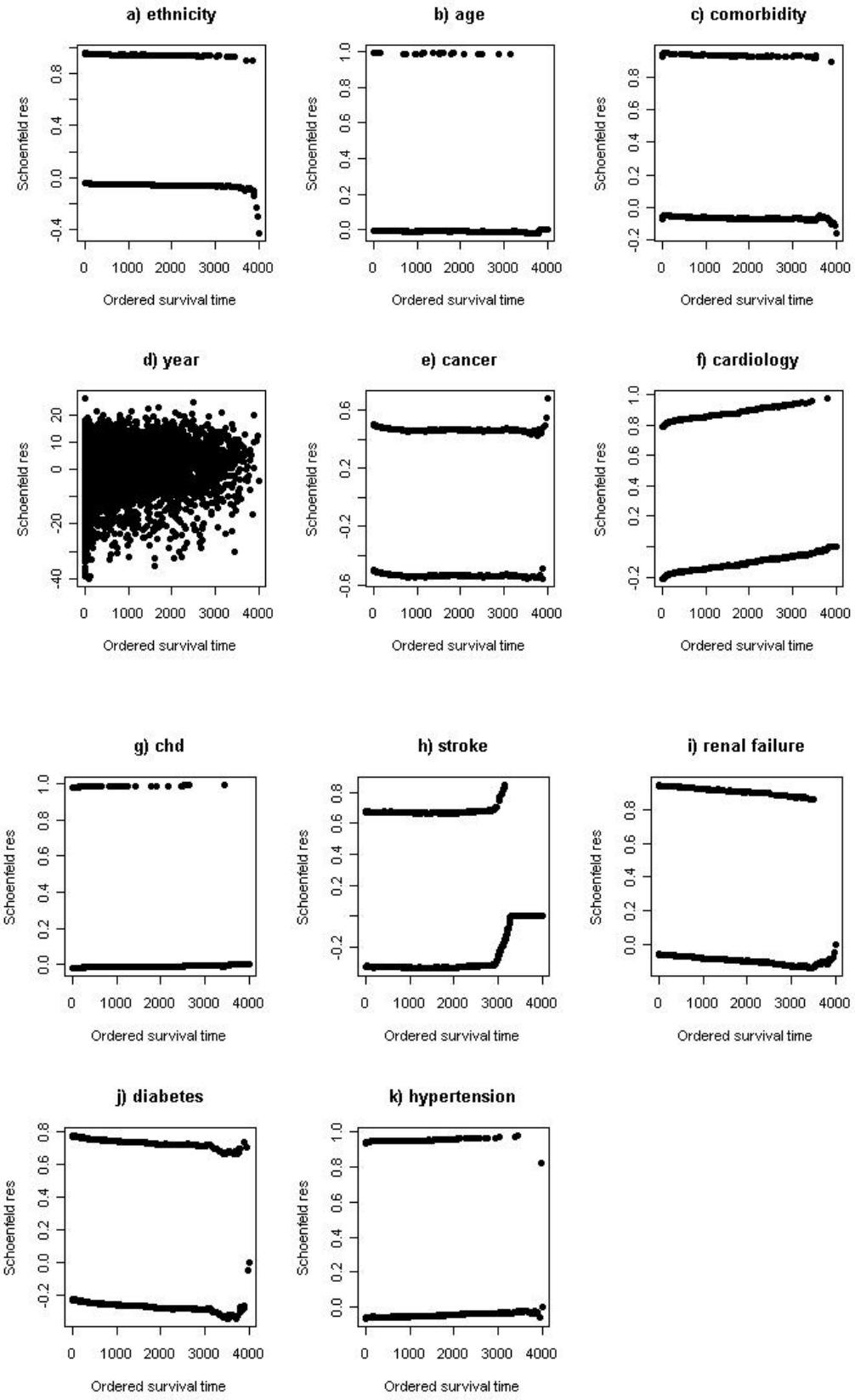
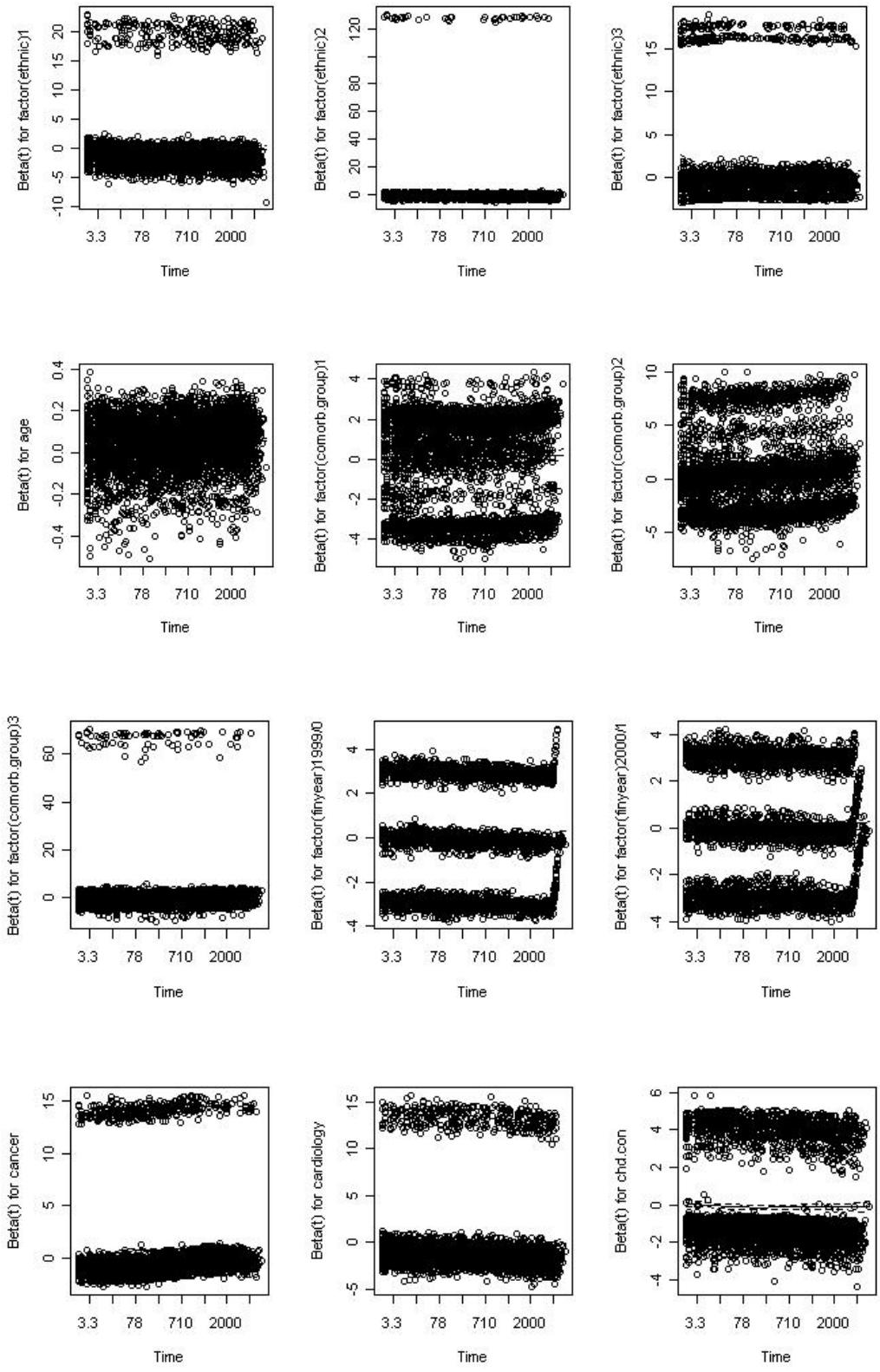
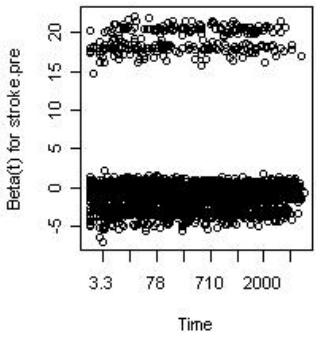


Figure A5 Diagnostics for Cox PH-AIC model for all-cause mortality – beta(t) residuals

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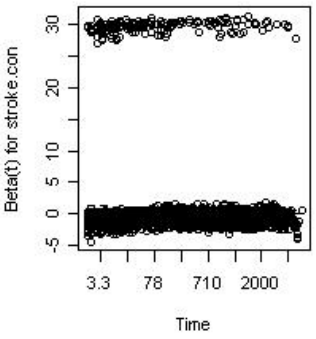
3.3 78 710 2000
Time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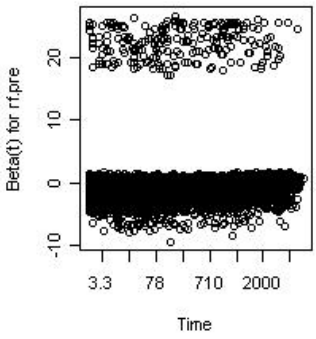
Time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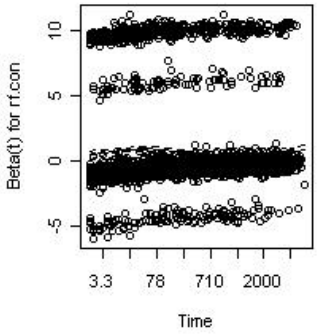
3.3 78 710 2000
Time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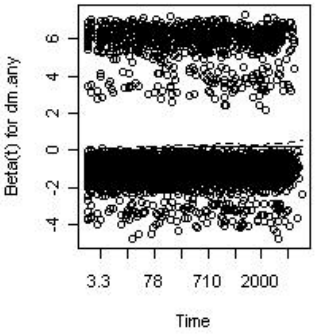
3.3 78 710 2000
Time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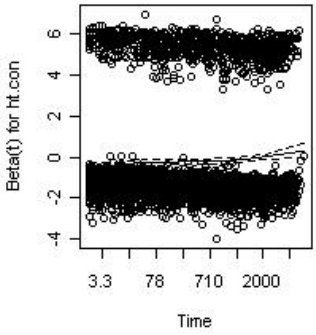
3.3 78 710 2000
Time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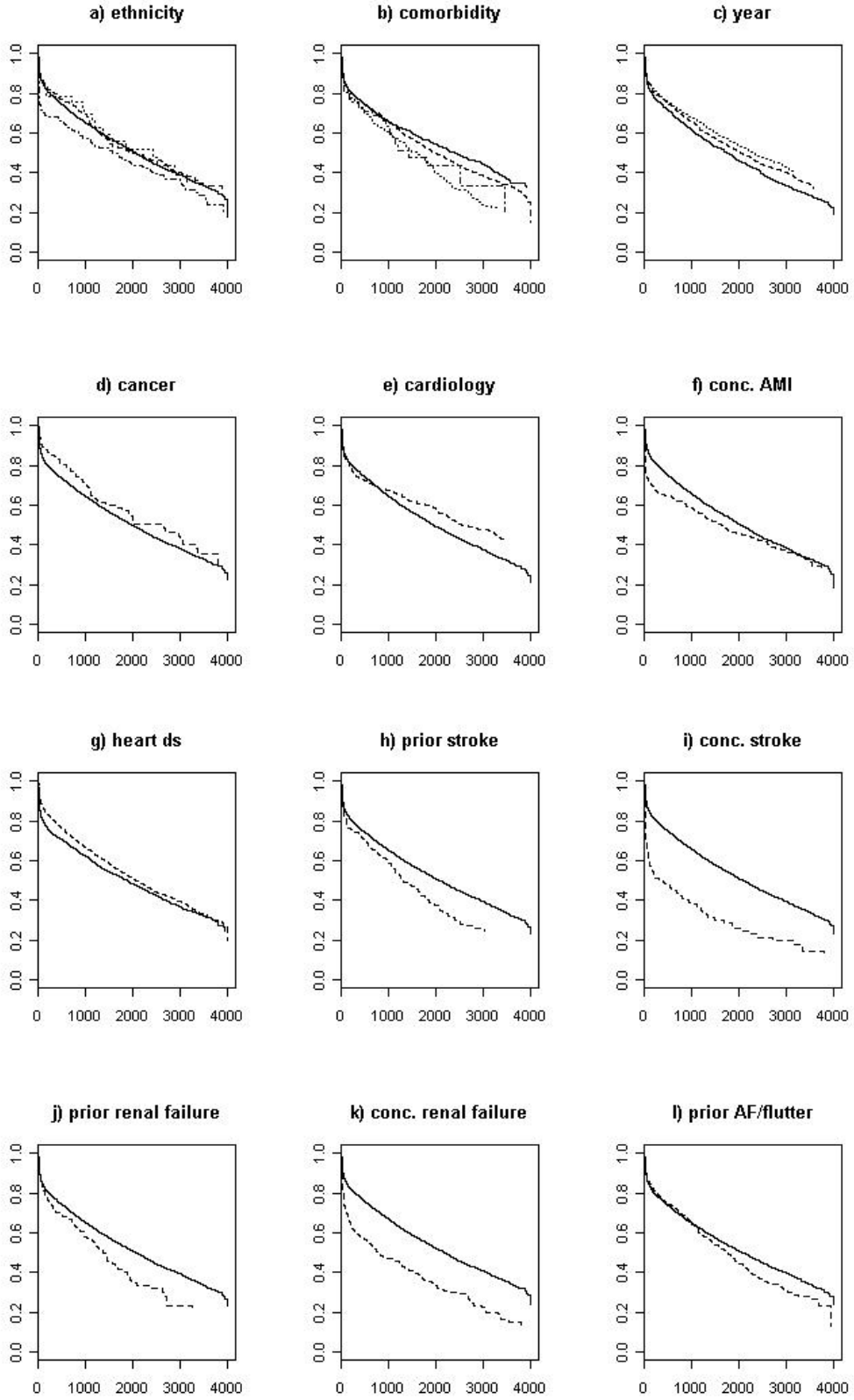
3.3 78 710 2000
Time

Figure A6 Stratified Cox PH-AIC model for cardiovascular mortality



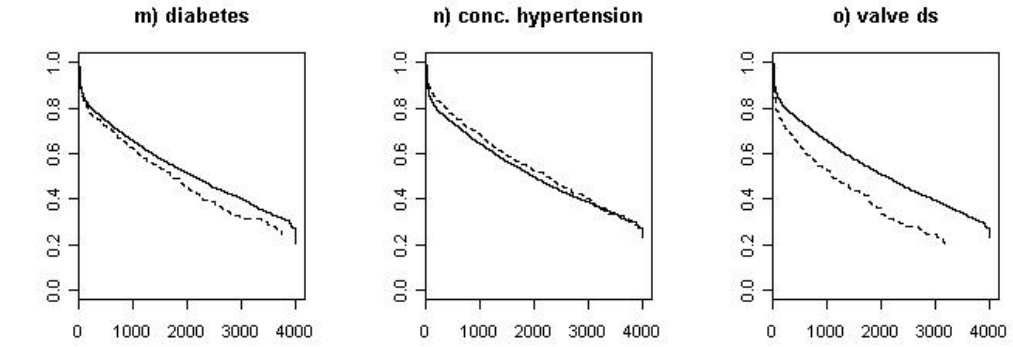


Figure A7 Diagnostics for CoxPH-AIC model for cardiovascular mortality – Cox-Snell and Martingale residuals

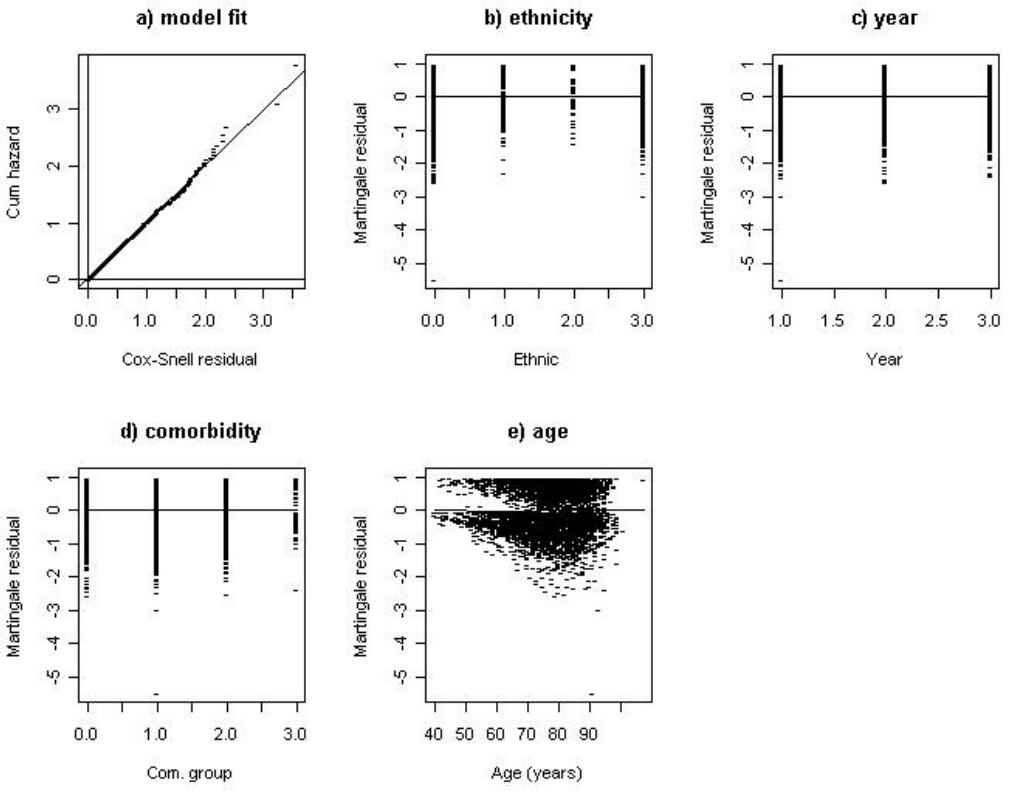


Figure A8 Diagnostics for Cox PH-AIC model for cardiovascular mortality – deviance residuals

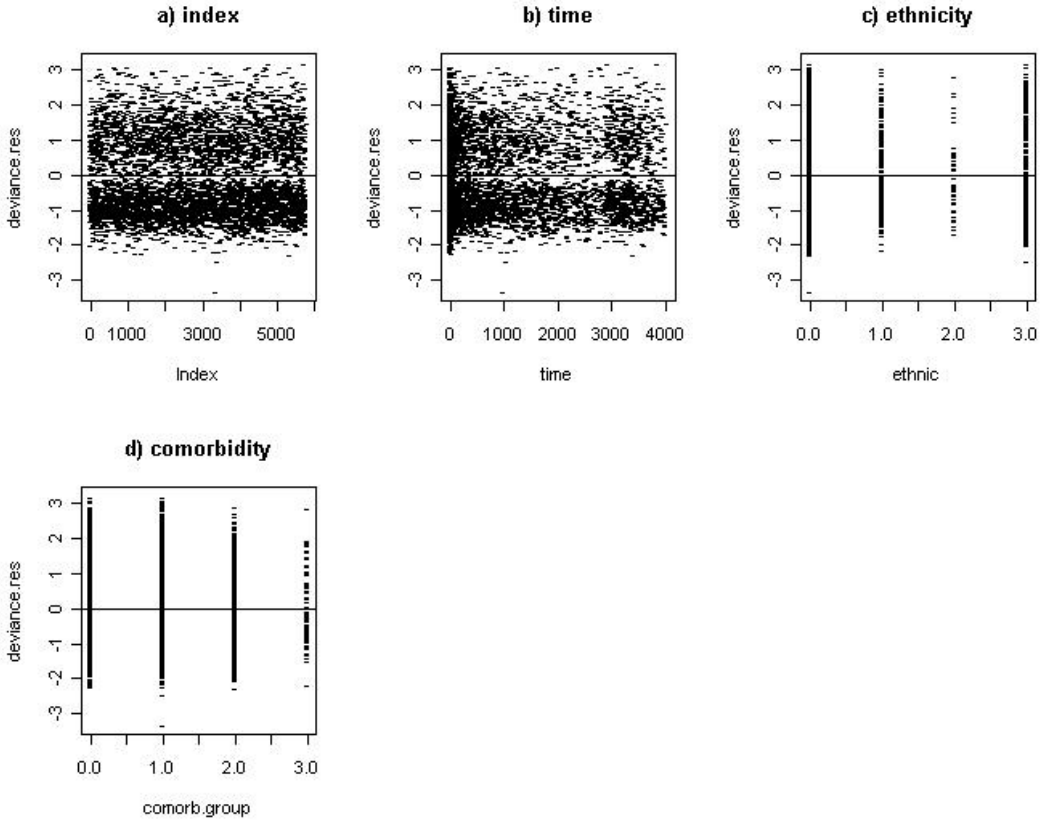


Figure A9 Diagnostics for Cox PH-AIC model for cardiovascular mortality – Schoenfeld residuals

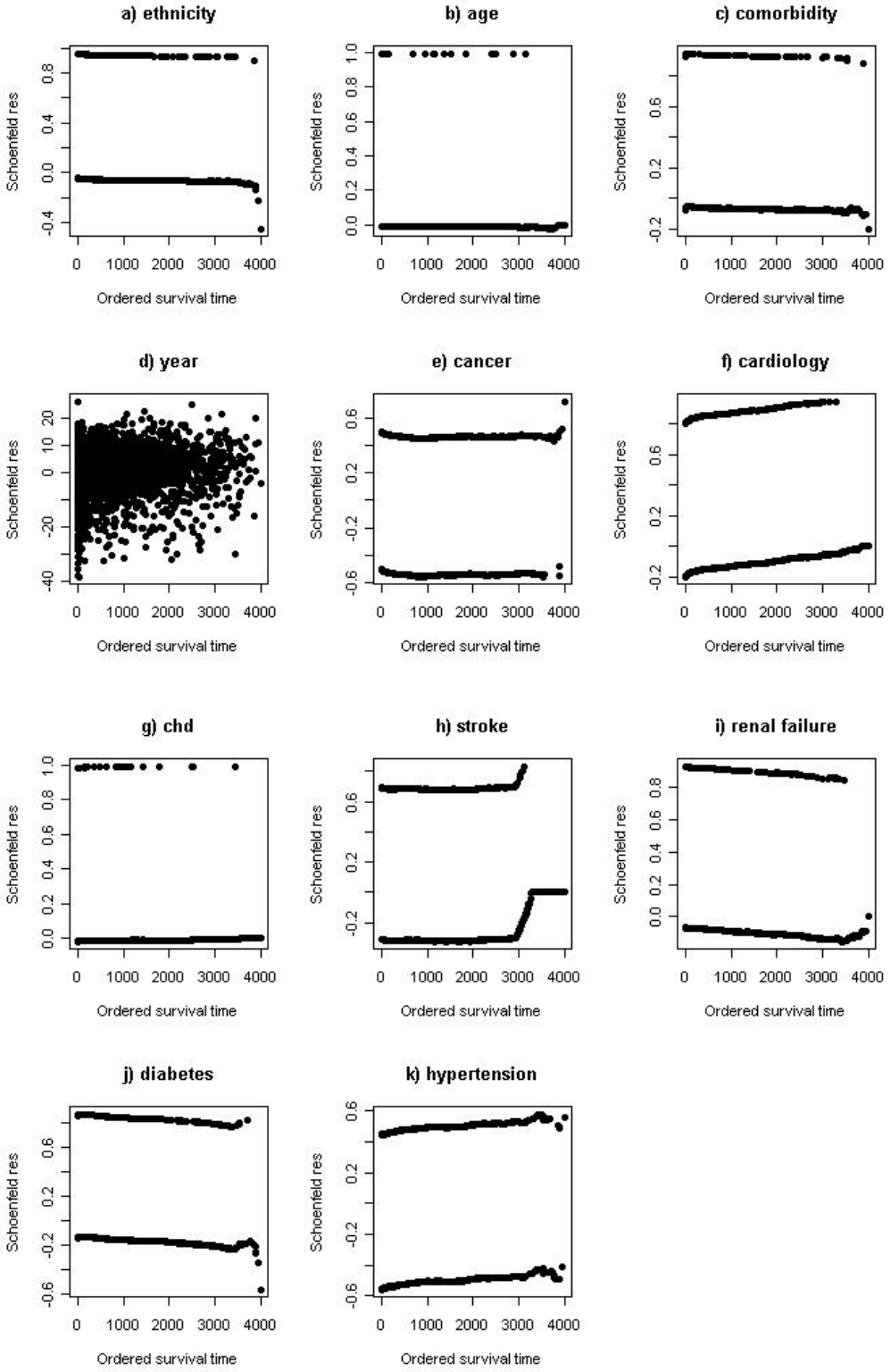
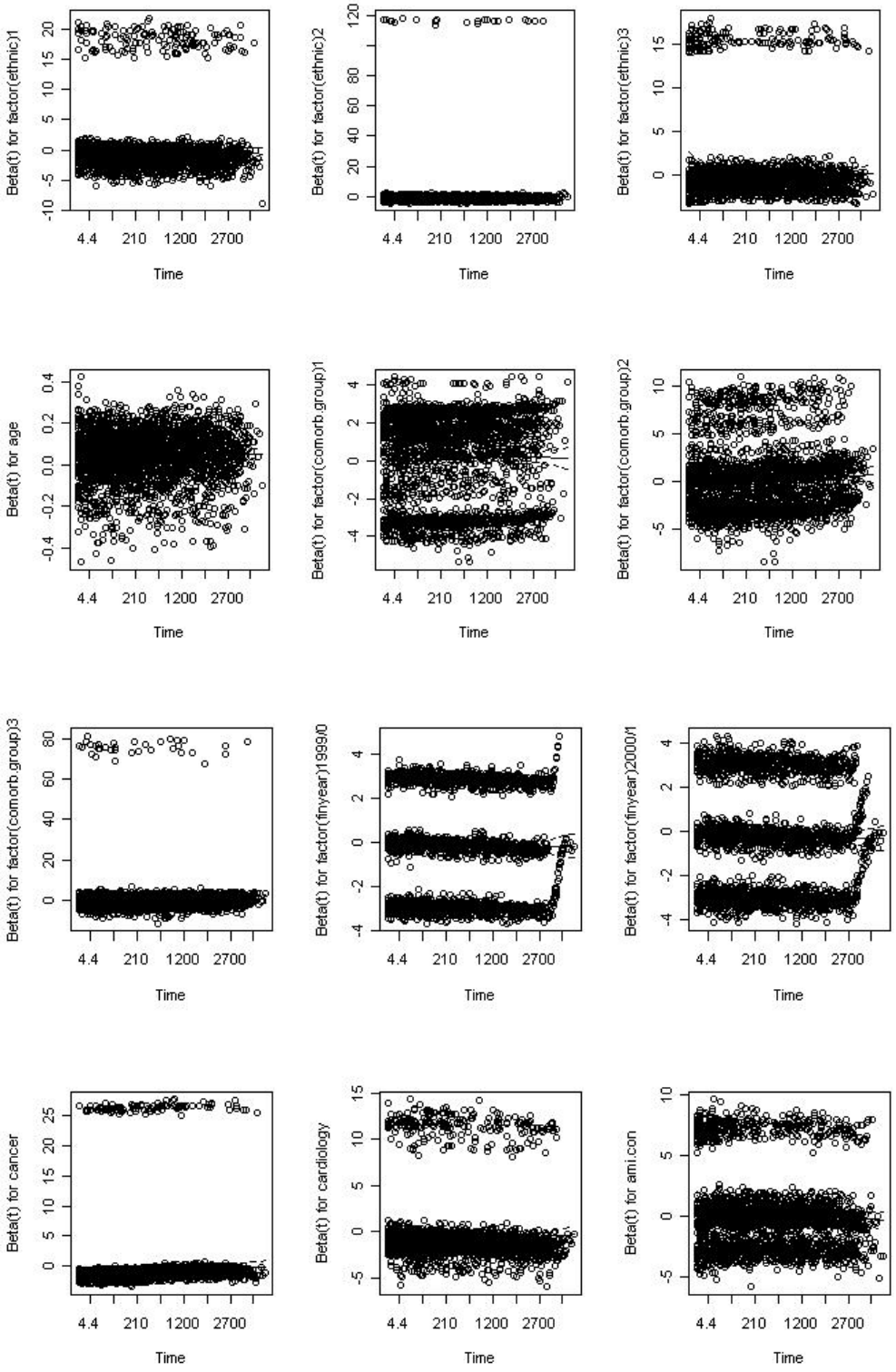


Figure A10 Diagnostics for Cox PH-AIC model for cardiovascular mortality – beta(t) residuals



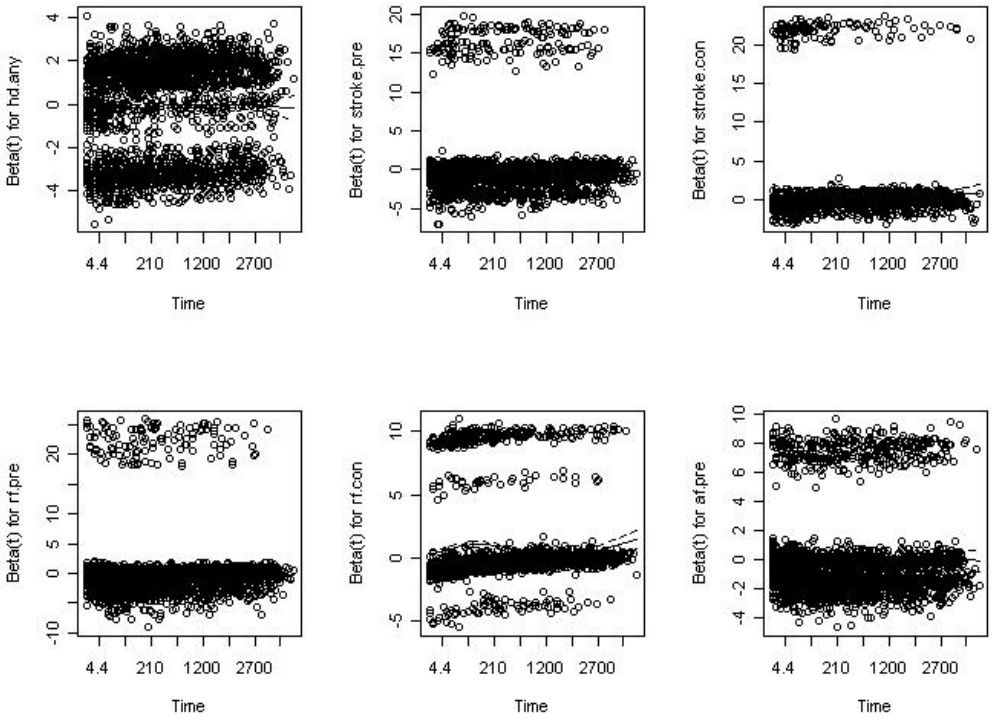
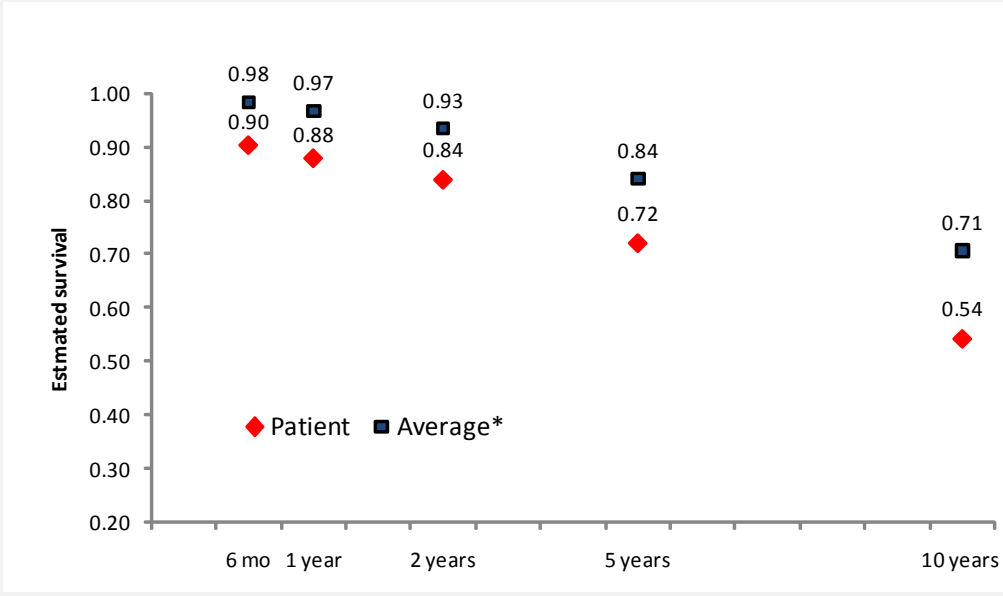

Beta(t) for hd.any
Beta(t) for stroke.pre
Beta(t) for stroke.con
Beta(t) for rf.pre
Beta(t) for rf.con
Beta(t) for af.pre
4.4
210
1200
2700
Time

Figure A11 Predictive survival modelling for a sample patient



Age (years):	**70**		
Sex:	**male**		
Ethnicity:	**white**		
Year of first admission:	**2001**		
Hospitalisation in past 5 years:	**< 7 days**		*none*
			<7 days per year
			7-30 days per year
			30+ days per year
Cancer	no		
Acute MI on admission	no		
Prior stroke	no		
Stroke on admission	**yes**		
Prior renal failure	no		
Renal failure on admission	no		
Atrial Flutter or Fibrillation	no		
Diabetes	**yes**		
Hypertension	**yes**		* average estimated survivorship in
Valve disease	no		a sex, age and year matched cohort

CARDIOVASCULAR MEDICINE

Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12 220 index admissions in Leicestershire 1993–2001

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Objective: To examine rates of, prognosis following, and the influences on first hospital admission with heart failure in Leicestershire during 1993–2001.
Design: Historical cohort study using record linked discharge and mortality data.
Setting: Leicestershire, England.
Patients: 12 220 individual patients newly hospitalised with heart failure between 1 April 1993 and 31 March 2001.
Main outcome measures: 30 day and one year survival, temporal trends in survival, and the influence on prognosis of age, sex, comorbidity, social deprivation, and year of hospital admission.
Methods and results: Between 1993/94 and 2000/01, rates of first hospitalisation increased by 62%, from 29 to 47/10 000 population, confined largely to those aged > 65 years. Rates did not increase after 1998. Median age at presentation increased from 74 years in 1993/94 to 77 years in 2000/01 for men but was unchanged (80 years) for women. Overall one and five year survival was 57% and 27%, 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. There was a clear influence on outcome of comorbidity but no influence of social deprivation score. Both one month and one year survival were lower for patients whose first heart failure admission was concomitant with acute myocardial infarction. Between 1993/94 and 2000/01 postdischarge cardiovascular survival improved by 50% ($p < 0.001$).
Conclusions: Rates of first hospital admission with heart failure reached a plateau in the late 1990s. Case fatality rates remain high and prognosis poor, in particular for those of increasing age, for men, and for patients with concomitant acute myocardial infarction. However, clear trends to improved survival were seen over this time.

Heart failure is a major public health issue in developed countries with increasingly elderly populations.[1 2] Clinical trials in the 1980s and 1990s showed mortality and morbidity benefits with a variety of treatments in chronic heart failure[3–6] and in heart failure following acute myocardial infarction (AMI).[7 8] In the years 1980–1993 studies from the UK (Scotland),[9] Sweden,[10] Spain,[11] New Zealand,[12] the Netherlands,[13] and the USA[14] showed increasing numbers of heart failure hospitalisations. Recent reports have suggested that admission numbers may have peaked in the early 1990s[15 16] and that prognosis improved over the period 1979–1996.[17]

The majority of first diagnoses of heart failure are made in hospital[18] and the prognosis for patients hospitalised is worse than for those remaining in the community. Accurate hospitalisation data thus provide relatively accurate measures of trends in incidence and prognosis for heart failure. Leicestershire has a mixed rural and urban population of approximately one million. All available routine measures of coronary heart disease (CHD) morbidity and mortality are in line with average national rates. The aim of this study was to investigate trends in outcome following a first ever hospitalisation with a diagnosis of heart failure in a large cohort of patients in the modern treatment era. We used record linked discharge data to investigate survival, potential aetiological conditions, and the influence on outcome of comorbidity, social deprivation, and demographic factors.

METHODS

Study population

Leicestershire Health Authority has a comprehensive record linkage system, which is linked to information held at the Office of National Statistics. This allows for follow up of all residents registered with primary care (956 000 in 2001) in terms of events such as hospitalisations and mortality. The system provides details of the dates of events, discharge diagnoses, and the patient's age, sex, and domicile postcode.

We obtained data on residents aged ⩾ 40 years who were admitted for a first heart failure to any of the hospitals serving the population of Leicestershire between 1 April 1993 and 31 March 2001. We excluded all those with a recorded heart failure diagnosis in the five years before the start of, and counted only the first heart failure hospitalisation during, the observation period. A heart failure admission was defined as heart failure (*International classification of diseases* (ICD) 10th revision or ICD 9th revision code I50* or 428*, respectively) in any discharge coding position. As a relatively small degree of migration occurs in those aged over 40, we included only patients resident in the district for at least five years before the index admission, thus omitting all those who may have had a diagnosis while resident outside the county. Although our data

Abbreviations: AMI, acute myocardial infarction; CHD, coronary heart disease; CI, confidence interval; ICD, *International classification of diseases*; IMD, index of multiple deprivation

Table 1 Demographic and clinical features of all newly diagnosed cases (including all secondary diagnoses)

Variable	Diagnosis in any position	Primary diagnosis
Total number	12 220	4335
Age (years)		
Mean (SD)	76.8 (10.2)	76.9 (10.0)
40–64	1429 (12%)	494 (11%)
65–74	3032 (25%)	1098 (25%)
⩾75	7759 (63%)	2743 (64%)
Sex		
Men	6055 (49%)	2207 (51%)
Women	6164 (51%)	2128 (49%)
Deprivation*		
Median (interquartile range)	16.6 (9.8–33.3)	17.2 (10.7–33.4)
Q1	1364 (11%)	447 (10%)
Q2	1497 (12%)	525 (12%)
Q3	1797 (14%)	629 (15%)
Q4	2400 (20%)	882 (20%)
Q5	5124 (42%)	1852 (43%)
Unknown	38 (1%)	0
Length of stay on admission (days)		
Median (interquartile range)	9 (5–16)	8 (5–14)
<7 days	4460 (37%)	1644 (38%)
7–29 days	6659 (55%)	2414 (56%)
30–89 days	1018 (8%)	259 (6%)
⩾90 days	83 (1%)	18 (0%)
Comorbidity (total length of stay per year in five years before admission)		
None	6258 (51%)	2240 (52%)
<7 days	4714 (39%)	1679 (39%)
7–29 days	1152 (9%)	384 (9%)
⩾30 days	97 (1%)	32 (1%)

*Index of multiple deprivation (DETR 2000) (Q1–least deprived, Q5–most deprived).

may have omitted a small number of residents, it constitutes a large cohort from a demographically varied population. Incidence data are presented as age standardised annual rates.

Survival

Mortality was identified from death certification records provided by the Office of National Statistics. Survival was measured from the date of admission to the date of death or to the end of follow up (30 September 2001), providing a minimum of six months of follow up for those alive at the end of the period. For patients who migrated from the area before 30 September 2001, the date of migration was taken as the end of follow up. Analysis was undertaken in respect of both all cause and cardiovascular mortality (ICD-9 39–45, diseases of circulatory system, excluding 43, cerebrovascular disease), as defined by the recorded cause of death. Demographic variables potentially affecting survival were age at the date of diagnosis and sex. As a proxy measure of social deprivation we used the index of multiple deprivation (IMD 2000)[19] at the electoral ward level, matched to the patient's domicile postcode, expressed as quintiles (quintile 5 being most deprived). Variables related to hospitalisation were year of admission, duration of index admission, and diagnoses related to the index and previous hospitalisations.

Previous hospitalisations

We used two measures of comorbidity. Firstly, we used diagnoses related to the index and to previous hospitalisations. In particular we focused on conditions associated with the development of heart failure; myocardial infarction, CHD, other heart disease, hypertension, and diabetes. Secondly, we used average length of hospital stay, by definition for causes other than heart failure, in each of the five years before the index admission. From these same five year data we obtained information on conditions associated with the development of heart failure: AMI (ICD 410/I21), other CHD (ICD 411–414/I20/I22–I25), heart disease other than CHD (ICD 415–429/I26–I52), hypertension (ICD 40/I1), heart valve disease (ICD 39/I0), and diabetes mellitus (ICD 250/E10–E14).

Statistical analysis

We used the χ^2 test for trend in ordered categories to analyse temporal changes in proportions and evaluated differences between population subsets using normal approximation confidence intervals. Crude survival was estimated using the Kaplan-Meier method, with log rank test to assess temporal (annual) trends in these estimates. Cox proportional hazards modelling was used to investigate the influence on outcome of potential explanatory variables. The stratified Cox procedure was used to analyse survival according to previous and concomitant diagnoses. The strategy for multivariate model selection was that published by Collett,[20] with the significance level for inclusion of variables at 10%. Statistical analyses were performed using SPSS software (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Patient characteristics

Between 1 April 1993 and 31 March 2001 a total of 12 220 patients were admitted to hospital for the first time with a diagnosis of heart failure. In 4335 (36%) heart failure was recorded as the primary diagnosis. Demographic features and duration of index admission were similar for patients with heart failure in the primary coding position and in the total cohort (table 1). Half of the patients were women and more than 60% were older than 75 years. The deprivation score, median 16.7, was similar to the national value of 16.9 for all English wards. More than half of the patients came from areas

Table 2 Annual trends in incidence, mean age of incident cases, and hospital mortality for any heart failure diagnosis (including all secondary codes)

Year	Number	Rate (95% CI)	Length of admission (days, median (interquartile range))	Median age (years (male/female))	Hospital deaths*	Median age (hospital deaths) (years)	Heart failure in first diagnostic position
1993/4	1100	29.2 (27.5 to 31.0)	9 (5–15)	78 (74/80)	248 (24.8%)	80	443 (37%)
1994/5	1157	30.5 (28.7 to 32.3)	9 (5–16)	77 (74/79)	214 (20.3%)	79	433 (34%)
1995/6	1361	35.3 (33.4 to 37.2)	8 (5–14)	78 (75/80)	281 (20.6%)	81	465 (34%)
1996/7	1381	35.3 (33.4 to 37.1)	8 (5–15)	78 (75/80)	271 (19.6%)	81	442 (32%)
1997/8	1636	41.3 (39.3 to 43.3)	9 (5–15)	77 (76/81)	302 (18.5%)	81	609 (37%)
1998/9	1957	49.0 (46.8 to 51.1)	8 (5–16)	78 (76/80)	409 (20.9%)	80	675 (34%)
1999/0	1912	47.3 (45.2 to 49.4)	8 (5–16)	78 (76/80)	376 (19.7%)	81	718 (38%)
2000/1	1920	46.8 (44.7 to 48.9)	9 (4–16)	79 (77/80)	393 (20.5)	82	702 (37%)

Rate is age and sex directly standardised rate per 10 000 resident population >40 years of age.
*Deaths during first heart failure admission.
CI, confidence interval.

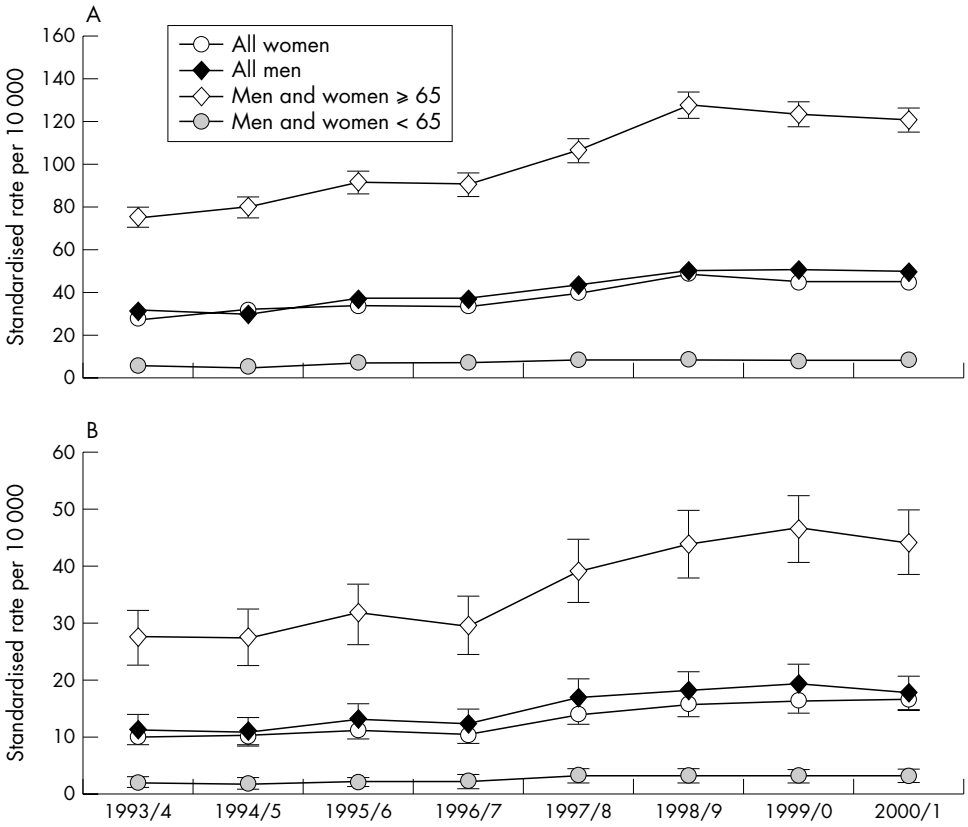

Figure 1 Trends in first heart failure admission rates between 1993 and 2001. (A) All diagnostic positions; (B) first diagnostic position. Rates for population older than 40, standardised for age and sex.

in the lowest two quintiles of deprivation score. With 30% of the population and 42% of cases, patients from the lowest quintile were over represented.

Over the study period there was a significant increase in the number and population rate of admissions. The age of men at presentation increased while that of women was unchanged (table 2). Age and sex adjusted hospital incidence rate among those aged ⩾ 40 rose by 62%, from 29/10 000 population in 1993/94 to 47/10 000 in 2000/01, with no sex difference (fig 1). This increase was seen primarily in those aged ⩾ 65 years, in whom the rate increased from 75 to 120 cases per 10 000 population. Corresponding trends were observed for heart failure in the primary coding position (fig 1, table 2). Rates also increased almost exclusively in those aged > 65 years, from 27 to 43/10 000. Overall numbers and population rates appeared to plateau after 1998/99 (fig 1, table 2). The median length of hospital stay was unchanged over the observation period (table 2).

Conditions leading to heart failure: previous hospitalisations

Table 3 shows the recorded frequency of comorbid conditions on the index and prior hospitalisations. Overall, in nearly 42% of patients (n = 5098) a form of CHD was recorded either before or during the first heart failure admission. A further 10% of patients (n = 1218) had other heart disease coded. With regard to the index admission, for one third of patients (n = 4195) there was a concomitant diagnosis of CHD, including 13% (n = 1542) with AMI.

Other potential contributory conditions such as hypertension or diabetes were recorded less commonly in the previous five years of hospitalisation data. Heart valve disease was recorded very infrequently (table 3). Nearly half of the patients either had no recorded hospitalisation (n = 3782, 31%) in the prior five years or had been hospitalised only for conditions not normally associated with heart failure (n = 1987, 16%).

Survival

For all 12 220 patients, mean follow up was 651 days (22 months) with a range of 0–3103 days (8.5 years). For those alive at the end of the study, length of follow up was 183–3103 days.

Table 4 presents Kaplan-Meier estimates of survival for all patients and for the subset with heart failure as the primary

Table 3 Numbers and proportions of all 12 220 incident cases in patients hospitalised for recognised aetiological conditions at any time during five years before or during the index admission

	Previous admissions	Index admission	Previous/index admission
AMI	803 (6.6%)	1542 (12.6%)	2187 (17.9%)
Other CHD (no AMI)	1610 (13.2%)	2653 (21.7%)	2911 (23.8%)
Other heart disease (no CHD or AMI)	1218 (10.0%)	8025 (65.7%)	7121 (58.3%)
Hypertension	1801 (14.7%)	1940 (15.9%)	3158 (25.8%)
Heart valve disease	179 (1.5%)	404 (3.3%)	534 (4.4%)
Diabetes mellitus	1281 (10.5%)	1724 (14.1%)	2040 (16.7%)
Admitted for reason other than above	1987 (16.3%)	0	0
No admission	3782 (31.0%)	0	0

AMI, acute myocardial infarction; CHD, coronary heart disease.

Table 4 Kaplan-Meyer survival estimate for the total cohort and the primary diagnosis subcohort: all cause and cardiovascular mortality

	All diagnoses (n=12 220)		Primary diagnosis (n=4335)	
Time from admission	All cause survival (95% CI)	Cardiovascular survival (95% CI)	All cause survival (95% CI)	Cardiovascular survival (95% CI)
1 month	79.1 (78.3 to 79.9)	83.8 (83.2 to 84.4)	80.8 (79.6 to 82.0)	84.5 (83.5 to 85.5)
6 months	64.4 (63.6 to 65.2)	73.2 (72.4 to 74.0)	66.5 (65.1 to 67.9)	73.6 (72.2 to 75.0)
1 year	57.1 (56.1 to 58.1)	67.7 (66.9 to 68.5)	58.6 (57.0 to 60.2)	67.6 (66.2 to 69.0)
3 years	38.9 (37.9 to 39.9)	52.6 (51.6 to 53.6)	37.6 (36.0 to 39.2)	49.6 (47.8 to 51.4)
5 years	27.0 (26.0 to 28.0)	41.8 (40.6 to 43.0)	24.4 (22.8 to 26.0)	37.9 (35.7 to 40.1)
6 years	23.2 (22.2 to 24.2)	38.0 (36.6 to 39.4)	20.4 (18.6 to 22.2)	34.1 (31.7 to 36.5)

diagnosis. Overall, 7818 patients (64%) died by the end of follow up, including 5364 (44%) from cardiovascular causes. One month and one year case fatality was 21% and 43%, respectively, the majority being cardiovascular. By six years of follow up case fatality was 75–80%, with slightly worse outcome for those with heart failure in the primary diagnostic position. Hospital mortality remained unchanged at around 20% over the period of observation. Patients dying during the index admission were on average 2–3 years older than the population as a whole (table 2).

Influence of demographic factors

Many of the measured demographic variables were strongly related to the risk of death (table 5). After adjusting for all other factors, there was a 43–45% increase in risk of death for each 10 years of age at the time of admission and a 14–17% increase associated with male sex. There was a clear relation to time spent in hospital in the prior five years, but no apparent influence on survival of social deprivation score.

We observed a number of associations between measures of comorbidity and prognosis. Our general measure of comorbidity—the average number of days in hospital in each of the previous five years—was strongly related to outcome (table 5). More specifically, when adjusted for other factors, prognosis for both all cause and cardiovascular mortality was worse for patients whose first heart failure admission was concomitant with AMI. For these 1542 patients, 30 day cardiovascular survival was 74% (95% confidence interval (CI) 72% to 76%) compared with 86% (95% CI 85% to 87%) in the non-myocardial infarction group. One year survival was also lower at 61% (95% CI 58% to 64%) compared with 70% (95% CI 69% to 71%) in those without concomitant AMI.

We observed no difference in survival between patients with (one month all cause survival 81%, 95% CI 79% to 83%) or without (80%, 95% CI 79% to 81%) diagnosed diabetes. At three years these probabilities were 37% (95% CI 34% to 40%) and 40% (95% CI 39% to 41%), respectively. Similarly, the diagnosis of diabetes did not alter cardiovascular mortality.

Trends in survival

When stratified by the year of index admission there was a clear trend to improvement in the Kaplan-Meyer estimate of survival between 1993/94 and 2000/01 ($\chi^2 = 13$, $p < 0.001$). Multivariate modelling confirmed this trend, showing up to 50% reduction in the relative risk of cardiovascular death over the period, most evident in the last three years (fig 2, table 5). Using a stratified model with adjustment for age, sex, and comorbidity, the one month, all cause survival estimates were 72% (95% CI 69% to 75%) in 1993/94 and 82% (95% CI 80% to 84%) in 2000/01. One year survival was 45% (95% CI 42% to 48%) in 1993/94 compared with 62% (95% CI 60% to 64%) in 2000/01. Similar improvements were seen in cardiovascular

Table 5 Results of Cox proportional hazards modelling of all cause and cardiovascular mortality in 12 220 patients with incident heart failure admissions: hazard ratios with corresponding 95% CI

		All cause mortality		Cardiovascular mortality	
		Univariate	Multivariate*	Univariate	Multivariate*
Sex	Male†				
	Female	1.03 (0.98 to 1.08)	0.86 (0.82 to 0.90)	1.00 (0.90 to 1.05)	0.83 (0.78 to 0.88)
Age	10 year	1.43 (1.39 to 1.46)	1.44 (1.40 to 1.48)	1.43 (1.38 to 1.47)	1.45 (1.41 to 1.50)
Deprivation‡	Q1†				
	Q2	1.01 (0.91 to 1.11)	1.03 (0.93 to 1.12)	0.99 (0.88 to 1.11)	1.01 (0.90 to 1.13)
	Q3	0.95 (0.87 to 1.04)	0.98 (0.89 to 1.07)	0.94 (0.85 to 1.05)	0.97 (0.87 to 1.08)
	Q4	0.96 (0.95 to 1.04)	1.00 (0.91 to 1.08)	0.96 (0.87 to 1.06)	1.00 (0.90 to 1.11)
	Q5	0.87 (0.86 to 0.94)	0.94 (0.87 to 1.01)	0.87 (0.79 to 0.95)	0.94 (0.85 to 1.03)
Comorbidity§	None†				
	<7 days	0.97 (0.92 to 1.02)	1.06 (1.00 to 1.12)	0.90 (0.85 to 0.96)	1.00 (0.93 to 1.07)
	7–29 days	1.52 (1.40 to 1.64)	1.56 (1.43 to 1.67)	1.35 (1.22 to 1.48)	1.43 (1.28 to 1.58)
	≥30 days	1.76 (1.39 to 2.22)	1.87 (1.47 to 1.36)	1.44 (1.06 to 1.94)	1.58 (1.17 to 2.15)
Year of diagnosis	1993/4†				
	1994/5	0.81 (0.73 to 0.89)	0.79 (0.71 to 0.87)	0.80 (0.71 to 0.89)	0.78 (0.69 to 0.87)
	1995/6	0.80 (0.73 to 0.88)	0.75 (0.68 to 0.82)	0.77 (0.68 to 0.86)	0.73 (0.65 to 0.81)
	1996/7	0.81 (0.73 to 0.89)	0.74 (0.66 to 0.81)	0.83 (0.74 to 0.92)	0.78 (0.69 to 0.87)
	1997/8	0.80 (0.73 to 0.88)	0.70 (0.63 to 0.77)	0.79 (0.70 to 0.88)	0.72 (0.63 to 0.80)
	1998/9	0.86 (0.78 to 0.94)	0.75 (0.68 to 0.83)	0.82 (0.73 to 0.91)	0.74 (0.66 to 0.83)
	1999/0	0.77 (0.69 to 0.84)	0.65 (0.59 to 0.72)	0.70 (0.62 to 0.78)	0.63 (0.55 to 0.71)
	2000/1	0.77 (0.70 to 0.85)	0.65 (0.59 to 0.72)	0.59 (0.52 to 0.67),	0.52 (0.45 to 0.59)

*Adjusted for age, sex, social deprivation, and comorbidity.
†Reference categories.
‡Index of multiple deprivation (DETR 2000) score by patient's ward of residence in quintiles (Q1–least deprived, Q5– most deprived).
§Defined as average annual stay in hospital in five years preceding the index heart failure admission.

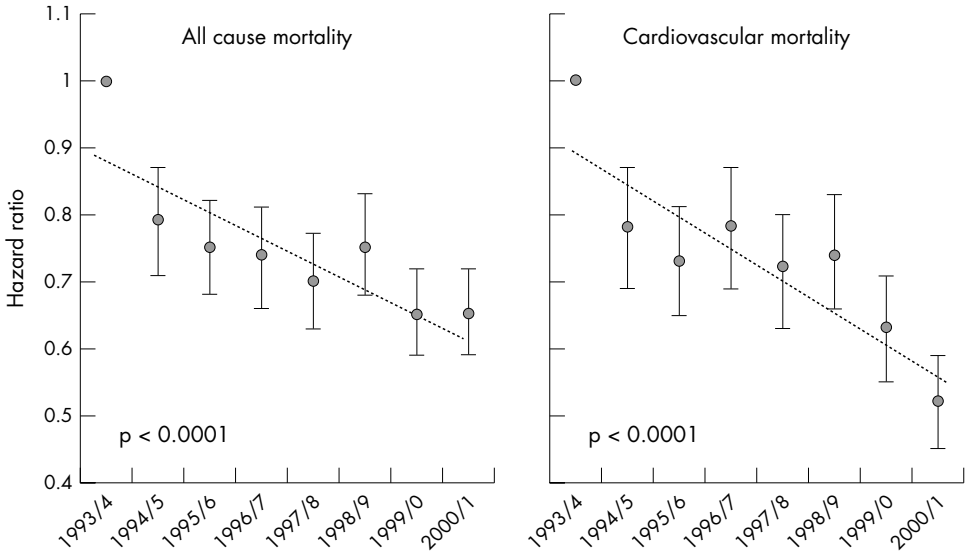

Figure 2 Estimated hazard ratios and their 95% confidence intervals for all cause and cardiovascular mortality in 12 220 patients, according to the year of first admission, adjusted for age, sex, comorbidity, and social deprivation. Probability (p) values represent the contribution of year of diagnosis to multivariate model. Dotted line indicates linear trend in hazard estimates.

survival, from 78% to 88% at one month and from 59% to 76% at one year. Trends were similar for heart failure as the primary diagnosis.

DISCUSSION

This study—the largest epidemiological study from England of patients newly admitted to hospital with heart failure—has three main findings. Firstly, numbers of heart failure related admissions increased dramatically between 1993 and 1998 but did not increase thereafter. Secondly, survival improved greatly over the period of the study. Thirdly, and importantly, the outlook for patients hospitalised with heart failure remains poor, with 20% dying within 30 days and 40% within one year of admission. Our observations add to those from earlier, large cohort studies from Scotland 1986–1995[15 17] and Canada 1994–1997[21] and a number of smaller studies.[10–14 16 22–26]

Rates of first hospitalisation

Following steady increases from 1993–98, we observed a plateau in numbers and population rates from 1998–2001. A slowing in admission rates in recent years has been noted in studies from Scotland[15] and the Netherlands.[16] While requiring further observation to clarify its reality, this finding is encouraging. Importantly, the increase in numbers of admissions in the current study was seen largely in those aged 65 years or more. The age of men continued to increase in the latter part of the 1990s, reaching a median of 79 in 2000/01. The median age of women in our study was unchanged at 80, in contrast to the increase in Scotland from 76 in 1986 to 79 in 1995.[17] Such findings have clear implications for increasingly elderly populations.

SURVIVAL TRENDS

Improved case fatality rates after heart failure hospitalisation were reported from 1980–1995.[17 25] We observed major improvement in both one month and one year survival over the period 1993–2001, despite a continuing increase in the age of the patients during this period. The current study and previous reports[17 21 25] cover two decades during which evidence accumulated of the benefits of various pharmacological treatments in heart failure.[3–8] The impact of such treatments in standard clinical practice is difficult to quantify. A plateau in heart failure hospital admissions coincident with increasing angiotensin converting enzyme inhibitor prescription was observed in the Netherlands.[16] While we cannot with certainty ascribe either improved outcomes or a plateau in numbers to prescription of such agents, it is tempting to do so.

Despite encouraging trends in admission rates, it is important to emphasise that the outlook for patients with heart failure remains poor. Overall one month and one year case fatality rates were 20% and 40%, respectively, and by five years nearly 75% of patients were dead. These figures are very similar to those reported in studies of hospitalised patients from Scotland during 1986–1995[17] and Canada during 1994–1997.[21] In-hospital mortality was high and unchanged at around 20% between 1993/94 and 2000/01, which compares with rates of approximately 29% in 1984 and 21% in 1992 reported from the Scottish database.[26] There is clearly a consistent proportion of patients for whom the prognosis is bleak at the point of first admission with heart failure. It is likely that their greater age is a major contributory factor.

Similarly, as in Scotland[17] and Canada,[21] unselected patients with heart failure in England are older and much more often women than those in heart failure trials. Moreover, case fatality rates in our population are much higher than those seen in these trials. This disparity between the populations in trials and in clinical practice is a consistent finding in epidemiological studies of heart failure.[17 18 21] This observation once again raises the issue of the relevance to the majority of those with the condition in everyday practice of the evidence base for the treatment of this condition.

Influence of age and sex

Our observed association of greater age and male sex with higher mortality are not unexpected. Moreover, the strengths of these associations (hazard ratio of 1.4/10 years of age and 0.87 for female sex) are strikingly similar to those seen in previous studies.[17 21] The differential risk associated with age and male sex has not changed over the period 1985–2001.

Influence of deprivation

In keeping with previous reports from the UK,[27] we observed no influence of deprivation on survival. However, a disproportionate number of index patients came from the most deprived areas, again in keeping with previous studies.[17] These areas clearly have a heavy burden of disease associated with heart failure. In Leicestershire these areas are in the vast majority urban, with a high demand for hospital care. A lower threshold for referral to hospital for residents of these areas may explain the apparent lack of effect of social deprivation on mortality but cannot be verified without information on disease severity at diagnosis. More detailed comparison of the characteristics of patients from the various quintiles of deprivation may help clarify this issue.

Influence of comorbidity

When adjusted for demographic factors, comorbidity, and year of diagnosis, mortality was higher in patients for whom heart failure was recorded concomitant with AMI. Once again this is in keeping with data from both large epidemiological[21] and small cohort[27] studies. Patients with AMI are an easily identifiable group at high risk of heart failure and to whom appropriate investigations and treatment should be targeted. Interestingly, only a small proportion of our cohort (7%) had a hospital discharge diagnosis of AMI in the previous five years, compared with 15% of first heart failure admissions in Scotland,[17] perhaps reflecting regional differences in the incidence of CHD.

Although a small percentage of our cohort spent any considerable amount of time in hospital in the previous five years, this very general measure of overall comorbidity associated strongly with outcome. This very simple observation perhaps emphasises the importance of concomitant pathology and interactions between covariables in the natural history of heart failure.[21]

Limitations of the study

Our study is constrained by the limitations inherent in all studies of historical, observational design. Inaccuracies in the diagnosis and coding of heart failure in routine data are well recognised[28] and we have of necessity relied on the accuracy of such data. While we identified only hospitalised patients, patients remaining in the community are likely to have a better prognosis. Temporal changes in referral and coding practices, in diagnostic accuracy, and in awareness of heart failure as a diagnostic entity may have influenced our findings. Similar comments can be applied to concomitant diagnoses potentially influencing prognosis such as AMI and diabetes. We have incomplete information on prior diagnoses, disease severity, and drug treatment at presentation. Similarly, we have not assessed the potential impact on trends in outcome of all relevant cofactors, such as renal impairment. These potential criticisms apply equally to previous studies of hospitalised patients, and the demographic features and short term and long term prognosis of our population are very much in keeping with these studies.[17 21] The duration of index admission and inpatient fatality rate did not change during our observation period and are very similar to those reported previously from Scotland for the year 1996.[15] This suggests that the severity of disease was on average similar throughout the study period. We feel that our work stands reasonable comparison with previous large, epidemiological studies of trends in heart failure hospitalisation and prognosis.

Summary

Following many years of increase, numbers of patients with first hospital admission with heart failure reached a plateau after 1998. Clear improvements in survival were observed between 1993 and 2001. However, the prognosis for patients newly admitted with heart failure remains poor, in particular for those of greater age, for men, and for those with heart failure recorded during admission with myocardial infarction. These groups are cohorts in whom screening for heart failure and asymptomatic left ventricular dysfunction are likely to be relatively cost effective. While the plateau in numbers and improvements in survival are welcome, the prevalence of heart failure remains high and the prognosis poor.

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Papers

Prognosis for South Asian and white patients newly admitted to hospital with heart failure in the United Kingdom: historical cohort study

Hanna M Blackledge, James Newton, Iain B Squire

Abstract

Objectives To compare patterns of admission to hospital and prognosis in white and South Asian patients newly admitted with heart failure, and to evaluate the effect of personal characteristics and comorbidity on outcome.

Design Historical cohort study.

Setting UK district health authority (population 960 000).

Participants 5789 consecutive patients newly admitted with heart failure.

Main outcome measures Population admission rates, incidence rates for first admission with heart failure, survival, and readmission rates.

Results When compared with the white population, South Asian patients had significantly higher age adjusted admission rates (rate ratio 3.8 for men and 5.2 for women) and hospital incidence rates (2.2 and 2.9). Among 5789 incident cases of heart failure, South Asian patients were younger and more often male than white patients (70 (SD 0.6) *v* 78 (SD 0.1) years and 56.5% (190/336) *v* 49.3% (2494/5057)). South Asian patients were also more likely to have previous myocardial infarction (10.1% (n = 34) *v* 5.5% (n = 278)) or concomitant myocardial infarction (18.8% (n = 63) *v* 10.7% (n = 539)) or diabetes (45.8% (n = 154) *v* 16.2% (n = 817), all $P < 0.001$). A trend was shown to longer unadjusted survival for both sexes among South Asian patients. After adjustment for covariables, South Asian patients had a significantly lower risk of death (hazard ratio 0.82, 95% confidence interval 0.68 to 0.99) and a similar probability of death or readmission (0.96, 0.81 to 1.09) compared with white patients.

Conclusions Population admission rates for heart failure are higher among South Asian patients than white patients in Leicestershire. At first admission South Asian patients were younger and more often had concomitant diabetes or acute ischaemic heart disease than white patients. Despite major differences in personal characteristics and risk factors between white and South Asian patients, outcome was similar, if not better, in South Asian patients.

Introduction

People of South Asian origin (Indian (subcontinent) origin) comprise the largest ethnic minority group in the United Kingdom—4.1% of the population in 2001. The incidence of coronary heart disease is around 40% higher among this group than among the indigenous white population.[1 2] Moreover, the onset of coronary heart disease has been suggested to be earlier and mortality higher in South Asian patients.[2–4] Some studies have shown a similar prognosis in South Asian and white patients after myocardial infarction.[5] A high prevalence of coronary heart disease in South Asian people might be expected to result in a higher prevalence of heart failure, a major sequela of coronary heart disease.

Population studies and clinical trials of heart failure have under-represented ethnic minority groups.[6 7] In a multiracial cohort admitted to hospital in Birmingham in the early 1990s, Indo-Asian patients were younger than white patients and had a higher prevalence of coronary heart disease and hypertension.[8] In the United States, disease progression, mortality, and response to treatment in heart failure are less favourable for black patients.[9 10] Thus it seems that outcomes from heart failure may differ with ethnicity.

Leicestershire has a population of around one million, with over twice the national average for people of South Asian ethnic origin. We compared population admission rates for heart failure and outcomes after first admission for heart failure in South Asian and white patients.

Methods

Data on admissions for heart failure were obtained from Leicestershire health information service. These data comprise self reported coding for ethnicity, for which local coverage is thorough. We defined an admission as a recorded episode of inpatient care with a diagnosis of heart failure (code I50; international classification of diseases, 10th revision) in primary or secondary position. Our denominator was from 1991 census data for the local ethnic population. Data were obtained for patients aged 40 or over. Our principal measure was the ratio of standardised admission rates (South Asian patients to white patients) for men and women.

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We obtained data on all Leicestershire residents, aged 40 or over, admitted with heart failure for the first time between 1 April 1998 and 31 March 2001. To counter the effect of migration we included only patients resident in Leicestershire for up to five years before the index admission, according to the family health service register. First admissions were defined as those where patients had no previous admission related to heart failure in these five years as a minimum. Ethnicity was that reported in the hospital discharge data. Validation checks of the South Asian cohort and a matched sample of white patients were performed with patient names.

Mortality was identified through the Office for National Statistics, and follow up hospital events were obtained from Leicestershire Health Authority data. Survival was measured from the date of first admission to the date of death, of readmission, or the end of follow up (30 September 2001). The main outcome measures were death from any cause (all cause survival) and all cause survival or emergency readmission for a cardiovascular event (event free survival).

Statistical analysis

We assessed the baseline characteristics of the cohorts with the χ^2 test for difference in independent proportions.[11] Crude survival was estimated with the Kaplan-Meier method, and Cox proportional hazards modelling was used to investigate the influence of covariates on outcome. The strategy for selection of the multivariate model was as published by Collett, with a 10% univariate significance level for inclusion of variables.[12] Potential modifiers of outcome included in the multivariate analysis were age, sex, ethnicity and social deprivation, and hospital comorbidity, such as diabetes, hypertension, renal insufficiency, stroke, and myocardial infarction.

We retrospectively estimated that, given the proportion of 10% for South Asian people in Leicestershire, an α of 0.05, a β of 0.1, and a 58% survival rate at one year, the observed number of deaths (n=2746) in the two principal ethnic groups should be large enough to detect at least a 20% difference in all cause mortality.

Our proxy measure of social deprivation was from the index of multiple deprivation 2000 at electoral ward level expressed in fifths (lowest fifth being most deprived), matched using the domicile postcode of the patient at admission. As a proxy of general comorbidity, we took the average hospital stay in each of the five years before the index admission. From this same five years we obtained information on conditions associated with heart failure, including acute myocardial infarction (code 410/I21), other coronary heart disease (411-414/I20/I22-I25), other than coronary heart disease (415-429/I26-I52), hypertension (40/I1), heart valve disease (39/I0), diabetes (250/E10-E14), stroke (434,436/I60-I64), renal failure (584-586/N17-N19), and atrial fibrillation or flutter (427.3/I48). Statistical analyses were performed with SPSS, version 9.

Results

Admission and incidence rates

From 1 April 1998 to 31 March 2001, 14 797 patients were admitted with heart failure; heart failure was the primary diagnosis in 4838 (32.7%). Ethnicity could not be established in 1776 (12.0%) patients.

White patients accounted for 90% (n=11 547) of all admissions and South Asian patients accounted for 8% (1037); 87% (3732) and 10% (435), respectively, with heart failure in the first diagnostic position.

When South Asian patients were compared with white patients of the same sex, the crude annual rates for admission (heart failure in any position) per 10 000 population were higher for both South Asian men (161 *v* 101) and South Asian women (144 *v* 93). Differences in crude incidence rates (first admission) were less noticeable (56 *v* 44 for men and 43 *v* 41 for women). The South Asian population in Leicestershire is significantly younger that its white counterpart. Figure 1 shows that age standardised admission and incidence rates were higher for South Asian patients of both sexes.

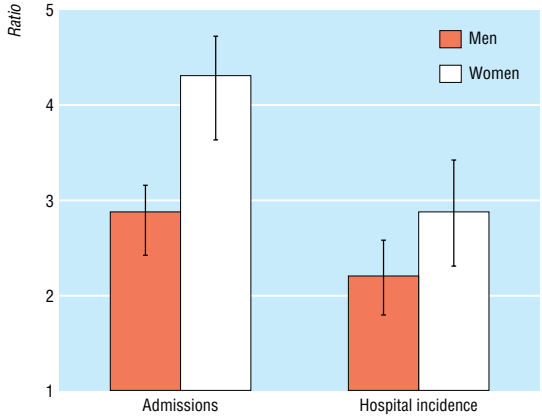
Personal characteristics of incident cohort

Between 1 April 1998 and 31 March 2001, 5789 patients were newly admitted with heart failure; 5057 (87.4%) of these were white patients and 336 (5.8%) South Asian patients (table 1). Follow up ranged from 183 to 1279 days, a minimum of six months for those alive at the end of the observation period. Ethnicity was recorded as not given for 347 (5.9%) patients, but personal characteristics suggested this group to be predominantly white.

Patients in the South Asian cohort were on average eight years younger than those in the white cohort. The South Asian cohort also contained a higher proportion of men (190; 56.5%) than the white cohort (2494; 49.3%). Less than 10% (519) of patients were treated within a cardiological setting within seven days before or after the index admission. No difference was found between cohorts in this respect.

Comorbidity

Acute myocardial infarction, both before and concomitant with the first admission for heart failure, was more prevalent in South Asian than white patients (before,



Total No of cases:				
South Asian patients	549	488	190	146
White patients	5656	5888	2493	2564

Fig 1 Ratios of age standardised admission (heart failure in any position) and incidence rates of first admission for heart failure for South Asian and white patients (95% confidence intervals), 1998-2001

Table 1 Personal and clinical characteristics of 5789 patients with newly diagnosed heart failure. Values are numbers (percentages) of patients unless stated otherwise

Variable	White patients (n=5057)	South Asian patients (n=336)	Other (n=49)	Not known (n=347)
Mean (SD) age (years); range	78 (9.8); 42-107	70 (10.4); 42-97	75 (11.6); 41-96	78 (11.0); 42-99
Men	2494 (49)	190 (57)	23 (47)	169 (49)
Women	2563 (51)	146 (43)	26 (53)	178 (51)
Deprivation*:				
Q1-Q4	3114 (62)	51 (15)	17 (35)	218 (63)
Q5	1943 (38)	285 (85)	32 (65)	129 (37)
Comorbidity†:				
None	1501 (29.7)	98 (29.2)	24 (49.0)	227 (65.4)
<7	2714 (53.7)	186 (55.4)	23 (46.9)	113 (32.6)
7-29	766 (15.1)	49 (14.6)	2 (4.1)	7 (2.0)
≥30	76 (1.5)	3 (9.0)	—	—
Median follow up (months)	11	17	14	4
No of deaths (% of total)	2623 (51.9)	123 (36.6)	18 (36.7)	210 (60.5)

*Index of multiple deprivation; Q1=least deprived, Q5=most deprived.
†Length of stay (days) per year, in five years before admission.

Table 2 Patterns of in-hospital comorbidity in five years before or concomitant with diagnosis of heart failure among white and south Asian patients. Values are numbers (percentages) of patients (95% confidence intervals), unless stated otherwise

Comorbidity	White patients (n=5057)	South Asian patients (n=336)	P value*
Acute myocardial infarction:	769 (15.2, 14.2 to 16.2)	91 (27.1, 22.4 to 32.2)	<0.001
Before admission with heart failure†	278 (5.5, 4.9 to 6.1)	34 (10.1, 6.9 to 13.3)	<0.001
Concomitant with heart failure	539 (10.7, 9.8 to 11.5)	63 (18.8, 14.6 to 22.9)	<0.001
Other coronary heart disease‡	1264 (25.0, 23.8 to 26.2)	98 (29.2, 24.4 to 34.3)	0.1
Other heart disease§	3024 (59.8, 58.4 to 61.2)	147 (43.8, 38.4 to 49.2)	<0.001
Hypertension	1484 (29.3, 28.1 to 30.6)	147 (43.8, 38.4 to 49.2)	<0.001
Valve disease	250 (4.9, 4.4 to 5.6)	6 (1.8, 0.7 to 3.8)	0.01
Diabetes	817 (16.2, 15.2 to 17.2)	154 (45.8, 40.4 to 51.3)	<0.001
Stroke	393 (7.8, 7.0 to 8.5)	26 (7.7, 4.9 to 10.6)	0.98
Renal failure	756 (14.9, 14.0 to 15.9)	56 (16.7, 12.7 to 20.7)	0.39
Atrial fibrillation or flutter:	174 (434.5, 33.2 to 35.8)	46 (13.7, 10.0 to 17.4)	<0.001
Before admission with heart failure†	646 (12.8, 11.9 to 13.7)	15 (4.5, 2.3 to 6.7)	<0.001
Concomitant with heart failure	148 (729.4, 28.1 to 30.7)	37 (11.0, 7.7 to 14.4)	<0.001

*Derived with χ^2 statistic.
†Diagnosed in hospital at any time within five years before, and excluding, first admission with heart failure.
‡No acute myocardial infarction.
§No acute myocardial infarction or coronary heart disease.

10.1% *v* 5.5%; concomitant, 18.8% *v* 10.7%). Similarly, diabetes mellitus and hypertension were more commonly recorded among South Asian patients. In contrast, white patients were more likely to have atrial arrhythmias, both before or concomitant with the admission for heart failure (table 2).

Survival

Over half of all patients (51.4%; 2974) died before the end of follow up. Two thirds of all mortality (65.5%; 1948) was due to cardiovascular events. Crude survival analysis gave all cause case fatality rates at 30 days and one year of 21% and 42%, respectively, for the whole cohort and a median survival of 21 months (95% confidence interval 20 to 22).

Unadjusted inhospital case fatality rates were lower in South Asian patients than in white patients (13% *v* 19%). Estimates of survival at 30 days, one year, and two years (both to death and to combined event) were consistently higher for South Asian patients (table 3). Univariate Cox regression showed a 38% lower risk of death and a 17% lower risk of readmission or death among South Asian patients.

Adjusted survival analysis

On multivariate analysis the risk of death remained lower (18%) for South Asian patients whereas the risk of readmission was similar to white patients (table 4). Among the factors influencing outcome were age (44% increase in the risk of death per decade of life) and comorbidity, particularly stroke and renal failure. Adjusted outcomes were better for women. A diagnosis

Table 3 Unadjusted estimates of event free survival for white and South Asian men and women for overall all cause survival and survival to death or readmission for any cause or cardiovascular event. Values are percentages (95% confidence intervals)

	Men		Women	
Survival	White patients (n=2494)	South Asian patients (n=190)	White patients (n=2563)	South Asian patients (n=146)
Patients aged <75				
Survival:				
30 days	85 (83 to 87)	85 (76 to 91)	87 (84 to 90)	91 (85 to 97)
1 year	70 (67 to 73)	72 (64 to 80)	68 (64 to 72)	79 (71 to 87)
2 years	63 (60 to 66)	66 (57 to 75)	59 (55 to 63)*	75 (65 to 85)*
Survival to event (death or readmission):				
30 days	81 (80 to 82)	82 (75 to 89)	84 (81 to 87)	88 (81 to 95)
1 year	51 (48 to 54)	54 (44 to 64)	51 (47 to 55)	54 (44 to 64)
2 years	37 (34 to 40)	35 (25 to 45)	35 (31 to 39)	37 (26 to 48)
Patients aged ≥75				
Survival:				
30 days	77 (75 to 79)	77 (67 to 87)	78 (76 to 80)	85 (75 to 95)
1 year	49 (46 to 52)	62 (51 to 73)	54 (52 to 56)	62 (48 to 76)
2 years	38 (35 to 41)	50 (36 to 64)	43 (40 to 46)	52 (36 to 68)
Survival to event (death or readmission):				
30 days	74 (72 to 76)	72 (61 to 83)	77 (75 to 79)	83 (73 to 93)
1 year	36 (34 to 38)	37 (25 to 49)	41 (39 to 43)	44 (30 to 58)
2 years	22 (20 to 24)	20 (8 to 32)	25 (23 to 27)	30 (16 to 44)

*Statistically significant difference.

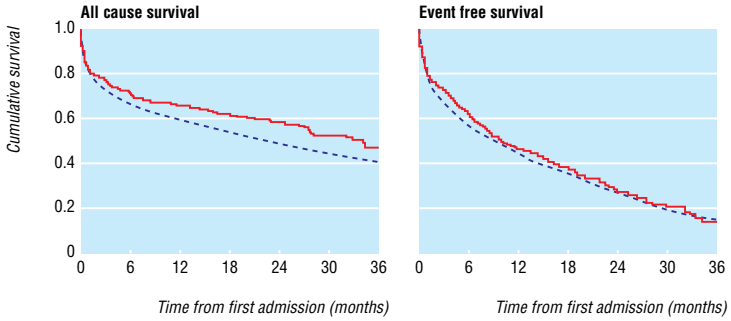


Fig 2 Survival model for South Asian and white patients in cohort of new cases diagnosed with heart failure in hospital between 1 April 1998 and 31 March 2001

of diabetes or concomitant acute myocardial infarction was associated with poorer event free survival. A lower risk was found in patients with hypertension (hazard ratio for death and event free survival 0.77 and 0.88, respectively) or atrial arrhythmias (0.86 and 0.94). Between 1998 and 2000 the risk of death fell, but the risk of readmission increased. No clear relation was found between deprivation and outcome. Indeed patients living in the most disadvantaged areas (lower fifth) had lower mortality.

Influence of ethnicity

After correction for covariates, the hazard ratio for all cause mortality was lower in South Asian patients than in white patients and similar for combined events (all cause, 0.82, 0.68 to 0.99; combined events, 0.94, 0.81 to 1.09; see table 4). Figure 2 presents the adjusted survival in both groups over the follow up period.

Revascularisation rates

In the five years before the admission with heart failure, 3.3% (n=11) of South Asian patients had undergone a revascularisation procedure compared with 2.1% (n=105) of white patients ($\chi^2=1.6$, $P<0.2$). For procedures in the follow up period, values were 6.5% (n=22) and 3.1% (n=158), respectively ($\chi^2=10.4$, $P=0.001$).

Discussion

Our report is the first of ethnicity specific outcomes in heart failure from a large UK cohort. South Asian patients admitted for the first time with heart failure were younger and more often had a recorded diagnosis of diabetes or myocardial infarction than white patients. Despite these differences, outcomes were similar for the two groups, and overall mortality was lower for South Asian patients.

Our study has the advantage of a homogeneous South Asian cohort (94% of the South Asian population in Leicestershire is of Indian descent), but we cannot assume that our observations apply to other ethnic groups, among whom cardiovascular risk profiles differ.[13] Similar results were, however, shown in another study, where South Asian people of Pakistani or Bangladeshi descent were in the majority.[7]

Table 4 Results of Cox proportional hazards modelling for all cause and cardiovascular mortality and for unplanned readmissions to hospital. Values are hazard ratios (95% confidence intervals)

	All cause survival		Event free survival*	
Variable	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Sex (female *v* male)	1.01 (0.94 to 1.09)	0.88 (0.82 to 0.96)	0.99 (0.93 to 1.06)	0.92 (0.85 to 0.98)
Age (per 10 year increase)	1.44 (1.38 to 1.50)	1.42 (1.36 to 1.48)	1.24 (1.20 to 1.28)	1.24 (1.20 to 1.28)
Ethnicity:				
White	1.00	1.00	1.00	1.00
South Asian	0.62 (0.51 to 0.75)	0.82 (0.68 to 0.99)	0.83 (0.72 to 0.95)	0.94 (0.81 to 1.09)
Other	0.69 (0.43 to 1.10)	0.80 (0.50 to 1.27)	0.71 (0.47 to 1.04)	0.78 (0.52 to 1.13)
Not known	1.46 (1.27 to 1.69)	1.62 (1.39 to 1.87)	1.02 (0.89 to 1.18)	1.15 (0.99 to 1.31)
Gross comorbidity:				
None	1.00	1.00	1.00	1.00
<7 days	1.03 (0.95 to 1.12)	1.07 (0.98 to 1.17)	1.15 (1.07 to 1.23)	1.14 (1.06 to 1.22)
7-29 days	1.60 (1.40 to 1.75)	1.46 (1.30 to 1.64)	1.60 (1.45 to 1.76)	1.44 (1.30 to 1.59)
≥30 days	1.75 (1.32 to 2.30)	1.55 (1.17 to 2.05)	1.77 (1.39 to 2.26)	1.59 (1.24 to 2.03)
Deprivation†:				
Q1	1.00		1.00	1.00
Q2	0.94 (0.81 to 1.08)	0.96 (0.83 to 1.12)	0.99 (0.87 to 1.13)	1.01 (0.89 to 1.15)
Q3	0.90 (0.78 to 1.04)	0.94 (0.81 to 1.07)	1.01 (0.89 to 1.13)	1.04 (0.92 to 1.17)
Q4	0.90 (0.78 to 1.02)	0.95 (0.83 to 1.08)	0.99 (0.88 to 1.11)	1.02 (0.91 to 1.15)
Q5	0.81 (0.71 to 0.91)	0.88 (0.77 to 0.99)	0.94 (0.84 to 1.04)	0.98 (0.88 to 1.08)
Diabetes (yes *v* no)	0.85 (0.77 to 0.94)	0.98 (0.88 to 1.09)	1.06 (0.97 to 1.14)	1.11 (1.02 to 1.21)
Concomitant acute myocardial infarction (yes *v* no)	0.96 (0.85 to 1.08)	1.07 (0.94 to 1.17)	1.04 (0.94 to 1.14)	1.13 (1.02 to 1.24)
Hypertension (yes *v* no)	0.76 (0.70 to 0.83)	0.77 (0.71 to 0.84)	0.91 (0.85 to 0.97)	0.88 (0.82 to 0.94)
Stroke (yes *v* no)	1.57 (1.38 to 1.77)	1.46 (1.28 to 1.65)	1.34 (1.22 to 1.53)	1.26 (1.12 to 1.41)
Renal insufficiency (yes *v* no)	1.88 (1.70 to 2.06)	1.85 (1.68 to 2.03)	1.65(1.51 to 1.80)	1.57 (1.44 to 1.72)
Atrial fibrillation or flutter (yes *v* no)	0.93 (0.86 to 1.00)	0.86 (0.79 to 0.92)	0.99 (0.92 to 1.06)	0.94 (0.88 to 1.00)
Year of diagnosis:				
1998-9	1.00	1.00	1.00	1.00
1999-2000	0.89 (0.81 to 0.97)	0.89 (0.81 to 0.97)	1.06 (0.98 to 1.15)	1.06 (0.98 to 1.14)
2000-1	0.89 (0.80 to 0.97)	0.88 (0.78 to 0.96)	1.17 (1.07 to 1.27)	1.14 (1.05 to 1.24)

*Survival to death from any cause or emergency readmission for cardiovascular event.
† Q1=least deprived, Q5=most deprived.

Study limitations

Our study is limited by lack of information on disease severity, non-invasive investigations, and pharmacological treatment before and after admission, all potential modifiers of outcome. We are confident about the robustness of the record linkage system, which allowed identification of all mortality and inhospital events. Although the limitations of hospital discharge data cannot be ignored, such caveats apply equally to both ethnic cohorts and are unlikely to have introduced bias.[7] In identifying incident cases we included all admissions with heart failure diagnosed in any position. Although this may cause some overestimate, excluding cases with a diagnosis of secondary heart failure may have led to more underestimation.

Admission and incidence rates

Coronary heart disease, the commonest cause of heart failure, is around 40% more common in patients from South Asian ethnic minorities in the United Kingdom and other countries compared with indigenous populations.[1 2 14] Moreover, coronary heart disease has been reported to have earlier onset, to be more extensive, and to have a worse prognosis in South Asian people.[2–4 15] Our data are compatible with a greater prevalence of coronary heart disease in South Asian people, with concomitant or previous myocardial infarction being nearly twice as common than in white patients. The younger age of the South Asian patients also supports earlier onset of disease. As might be expected, age adjusted rates for admission and incidence of heart failure were higher for South Asian patients.

Prognosis of heart failure

Our study concurs with recently reported annual case fatality rate of 40% after a first admission for heart failure.[16 17] A small proportion of our cohort was treated in a cardiological setting at the time of the index admission. In the context of previous reports from UK centres, indicating similar outcomes in South Asian and white patients after myocardial infarction and after coronary artery surgery, the lower mortality for South Asian patient newly admitted with heart failure is of note.[5 18] This phenomenon is likely to be multifactorial and could be explained by heart failure being less advanced at the point of first admission, by a differing cause of heart failure in ethnic minority populations, or by better family support after discharge. Better prognosis among South Asian patients remained after adjustment for other prognostic variables and despite higher rates of coronary heart disease and diabetes. The higher prevalence of hypertension and diabetes in South Asian patients perhaps suggests that this cohort may have a higher prevalence of heart failure with preserved left ventricular systolic function. The protective effect of hypertension in our cohort lends some support to this postulate.

Our data are in keeping with the previous observation in heart failure of better outcome with a diagnosis of atrial fibrillation.[19] Although this arrhythmia was less prevalent for South Asian patients than for white patients, the small numbers of South Asian patients with this comorbidity makes interpretation difficult.

Heart failure in South Asian patients

In the United States, black patients show more rapid disease progression with heart failure and are readmitted more frequently than white patients.[9 20] Poorer prognosis for black and Asian patients in the United States after myocardial infarction has been ascribed in part to inequities in access to invasive procedures.[21 22] Our observations do not support such phenomena in South Asian patients in Leicestershire, for whom coronary revascularisation rates were higher than in white patients. There is, however, a parallel to a large study from California where Asian patients (likely to be ethnically different to our South Asian population) had lower rates for admission to hospital, incidence, mortality, and readmission than white patients.[23]

Diabetes and insulin resistance are more prevalent in South Asian patients, and poor glycaemic control may be important in the development of heart failure.[19 24 25] In our study a previous hospital diagnosis of diabetes was recorded for over 45% of South Asian patients, three times the rate in the white cohort. Prospective studies are needed to clarify the importance of diabetes, and its control, in the development and progression of heart failure in ethnic minority populations.

It may be argued that the younger average age of South Asian patients with heart failure simply reflects the age distribution of the local population. However the importance of this observation lies in the fact that the proportion of individuals of an age that puts them at risk of heart failure is increasing disproportionately in the South Asian population. The number of cases of coronary heart disease among this population is predicted to increase markedly by 2008.[26] Although estimated all cause survival was better for South Asian patients, the combined end point of survival or readmission was similar to white patients. It is likely that the phenomenon of competing risks at least partly explains this observation; survivors have longer in which to experience readmission. Our observations have clear implications for the allocation of healthcare resources in this population.

Better outcome for patients from areas of high deprivation is puzzling. As with all such measures, the index of multiple deprivation is a sum of indicators more relevant to the working age population than to elderly patients, who primarily comprised our cohort. Only two of the six domains in the index—housing and access to services (contributing no more than 20% of the overall weight)—could feasibly reflect the level of social deprivation among elderly patients. This indicates that the index is a relatively inappropriate measure of deprivation in this type of population. However short of knowing the current income or housing conditions, it is difficult to measure social deprivation in elderly patients.

Conclusions

Age adjusted admission and incidence rates for heart failure are higher among the South Asian ethnic population of Leicestershire than they are among the white population. Survival data suggest better outcomes for South Asian patients compared with white patients, this on a background of markedly differing risk factor profiles. The observations are clinically important to the UK South Asian population, among whom coronary heart disease and diabetes are common, and in whom the proportion of patients of an age that puts them at risk of heart failure is increas-

What is already known on this topic

Coronary heart disease is more prevalent among South Asian people than white people, with an earlier onset and higher mortality

Ethnic minority patients are under-represented in clinical trials

Little is known about the clinical features of heart failure and outcomes in South Asian patients in the United Kingdom

What this study adds

Admission and incidence rates for heart failure are higher in South Asian patients than in white patients

South Asian patients newly admitted with heart failure are younger (average eight years) and have a history of a higher prevalence of acute myocardial infarction, diabetes, and hypertension than white patients

Even after adjusting for age and in-hospital comorbidity factors, survival is similar, if not better, for South Asian patients

ing. The data indicate that ethnicity is a significant factor in the development and course of the disease. Further studies are required to delineate the cause, clinical course, and prognosis of heart failure in different communities worldwide.

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Competing interests: None declared.

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CARDIOVASCULAR MEDICINE

Ethnicity and variation in prognosis for patients newly hospitalised for heart failure: a matched historical cohort study

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Objectives: To compare mortality and factors predictive for outcome in age matched white and South Asian cohorts after first admission for heart failure.
Design: Matched historical cohort study.
Setting: One National Health Service trust comprising three acute care hospitals.
Participants: 176 South Asian (mean age 68 (10) years, 45% women) and 352 age and sex matched white (70 (11) years, 42% women) patients hospitalised for the first time with heart failure.
Main outcome measures: All cause survival, measures of disease severity, and the association of clinical variables with outcome.
Results: Compared with white patients, South Asian patients had similar rates of prior coronary heart disease but more often had prior hypertension (45% *v* 33%, p = 0.006) and diabetes (46% *v* 18%, p < 0.0001). Atrial fibrillation (15% *v* 31%, p = 0.0002) and prior diuretic use (39% *v* 48%, p = 0.041) were less common among South Asians. Left ventricular function was more often preserved (38% *v* 23%, p = 0.002) and less often severely impaired (18% *v* 28%, p = 0.025) among South Asians. During follow up (range 520–1880 days) 73 of 176 (41.2%) South Asian and 167 of 352 (47.4%) white patients died. South Asian ethnicity was associated with lower all cause mortality (odds ratio 0.71, 95% confidence interval 0.53 to 0.96, p = 0.02). Other predictors of outcome (admission age, lower systolic blood pressure, higher creatinine, higher plasma glucose, and lower haemoglobin) were similar in each cohort.
Conclusions: At first hospitalisation, heart failure appears less advanced in South Asians, among whom diabetes and hypertension are more prevalent. Survival is better for South Asian than for white patients. Higher glucose and lower haemoglobin at admission provide useful prognostic information in heart failure.

As the only manifestation of heart disease which is increasing in prevalence, chronic heart failure (CHF) constitutes an increasingly important public health issue.[1] Conditions contributing to the development of CHF, such as coronary heart disease (CHD) and hypertension, vary in prevalence among ethnic populations, and it has been suggested that important differences may exist among ethnic groups in the response to treatment and prognosis for heart failure.[2] Reports from the USA suggested that disease prevalence,[3] progression,[4] prognosis,[4] and the response to pharmacological treatments[5 6] may be less favourable in black American patients. In contrast, other studies have suggested lower mortality but higher readmission rates among black patients in the USA.[7]

People whose ethnic origin is South Asian (countries of the Indian subcontinent) constitute one of the largest ethnic groups in the world and the largest ethnic minority population in the UK. These populations have high prevalence of CHD and diabetes, factors that may be expected to lead to greater prevalence of CHF. Few studies have examined the prevalence of and outcome from CHF in South Asian patients in the UK. Data from our own[8] and one other centre[9] suggest that patients of South Asian ethnicity have about a threefold higher risk of hospitalisation with heart failure than the white population. In our description of the demographic characteristics of patients hospitalised for the first time with heart failure, diabetes, hypertension, and prior myocardial infarction were more prevalent among South Asians. Despite this adverse risk factor profile, in terms of both mortality and readmission outcome was better among South Asians.[8] An earlier study noted younger average age among South Asians admitted to hospital with heart failure,[9] a finding that led to the suggestion that this condition may have earlier onset in this population.[2] In our study of unselected hospital admissions for heart failure over the period 1998 to 2001, the average age of white patients was 78 years compared with 70 years among South Asians. Thus, it was suggested that our observation of better prognosis for South Asians hospitalised with heart failure is artefactual[10] and simply reflects the age structure of the ethnic South Asian population in the UK.

We wished to explore further our prior observations. The objective of the current study was to compare the clinical characteristics of, and the relative prognosis for, South Asian and white patients hospitalised for the first time with heart failure after correcting for disease severity, access to investigations, and pharmacological treatment in the two populations. We also wished to assess possible aetiological factors in these cohorts.

METHODS

The strategy for patient identification has been described elsewhere.[8] We used routine hospital discharge data from Leicestershire's health information service to identify, for residents of Leicestershire, all first hospitalisation episodes

Abbreviations: CHARM, candesartan in heart failure assessment of reduction in mortality and morbidity; CHD, coronary heart disease; CHF, chronic heart failure; LV, left ventricular; RENAISSANCE, randomized etanercept North American strategy to study antagonism of cytokines

for which heart failure was coded between 1 April 1998 and 31 March 2001. First admissions were those where patients had no previous heart failure related hospitalisation in a minimum of the preceding five years. Ethnicity, information recorded routinely locally, was that reported in the hospital discharge data. We obtained all available hospital records pertaining to the three local acute care hospital sites, constituting a single acute care National Health Service trust. The validity of the diagnosis required documentation of appropriate symptoms (shortness of breath, peripheral oedema, and fatigue) and physical findings (pulmonary crepitations, peripheral oedema, gallop rhythm, and jugular venous distension). We sought supportive documentation from reports of chest radiography. If doubt remained, an appropriate response after diuretic treatment was accepted. Patients for whom the diagnosis of heart failure on the index admission could not be confirmed were excluded.

A single investigator (JDN) abstracted baseline clinical characteristics, including demographic features, clinical history, physical findings, and biochemical and haematological information relevant to the index heart failure admission. Biochemical and haematological data recorded were the first available from the admission episode. A history of CHD was recorded if the patient had a history of angina, myocardial infarction, or coronary revascularisation. Diabetes was recorded for patients treated with insulin, oral hypoglycaemic drugs, or dietary restriction. Hypertension was recorded for patients with a history of treated hypertension or who were taking antihypertensive treatment. Details of baseline and discharge drug treatment were abstracted from the notes, as was information regarding the timing and findings of echocardiographic examination.

We matched each South Asian patient with two sex and age matched white patients. The principal outcome measure was all cause mortality, identified from death certification records provided by the Office for National Statistics to Leicestershire Health Authority. Survival was measured from the date of first admission to the date of death. Follow up was censored at 31 March 2003.

Statistical analysis

Crude survival was estimated by the Kaplan-Meier method and Cox proportional hazards modelling was used to assess the influence on outcome of covariates.[8] Covariates assessed for such an influence were age, prior myocardial infarction, hypertension, renal insufficiency, diabetes, and stroke, and the baseline serological variables sodium, creatinine, haemoglobin, and glucose. To examine for linearity of associations between outcome and continuous variables, these were categorised by quartiles. Missing continuous variables were imputed by the expectation maximisation method based on correlation between each variable with absent values and all other variables as estimated from the set of complete patients. Differences between ethnic groups were examined by the χ^2 test for categorical variables and Mann-Whitney test for continuous variables. Data are presented as mean (SD) for continuous variables and as proportions for categorical variables. Two sided $p < 0.05$ was considered significant.

RESULTS

Demographic characteristics of incident cohort

Between 1 April 1998 and 31 March 2001, a total of 332 first admissions to hospital with heart failure were recorded for South Asian patients. Case records for 210 (63%) were available for review, and these were matched with 419 white patients. The 210 patients for whom case records were available (59% men, mean age 69 years (range 42–93 years), 43% died by end of follow up) did not differ significantly from the 122 for whom case records were not accessed (56% men, $p = 0.556$, mean age 69 years (range 42–96 years, $p = 0.990$), 41% died, $p = 0.739$). On review of the 629 available case notes, evidence was insufficient for a new diagnosis of heart failure for 101 (16%) patients. Thus, the final analysis was based on 528 patients, 176 (33%) of whom

Table 1 Baseline characteristics stratified by ethnic origin

Variable	Whites (n = 352)	South Asians (n = 176)	All (n = 528)	p Value*	Missing values
Demographics					
Age (years)	70 (11)	68 (10.0)	69 (10.5)	0.106	0
Women	147 (42%)	79 (45%)	226 (43%)	0.494	0
Medical history					
Heart failure	44 (13%)	18 (10%)	62 (12%)	0.444	0
Angina	75 (21%)	47 (27%)	122 (23%)	0.165	0
Myocardial infarction	75 (21%)	36 (20%)	111 (21%)	0.821	0
Coronary revascularisation	20 (6%)	10 (6%)	30 (6%)	1.0	0
Hypertension	117 (33%)	80 (45%)	197 (37%)	0.006	0
CVA	37 (11%)	20 (11%)	57 (11%)	0.766	0
Diabetes	62 (18%)	81 (46%)	143 (27%)	<0.0001	0
COPD	38 (11%)	9 (5%)	47 (9%)	0.031	0
Physical examination					
Pulse rate (beats/min)	95 (24.7)	92 (20.8)	94 (23.5)	0.115	40 (7.6%)
SBP (mm Hg)	140 (27.5)	145 (28.4)	142 (27.9)	0.063	59 (11.2%)
DBP (mm Hg)	83 (17.9)	83 (18.0)	83 (17.9)	0.559	58 (11%)
Atrial fibrillation	94 (31)†	24 (15)†	118 (25)†	0.0002	63 (12%)
QRS duration	107 (21.7)†	99 (19.9)†	104 (21.4)†	0.0001	63 (12%)
Biochemical data					
Sodium (mmol/l)	137 (4.6)	137 (4.6)	137 (4.6)	0.149	1 (0.2%)
Potassium (mmol/l)	4.2 (0.71)	4.2 (0.64)	4.2 (0.69)	0.438	1 (0.2%)
Creatinine (μmol/l)	121 (75.8)	128 (86.3)	123 (79.4)	0.657	1 (0.2%)
Serum glucose (mmol/l)	8.4 (5.2)	9.6 (3.7)	8.8 (4.3)	0.019	96 (8.2%)
Haemoglobin (g/l)					
All	131 (20)	125 (22)	129 (21)	0.002	2 (0.4%)
Males	134 (18)	131 (22)	133 (21)	0.235	1 (0.2%)
Females	126 (21)	117 (20)	123 (19)	0.001	1 (0.2%)

All values are mean (SD) or number (%).
*Difference between whites and South Asians; †465 (88%) patients had an ECG available, 308 (88%) whites and 157 (89%) South Asians.
COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2 Admission and discharge treatment after first hospitalisation with heart failure

	Whites (n = 352)	South Asians (n = 176)	p Value
Admission			
Aspirin	98 (28%)	50 (28%)	0.891
ACEI or ARB	91 (26%)	54 (31%)	0.241
Diuretic	169 (48%)	68 (39%)	0.041
Loop	149 (42%)	61 (35%)	0.090
Thiazide	20 (6%)	7 (4%)	0.402
β Blocker	32 (9%)	34 (19%)	0.001
CCB	56 (16%)	50 (28%)	0.001
Digoxin	31 (9%)	5 (3%)	0.010
Nitrate	34 (10%)	27 (15%)	0.054
Spironolactone	3 (1%)	1 (1%)	1.000
Statin	26 (7%)	9 (5%)	0.322
Discharge			
Aspirin	131 (43%)	79(51%)	0.139
ACEI or ARB	183 (61%)	101 (65%)	0.386
Diuretic	237 (78%)	115 (74%)	0.289
Loop	235 (78%)	111 (72%)	0.136
Thiazide	2 (1%)	4 (3%)	0.187*
β Blocker	46 (15%)	32 (21%)	0.154
CCB	30 (10%)	35 (22%)	0.0003
Digoxin	65 (22%)	11 (7%)	<0.0001
Nitrate	40 (13%)	35 (20%)	0.012
Spironolactone	21 (7%)	8 (5%)	0.447
Statin	54 (18%)	22 (14%)	0.303

*Fisher's exact test.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

were South Asian (table 1). Follow up ranged from 520–1800 days, with a mean of 1257 days.

Co-morbidity and drug treatment

A history of heart failure was recorded for 10% of South Asian and 13% of white patients. CHD was recorded for about 40% of each cohort. Diabetes and hypertension were more often recorded for South Asians and COPD more often for white patients (table 1). A greater proportion of the South Asian cohort (27% *v* 20% whites, p = 0.043) reported symptom duration of less than 24 hours before hospitalisation. Mean plasma glucose was higher among South Asians. Haemoglobin was lower among South Asian women (table 1). Atrial fibrillation was twice as common in white as in South Asian patients (31% *v* 15%).

At admission, more South Asians were taking β blockers and calcium antagonists; South Asians also tended to have more nitrates prescribed (table 2). Loop diuretic treatment was uncommon, although more common in the white cohort. In keeping with their greater prevalence of atrial fibrillation, white patients more commonly had digoxin prescribed both at admission and at discharge. Rates of discharge prescription of diuretics, β blockers, and renin–angiotensin system antagonists did not differ at discharge.

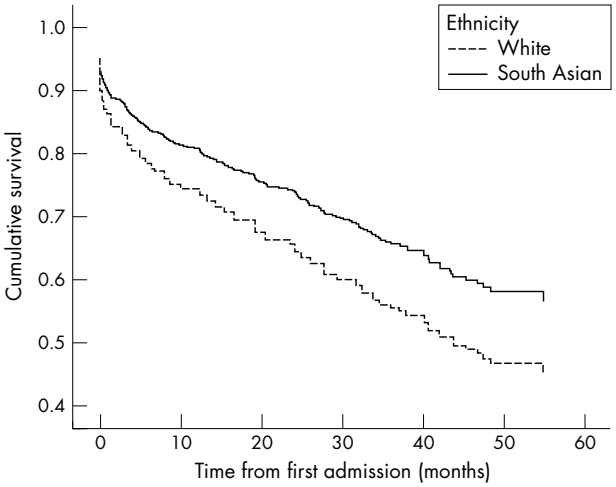

Figure 1 Adjusted survival estimates stratified by ethnicity.

Survival

During a mean follow up of 3.5 years, 73 of 176 (41.2%) South Asian and 167 of 352 (47.4%) white patients died. Crude in-hospital, 30 day, one year, and two year survival rates were consistently better for South Asian patients (table 3). For the entire study population, 30 day and one year case fatality rates were 15% and 27%, respectively.

Adjusted survival analysis: influence of ethnicity

Multivariate analysis confirmed an independent association of South Asian ethnicity with better survival (fig 1).

Table 4 shows independent predictors of survival, with continuous variables categorised by quartile. As expected, age and risk of mortality were linearly related. Current prescription of diuretic, higher creatinine, and lower haemoglobin at admission were each associated with adverse outcome. Higher glucose concentrations at admission were associated with poor outcome, and this relation reached significance for concentrations above the highest quartile. For glucose, haemoglobin, and creatinine the strength of association with death was statistically stronger for white patients.

Notably, plasma glucose at admission remained independently predictive of poor outcome among patients discharged without any treatment for diabetes (odds ratio 1.081, 95% confidence interval 1.037 to 1.128, p = 0.0002). Indeed among diabetic patients the relation between glucose at admission and subsequent mortality was non-significant (odds ratio 1.018, 95% confidence interval 0.737 to 1.687).

Echocardiography

Sixty nine per cent of patients underwent echocardiographic examination and the timing and findings of this investigation differed between South Asian and white patients (table 5).

Table 3 Unadjusted and adjusted survival estimates for white and South Asian patients

	Unadjusted			Adjusted		
Survival	White	South Asian	All	White	South Asian	All
In hospital	88 (84 to 91)	93 (88 to 96)	89 (86 to 92)	NA	NA	NA
30 days	83 (79 to 87)	90 (85 to 94)	85 (82 to 88)	85 (82 to 88)	91 (87 to 95)	88 (85 to 90)
1 year	70 (65 to 75)	78 (72 to 84)	73 (69 to 83)	73 (68 to 78)	82 (77 to 87)	77 (73 to 81)
2 years	62 (64 to 67)	70 (64 to 77)	65 (61 to 69)	64 (59 to 69)	75 (69 to 81)	68 (64 to 72)

Values are percentage (95% confidence interval (CI)).
NA, not applicable.

Table 4 Independent predictors of all cause mortality

Predictor	HR (95% CI) All	p Value	Whites	South Asians
Ethnicity				
White	1.00		NA	NA
South Asian	0.71 (0.53 to 0.96)	0.020	NA	NA
Age (years)				
<63	1.00		1.00	1.00
63–70	1.597 (1.043 to 2.443)	0.041	1.917 (1.133 to 3.245)	1.039 (0.472 to 2.288)
71–77	1.799 (1.186 to 2.730)	0.008	1.604 (0.951 to 2.703)	1.992 (0.942 to 4.212)
>77	2.136 (1.404 to 3.251)	0.002	1.972 (1.170 to 3.323)	2.251 (1.067 to 4.748)
SBP (mm Hg)				
>158	1.00		1.00	1.00
140–158	1.583 (1.090 to 2.300)	0.022	1.709 (1.065 to 2.743)	1.738 (0.907 to 3.329)
122–139	1.206 (0.801 to 1.816)	0.513	1.369 (0.820 to 2.285)	1.371 (0.650 to 2.890)
<122	1.624 (1.103 to 2.391)	0.017	1.633 (1.023 to 2.605)	1.527 (0.695 to 3.354)
Serum creatinine (μmol/l)				
<85	1.00		1.00	1.00
85–104	1.529 (1.003 to 2.331)	0.089	2.020 (1.191 to 3.427)	0.850 (0.405 to 1.784)
105 to 133	1.444 (0.946 to 2.203)	0.076	1.695 (0.991 to 2.900)	1.093 (0.537 to 2.224)
>133	2.627 (1.746 to 3.951)	<0.0001	4.129 (2.447 to 6.967)	1.158 (0.570 to 2.351)
Serum glucose (mmol/l)				
<6.0	1.00		1.00	1.00
6.0–7.6	1.218 (0.829 to 1.790)	0.285	1.373 (0.866 to 2.179)	0.881 (0.417 to 1.860)
7.7–10.0	1.183 (0.810 to 1.728)	0.313	1.174 (0.750 to 1.838)	1.572 (0.732 to 3.374)
>10.0	2.032 (1.420 to 2.906)	<0.0001	2.474 (1.603 to 3.821)	1.569 (0.789 to 3.118)
Serum haemoglobin (g/l)				
>143	1.00		1.00	1.00
131–143	1.493 (0.989 to 2.255)	0.034	1.467 (0.902 to 2.387)	1.499 (0.641 to 3.506)
116–130	1.620 (1.064 to 2.467)	0.030	1.909 (1.160 to 3.139)	0.964 (0.425 to 2.184)
⩽115	1.919 (1.275 to 2.886)	0.002	2.111 (1.288 to 3.462)	1.666 (0.769 to 3.612)
Diuretic on admission	1.300 (1.003 to 1.686)	0.039	1.173 (0.856 to 1.609)	1.616 (0.981 to 2.664)

HR, hazard ratio.

While similar minorities had undergone echocardiography before the index admission, a greater proportion of white patients underwent this examination during, and a smaller proportion after, the index admission. Left ventricular (LV) systolic function was more often reported as normal in the South Asian than in the white cohort (38% *v* 23%, p = 0.002). In contrast, severe LV systolic dysfunction was recorded for 28% of white and 18% of South Asian patients (p = 0.025).

Figure 2 shows Kaplan-Meier survival curves for patients discharged alive from the index admission. Preserved LV systolic function was associated with better prognosis among patients who underwent echocardiography than among both patients with impaired systolic function and particularly among patients who did not undergo echocardiography.

We considered whether the higher proportion of South Asian patients recorded as having normal LV function may have biased survival in their favour. Our analyses in this regard indicated very similar survival in each cohort for patients with "normal" LV function. Outcome for South Asian patients was driven by better survival for those with moderate or severe LV systolic dysfunction.

DISCUSSION

This study extends our previous report of outcomes for South Asian and white patients with heart failure.[8] After correcting for differences in population ages, survival is better for South Asian than for white patients. Heart failure appears to be more advanced in white patients at first hospitalisation.

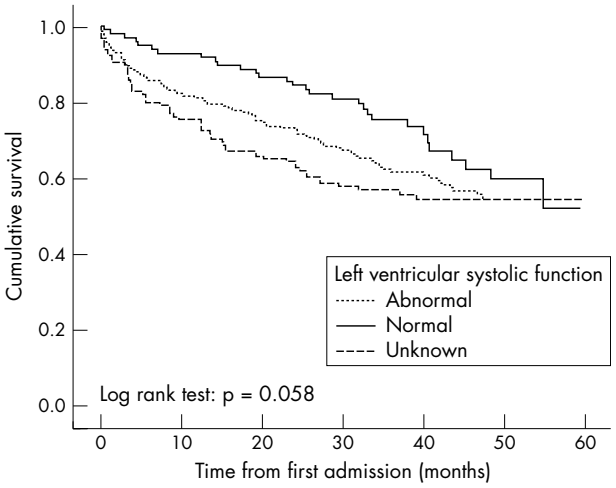

Figure 2 Kaplan-Meier survival estimates stratified by left ventricular systolic function where known (survivors of index admission only).

Table 5 Echocardiography details

	All	White	South Asian	p Value
Echocardiography performed	364 (69%)	244 (69%)	120 (68%)	0.790
Before admission	51 (14%)	38 (16%)	13 (11%)	0.221
During admission	183 (50%)	131 (54%)	52 (40%)	0.063
After admission	130 (36%)	75 (31%)	55 (46%)	0.005
Normal LV function	102 (28%)	56 (23%)	46 (38%)	0.002
Mild LVSD	85 (23%)	60 (25%)	25 (21%)	0.426
Moderate LVSD	87 (24%)	59 (24%)	28 (23%)	0.859
Severe LVSD	90 (25%)	69 (28%)	21 (18%)	0.025

LV, left ventricular; LVSD, left ventricular systolic dysfunction.

Strengths and limitations of study

This study examined the largest cohort of South Asian patients for whom the hospital discharge diagnosis of heart failure has been verified and for whom clinical information and outcome data are available. The number of patients is large and proportion of events high. Unlike our previous study[8] this report has the advantage of careful verification of the admission diagnosis and prior medical history through review of hospital records.

While we may have missed cases of heart failure that were not coded as such, this is unlikely to have introduced systematic bias. A significant number of hospital records were not available and a proportion of patients included had not undergone important investigations such as echocardiography. While some data were incomplete, these were split proportionately between cohorts. Moreover, the demographic features of South Asian patients were included and those for whom case records were not available were very similar demographically.

Patient management

Sixty nine per cent of our cohort had undergone echocardiography, a figure similar to that reported from the EuroHeart failure survey 2000 to 2001.[11] The poorer prognosis for patients with impaired LV function is in keeping with the results of EuroHeart failure.[11] However, among patients discharged alive from the index admission, mortality was highest for patients without documented echocardiographic examination. Perceived futility, death before the investigation, and co-morbidity may all contribute. In this regard the nature of the care of these patients with regard to the specialty of the hospital unit and physician merit further study.

The rates of use of diuretic (75%) and antagonists of the renin–angiotensin system (60%) at discharge are similar to those reported in EuroHeart failure (87% and 62%, respectively).[12] The relatively low rates of prescription of β blockers likely reflect the time period of this study and the difficulties of using these agents in standard CHF populations.

Prognosis of heart failure

We studied relatively young patients age matched to the average of 69 years in the South Asian cohort, younger than the average of 78 years for white patients in our previous report.[8] Very few of our cohort had a history of heart failure. Nevertheless, case fatality at one year was 27%. This can be compared with the one year case fatality of less than 10% in the recent CHARM (candesartan in heart failure assessment of reduction in mortality and morbidity) trial.[13] Indeed our observed mortality rate compares closely with that seen in recent trials in advanced heart failure.[14] The significance of this is clear: even at the point of first hospitalisation, the prognosis for heart failure is very poor.

As in non-white populations the risk factor profiles differed between ethnic groups.[15] However, the markers of poor prognosis appear to be very similar for South Asian and white patients. As expected, increasing age, lower systolic blood pressure, and renal impairment were associated with higher case fatality rate. However, we also observed that ethnicity itself, plasma glucose, and anaemia influenced prognosis.

Heart failure: influence of ethnicity

We previously observed that at the time of first hospital admission for heart failure, South Asian patients are younger than their white counterparts.[8] Findings were similar in a separate study of a small number (n = 31) of Indo-Asian patients.[16] For both studies it was suggested that better survival may be the result of younger age in the South Asian patients.[10 16] Some observations suggest that the better prognosis for South Asian patients more likely reflects less advanced heart failure. Normal LV systolic function was recorded for 38% of South Asians and 23% of white patients. When preserved LV systolic function was defined more broadly[17] (normal or mildly reduced function), this proportion remained higher in South Asians (59%) than in whites (48%). Severe LV systolic dysfunction was less prevalent and surrogate indicators of disease severity suggest less advanced disease among South Asians: symptom duration of less than 24 hours was more common, mean QRS duration shorter, and loop diuretic use at admission less prevalent.

Small UK studies suggested that CHD may be treated less aggressively in South Asians.[18 19] Recent UK prospective studies indicate a higher use of cardiac procedures among South Asians, even allowing for co-morbidity.[20] Our observations suggest that in the UK South Asian patients access secondary health care earlier in the course of CHF than do white patients, as seen with angina.[21] Such a phenomenon may contribute to better survival. Alternatively, or additionally, survival for South Asians may be due to greater prevalence of heart failure with preserved systolic function. The prevalence of hypertension and diabetes among South Asians and the echocardiographic data are in keeping with this. However, our findings were not biased by better survival of South Asian patients with preserved LV function. Rather, survival was better for South Asian patients with ''moderate'' LV systolic dysfunction on echocardiography. This is likely to reflect the inaccuracy of echocardiographic assessment of LV function and the relative poverty of echocardiography as a prognostic marker.

South Asians were taking both angiotensin converting enzyme inhibitor and β blocker more commonly at presentation. Whether early use of these agents in stable coronary disease results in benefit is controversial; some studies showed benefit[22] but others failed to do so.[23] Our data are compatible with the possibility of disease modification by pharmacological treatments known to improve outcome in heart failure.

Glucose and haemoglobin

Our data indicate for the first time that haemoglobin measured at the first hospital admission is a predictor of mortality in an unselected CHF population. Of note is the predictive independence of haemoglobin and creatinine, suggesting anaemia in heart failure to be more than a manifestation of renal impairment, also in keeping with previous studies.[24]

Applying the World Health Organization criteria of anaemia, haemoglobin < 130 g/l in men and < 120 g/l in women, we observed surprisingly high rates of anaemia of 37% among men in each cohort and 43% among women (52% of South Asian and 38% of white women). In a subset of the RENAISSANCE (randomized etanercept North American strategy to study antagonism of cytokines) trial population, haemoglobin $\leqslant 120$ g/l was seen in only 12% of patients but was associated with poor outcome.[25] Dietary habits and haemoglobinopathies are likely to contribute to anaemia in South Asians. In white patients, anaemia is likely due to other causes, possibly as a consequence of more advanced heart failure.

Our observation of plasma glucose at admission as a marker of poor outcome in heart failure is, to our knowledge, novel. Diabetes is a risk factor for the development of heart failure[26] and confers worse prognosis once heart failure is established.[27] Increased glucose concentrations are associated with increased short term mortality in non-diabetic patients sustaining an ischaemic stroke[28] or acute coronary syndromes.[29] Other studies have suggested this association to

apply irrespective of diabetic status.[30] A previous study of non-diabetic patients with CHF observed no association of random blood glucose concentrations with mortality.[31]

The reasons for the less powerful prognostic value of glucose in diabetics in our study are unclear. The degree of hyperglycaemia may be blunted in diabetic patients receiving antihyperglycaemic treatment. Our observations pertain to glucose concentration rather than diabetic status, which are hampered in our cohort by the lack of standard assessment of glucose tolerance. The correction of anaemia in heart failure may improve prognosis[32] and randomised clinical trials of the benefit of correction of anaemia are in progress. Studies of the aggressive control of blood glucose in CHF may be appropriate.

Conclusions

After the first hospital admission with heart failure, survival is better for South Asian than for white patients. The predictors of adverse prognosis are similar in South Asian and white patients. At the time of first admission to hospital South Asian patients are more likely to have preserved LV systolic function and less likely to have advanced heart failure than their white counterparts. Admission concentrations of glucose and haemoglobin provide useful prognostic information in patients hospitalised with heart failure.

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Improving long-term outcomes following coronary artery bypass graft or percutaneous coronary revascularisation: results from a large, population-based cohort with first intervention 1995–2004

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ABSTRACT

Objective: To describe recent trends in outcome after first coronary revascularisation in routine clinical practice, with a focus on the influence of co-morbidity, demographics and ethnicity.

Design: Historical cohort study.

Setting: Leicestershire, UK (resident population 946 000).

Patients: All consecutive patients (n = 6068) after first-ever coronary revascularisation by coronary artery bypass graft surgery (CABG, n = 2520) or percutaneous coronary intervention (PCI, n = 3548) in the period between 1995–6 and 2003–4.

Outcome measures: Mortality (all-cause and cardiovascular), repeat revascularisation, unplanned readmission, acute myocardial infarction (MI), stroke and the combination of these outcomes.

Results: Among inpatients undergoing their first revascularisation, hospital co-morbidity increased significantly between 1995–6 and 2003–4. In contrast, operative outcomes improved, particularly among the PCI patients experiencing a two-year event-free survival of 83% in the latter period (2001–4), compared to just 73% in the earlier period (1995–8). After statistical adjustment for the temporal increase in preoperative co-morbidity and changing patient demographics, the rates of all-cause and cardiovascular mortality were similar after PCI when compared to CABG, generally less than 5% in the first two years following the index procedure. However, the risk of further revascularisation was much higher (10-fold) with index PCI. The adjusted risk for the need for further procedure was lower after PCI with a coronary stent (HR 0.61, 95% CI 0.49 to 0.74), compared to without, a coronary stent. Except for the risk of readmission, outcome was independent of patients' ethnicity, and for women the risk of death was lower (HR 0.73, 95% CI 0.61 to 0.87).

Conclusions: On a background of increasingly complex preoperative profile, outcomes after first coronary revascularisation procedure seem to have improved in routine clinical practice since the 1990s, and compare well to those seen in clinical trials. In contemporary, routine clinical practice survival is very similar after CABG or PCI, but rate of further revascularisation procedure remains much higher after PCI, despite increasing use of coronary stenting.

Obstructive coronary artery disease may be addressed by coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI). Together, CABG and PCI are among the most common procedural interventions in industrialised society. While CABG is associated with early morbidity and mortality, PCI is less invasive but is less likely to achieve complete revascularisation and more likely to be followed by the need for further intervention.[1]

Clinical outcomes have been assessed in several trials comparing PCI with CABG in patients with similar coronary artery pathology.[2] Such trials usually include selected populations and capture relatively few end points and with short follow up. Indeed, it has been suggested that rapid advances in revascularisation technology may preclude the setting up of appropriately sized or longer term studies.[2] Recent developments in operative technology include coronary artery stenting, which is proved to reduce restenosis and the need for further coronary intervention. However, the effect of stenting on the overall mortality and myocardial infarction is less clear.[3]

Coronary heart disease (CHD) and revascularisation are common, and adverse events following these procedures are potentially serious. Thus, the evaluation of outcomes after CABG or PCI is an important public health issue. Such assessment must include population based outcomes using routine data, enabling monitoring of temporal trends in procedure rates, outcomes and adverse events. Routine sources have important limitations, such as inaccuracy, incomplete coverage or lack of reliable information on potentially important modifying factors such as disease severity or details of clinical management. However, they do have the undoubted advantage of capturing relatively unbiased information on timing of procedures and main clinical outcomes in a totality of the population, managed in standard clinical practice and followed over long periods of time.

OBJECTIVES

The two main aims of this study were:

a. To investigate trends in clinical outcomes following first coronary revascularisation procedure undertaken in a contemporary period, 1995–6 to 2003–4
b. To assess the impact of major co-morbid conditions on outcome of revascularisation.

METHODS

Study population

The setting was the population of Leicestershire, with a resident population estimated at 946 000 in

Table 1 Baseline characteristics of 6068 patients undergoing index revascularisation

Variable	CABG (n = 2520) (%)	PCI (n = 3548) (%)	p Value*
Age (years)			
<45	51 (2.0)	173 (4.9)	
45 64	1065 (42.3)	1823 (51.4)	
65 74	1150 (45.6)	1228 (34.6)	
75 84	245 (9.7)	297 (8.4)	
85+	9 (0.4)	27 (0.8)	<0.001
Sex			
Men	1990 (79.0)	2631 (74.2)	
Women	530 (21.0)	917 (25.8)	<0.001
Social deprivation			
Q1 (deprived)	498 (19.8)	680 (19.2)	
Q2	519 (20.6)	718 (20.2)	
Q3	520 (20.6)	703 (19.8)	
Q4	526 (20.9)	741 (20.9)	
Q5 (affluent)	457 (18.1)	706 (19.9)	0.409
Ethnicity			
White	2152 (85.4)	3055 (86.1)	
South Asian	301 (11.9)	359 (10.1)	
Black	9 (0.4)	15 (0.4)	
Other	41 (1.6)	64 (1.8)	
Unknown	17 (0.7)	55 (1.6)	0.248
Year of surgery†			
1995 6	217 (47.3)	242 (52.7)	
1996 7	285 (46.8)	324 (53.2)	
1997 8	300 (52.7)	269 (47.3)	
1998 9	282 (51.2)	269 (48.8)	
1999 2000	297 (42.1)	408 (57.9)	
2000 1	299 (42.8)	399 (57.2)	
2001 2	277 (37.0)	471 (63.0)	
2002 3	249 (29.5)	596 (70.5)	
2003 4	314 (35.5)	570 (64.5)	<0.001
Type of admission			
Elective	1905 (75.6)	2049 (57.8)	
Emergency	450 (17.9)	1145 (32.3)	
Other	165 (6.5)	354 (10.0)	<0.001
Gross co morbidity			
No admissions	863 (34.2)	1646 (46.4)	
<7 days per year	1002 (39.8)	1268 (35.7)	
7+ days per year	655 (26.0)	634 (17.9)	<0.001
Co morbidity			
Heart failure			
Prior	210 (8.3)	162 (4.6)	<0.001
Concomitant	133 (5.3)	155 (4.4)	<0.001
Renal failure			
Prior	42 (1.7)	57 (1.6)	0.94
Concomitant	43 (1.7)	42 (1.2)	0.11
Acute MI‡			
>90 days	415 (16.5)	418 (11.8)	<0.001
⩽90 days	208 (8.3)	398 (11.2)	<0.001
Diabetes			
Prior/concomitant	537 (21.3)	566 (16.0)	<0.001
Stroke			
Prior	61 (2.4)	66 (1.9)	0.16
Concomitant	173 (6.9)	49 (1.4)	<0.001
Angina			
Prior	195 (7.7)	237 (6.7)	0.13
Concomitant	2143 (85.0)	2673 (75.3)	<0.001
Arrhythmia			
Prior	202 (8.0)	196 (5.5)	<0.001
Concomitant	408 (16.2)	442 (12.5)	<0.001
Liver disease			
Prior	33 (1.3)	6 (0.2)	<0.001
Concomitant	3 (0.1)	3 (0.1)	0.99
Chronic lung disease			
Prior	56 (2.2)	110 (3.1)	0.047
Concomitant	191 (7.6)	196 (5.5)	<0.001
Cancer			
Prior	38 (1.5)	67 (1.9)	0.31
Concomitant	22 (0.9)	24 (0.7)	0.47

*Statistical difference between CABG and PCI, χ^2 or χ^2 for trend.
†Values are number (%), percentage of total procedures in all years, except for year of surgery where percentage of total procedures in a given year.
‡For acute MI, prior defined as >90 days before revascularisation, concomitant ⩽90 days before; for all other conditions concomitant defined as within three days of admission for revascularisation.
CABG, coronary artery bypass graft surgery; MI, myocardial infarction; PCI, percutaneous coronary intervention.

2004[4]). It has a higher than average proportion of South Asian minority (11% compared with 4% in England and Wales in 2001), but the overall CHD incidence and cardiovascular mortality have been historically very similar to the national rates. Thus, observations in this population are likely to be representative of those in the UK population.

We used hospital inpatient data, record linked to mortality records and to the local primary care population register as described previously.[5] Included were all patients resident in Leicestershire at the time of, and for at least three years before, their first coronary revascularisation carried out between April 1995 and March 2004, classified as CABG (OPCS 9: K40 K44) or PCI (K49 K50) procedures without and with (an additional code of Y02.1 or Y20.2) the use of coronary artery stent.

We analysed all hospital inpatient episodes within the three years before the index revascularisation, to record any acute myocardial infarction (MI) (ICD10: I21 22), arrhythmia (I44 49), cerebrovascular disease (I60 69), diabetes (E10 14), renal failure (N17 19), heart failure (I50), angina (I20), liver disease (K70 77), chronic lower respiratory disease (J40 47) or cancer (C00 99). These conditions were classified as concomitant (within the same spell of treatment as the index revascularisation) or prior (at any other time in the preceding three years). In addition, we assessed a summary measure of hospital co morbidity, defined as average annual length of hospitalisation for any cause in each of the three years preceding index revascularisation: patients were stratified into categories with (a) no overnight hospital stays, (b) less than seven days or (c) seven days or more. To avoid bias in ascertainment of the impact of co morbidities, we excluded from the analysis all patients for whom residence within Leicestershire in the preceding three years could not be confirmed. Patients were followed up to the end of December 2004, allowing a minimum follow up of nine months.

Recorded variables relating to index procedure included the mode of admission, patient age, gender, social deprivation (Index of Deprivation 2004[6] based on postcode of domicile), ethnicity and co morbidity as described above. Subsequent cardiovascular and non cardiovascular mortality (Office for National Statistics), hospital readmissions and repeat revascularisation procedures were identified through record linkage.

Statistical analysis

Baseline characteristics of patients were evaluated using goodness of fit χ^2 test and χ^2 test for trend. Outcome measures

Table 2 Trends in baseline co-morbidity (except for the annual totals and p values, all values are percentages)

	CABG				PCI			
	1895 7*	1998 2000	2001 3	p Value†	1995 7	1998 2000	2001 3	p Value†
Total number	802	878	840		835	1076	1637	
Demographics								
Age ⩾70 years	28.7	31.9	41.2	<0.001	23.2	25.9	28.6	0.005
Female sex	18.6	21.5	22.9	0.033	28.1	25.0	25.2	0.12
Heart failure								
History	7.5	8.2	9.3	0.21	4.6	4.8	4.4	0.92
Concomitant	3.5	5.9	6.3	0.009	2.6	2.7	3.9	0.11
Renal failure								
History	2.1	1.6	1.3	0.25	2.3	0.8	1.8	0.44
Concomitant	2.1	1.5	1.5	0.46	0.7	1.1	1.5	0.12
Acute MI								
History	16.3	17.2	15.8	0.79	9.0	12.7	12.6	0.007
Concomitant	1.6	2.8	4.2	0.003	26.0	14.9	18.8	<0.001
Diabetes	15.6	22.0	26.1	<0.001	12.9	13.7	19.0	<0.001
Stroke								
History	2.0	2.1	3.2	0.13	1.4	1.7	2.2	0.22
Concomitant	3.7	6.8	9.9	<0.001	1.1	1.3	1.6	0.37
Angina								
History	5.2	6.4	11.5	<0.001	5.5	6.7	7.3	0.11
Concomitant	89.8	87.1	78.3	<0.001	66.0	77.3	78.8	<0.001
Arrhythmia								
History	8.7	7.1	8.3	0.79	2.6	4.8	7.5	<0.001
Concomitant	6.2	18.9	22.9	<0.001	9.2	11.0	15.1	<0.001
Liver disease								
History	0.0	0.1	3.8	<0.001	0.4	0.2	0.1	0.12
Concomitant	0.0	0.2	0.1	1.00	0.0	0.1	0.1	0.55
Chronic lung disease								
History	2.6	1.9	2.1	0.63	2.4	2.4	3.9	0.06
Concomitant	7.9	7.7	7.1	0.64	3.8	5.3	6.5	0.006
Neoplasm								
History	0.9	1.5	2.1	0.043	1.6	1.6	2.3	0.29
Concomitant	1.1	0.7	0.8	0.62	0.5	0.7	0.8	0.45

*1995 7, April 1995 to March 1998; 1998 2000, April 1998 to March 2001; 2001 3, April 2001 to March 2004.
†Two sided Fisher's exact test for difference between proportions in 1995 7 and 2001 3.
CABG, coronary artery bypass graft surgery; MI, myocardial infarction; PCI, percutaneous coronary intervention.

included all cause and cardiovascular mortality, and survival to individual major adverse outcomes, including hospitalisation for acute MI, stroke, further coronary revascularisation, or the combination of major adverse cardiovascular/cerebrovascular events (MACCE: MI, further revascularisation, stroke or cardiovascular death). The relations between the variables and outcome measures were first explored using univariate meth ods. Multivariate models (using Cox proportional hazards) were developed to explore the relation between survival rates and underlying variables, in particular patient demographics and co morbid conditions. Multivariate models were evaluated for each end point and tested for proportional hazards assumptions using partial residuals and for potential interactions between all significant pre existing risk factors namely, age, ethnicity and co morbidities.

Differences between CABG and PCI cohorts in the relative prevalence of individual co morbid conditions, between the earlier (April 1995 to March 1998) and later (April 2001 to March 2004) study period were examined using Fisher's exact test. All statistical analyses were carried out using SPSS version 12.

RESULTS

Patient characteristics and temporal trends in revascularisation

From 1 April 1995 to 31 March 2004, a total of 6365 first revascularisation procedures were recorded. For 5% of these (n = 286), local residency of patients over the preceding three years could not be established, thus the final analysis included 6068 patients (table 1). The maximum follow up was 121 months with a median of 47 months (interquartile range 25 75). On average, patients undergoing PCI were younger (median 63 years, interquartile range 55 70) than those having CABG (66 years, interquartile range 59 72). Nearly 57% of first PCI procedures were performed under the age of 65 years, compared to 44% of CABG.

There were no meaningful differences in terms of social deprivation or ethnicity between patients undergoing CABG or PCI, but noticeable difference in case mix (table 1). As can be expected of an older population, patients undergoing CABG had greater gross co morbidity; 34% had no hospital admissions in previous three years, compared to 46% for PCI. Specific co morbidity rates were also higher among CABG patients, with the exception of concomitant MI, which was more prevalent in PCI. A higher proportion of PCI procedures occurred in the context of emergency hospitalisation.

The total number of procedures carried out annually nearly doubled between 1995 6 and 2003 4, largely a consequence of increase in PCI numbers. As a proportion of all PCI procedures, stent usage increased from 0.4% in 1995 6 to 46% in 1997 8, 87% in 2001 2 and reaching 88% (n = 503) in 2003 4, constituting around 60% of all first revascularisations in more recent years.

Table 3 Outcomes following index revascularisation: survival estimates after index CABG or PCI

	CABG (n = 2520)		PCI (n = 3548)	
	Adjusted (95% CI)*	Crude (95% CI)†	Adjusted (95% CI)*	Crude (95% CI)†
All cause mortality:				
30 days	99.1% (98.7% to 99.5%)	97.6% (97.0 to 98.2%)	99.0% (98.6% to 99.4%)	98.2% (97.8% to 98.6%)
1 year	97.2% (96.6% to 97.8%)	95.1% (94.2% to 96.0%)	97.2% (96.6% to 97.8%)	95.6% (94.9% to 96.3%)
2 years	96.0% (95.2% to 96.8%)	93.1% (92.1% to 94.1%)	95.0% (94.2% to 95.8%)	93.9% (93.1% to 94.7%)
Hazard ratio (95% CI):			1.09 (0.92% to 1.28)	0.92 (0.79% to 1.06)
Cardiovascular mortality:				
30 days	99.2% (98.8% to 99.6%)	97.7% (97.1% to 98.3%)	99.0% (98.6% to 99.4%)	98.3% (97.9% to 98.7%)
1 year	98.1% (97.5% to 98.7%)	95.9% (95.1% to 96.7%)	98.2% (97.8% to 98.6%)	96.6% (96.0% to 97.2%)
2 years	97.1% (96.5% to 97.7%)	94.6% (93.7% to 95.5%)	97.1% (96.5% to 97.7%)	95.5% (94.8% to 96.2%)
Hazard ratio (95% CI):			0.93 (0.76% to 1.13)	0.83 (0.69% to 0.98)
Readmission:				
30 days	88.4% (87.2% to 89.6%)	88.2% (86.9% to 89.5%)	90.4% (89.4% to 91.4%)	91.5% (90.6% to 92.4%)
1 year	73.9% (72.1% to 75.7%)	72.4% (70.6% to 74.2%)	69.9% (68.3% to 71.5%)	71.5% (70.0% to 73.0%)
2 years	66.4% (64.4% to 68.4%)	64.7% (62.7% to 66.7%)	61.2% (59.4% to 63.0%)	63.4% (61.7% to 65.1%)
Hazard ratio (95% CI):			1.12 (1.12% to 1.32)	1.05 (0.97% to 1.13)
Repeat revascularisation procedure:				
30 days	98.1% (97.7% to 98.5%)	99.9% (99.8% to 100.0%)	97.4% (96.8% to 98.0%)	99.2% (98.9% to 99.5%)
1 year	95.6% (94.8% to 96.4%)	99.0% (98.6% to 99.4%)	84.5% (83.3% to 85.7%)	88.3% (87.2% to 89.4%)
2 years	93.8% (92.8% to 94.8%)	98.7% (98.3% to 99.1%)	79.0% (77.6% to 80.4%)	83.9% (82.7% to 85.1%)
Hazard ratio (95% CI):			10.56 (8.20% to 13.60)	8.50 (6.67% to 10.88)
MACCE				
30 days	97.9% (97.3% to 98.5%)	97.3% (96.7% to 97.9%)	96.7% (96.1% to 97.3%)	96.6% (96.0% to 97.2%)
1 year	95.0% (94.2% to 95.8%)	93.8% (92.9% to 94.7%)	83.6% (82.4% to 84.8%)	83.5% (82.3% to 84.7%)
2 years	93.0% (92.0% to 94.0%)	91.2% (90.1% to 92.3%)	78.4% (77.0% to 79.8%)	78.4% (77.0% to 79.8%)
Hazard ratio (95% CI):			2.67 (2.35% to 3.03)	2.20 (1.90% to 2.40)

*Adjusted survival and hazard ratio estimates (demographics, year, co morbidities, deprivation and type of admission).
†Unadjusted cumulative survival estimated using Kaplan Meier method.
CABG, coronary artery bypass graft surgery; MACCE, cardiovascular mortality, non fatal MI, stroke or repeat procedure; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Main risk factors and co-morbidity

Table 2 shows changes in recorded risk factors in patients undergoing index revascularisation procedure in three year periods between April 1995 and March 2004. In the more recent period of the study, there were significantly more patients over 70 years of age undergoing CABG surgery, those with concomitant heart failure, acute MI, diabetes, stroke, arrhythmia or history of angina, liver disease or cancer.

Patients undergoing PCI were also proportionately older in the last three years of the study, with increase in acute MI reported previously, arrhythmias or lung disease, but also with a significant fall in concomitant MI. The generally low rate of reporting of angina is of note; concomitant angina rose for PCI procedures and fell for CABG, for which the percentage of patients with the history went up significantly. According to hospital records, over 13% (n = 820) of patients apparently had no angina on admission or in the preceding years; however, a large proportion of these had a history of acute MI (n = 541, 9%), leaving only a small fraction of patients (4%) without any record of angina or acute coronary event.

Outcomes

During the follow up, a total of 773 (12.7%) patients died. Sixteen per cent (n = 124) of all deaths occurred within 30 days of the index revascularisation and nearly 50% within two years.

Table 3 shows the adjusted and crude survival estimates following the first coronary revascularisation, obtained from Cox models at one month, one year and two years after the procedure. Patterns of mortality were broadly similar after CABG and PCI, with one year, all cause mortality of less than 5% in both groups. In crude terms, there were no substantial differences between cohorts in rates of unplanned re hospitalisation after the initial

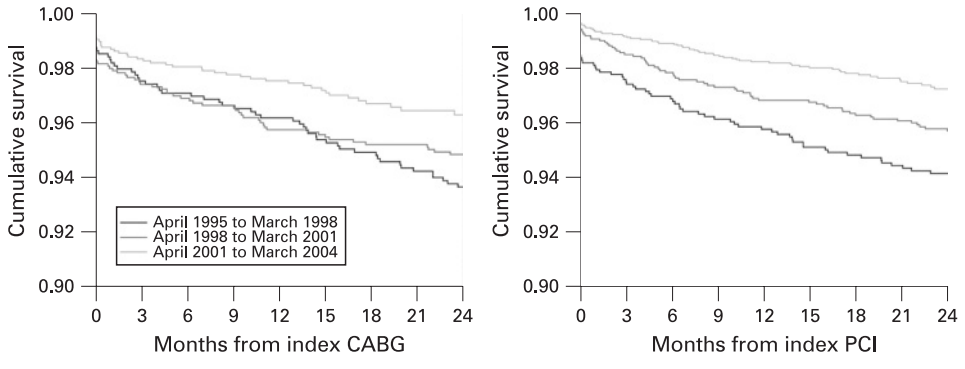

Figure 1 Survival curves for all-cause mortality following index coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI), adjusted for patient demographics and co-morbidities in a Cox proportional hazards, stratified by three-year periods of the study.

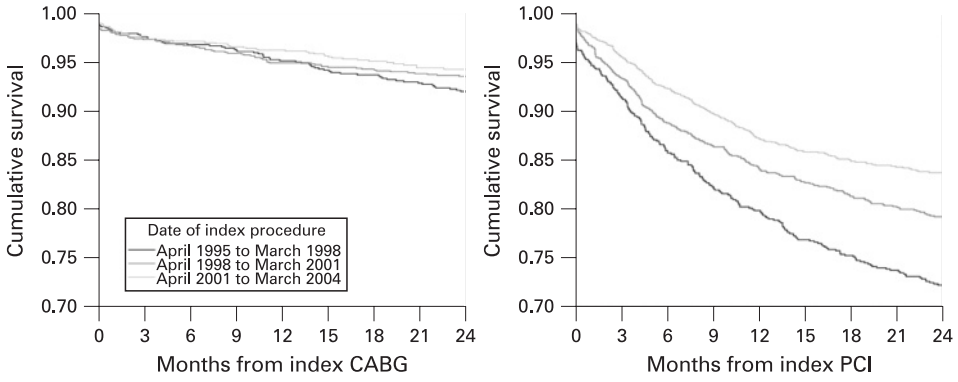

Figure 2 Adjusted survival free of any adverse cardiovascular/cerebrovascular event (MACCE) for coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) patients, stratified by three-year periods of the study.

30 day postoperative period. However, adjustment for covariates revealed a small but significant increase in risk of readmission following PCI. The likelihood of a further revascularisation procedure (77% of those were PCIs) was at least seven fold greater after index PCI, with a total of 71 (2.8%) patients undergoing a repeat procedure after index CABG, and 702 (19.8%) after PCI in our cohort, with adjusted procedure free survival significantly higher in the CABG group (94% compared with 79%). Overall, 93% of CABG patients were likely to remain without an adverse event after the index procedure, compared to just 78% after PCI.

Table 3 also shows the overall adjusted and unadjusted hazards ratios for all outcomes for PCI versus CABG. They indicate a nearly 11 fold increase in risk of repeat procedure after PCI, resulting in a nearly threefold increase in risk of MACCE.

Figure 1 shows adjusted survival curves for patients undergoing either a CABG or PCI as index procedure. Against a background of increasing co morbidity across the study periods, the absolute survival appears to have remained similar for CABG patients and improved after PCI. At 24 months after CABG, survival was 93.7% (95% CI 91.9% to 95.5%) in first three year period and 96.1% (95% CI 94.9% to 97.3%). The corresponding rates following a PCI were 94.0% (95% CI 92.4% to 95.6%) and 97.2% (95% CI 96.4% to 99.0%), showing a statistically significant difference between the periods of the study.

Figure 2 shows a comparison of the adjusted cumulative MACCE free survival in the three year intervals, for CABG and

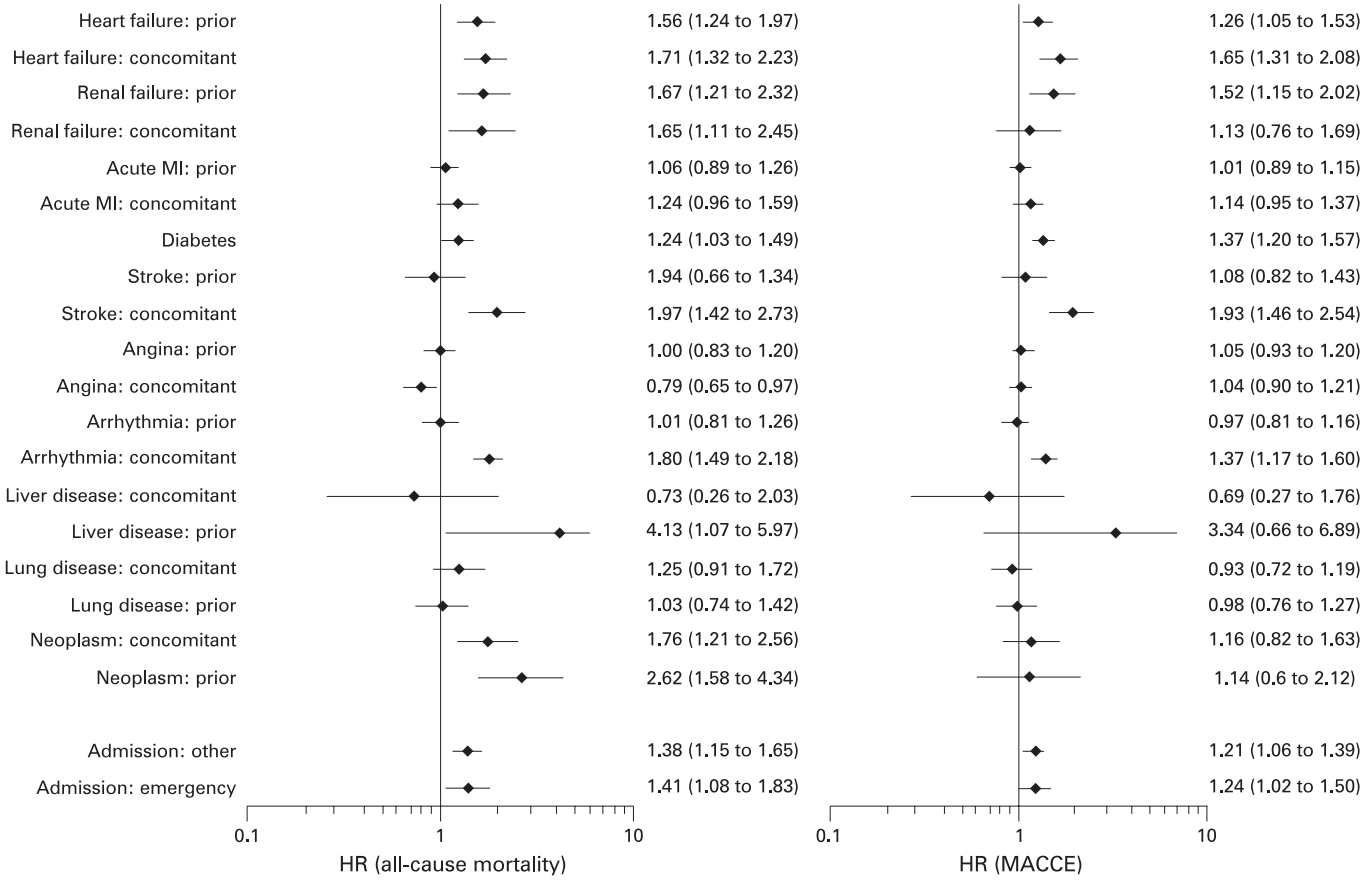

Figure 3 Hazard ratios (95% CI) for co-morbidities from multivariate Cox models for all-cause mortality and combined cardiovascular outcome (MACCE).

Table 4 Comparison of adverse outcomes after PCI with stent compared to PCI alone: risk estimate adjusted for age, gender, ethnicity, deprivation, year and type of admission, and comorbidity and unadjusted hazard ratios

	Number: stent/PTCA	Adjusted HR* (95% CI)	Crude HR (95% CI)
All cause mortality	178/237	0.73 (0.55 to 0.95)	0.60 (0.48 to 0.73)
Cardiovascular mortality	108/162	0.65 (0.46 to 0.92)	0.50 (0.38 to 0.64)
Acute MI	127/95	0.89 (0.61 to 1.30)	1.03 (0.77 to 1.38)
Readmission	1006/674	0.88 (0.77 to 1.00)	0.87 (0.78 to 0.96)
Repeat procedure	365/337	0.61 (0.49 to 0.74)	0.60 (0.51 to 0.70)
MACCE†	527/508	0.64 (0.54 to 0.76)	0.61 (0.53 to 0.69)

*Hazard ratio for PCI with stent compared to PCI alone.
†Defined as cardiovascular mortality, non fatal MI, stroke or repeat procedure.
HR, hazard ratio; MACCE, cardiovascular mortality, non fatal MI, stroke or repeat procedure; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

PCI patients. It is apparent that while a greater proportion of patients remained event free 24 months post CABG, a signifi cant improvement over time occurred after PCI, from 72.1% (95% CI 68.9% to 75.35%) in the first three year period to 83.6% (95% CI 81.6% to 85.6%) in the last three years of the study. There were no statistically significant differences in survival estimates following CABG in the 24 month following the procedure, between the three periods of the study.

Factors affecting survival

The results of multivariate modelling (see supplemental online table on *Heart* website) showed that for each decade of life, there was 75% increase in the risk of mortality, 13% increase in likelihood of readmission, but a reduction in the likelihood of repeat revascularisation. As a result, the risk of the combined outcome (MACCE) associated with greater age was moderate (8% per decade). Combined outcomes were also poorer in patients under going a non elective procedure (HR 1.23, 95% CI 1.06 to 1.39).

Women in our cohort had a lower risk of death (by 28%) and a slightly higher risk of readmission. South Asian patients had very similar outcomes to the white population, other than for a 23% increased risk of hospital readmission. There was no clear relation to social deprivation.

We found no statistically significant interaction between the variables in the model; notably there were no such interaction between the year of index procedure and individual demo graphic or co morbidity factors.

The risk of death (cardiovascular or other) was very similar after PCI or CABG. Although PCI procedures appeared to bear a threefold greater risk of MACCE (HR 2.7), this was mainly a result of an over 10 fold excess risk of further procedure and, to a lesser extent, of emergency hospitalisation (HR 1.21).

The excess risks related to individual co morbidities and type of admission are presented in figure 3. Co morbidity was generally correlated with adverse outcome, but for individual conditions patterns were variable. Diabetes was associated with increased risk for all measured outcomes, including further revascularisation. Heart failure and renal failure were both associated primarily with greater mortality; concomitant angina was linked to lower risk of all cause and cardiovascular mortality but also to greater risk of further revascularisation. The powerful, adverse effects on survival of concomitant stroke or liver disease were also clear.

Impact of stenting

We compared outcome in patients receiving PCI with or without stent procedure. Results were adjusted for major cofactors, including year of the procedure (table 4). When compared to PCI, the risk of repeat procedure (HR 0.61, $p<0.001$), all cause or cardiovascular mortality (HR 0.73 and 0.65 respectively, $p = 0.02$) and hospital readmission (HR 0.86, $p = 0.004$) were all lower with the use of stent, which was reflected in the overall lower risk of MACCE (HR 0.64, $p<0.001$). The risk of a non fatal MI following the procedure was similar in both intervention groups.

DISCUSSION

This report is the most contemporary population based assess ment of outcome trends after coronary revascularisation in standard clinical practice in the United Kingdom. Our study highlights a number of clinically relevant observations.

Most important is the clear improvement during the study period in outcome for patients undergoing PCI on a background of a substantially greater burden of reported co morbidity and a marked increase in overall PCI intervention rate, in response to published reports of their effectiveness.[7 8] Clinical outcomes were similar after PCI or CABG with the exception of further revascularisation, which was 10 times more common after index PCI.

Coronary artery revascularisation is one of the most common interventional procedures carried out in industrialised society. In the context of increasing public awareness of coronary heart disease, and the introduction of national guidelines, population rates of coronary revascularisation have increased over recent years, and continue to do so.[9] Both PCI and CABG require appropriate facilities and highly skilled operators, and are associated with potentially serious adverse outcomes. With this background, it is important to assess clinical outcomes and their temporal trends in standard clinical practice.

Outcomes

The observed one year mortality of 4.4% and 4.9% after PCI and CABG, respectively, should be considered in the context of previous clinical trials and population based reports. Despite their methodological superiority, clinical trials recruit highly selected populations, often with limited follow up and small numbers of observed end points. This is exemplified by a recent meta analysis,[1] which although reporting no statistical differ ence in one year mortality between PCI (with stent) and CABG (0.8% and 2.4%, respectively), did so on the basis of only 75 deaths. An earlier meta analysis, covering a period largely predating the stent usage, indicated one year case fatality of 2.9% and 4.4% after PCI and CABG, respectively.[10] In the context of routine practice, registry based reports may be more informative, including a large Scottish cohort,[11] where one year case fatality was 1.5% after PCI and 4.4% after CABG.

However, exclusion in that report of emergency revascularisation and interventions on left main stem coronary artery stenosis, likely to account for some 25% of all procedures, reduces its applicability in the assessment of routine outcomes and outcome trends.

However, it is reassuring that in our more contemporary but unselected cohort, survival was broadly comparable to that in clinical trial populations, or after elective revascularisation in registry patients. In addition, we observed favourable trends in survival after revascularisation, with significant reduction in risk of death over the period of the study, both for CABG and PCI.

It has been suggested recently that improving temporal trends in survival after coronary revascularisation may be a consequence of improved surgical practice resulting from the publication of hospital specific and surgeon specific outcome data.[12] The previous study suggested a cut off of 2001, coinciding with time of data publication and public disclosure, as the time at which clinical improvements were first evident. Our results indicate that improving outcomes for all revascularisations were evident before 2001. Moreover, outcomes other than mortality have also shown significant improvement. Our data call into question the relevance of performance data to improvements in outcome after CABG or PCI.

Previous reports indicated fivefold[1] to 10 fold[9 11 13] excess requirement for further revascularisation after PCI compared to CABG. As recently as 1997–9, a 17 fold excess was evident after elective or emergency index procedures within the Scottish registry database.[11] In our cohort, PCI was more than 10 times more likely than CABG (11% compared with 1% within a year) to be followed by further revascularisation.

Our findings regarding improving outcome are reassuring and important in routine practice. Griffin *et al*[14] reported recently that, based on routinely collected data in 1996–7, PCI may be a less cost effective option for many patients, when compared to CABG, primarily because of the rate of repeat procedures. Our study indicates that the following years in routine practice, significantly fewer patients underwent repeat revascularisation after index PCI. Procedural advances, including the increasing use of internal mammary artery conduits and more aggressive secondary prevention are likely to have contributed to improved clinical outcomes and have implications for individual patients and for healthcare planning.

Predictors of outcome and trends over time

The improvements in clinical outcomes over the decade of our study occurred in a background of increasing acute and chronic co morbidity. For patients undergoing CABG this is in keeping with data from Scotland,[11] UK national data[15] and with reports from Canada[16] and Australia.[17] Ferguson *et al*[18] estimated that operative risk in patients undergoing CABG increased in the order of 30% through the 1990s, and also reported concurrent improvement in outcome.

Our observations emphasise the impact of routine clinical factors on prognosis after PCI or CABG. Diabetes, heart failure, renal impairment and age were all associated with greater risk of all cause mortality. The phenomenon of competing risks is one likely contributor to the lower likelihood of repeat revascularisation in cases with higher risk of mortality.

Previous population based studies suggested small[19] or large[14 20] excess risk of adverse outcome in women. In contrast, we observed a lower risk of death, by nearly 30%, but slightly greater risk of emergency hospitalisation, among women. These results are in keeping with a recent population based study from the United States.[21] However, despite equality in outcome following surgery, the current lower rates of revascularisation in women may not reflect the true need for these procedures. Indeed, a recent Finnish study has shown that angina rates in women are similar to those in men and outcomes may well be worse.[22] Again, further studies are required to explore gender differences in CHD prevalence and outcomes.

Contrary to previous reports,[23 24] we did not find any clear relation between socioeconomic deprivation and outcome following coronary revascularisation, after adjusting for other risk factors. Possible sources of confounding, inherent in routine data, may include referral patterns favouring earlier intervention in patients from more deprived inner city areas, and unmeasured risk factors, such as hypercholesterolaemia or hypertension. However, the lack of association with deprivation, if true, is encouraging with regard to equity of health care outcome.

Robust comparative data for different ethnic groups are scarce. Racial disparities for CHD have been studied in the United States[25] but mainly for African American minorities. South Asian populations in the United Kingdom appear to have high CHD prevalence, through a variety of mechanisms including higher rates of insulin resistance.[26] We observed no excess in mortality outcomes for South Asian patients after coronary revascularisation, when compared to the native white population, but 23% higher hospital readmission rate.

Study limitations

There are inherent limitations due to the source of our data. We used routinely recorded information and had little information on the extent of coronary artery disease before index revascularisation or on the extent of left ventricular dysfunction. We were unable to capture data from the independent healthcare sector, possibly omitting some 10–20% of procedures[23]; it was also impossible to account for the improvements in stent technology or increasing arterial conduit usage in CABG, for example. Similarly, we recognise that improved outcomes in the face of apparent greater burden of co morbidity over time may reflect improvements in routine capture of such information in recent years. However, it is likely that changes in the recording of such information were similar for patients undergoing CABG or PCI, and are thus unlikely to influence the comparison of outcomes between the two procedures. We also recognise that our study is dependent upon accurate recording of routine discharge coding information. Such information has been shown to be over 90% accurate in our area. However, our study would be improved by data validation. All of these points simply emphasise the importance of accurate recording of data pertaining to those factors likely to impact upon outcome.

In spite of these limitations, our data demonstrate that when used appropriately, routine hospital data can give valid predictive models for outcome following surgery[27]; the observed operative outcomes are likely to be related closely to technical, pharmacological and procedural advances in revascularisation in the past decade.

CONCLUSIONS

Routine monitoring of postoperative outcomes is paramount in areas where clinical practice changes rapidly. Our results, based on a large cohort representative of the overall population undergoing revascularisation in the United Kingdom, show improving event free survival after PCI or CABG, and on a background of a worsening risk profile.

We highlight the importance of routine monitoring of health outcome in cardiac patients.

Our study, using routinely available population data, confirms the extension into routine clinical practice of the excellent clinical outcomes seen in clinical trials of coronary revascularisation. In the context of the difficulty in performing adequately sized clinical trials, outcomes in standard practice can be usefully and inexpensively monitored using routine data sources. These observations have profound clinical as well as economic implications, which merit a separate in depth analysis.

Competing interests: None.

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