Studies of the Epidemiology and Prognosis of Patients with Heart Failure in Leicestershire

Thesis submitted for the degree of Doctor of Medicine at the University of Leicester

By

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Declaration

The work presented in this thesis is my own and was carried out with the supervision of Dr Iain Squire, and financial support provided by the Leicester Nuffield Hospital and the Department of Cardiovascular Sciences at the University of Leicester.

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Abstract

Background

Heart failure (HF) is a major disease with high mortality despite many therapeutic options. Little is known on the epidemiology and prognosis of HF in Leicestershire, which includes a large proportion of South Asians.

Hypotheses

The epidemiology of heart failure in Leicestershire is different to that of published national and international cohorts. South Asians have more severe coronary disease compared to Caucasians, and will have more severe HF and increased mortality. Simple clinical data on admission can be used to predict survival.

Methods

Matched cohort design with retrospective data collection on 528 patients - 176 South Asians age and sex matched to 352 Caucasians admitted with a validated new diagnosis of HF between April 1998 and March 2001. Cox proportional hazards modelling to test variables associated with outcome and develop a prognostic model.

Results

The majority of HF is secondary to ischaemic heart disease or hypertension. Two-thirds of patients undergo echocardiography. Only 60% of patients are discharged with an ACE inhibitor, just 17% receive a beta blocker. 11% died during admission, and by the end of follow up 45% had died. South Asians have higher rates of hypertension and diabetes and present earlier with less severe impairment of systolic function. South Asians have lower mortality - odds ratio of 0.71 (95% CI 0.53 – 0.96, p=0.02) compared to Caucasians. A prognostic score based on five simple variables stratifies patients into low or high risk with a sensitivity 78% of and specificity of 57%.

Conclusion

The epidemiology of patients admitted with HF in Leicestershire is not significantly different to published cohorts. South Asian patients present with less severe ventricular dysfunction and survive for longer with no differences in the investigations or treatment given compared to Caucasians. A pragmatic risk prediction model using easily available clinical variables can identify high risk individuals.

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Publications and Presentations

This thesis has lead to the following publications and presentations at various scientific meetings:

1. Newton JD**,** Squire IB. Glucose and haemoglobin in the assessment of prognosis after first hospitalisation for heart failure. Heart, Oct 2006; 92: 1441 - 1446.

2. Newton JD, Squire IB, Blackledge HM. Ethnicity and variation in prognosis for patients newly hospitalised for heart failure: a matched historical cohort study. Heart, Dec 2005; 91: 1545 - 1550.

3. Newton JD, Squire IB. Multiple medical treatments for heart failure in the community: what is first-line, second-line and held in reserve? Journal of Practical Cardiovascular Risk Management, October 2003; 1: 12-15.

4. Blackledge HM, Newton JD, Squire IB. Prognosis in South Asian and white patients newly hospitalised with heart failure. British Medical Journal, Sep 2003; 327: 526 - 531.

Presented Abstracts

1. Newton JD, Squire IB. Clinical factors associated with the use of recommended therapy on discharge after a first admission with heart failure – British Cardiac Society 2005

2. Newton JD, Squire IB. Difference in risk factors for mortality between heart failure patients with and without diabetes mellitus – British Cardiac Society 2005

3. Newton JD**,** Squire IB. Elevated serum glucose as an independent risk factor for mortality in patients admitted to hospital with a new diagnosis of heart failure – British Cardiac Society 2005

4. Newton JD, Squire IB. Ethnicity and variation in prognosis for patients newly hospitalised for heart failure – British Cardiac Society 2005

5. Newton JD, Squire IB. Routine clinical variables associated with increased mortality following hospital admission with a new diagnosis of heart failure – British Cardiac Society 2005

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Abbreviations and Trial Acronyms

ACE	Angiotensin Converting Enzyme
AIRE	Acute Infarction Ramipril Efficacy study
ARB	Angiotensin Receptor Blocker
AUC	Area under the curve
BNP	Brain Natriuretic Peptide
CARE-HF	Cardiac Resynchronisation in Heart Failure study
CHARM	Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity programme
CHF	Chronic Heart Failure
CI	Confidence Interval
CIBIS	Cardiac Insufficiency Bisoprolol Study
CRT	Cardiac Resynchronisation Therapy
ECG	Electrocardiogram
GFR	Glomerular Filtration Rate
HFNEF	Heart Failure with Normal Ejection Fraction
MERIT	Metoprolol Randomized Intervention Trial in Congestive Heart Failure
NYHA	New York Heart Association
OPTIMIZE-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure
ROC	Receiver-operator characteristic
SOLVD	Studies of Left Ventricular Dysfunction
USA	United States of America
V-HEFT	Vasodilator Heart Failure Trial

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Chapter 1 - Epidemiology

1 – 1 Introduction

In order to provide data on the epidemiology, aetiology and treatment of patients admitted to hospitals in Leicester with heart failure it is vital to have knowledge of the relevant data in the wider heart failure population and an understanding of what constitutes optimal medical therapy. In this chapter I will discuss the current knowledge of the epidemiology, aetiology and diagnosis, framed around a relevant definition of heart failure, along with discussion on the burden of heart failure on the health care services and cost of treatments. This will then be followed by a review of the evidence for heart failure therapy, focussing principally on medical therapy. Following this review I will propose the hypothesis and subsequent research questions that this thesis aims to address.

1 – 2 Overview

Heart failure is an epidemic placing major burden on health care in Western Societies. In the general population the prevalence of symptomatic heart failure is around 0.4 – 2% (Swedberg, Cleland et al. 2005). This figure increases significantly with age, and up to 10% of elderly patients (over 75) have heart failure. Heart failure is a leading cause of morbidity and mortality and a common reason for hospital admission, and in contrast to other major cardiovascular disorders the age-adjusted mortality continues

to increase. Half of all patients diagnosed with heart failure will die within four years or within one year if they have severe heart failure. Overall health care expenditure on heart failure diagnosis and treatment is of the order of 1.5 to 2% of total expenditure in the United Kingdom (Malek 1999). Although there is emerging evidence that heart failure incidence has reached a plateau, successful treatment of myocardial infarction and increased survival from acute coronary syndromes are likely to lead to further increases, as will a rise in the prevalence of diabetes mellitus, obesity and hypertension. Furthermore the diagnosis and therapy of heart failure is becoming more complex and costly.

1 – 3 Definition

As the understanding of the patho-physiology of the syndrome of heart failure has evolved, so has its definition. It is challenging to develop a single definition which encompasses all possible clinical presentations and causes of heart failure. For the purposes of this thesis – based on clinical patients with a clinical diagnosis of heart failure – the definition provided by the European Society of Cardiology (Swedberg, Cleland et al. 2005) is used. The recently updated consensus statement defines chronic heart failure as:

'Symptoms of heart failure (at rest or during exercise) *and* objective evidence of cardiac dysfunction (systolic or diastolic) *and* response to treatment directed towards heart failure.'

The italicised operators (mine) emphasise the fact that it is difficult to diagnose heart failure on symptoms alone and further data on cardiac function along with definite improvement with heart failure therapy such as diuretics is required. There is clear evolution from a previous definition published in 1994 by the Agency for Health Care Policy and Research which stated: 'Heart failure is a clinical syndrome or condition characterized by (1) signs and symptoms of intravascular and interstitial volume overload, including shortness of breath, rales, and oedema, or (2) manifestations of inadequate tissue perfusion, such as fatigue or poor exercise tolerance. These signs and symptoms result when the heart is unable to generate a cardiac output sufficient to meet the body's demands' (Konstam, Dracup et al. 1995). This additional detail builds on an earlier definition by Braunwald in 1986 '…a patho-physiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues…'

As the understanding of the patho-physiology of heart failure has developed the definition has evolved. In the 1950s heart failure was considered to be a cardio-renal disease caused by renal hypoperfusion. An expanded haemodynamic model was developed in the 1970s to reflect the response of myocardium to altered dynamics and stress. Further research then led to the current neuro-hormonal model reflecting the importance of the sympathetic nervous system and renin-angiotensin-aldosterone axis (Pepper and Lee 1999). It is probable that the definition will further change as research into the disease process and new underlying abnormalities of cardiac function appear – current research is focussing on the potential links between

inflammation, oxidative stress and heart failure (Felker and Cotter 2006; Kotlyar, Vita et al. 2006).

It is usual to define the severity of heart failure using the classification system proposed by the New York Heart Association (NYHA), this is shown in Table 1.

Table 1: New York Heart Association Classification of Heart Failure Severity

Class I	Patients with documented heart disease of any type who are completely symptom free
Class II	Slight limitation of physical activity because symptoms (shortness of breath, chest pain) occur only with more than ordinary physical activity
Class III	Marked limitation of physical activity because symptoms occur even with ordinary physical activity (e.g., eating meals)
Class IV	Severe limitation of physical activity because symptoms occur even at rest (e.g., in a sitting or lying position)

1 – 4 Epidemiology

Worldwide population studies have provided clear data on the incidence and prevalence of heart failure in the general population, with longitudinal studies demonstrating a progressive increase in the incidence of new cases. This is due to the increasing age of the population as a whole and improved survival from acute coronary syndromes, along with enhanced surveillance and diagnosis.

The landmark Framingham cohort study provided the first robust data on the rates of heart failure in a general population. The incidence of heart failure in patients aged between 45 and 54 years was 1 case per 1000 patient years in women and twice that in men. This figure doubles with each decade reaching 8 to 10 cases per 1000 patient years in men over 80 years of age (McKee, Castelli et al. 1971). In the United Kingdom the prevalence of heart failure stands at 0.4 – 2.0% and leads to 120,000 hospital admissions per year – this represents around 5% of all acute admissions to medical services (Sutton 1990; Dargie and McMurray 1994). During the 1980s hospital admissions due to heart failure were increasing in the United States and the United Kingdom while the average length of hospital stays was decreasing in the same period (Ghali, Cooper et al. 1990; McMurray, McDonagh et al. 1993). More recent data from Scotland analysing more than 150,000 heart failure hospitalisations between 1990 and 1996 demonstrates that heart failure admissions peaked in 1993 and have since fallen (Stewart, MacIntyre et al. 2001). While this apparent success prompted relief that the expected epidemic was not developing, re-admission rates remain very high (Vinson, Rich et al. 1990) and there has been little appreciable fall in mortality despite new therapies being developed. High rates of re-admission are expected in a complex disease state such as heart failure, but may in part reflect inappropriately short hospital admissions. Care within a hospital is the most expensive proportion of all expenditure on heart failure management and yet also potentially the most preventable (McMurray and Davie 1996).

Recently published data from the United States studying a cohort of 2029 patients aged ≥ 45years demonstrates a prevalence of asymptomatic ventricular dysfunction in 34% of the cohort, of these 60% had diastolic dysfunction and 10% had systolic

dysfunction (Ammar, Jacobsen et al. 2007). The presence of left ventricular dysfunction – systolic or diastolic – is associated with eventual heart failure and predictive of all-cause mortality. With regards to the incidence of heart failure, 10 per 1000 population over 65 have heart failure and 75% of these have antecedent hypertension. The lifetime risk of developing heart failure for a patient aged 40 is 1 in 5 irrespective of sex, and this doubles for those with a blood pressure greater than 160/90 mmHg (Rosamond, Flegal et al. 2007).

1 – 5 Aetiology

The diagnosis of heart failure is never solitary – a search for the cause must always be undertaken in order that cause-specific treatment can be undertaken, as well as allowing identification of important co-morbid conditions that may influence treatment. Common causes of heart failure include myocardial dysfunction (systolic or diastolic) which may follow acute coronary syndromes or prolonged hypertension, valvular heart disease, arrhythmia, pericardial disease, anaemia, renal dysfunction and thyroid disease. Table 2 lists the common causes of heart failure with approximate prevalence. Details on the 5% listed as ‘other’ appear in Table 3.

Table 2: Common causes of heart failure (Baldasseroni, Opasich et al. 2002)

Aetiology	Prevalence	Examples
Coronary artery disease	40%	Myocardial infarction
Cardiomyopathy	32%	Idiopathic, alcoholic
Hypertension	11%	Chronic hypertension
Valvular dysfunction	12%	Aortic stenosis, mitral regurgitation
Other	5%	See table below

Table 3: Rare causes of heart failure (Felker, Thompson et al. 2000)

Aetiology	Prevalence	Examples
Idiopathic	50%	Dilated cardiomyopathy
Myocarditis	13%	Viral, Chagas disease, HIV
Infiltrative	5%	Sarcoidosis, Amyloidosis
Peripartum	4%	Peripartum cardiomyopathy
Connective tissue disease	3%	Sclerodema, Marfan's
Substance abuse	3%	Cocaine, alcohol
Toxicity	1%	Anthracycline, steroids
Pericardial disease	2%	Restrictive cardiomyopathy
Familial	2%	Familial cardiomyopathy
Nutritional	< 1%	Beri-Beri
Endocrine	< 1%	Acromegaly, thyroid disease
Other	16%	Congenital heart disease, critical illness, radiation, neuromuscular, post surgery

In Western societies the commonest aetiology is myocardial dysfunction secondary to coronary artery disease causing myocardial infarction, often with concomitant hypertension (Sutton 1990; Levy, Larson et al. 1996). Elucidating an exact cause may be challenging in elderly patients with less clear symptoms and signs and multiple potential confounding diagnoses such as pulmonary disease, anaemia and arthritis. Acute coronary events are common in heart failure and a cause of sudden death in at least 33% of patients treated for chronic heart failure (Uretsky, Thygesen et al. 2000). Why is a search for the underlying aetiology important? Given the poor prognosis once heart failure is established any potentially treatable and hopefully reversible cause may improve the outcome. Factors such as myocardial ischaemia, hypertension, progressive valvular disease, renal dysfunction and compliance with drug therapy are all modifiable and may influence prognosis considerably.

1 – 6 Diagnosis

As evident from the definition of heart failure explained previously, the diagnosis of heart failure requires integrations of data from the patients' symptoms, clinical signs, investigations to assess for cardiac dysfunction, and assessment of a response to heart failure therapy – typically diuretics. If a patient presents with symptoms of breathlessness on effort along with fatigue, with an obvious aetiology such as a recent myocardial infarction, the diagnosis is easily secured by confirming regional wall motion abnormalities of the left ventricle on echocardiography with an overall reduction in left ventricular systolic function, and good relief of symptoms with a diuretic expected. Unfortunately many patients present with more nebulous

symptoms, an aetiology obscured by multiple co-morbidities, challenging or unhelpful investigation data, and a limited response to heart failure therapy. In these patients securing a robust diagnosis of heart failure is more challenging. It is clear that a thorough understanding of the symptoms, signs and clinical investigation data in heart failure is vital to allow accurate diagnosis across a range of patients with heart failure.

1 – 6 – 1 Symptoms

Few – if any – patients present to a health care professional asking for help with an exact disease. Patients typically seek medical help because they have a new or more intrusive symptom. A symptom is a change from normal function, sensation or appearance and is therefore a subjective statement. Physicians often 'translate' the description given by the patient into medical terms to abbreviate the account and provide a diagnostic label. As symptoms are subjective they may be influenced by the patients' mood, anxiety, lifestyle and prior experience. Clearly they may change over time and evolve.

The two main symptoms of heart failure are breathlessness – usually on effort but may occur at rest – and fatigue (Parshall, Welsh et al. 2001). These symptoms are intuitive to understand for both patient and physician as a reflection of reduced function of a failing heart. In reality the pathophysiological explanation of fatigue in particular is complex, and is related more with skeletal muscle metabolism and response to under-perfusion than to the degree of cardiac dysfunction itself (Clark, Poole-Wilson et al. 1996). While fatigue and breathlessness are the bedrock of the

NYHA classification of heart failure severity – an assessment that has been in use for over 30 years – patients may describe as many as 20 symptoms to describe the physical sensations of heart failure (Nordgren and Sorensen 2003). The description varies between men and women despite a similar level of cardiac dysfunction which is likely a reflection of the impact of their disease on lifestyle, function and social restrictions (Ekman, Cleland et al. 2005).

If a patient describes the sensation of breathlessness during the history it is usual to label this as dyspnoea – defined as difficult or laboured respiration. Clearly there are many causes of dyspnoea, and the exact phraseology used by the patient may offer diagnostic clues – heart failure patients typically describe a 'suffocating' sensation or 'inability to breathe deeply' (Scano, Stendardi et al. 2005). This detail may help to differentiate from other common causes of dyspnoea such as chronic obstructive airways disease (Han, Zhu et al. 2005). Given that symptom severity can aid in prognosis determination (Ekman, Cleland et al. 2005) it is important to carefully and completely elucidate the patients' experience. Interest is being shown in the use of natural language processing – a technique of computer analysis of verbatim text of the patients symptom description – in the assessment of chest pain and diagnosis of angina, a disease which also relies heavily on patient symptom description (Pakhomov, Hemingway et al. 2007). These techniques may be applicable to patients presenting with breathlessness and assist physicians in elucidating the diagnosis.

1 – 6 – 2 Signs of heart failure

The principal pathological process in heart failure is inappropriate retention of sodium and water by the kidney in response to reduced renal perfusion, mediated by activation of the renin-angiotensin-aldosterone axis and stimulation of the sympathetic nervous system. The deleterious effects of this response lead to excess fluid accumulation, vasoconstriction, tachycardia, increased preload and afterload, and arrhythmia. These cause progressive damage to an already failing heart and further deterioration. The clinical signs apparent in a patient with heart failure depend on the severity and location of the cardiac dysfunction, along with the hearts adaptive response to altered wall stress. A patient who sustains a myocardial infarction of the left ventricle leading to acute left ventricular dysfunction will typically manifest tachycardia, gallop rhythm and pulmonary congestion – this may vary from minor crepitations in the lung fields to acute severe pulmonary oedema. Chronic heart failure may manifest with these signs along with oedema and elevated venous pressure. Additional signs present may reflect the aetiology of cardiac dysfunction – a murmur in valve disease for example - other signs may occur in response to drug therapy and co-morbid conditions. Criteria have been developed to assist in the clinical diagnosis of heart failure; these are listed in Table 4 (Ho, Pinsky et al. 1993).

Table 4: Criteria for diagnosis of heart failure (Ho, Pinsky et al. 1993)

Major criteria		
Paroxysmal nocturnal dyspnoea	S3 Gallop rhythm	Elevated venous pressure
Crepitations in lung fields	Cardiomegaly	Hepatojugular reflux
Acute pulmonary oedema	Weight loss of > 4.5kg in 5 days with diuretics	
Minor criteria		
Bilateral ankle oedema	Pleural effusion(s)	Nocturnal cough
Hepatomegaly	Heart rate > 120/min	Dyspnoea on exertion
Reduced vital capacity by 1/3		

Two major criteria, or one major and two minor criteria required to diagnose heart failure

The elucidation of clinical signs is clearly important to make a diagnosis of heart failure and identify aetiology, but in addition they may also provide prognostic information, particularly when combined with symptoms. Analysis of data from the large scale valsartan Heart Failure Trial (Cohn and Tognoni 2001) in which over 5,000 patients with heart failure of NYHA class II to IV were treated with either valsartan or placebo demonstrated that mortality could be predicted based on the detection and grading of symptoms and signs of heart failure (Wong, Staszewsky et al. 2006). Patients with more severe symptoms and more florid signs of heart failure had a higher risk of hospitalisation and death. Furthermore signs and symptoms were both independent and incremental predictors of outcome emphasising the need to elucidate both aspects clearly.

1 – 6 – 3 Echocardiography in heart failure

Echocardiography – ultrasound of the heart – is the most practical tool for the detection of ventricular dysfunction as it is rapid, safe, portable and cost effective. It is recommended as the investigation of choice in the assessment of heart failure in many guidelines, including those by the National Institute of Clinical Excellence (The National Collaborating Centre for Chronic Conditions 2003). It is held as the single most useful test in the diagnosis of heart failure as both the extent and severity of cardiac dysfunction as well as its aetiology can be detected, along with its ability to monitor response to treatment and aid development of new treatment strategies (Oh 2007).

Heart failure due to systolic dysfunction is usually relatively simple to diagnose with echocardiography – typically a dilated left ventricle with a reduced ejection fraction is demonstrated. Furthermore data on cardiac dimensions, shape, function and subsequent valve dysfunction have prognostic implications (Grayburn, Appleton et al. 2005). The correlation of abnormal systolic function with patients' symptoms and clinical signs is reassuring and conceptually straightforward. It has however been demonstrated in multiple studies that up to half of patients presenting with symptoms and clinical signs of heart failure have preserved – in other words normal – systolic function (Hogg 2004). The concept of dysfunction of diastole causing heart failure is now established (Aurigemma and Gaasch 2004) and current guidance recommends the term 'heart failure with normal ejection fraction' (HFNEF) to indicate that it may be a precursor of systolic dysfunction, and also because the distinction between systolic and diastolic dysfunction is difficult – many patients with HFNEF do have

abnormal tissue Doppler velocities which is a more sensitive indicator of systolic function than assessment of ejection fraction alone (Sanderson 2007), suggesting that in patients with HFNEF subtle abnormalities of systolic function do already exist (Yip, Wang et al. 2002). Conditions such as severe valvular disease or constrictive pericarditis can lead to heart failure with normal systolic performance of the ventricles, but intrinsic dysfunction of the myocardium with no other structural abnormality can also lead to the same clinical scenario. Unfortunately clinical findings alone cannot distinguish heart failure with impaired systolic function from heart failure with normal ejection fraction (Zile and Brutsaert 2002), hence identification of HFNEF requires more detailed echocardiographic assessment (Oh, Hatle et al. 2006). Doppler assessment of mitral valve inflow velocities, flow in pulmonary and hepatic veins, and measurement of myocardial tissue displacement velocity are required. Diagnostic criteria have been published to aid in the identification of HFNEF (Paulus, Tschope et al. 2007), although there is variation in proposed criteria and others have called for a more standardized approach (Vasan and Levy 2000). Exploration of the patho-physiology of HFNEF has led some to suggest it is a precursor of eventual systolic function and represents a different phenotype of the same disease, one where symptoms develop early and before frank systolic dysfunction is detectable (De Keulenaer and Brutsaert 2007). In contrast to many heart failure studies, the studies described in this thesis have not restricted analysis to patients with proven systolic dysfunction.

1 – 6 – 4 Additional diagnostic testing

Echocardiography is the gold standard for diagnosing heart failure but as can be seen it may be complex and difficult. Given the cost of echocardiography – albeit low compared to alternative diagnostic imaging – different strategies for diagnosing heart failure have been developed. Alternative diagnostic approaches in clinical use include the electrocardiogram (ECG) and biomarkers of cardiac dysfunction detectable in the blood such as brain natriuretic peptide (BNP) and its precursors.

1 – 6 – 4.1 ECG in heart failure

A simple 12-lead ECG can detect left ventricular systolic dysfunction, with a sensitivity of 85% and specificity of 58% (Khunti, Squire et al. 2004). This low specificity will lead to a high rate of false-positive examinations and impair its cost effectiveness at detecting left ventricular dysfunction. An entirely normal ECG does however strongly suggest normal left ventricular systolic function (Davie, Love et al. 1996) with a sensitivity of 94% and a negative predictive value of 98%. Beyond diagnosing heart failure, the ECG does have a clear role in predicting outcome and also development of heart failure. Left bundle branch block confers a risk of heart failure and furthermore carries a worse prognosis once ventricular dysfunction is established (Zannad, Huvelle et al. 2007), although whether the predictive power of left bundle branch block is independent of the effect of abnormal ventricular activation on left ventricular ejection fraction is less clear. Analysis of a registry of more than 11,000 patients with heart failure and ejection fraction measurements identified left bundle branch block as an independent predictor of one-year mortality.

However this only held true when the analysis was not adjusted for left ventricular ejection fraction (Stenestrand, Tabrizi et al. 2004).

1 – 6 – 4.2 Brain natriuretic peptide (BNP)

BNP is released from cardiac myocytes when increased stretch occurs. Any condition leading to increased wall stress and myocyte strain can lead to an elevation in BNP. Assessment of the precursor NTproBNP as a marker for heart failure yields a sensitivity of 80% and a specificity of 88%. In large scale studies of the use of BNP measurement in the assessment of breathless patients, BNP outperformed clinical assessment including history, examination and chest X-ray findings (McCullough, Nowak et al. 2002). Its most reliable role is in the exclusion of heart failure – a normal BNP value has a negative predictive value of 96% (Maisel, Krishnaswamy et al. 2002). Many updated guidelines on the diagnosis of heart failure therefore recommend the use of BNP to screen patients requiring further investigations such as echocardiography; this strategy has proven to be cost effective. A study in Switzerland randomised 452 patients present with acute dyspnoea to conventional investigation and management or assessment following BNP testing. Patients who had BNP measured received appropriate therapy earlier and were less likely to be admitted to hospital, those that were admitted had shorter in-patient stays. At the time of the study a BNP assay cost $47 per patient but total costs of treatment were $1804 lower for the initial in-hospital therapy (Mueller, Laule-Kilian et al. 2006).

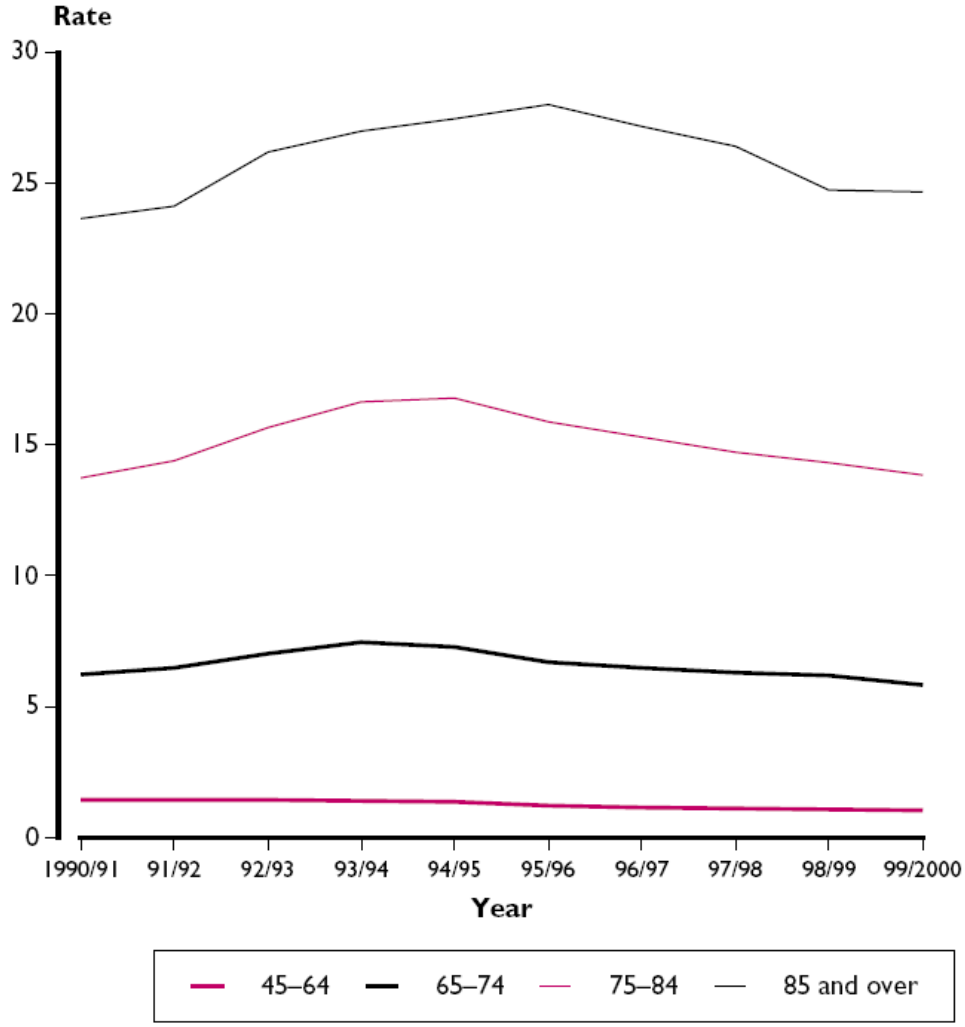
As the use of BNP measurement increases it is clear that its role in clinical practice is not fully established – for example one study of 76 outpatients with diabetes in Italy

were assessed with BNP measurement and echocardiography, and 51% were found to have evidence of diastolic dysfunction. There was no significant difference in the BNP measurements between those with normal echocardiograms and those with asymptomatic diastolic dysfunction suggesting BNP cannot detect subclinical cardiomyopathy (Valle, Bagolin et al. 2006).

1 – 7 Burden of disease

Identifying heart failure admissions as a source of high levels of health care expenditure has lead to efforts to reduce the public health burden of heart failure and reduce costs, principally by reducing the number of admissions to hospital. Strategies have included identifying at-risk populations and prescribing preventive therapies, and early initiation of heart failure therapy by the patient's primary care physician before symptoms severe enough to warrant hospital admission develop. The National Service Framework for Coronary Heart Disease in the United Kingdom published in 1999 lays out standards for prevention and treatment of heart failure with emphasis on the key role of the primary care physician in managing heart failure in the community. Despite these measures the rates of heart failure admissions have climbed by 5% for men and 4% for women from 1990 to 2000 (Gnani 2002), although the rates peaked in 1993 and have been declining since as shown in Figure 1.

Figure 1: Heart failure admission rates per 1,000 men in England by age and financial year, 1990/91 to 1999/2000 (Gnani 2002)



Projections based on these data have suggested that in 2011 there will be a total of 86,900 admissions for heart failure rising inexorably to 113,100 by 2026. This is a crude prediction and may be an over-estimation as a recently published review of heart failure hospitalisations in Australia has demonstrated a fall in age- and sex-standardised heart failure admissions from 2.0 per 1000 population to 1.6 per population between 1996 and 2004 (Najafi, Dobson et al. 2007). Data from our own local heart failure population paints a similar picture – heart failure admission rates

peaked in the early 1990s but have since started to decline, although overall mortality remains high (Blackledge, Newton et al. 2003).

It is challenging to explain the apparent decline in heart failure admission rates despite increased prevalence of heart failure risk factors such as diabetes mellitus, obesity and hypertension as well as improved survival from myocardial infarction. It is tempting to hypothesise that advances in treatment with angiotensin converting enzyme inhibitors, angiotensin receptor and beta blockers along with improved out-patient diagnosis and care have lead to this reduction, particularly when good heart failure care has been shown to reduce the rate of admissions by up to 40% (Michalsen, Konig et al. 1998). A counter-argument is that heart failure is a difficult condition to diagnose and therefore hospital event coding may be inaccurate, changes in hospital admission policies and evolution in guidelines and diagnostic practice may impact on admission trends.

1 – 8 Cost of hospitalisation and treatment

The total annual cost to the National Health Service from heart failure is around £550 million, mainly driven by hospital admissions - this accounts for up to 75% of the total treatment cost for a single patient and costs £350 million. The severity of heart failure is also positively correlated with the cost incurred - for example annual care for a patient with NYHA Class IV symptoms costs seven times that of a patient with NYHA Class II symptoms (Malek 1999). The average cost of a hospital admission is around £2000 compared to a cost of £250 for an outpatient attendance. The cost of

drug treatment varies widely, and the overall cost-effectiveness is difficult to calculate – for example extending a patient's life by 12 months may lead to additional hospital admissions - both for heart failure and other reasons - which may then offset the initial cost saving of the effective therapy. Detailed analysis of the major drug therapy trials has demonstrated their cost effectiveness when given early and used long term (Delea, Vera-Llonch et al. 1999) – the cost per life-year saved with the beta blocker carvedilol is between $12,799 and $29,477. It is important to emphasise these cost-benefit analyses were performed before generic carvedilol became available, although there is some evidence suggesting the generic versions are less potent (Smith, Tarocco et al. 2006). In the United States the estimated direct and indirect cost of heart failure in 2007 is $33.2 billion from a total expenditure on cardiovascular disease and stroke of $431.8 billion (Rosamond, Flegal et al. 2007).

1 – 9 Heart failure therapy

A large evidence base now exists for the use of pharmacotherapy in heart failure. Guidelines recommend the use of first-line agents in all patients with the introduction of second line therapy for those who remain symptomatic despite this. In this section I will briefly review the evidence for each major class of heart failure therapy and their indications for use. Additional data on the effect of drug therapy on survival are presented and discussed in chapter 2.

1 – 9 – 1 First line therapy

First line therapy in heart failure consists of combination therapy with a diuretic for symptom relief, an ACE inhibitor or ARB, and a beta blocker. Each of these drugs will be discussed in turn.

1 – 9 – 1.1 Diuretics

These are essential for treatment of symptoms due to fluid overload. They clearly improve fluid and sodium excretion, reduce symptoms and improve exercise tolerance but have no proven mortality benefit. For this reason, every patient treated with a diuretic for left ventricular dysfunction should also receive an ACE inhibitor and a beta blocker. Adequate dosing is essential; as fluid overload reduces ACE inhibitor effectiveness and increases the risk of beta blocker induced decompensation of heart failure. However once an optimum fluid balance has been achieved and the patient established on an ACE inhibitor, it may be possible to reduce the dose of diuretic.

1 – 9 – 1.2 ACE inhibitors

Data from more than 12,000 patients have been evaluated in randomised, double blind, placebo controlled trials. In clinical trials, ACE inhibitors slow disease progression, improve symptoms and reduce hospitalisation rates. Mortality is consistently reduced by 15-30% in all grades of heart failure, again in the clinical trial setting. ACE inhibitors are indicated in all stages of left ventricular dysfunction irrespective of symptoms. They should be started early before excessive diuresis and

hypotension. Abnormal renal function, commonly seen in patients with heart failure and reduced GFR, is not a contraindication to therapy. However a 10-15% increase in serum creatinine is common after ACE inhibitor initiation and regular monitoring of renal function and potassium levels is essential.

1 – 9 – 1.3 Beta blockers

The evidence for beta blockade in heart failure equals or surpasses that for ACE inhibition (Cleland, McGowan et al. 1999). Data from more than 6,000 patients in randomised double-blind clinical trials show that beta blockers reduce symptoms, hospitalisation, and mortality by over 30% when added to ACE inhibitors and diuretics.

Beta blockers are indicated in patients established on an ACE inhibitor and diuretic, with no signs of fluid overload, and who are stable clinically. They should be avoided in patients with evidence of fluid overload or unstable disease. The majority of trials enrolled patients in class I-III, but carvedilol has now been shown to also reduce mortality and hospitalisations in class IV patients (Packer, Coats et al. 2001). Specialist input is currently recommended for initiation of beta blockers. Careful, slow dose titration over weeks is mandatory until target dose is achieved or limited by side effects.

1 – 9 – 2 Second line therapy

Second line therapy in heart failure is instituted for patients demonstrating inadequate benefit with first line therapy, and includes treatment with an ARB, nitrates, spironolactone and digoxin.

1 – 9 – 2.1 Angiotensin Receptor Blockers

Angiotensin receptor blockers (ARBs) have not been shown to be superior to ACE inhibitors in heart failure. Both the ELITE-II trial in chronic heart failure (Pitt, Poole-Wilson et al. 2000), and OPTIMAAL trial in post myocardial infarction (Dickstein and Kjekshus 2002), failed to show superiority of losartan compared to captopril. Indeed, the latter trial failed to show equivalence of these treatments. However losartan was better tolerated in both studies. Initial reports suggested some evidence of increased mortality and morbidity if an ARB is used in conjunction with both an ACE inhibitor and beta blocker (Cohn and Tognoni 2001) but the large-scale series of trials of candesartan in heart failure (Pfeffer, Swedberg et al. 2003) demonstrated clear benefit of this ARB in both patients intolerant of an ACE inhibitor (Granger, McMurray et al. 2003) and those already treated with ACE inhibitor (McMurray, Ostergren et al. 2003) with no evidence of increased mortality with triple neurohormonal blockade. ARB therapy is indicated in patients who are truly intolerant of an ACE inhibitor; furthermore the addition of ARB therapy to ACE inhibitor therapy improves morbidity and mortality in patients with impaired systolic function. Careful monitoring is required as rates of hypotension, renal impairment and hyperkalaemia are higher with dual ACE-inhibition and ARB therapy.

1 – 9 – 2.2 Nitrates

Nitrates in combination with hydralazine may be useful in the rare instance of a patient truly intolerant of both ACE inhibitors and ARBs, who remains symptomatic despite diuretic and beta blocker therapy. There is no evidence suggesting benefit of adding nitrate alone to standard therapy, although it is often used in concomitant angina.

1 – 9 – 2.3 Aldosterone antagonists

Aldosterone promotes vascular fibrosis, sympathetic activation and parasympathetic inhibition – all deleterious in heart failure. Two aldosterone antagonists are currently available – spironolactone and eplerenone. The RALES study compared the effect of adding spironolactone at a target dose of 25 mg to standard therapy to placebo in 1663 patients with class III or IV heart failure, and demonstrated a significant reduction in morbidity and death (Pitt, Zannad et al. 1999). However, this trial pre-dated the widespread use of beta blockers in heart failure. Careful monitoring of serum potassium is essential. Spironolactone is best reserved for patients remaining symptomatic despite optimum diuretic, ACE inhibitor and beta blocker, and is usually initiated by hospital specialists.

Eplerenone has been studied in patients with systolic dysfunction post acute myocardial infarction in the Ephesus study (Pitt, White et al. 2005). Eplerenone 25 – 50mg demonstrated a 15% reduction in mortality and fewer heart failure hospitalisations.

1 – 9 – 2.4 Digoxin

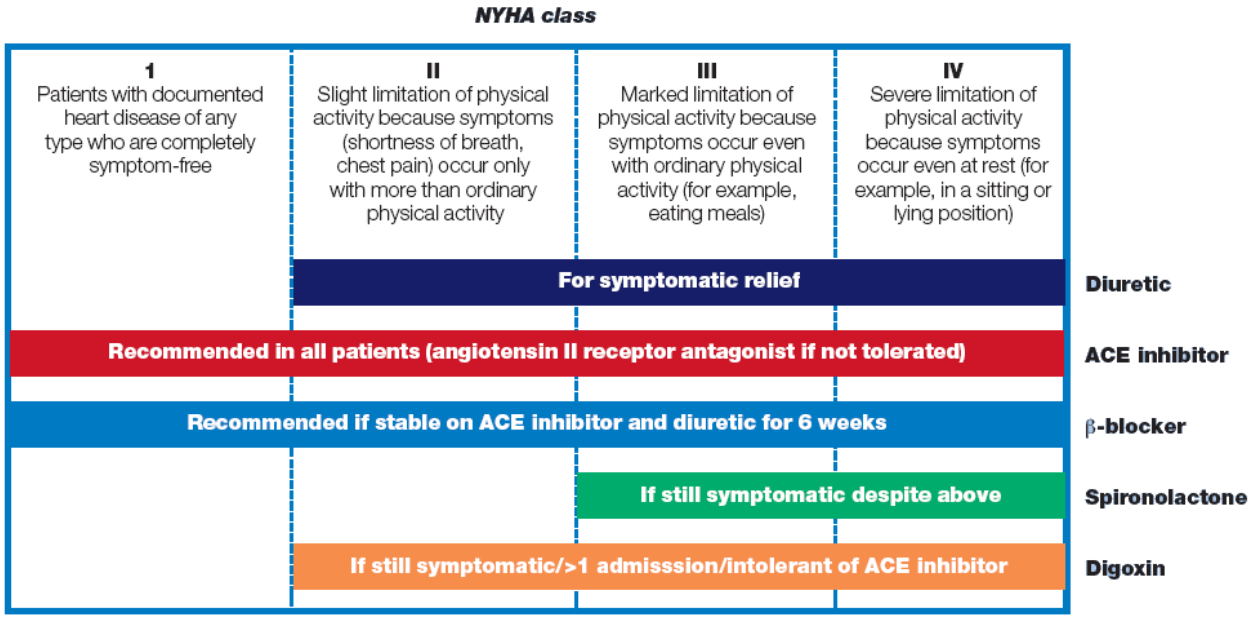
Patients in atrial fibrillation with heart failure benefit from the effect of digoxin on heart rate and myocardial contractility, although other agents such as amiodarone and beta blockers are also used. However its role in patients in sinus rhythm is less clear. The DIG study showed no reduction in mortality, but reduced hospitalisation rates, when digoxin was added to standard therapy in patients with chronic heart failure in sinus rhythm, and an ejection fraction < 45% (Garg 1997). The greatest benefit was seen in patients with more severe heart failure. However in a separate arm studying patients with an ejection fraction >45%, digoxin again improved functional capacity and reduced hospitalisations.

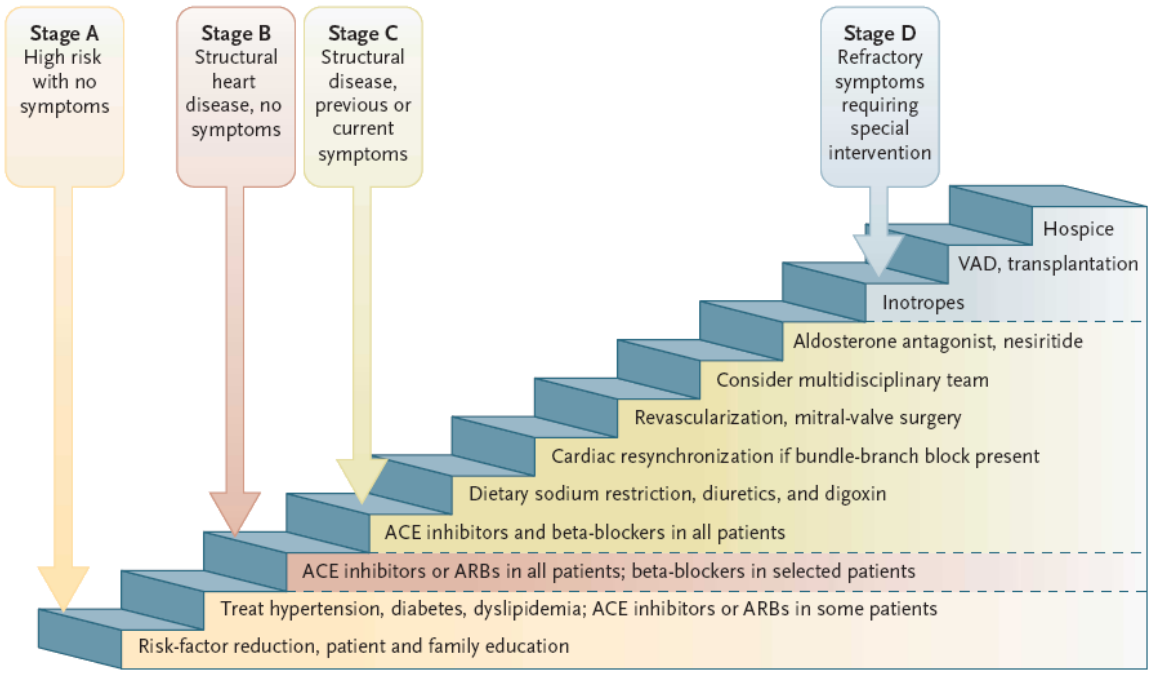
At present it is indicated in patients who remain symptomatic despite diuretic and an ACE inhibitor, who have had more than one admission with heart failure, or those who cannot tolerate an ACE inhibitor or ARB. Again, this is usually introduced under specialist supervision.

1 – 9 – 3 Stepwise approach to therapy

It can be seen that the treatment of heart failure follows a step-wise approach with the introduction of agents dependent on the severity of heart failure and response to previous therapy. Drug therapy is however only one aspect of the management of heart failure and this is demonstrated in the lower part of Figure 2 with the upper portion detailing the drug therapy discussed.

Figure 2: Stepwise approach to drug therapy in heart failure (Jessup 2003; Newton 2003)





1 – 9 – 4 Advanced heart failure therapy

Many patients with heart failure will make good symptomatic improvement with the above treatments, and undoubtedly live for longer. A proportion of patients will not improve sufficiently and remain burdened with intrusive symptoms. These patients may be considered for additional non-pharmacological therapy. Options include advanced pacemaker therapy, surgical therapy and cardiac support devices as mechanical pumps to act as a bridge to transplantation.

1 – 9 – 4.1 Pacemaker therapy for heart failure

A consequence of cardiac dysfunction can be myocardial and electrical remodelling which may disrupt the synchronised contraction induced during cardiac systole. During studies of patients with left bundle branch block it was noted that dyssynchronous contraction of the inter-ventricular septum and the free wall of the left ventricle occurred, impairing the mechanical efficiency of the left ventricle (Wyndham, Smith et al. 1980). This paradigm shift in the concept of electrical and mechanical dyssynchrony led to the development of bi-ventricular pacemaker therapy whereby both the left and right ventricles are stimulated to restore coordinated contraction and improve left ventricular ejection fraction (Cazeau, Ritter et al. 1996). Successful cardiac resynchronisation therapy (CRT) with biventricular pacemaker therapy leads to increased ejection fraction, pulse pressure and cardiac index with a reduction in left atrial pressure but no appreciable increase in myocardial energy consumption (Leclercq, Cazeau et al. 1998). Prolonged benefits include reversal of

left ventricular remodelling and reduced arrhythmia potential (Higgins, Yong et al. 2000).

Clinical trials of CRT have evolved from small scale studies of short duration through to large scale studies of the effect of CRT on heart failure survival. Current selection criteria based on the most recent trials require a patient to have persistent NYHA class III or class IV symptoms despite maximal tolerated medical therapy, an ejection fraction of 35% or less and a QRS interval prolonged beyond 150ms on the surface ECG. In the more recent CARE-HF study these patients had a hazard ratio for all cause mortality of 0.64 compared to those treated with standard medical therapy (Cleland, Daubert et al. 2005). Despite the impressive benefits of CRT up to 30% of patients derive no appreciable improvement following device implantation. Identification of patients who will benefit from CRT is vital to ensure correct tailoring of therapy, minimising unnecessary risks and reducing health care costs. A number of echocardiographic approaches to patient selection have been described, ranging from simple Doppler measurements to advanced 3-dimensional echocardiography parameters such as displacement time dispersion (Yu 2004). Furthermore there are sparse data on the benefit of CRT in patients with atrial fibrillation, those with a normal QRS duration but echocardiographic dyssynchrony and those with NYHA class II symptoms. A number of studies are underway to assess these factors.

Applying the current criteria for CRT to two cohorts of both patients discharged from hospital with new primary diagnosis of heart failure and those in a specialist heart failure clinic suggests that only 1% of patients discharged and 18% of those under specialist care qualify for CRT (McAlister, Tu et al. 2006). This apparently low

figure – in conflict with other analyses – may be due to the restricted cohorts chosen as dyssynchrony may develop with more chronic heart failure; furthermore patients with recent myocardial infarctions were also excluded. Review of 566 patients with dilated cardiomyopathy identified that between 7% and 14% of stable outpatients with heart failure were suitable for CRT depending on whether strict or less restrictive selection criteria were utilised (Grimm, Sharkova et al. 2003).

1 – 9 – 4.2 Implantable cardioverter defribillator therapy

Patients with heart failure and significant systolic dysfunction are at risk of ventricular arrhythmia and sudden death and benefit from implantation of an implantable cardioverter defibrillator (ICD). ICD therapy is recommended for patients with class III – IV heart failure and both an ejection fraction under 35% and QRS duration over 120ms. Survivors of cardiac arrest or patients with sustained ventricular tachycardia and impaired systolic function should also received ICD therapy.

In a study of 1232 patients with a myocardial infarction more than 30 days before and an ejection fraction of under 30%, ICD therapy was associated with a 31% relative risk reduction of mortality – an absolute risk reduction of 6% (Moss, Zareba et al. 2002).

As this study was performed in patients with heart failure post myocardial infarction the outcome cannot be applied to the general heart failure population. Additional studies have assessed the role of ICD therapy in patients with non-ischaemic cardiomyopathy (Kadish 2004), heart failure with dyssynchrony (Bristow 2004) and

those with symptomatic heart failure and an ejection fraction under 35% (Bardy, Lee et al. 2005). The majority have demonstrated mortality benefit with ICD therapy although interestingly there was no survival benefit from a CRT device combined with ICD therapy compared to CRT alone. A number of meta-analyses have agreed that the use of ICD therapy in patients with symptomatic heart failure and reduced ejection fraction reduces mortality, with a hazard ratio of 0.69 – 0.75 (Desai 2004; Nanthakumar 2004).

1 – 9 – 4.3 Left ventricular assist device therapy

A number of mechanical cardiac support devices exist and are able to support one of both ventricles(Mancini and Burkhoff 2005). Bi-ventricular devices exist to support both the left and right ventricle but only with external blood pumps limiting their role to short term support while awaiting transplantation.

Fully implantable left ventricular assist devices have been developed and while initially used as short term bridge-to-transplant therapy a number of patients have received long term support with such devices. Novel strategies of cardiac support with an implantable assist device and aggressive pharmacological therapy to promote reverse remodelling have been trialled, with the mean duration of device support being 320 days and a recovery rate of 46% (Birks 2006). Notably this study enrolled patients with non-ischaemic cardiomyopathy and no evidence of active myocarditis.

1 – 9 – 4.4 Surgical therapy for heart failure

Surgery can be directed at treating the cause of heart failure or attempting to improve the efficiency of the ventricular pump. Ischaemic heart failure due to coronary disease can be treated with coronary artery bypass surgery; similarly patients with valve disease such as aortic stenosis or mitral regurgitation are treated surgically where appropriate. For patients with impaired ventricles further options include surgery to restore the normal ventricular dimensions and shape – so called 'La Place' surgery as it attempts to reduce wall strain and improve haemodynamic function (Large 2007). Resection of aneurysmal sections of the ventricle or insertion of ventricular splinting devices such as the CorCap (Mann, Acker et al. 2004) is feasible although there is little convincing evidence to date to support widespread introduction. Further surgical options include attempts to improve the power of a failing ventricle. This can be achieved with cardiac myoplasty where skeletal muscle is wrapped around the ventricle and entrained to pump with the ventricle.

The ultimate definitive surgical therapy is cardiac transplantation – usuallya very successful treatment with a 5 year survival as high as 80% in carefully selected patients (Jeffrey, Leah et al. 1999). The obvious limitation is the scarcity of donor hearts... Given the dramatic developments in the medical therapy of heart failure selection of transplant candidates is becoming more challenging, not least because many of the prognostic models were developed before the widespread use of ACE inhibitors and beta blockers. Zugck found that the prognostic value of variables traditionally used for risk stratification and transplant selection is markedly influenced by beta blocker therapy (Zugck, Haunstetter et al. 2002). Cardio-pulmonary exercise

testing to calculate oxygen consumption and derive a peak VO_2 measurement is an accepted reference standard for entry into a transplant program. In this study at any level of peak VO_2 the use of a beta blocker was associated with a better prognosis, even in patients with severe heart failure.

Future options may include gene therapy, such as delivery of pluripotent stem cells to the myocardium in order to facilitate formation of new cardiac tissue (Stamm, Westphal et al. 2003).

1 – 10 Summary

This chapter has reviewed the definition and aetiology of heart failure along with discussion on the epidemiology, cost burden and optimal medical therapy of patients with heart failure. The hypothesis that patients admitted to hospitals in Leicester with newly diagnosed heart failure have the same demographics, aetiology, investigation and treatment during their admission as patients in published series is to be tested in this thesis.

The questions to be answered in this thesis relevant to this chapter can be summarised as follows:

1. How does the epidemiology of local heart failure patients compare with published data?

2. How long are patients admitted to hospital and what is the impact on service provision?

3. What proportion of patients admitted with heart failure receives specialist input from a cardiologist?

4. What proportion of patients admitted with heart failure undergoes appropriate investigations such as echocardiography?

5. Do patients admitted to hospitals in Leicester with heart failure receive optimal medical therapy on discharge?

6. What proportion of patients admitted with heart failure would be eligible for treatment with cardiac resynchronisation therapy?

The answers to these questions are discussed in chapter 4.

Chapter 2 – Survival and ethnicity

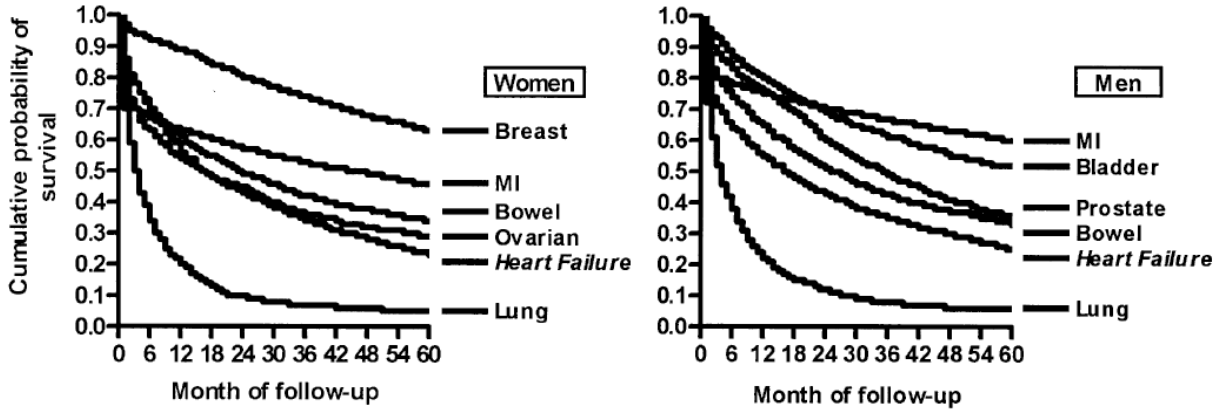
2 – 1 Introduction

Along with providing vital epidemiological data on patients admitted to hospitals in Leicester with heart failure as outlined in Chapter 1, another major aim of this study is to assess survival following a new diagnosis and compare this with published data. Furthermore the important impact of ethnicity on heart failure aetiology, therapy and outcome is a key component of the study. In this chapter I will review the current evidence on heart failure outcome and how this has changed, including details on the influence of medical therapy. A discussion on current prognostic techniques is also included. The importance of ethnicity with respect to heart failure aetiology and treatment will be emphasised and the current literature reviewed. I will conclude the chapter with further research questions which this thesis will address.

2 – 2 Survival

Heart failure is a malignant disease state with mortality comparable to many cancers. Despite the improvements in therapy detailed in Chapter 1, overall mortality rates remain high – in the order of 5 year mortality as high as 50% in men and 46% in women. Comparing these survival rates with those of common cancers demonstrated that only patients with lung cancer had higher 5 year mortality as shown in Figure 3.

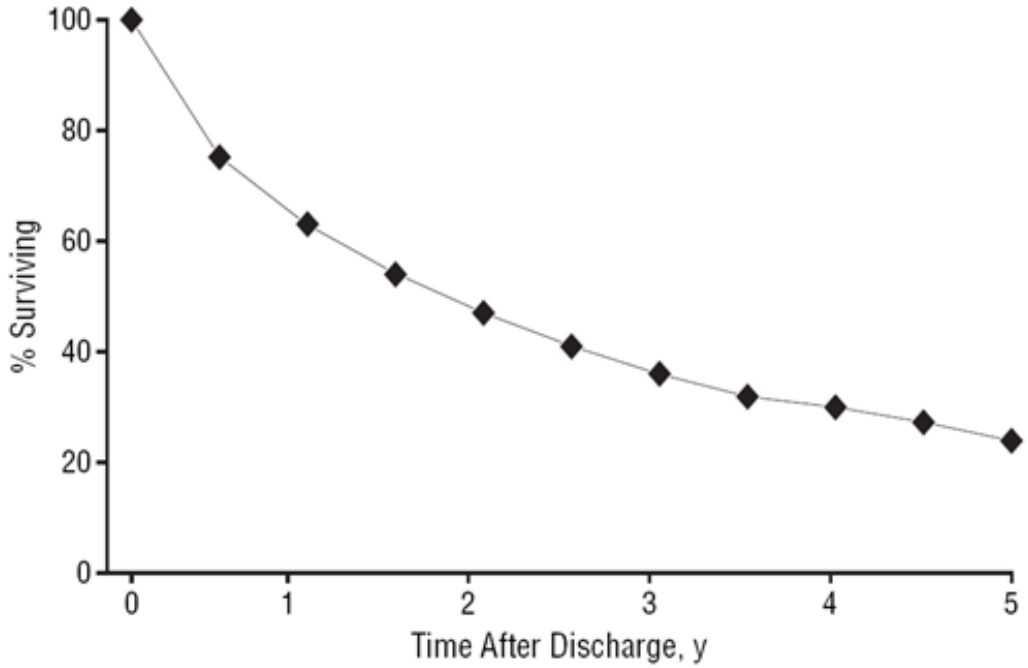
Figure 3: Five-year survival following a first admission to any Scottish hospital in 1991 for heart failure, myocardial infarction and the four most common sites of cancer specific to men and women (Stewart, MacIntyre et al. 2001)



Studies have repeatedly demonstrated modest improvements in heart failure survival with the introduction of new therapies but comment that the overall mortality remains high. Mortality from cancer is well known among both physicians and patients yet knowledge of the severity of a diagnosis of heart failure is poor. A recent European study into the awareness of heart failure identified that only 3% of the public could identify heart failure from its clinical description. Only 52% of people questioned correctly thought that heart failure is due to the heart becoming less efficient at pumping blood around the body – many felt it represented a heart rhythm disorder or a natural result of ageing. Furthermore 67% believed heart failure patients live longer than those with cancer, and only 58% would be concerned a colleague with heart failure could die suddenly (Remme, McMurray et al. 2005). A follow on from this general lack of awareness of heart failure is that many people are not aware of the burden on health care resources – many people chose cancer and HIV as diseases causing the greatest health care expenditure whereas heart failure consumes a larger

proportion of health care budgets than routine cancer and HIV therapy (Berry, Murdoch et al. 2001; Stewart, Jenkins et al. 2002). At the time of completing this thesis the most up to date estimate of heart failure survival demonstrates a one year mortality rate of 37% and 5-year mortality of 79% (Goldberg, Ciampa et al. 2007). These data are from a study of 2445 residents of Worcester metropolitan area in the USA who were discharged from one of 11 hospitals with a diagnosis of heart failure in 2000. The percentage of patients surviving over the 5 years of follow up after a hospital admission with heart failure is shown in Figure 4.

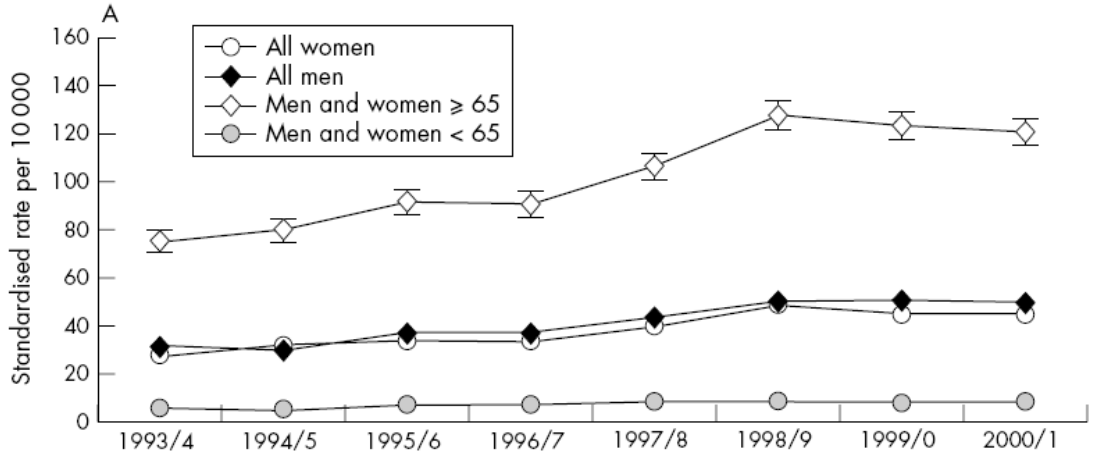
Figure 4: Percentage of patients surviving over 5 years of follow up after a hospital admission with heart failure (Goldberg, Ciampa et al. 2007)



2 – 3 Local data on heart failure epidemiology and survival

Blackledge et al. undertook a review of 12,220 index admissions with heart failure to hospitals in Leicestershire between 1993 and 2001 with cases identified through discharge coding of heart failure (Blackledge, Tomlinson et al. 2003). Overall 49% were male and 63% were aged over 75 years, the mean age being 77 years. The median admission duration was 9 days. Between 1993 and 2001 a significant increase in rates of heart failure admissions was noted, with a rise from 29 per 10,000 people to 47 per 10,000 – an increase by 62% as shown in Figure 5. It was noted that this increase principally constituted patients aged over 65 years.

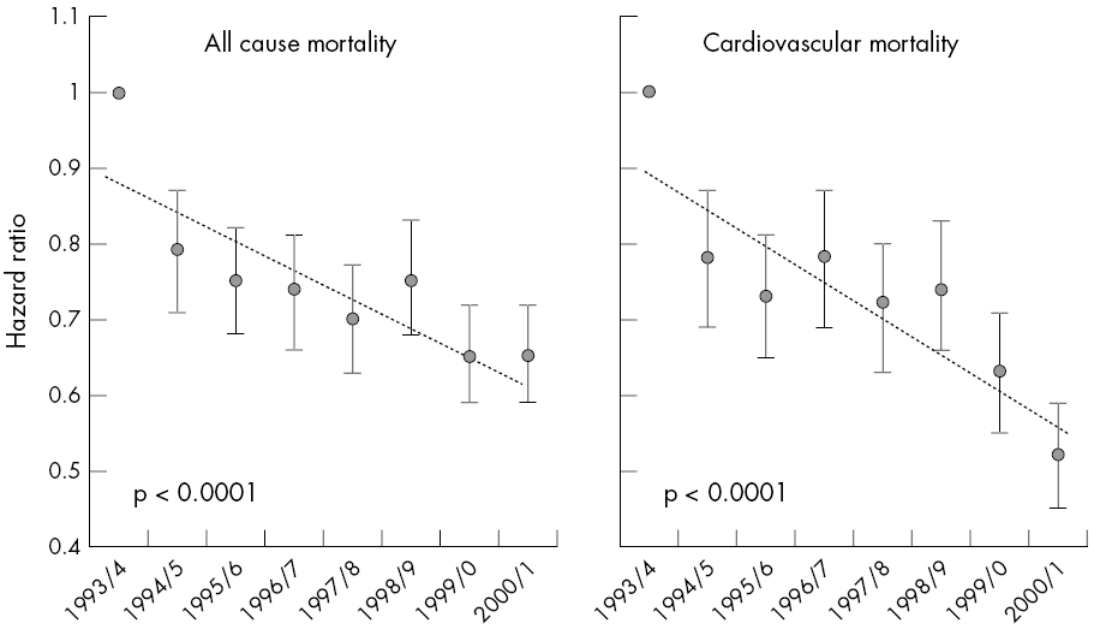
Figure 5: Trends in first heart failure admission rates between 1993 and 2001, rates for population older than 40, standardised for age and sex (Blackledge, Tomlinson et al. 2003)



Survival of patients following an index heart failure admission was poor – one month and one year case fatality rates were 21% and 43% respectively. At six years of

follow up 75 – 80% of patients had died. Over the study duration survival did appear to improve with one month survival rates climbing from 72% to 82% over the 8 years, with a similar increase in one year survival from 45% to 62% as shown in Figure 6.

Figure 6: 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, co-morbidity, and social deprivation (Blackledge, Tomlinson et al. 2003)



Probability (p) values represent the contribution of year of diagnosis to multivariate model. Dotted line indicates linear trend in hazard estimates

These data from local heart failure admissions compares with other studies demonstrating an increase in admissions followed by an apparent plateau in the late 1990s (Stewart, MacIntyre et al. 2001), with one study suggesting this correlated with increased prescription of angiotensin converting enzyme inhibitors (Mosterd, Reitsma et al. 2002). The case fatality rates are higher than those observed in clinical trials but similar to other population studies from Scotland (MacIntyre, Capewell et al. 2000) and Canada (Jong, Vowinckel et al. 2002).

2 – 4 Prognostication

Given the expense of heart failure therapy is principally driven by in-hospital care, estimating prognosis and survival may allow identification of high risk patients (Lee, Austin et al. 2003) who can be targeted with appropriate intensive investigations and therapy in order to reduce admissions and associated costs (Chin and Goldman 1997), and prolong survival. Unfortunately prognostication in heart failure is complex. This is due to the presence of multiple aetiologies in many patients, co-morbid disease, variable tolerability and response to therapy, and of course individual patient variation.

Most patients with heart failure do not have a discussion with health care professionals about the prognosis of their disease (Rogers, Addington-Hall et al. 2000; Murray, Boyd et al. 2002), perhaps because physicians lack confidence in estimating prognosis (Christakis and Iwashyna 1998) and have great difficulty in predicting the survival of an individual heart failure patient (Poses, Smith et al. 1997), and may

under or over-estimate prognosis based on memorable clinical experience (Hanratty, Hibbert et al. 2002). Failure to discuss prognosis may be denying the patient an opportunity to make fully informed decisions about their care, and will limit effective counselling. The estimation of prognosis is best achieved using a combination of clinical judgement and prognostic indices (Teno, Harrell et al. 2000), and has been endorsed as a key element of management of heart failure in recent guidelines (Swedberg 2005). In light of this, reports have recommended the development of risk models to quantitatively estimate prognosis are a research priority (Krumholz, Baker et al. 2000).

The majority of prognostic analyses so far published have been derived from large scale clinical trials of heart failure therapy, and given the restrictive nature of trial inclusion criteria it is questionable whether these data are applicable to the heart failure population as a whole. Furthermore the information from an estimation of prognosis is only valid at that time-point, and may be different to that derived during an acute decompensation and hospital admission. Prognosis may be modified by introduction of new treatments that were not included in the original study – beta blockers in addition to ACE inhibitors, for example. Contrast the 12 month death rate of 12% in the SOLVD trial (Jong, Yusuf et al. 2003) with an observed death rate of 38% in patients admitted to Hillingdon hospital with heart failure (Cowie, Wood et al. 2000). This difference was ascribed to trial selection criteria, low age of trial patients (mean of 60 years compared to 75 years) and low co-morbidity rates.

More than fifty biochemical, haemodynamic, clinical, demographic, functional, echocardiographic and electrophysiological factors have been identified as predictive

factors of mortality in patients with heart failure. Many different risk scores have subsequently been developed which utilise a combination of factors to provide an estimate of survival, or to predict those at risk from sudden cardiac death and direct device based therapy for heart failure. Table 5 gives an overview of predictive factors in heart failure with examples. Predictive models perform well in the cohort of patients it was developed for but can be inaccurate or impossible in other cohorts – for example there is a wide body of evidence supporting the use of cardiopulmonary exercise testing to determine oxygen consumption and measure peak VO2 max in order to select patients for cardiac transplantation. In such patients it does provide data on prognosis (Cohn 1996; MacGowan, Janosko et al. 1997). For the majority of patients admitted to hospital with heart failure these data are not available – in fact fewer than 5% of patients admitted to hospital undergo cardiopulmonary exercise testing (Cleland, Swedberg et al. 2003). Furthermore, the severity of their heart failure may not equate to that of the original study population. More pragmatic models have been developed which use more simple clinical variables and data widely available to most patients with heart failure, such as renal function, NYHA class, body weight, blood pressure, ankle oedema, quality of life assessment and drug therapy (Bouvy, Heerdink et al. 2003).

While such models are more widely applicable to the broader heart failure population they do not generally perform as robustly as those developed on purely invasive quantitative data. Simple biochemical parameters such as serum sodium can be used to estimate outcome as data from a study of over 48,000 patients with heart failure demonstrates (Gheorghiade, Abraham et al. 2007), with a 19.5% increase in the risk

of in-hospital mortality for each 3 mmol/L drop in serum sodium level below 140 mmol/L.

Estimating prognosis accurately and reliably in heart failure is challenging, but can provide useful information to adjust management as well as information for the patient regarding their disease and its likely progression. Moreover, estimating prognosis is a key step in modern heart failure guidelines (Hunt, Abraham et al. 2005; Swedberg 2005).

Table 5: Examples of prognostic factors in heart failure

Demographic	
Age	Increasing age is a robust independent predictor of mortality (Jong, Vowinckel et al. 2002)
Gender	Male gender is an independent predictor of mortality (Gustafsson, Torp-Pedersen et al. 2004)
Clinical measurement	
Blood pressure	Hypertension preceding heart failure is associated with increased mortality (Rosamond, Flegal et al. 2007)
Heart rate	Heart rate above 100/minute has a relative risk of 2.7 (Muntwyler, Abetel et al. 2002)
Biochemical	
Serum sodium	Serum sodium < 140mmo/l predicts increased mortality (Kearney, Fox et al. 2002)
Brain natriuretic peptide	A raised BNP or change in BNP independently predicts mortality (Gardner, Chong et al. 2007)
Haematological	
Anaemia	Anaemia is an independent predictor of outcomes in heart failure (Ezekowitz, McAlister et al. 2003)
HbA1c	Elevated HbA1c levels in diabetics associated with increased survival (Eshaghian, Horwich et al. 2006)
Echocardiographic	
Diastolic dysfunction	Heart failure with normal ejection fraction has a 25% five year mortality (MacCarthy, Kearney et al. 2003)
Left ventricular size	Increasing left ventricular size is a risk for heart failure developing (Vasan, Larson et al. 1997)
Electrocardiographic	
Atrial fibrillation	Atrial fibrillation is common and adversely affects morbidity and mortality (Corell, Gustafsson et al. 2007)
QRS duration	QRS prolongation is an independent predictor of mortality and sudden death (Iuliano, Fisher et al. 2002)
Functional	
NYHA class	Clear increase in mortality with more severe symptoms (Ekman, Cleland et al. 2005)
Peak O2 consumption	Robust identifier of high risk patients – used in transplant assessment (Lund, Aaronson et al. 2005)
Haemodynamic	
PCW pressure	Left ventricular end diastolic pressure correlated with survival (Grzybowski, Bilinska et al. 1996)
Ejection fraction	Ejection fraction is inversely correlated with mortality in heart failure (Brophy, Dagenais et al. 2004)
Examination	
Perfusion / congestion	Dividing patients into 4 simple groups predicts outcomes (Nohria 2003)
Ankle oedema	Independent predictor of mortality at 18 months (Bouvy, Heerdink et al. 2003)
Drug therapy	
Statin therapy	Use is independently associated with lower risk of death and hospitalization (Go, Lee et al. 2006)
Beta blocker therapy	The effect of beta blockade on outcome is similar to that of ACE inhibitors (Krum, Haas et al. 2005)

2 – 5 Improvements in survival

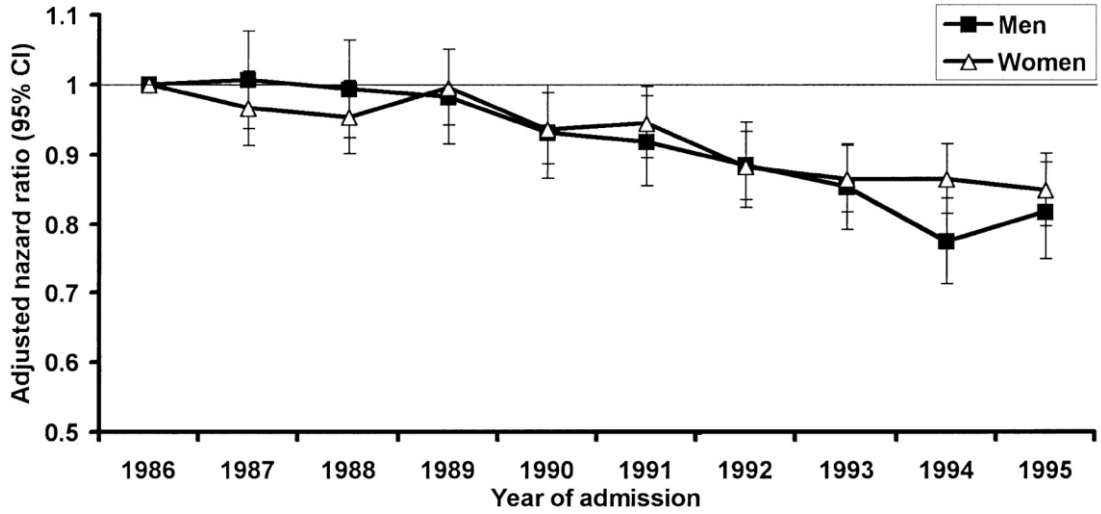
There is widespread evidence that the survival after onset of heart failure has improved. Further analysis of the Framingham cohort demonstrated a fall in the 1-year mortality rate from 28% to 24% between 1950-1969 and 1990-1999 in women and from 30% to 28% in men (Levy, Kenchaiah et al. 2002). Data from the United Kingdom has demonstrated a 36% decrease in case fatality rates from heart failure admissions between 1990 and 2000, with the largest change seen in patients aged less than 75 years (Gnani 2002). Similar data from Italy have shown a progressive increase in survival of outpatients with heart failure over a period from 1995 to 1999 with patients in 1993 having a 1.3 times greater risk of death when compared to those in 1999 (Senni, De Maria et al. 2005). Despite these improvements the overall survival from heart failure remains poor – the 5 year mortality remains as high as 50% in men and 46% in women in a population from 1996 – 2000 (Roger, Weston et al. 2004), and is worse than bowel cancer in men and breast cancer in women (Stewart, MacIntyre et al. 2001). Recent data from Australia suggests the in-hospital mortality of heart failure also remains poor with an overall age-standardized case fatality rate of 8.9% for men and 8.1% in women (Najafi, Dobson et al. 2007). The authors do point out that this has fallen by 21.9% and 14.4% in men and women respectively over a period from 1996 to 2004.

Data from a Swedish registry have also demonstrated a reduced incidence and improved prognosis following a first hospital admission with heart failure and link this trend with the introduction of ACE inhibitor and beta blocker therapy for heart failure along with home care programmes and more effective prevention. An annual

decrease in mortality of 9% in men and 10% in women was noted, although this is mainly in younger patients aged 45 – 54 years. Once again the overall one-year mortality remains high at 9% for men aged 45 – 54 and 36% for men aged 75 – 84, even in 2000. One-year mortality for women is similar at 8% and 29% for the same age groups (Schaufelberger, Swedberg et al. 2004). Data from the United States confirm increased mortality in men compared to women, and an overall one-year mortality of 1 in 5 (20%). Furthermore patients with heart failure are 6 to 9 times more likely to sustain sudden cardiac death than the general population. From 1994 to 2004 deaths from heart failure increased by 28% in the face of an overall fall in the population death rate by 2.0%.

Case fatality data from Scotland in patients admitted with a principal diagnosis of heart failure has shown an improvement in survival between 1986 and 1995, with a fall in 30-day mortality rates by 26% as shown in Figure 7. The high mortality in the elderly was noted, along with emphasis again that although progress is being made there is much room for improvement (MacIntyre, Capewell et al. 2000).

Figure 7: Decline in adjusted risk of dying after 30 days following a first heart failure admission between 1986 and 1995 (MacIntyre, Capewell et al. 2000)



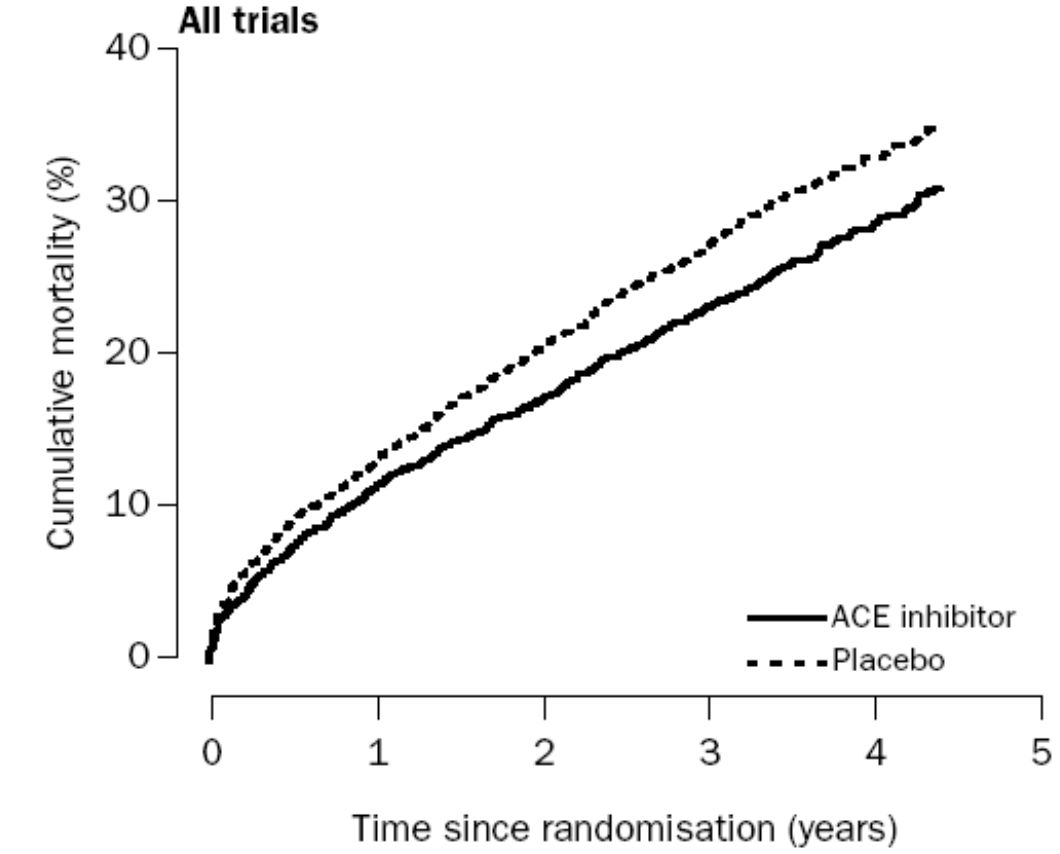
2 – 6 Impact of optimal current therapy on survival

I will now briefly review the evidence for the effect of ACE inhibitor, beta blocker and ARB therapy on heart failure survival.

2 – 6 – 1 Angiotensin Converting Enzyme inhibitors

The benefit of angiotensin converting enzyme inhibition in patients with chronic heart failure due to left ventricular systolic dysfunction on survival has been clearly demonstrated in several randomised clinical trials (Garg and Yusuf 1995; Flather, Yusuf et al. 2000) and is summarised in Figure 8.

Figure 8: Overall effect of angiotensin converting enzyme inhibitors on survival in chronic heart failure (Flather, Yusuf et al. 2000)



Number at risk

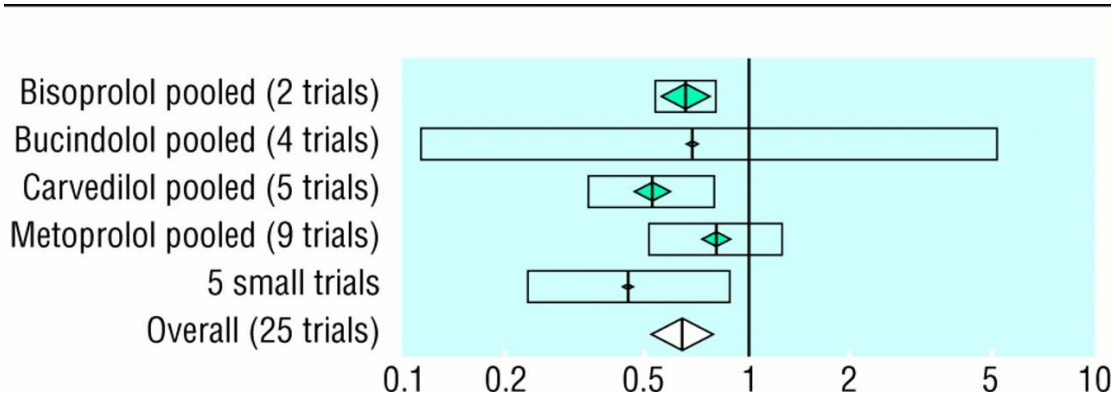
ACE-I	6391	5378	4204	2457	892
Placebo	6372	5279	4025	2364	742

Combining data from the five large scale randomised clinical trials of ACE inhibitors in chronic heart failure (SOLVD Investigators 1991; Pfeffer, Braunwald et al. 1992; SOLVD Investigators 1992; Acute Infarction Ramipril Efficacy (AIRE) Study Investigators 1993; Kober, Torp-Pedersen et al. 1995) has demonstrated an absolute event rate difference of 5.7%, with an estimation that for every 1000 patients treated with ACE inhibitors 60 deaths would be avoided.

2 – 6 – 2 Beta blocker therapy

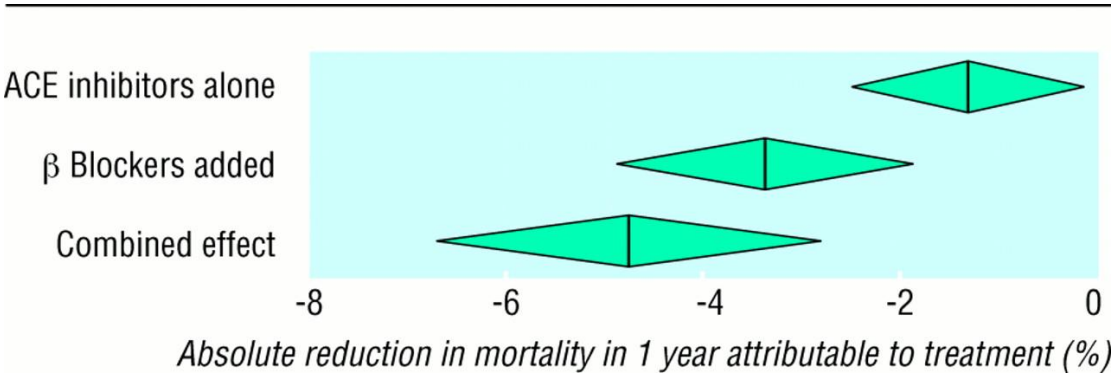
Randomised clinical trials of beta blocker therapy in heart failure have conclusively demonstrated a reduction in morbidity and mortality (Packer, Bristow et al. 1996; CIBIS-II Trial 1999; MERIT-HF Trial 1999; Packer, Coats et al. 2001). Repeated meta-analysis of available randomised trial data has shown a significant impact on mortality – a review in 2001 found an overall odds ratio of 0.65 for total mortality equating to 3.8 lives saved per 100 patients treated with beta blockers during the first year when adjusted for placebo mortality rates (Brophy, Joseph et al. 2001). An earlier meta-analysis performed before the CIBIS-II study concluded that beta blocker therapy reduced death by 37% (Lechat, Packer et al. 1998). A later review including this study along with 24 other randomised trials demonstrated a mortality reduction of 36% with 95% confidence intervals of 35% to 45% as shown in Figure 9, compared to a updated figure of 24% for ACE inhibitor therapy (Cleland, McGowan et al. 1999).

Figure 9: Pooled odds ratios (and 95% confidence intervals) describing the effect of beta-blockers on mortality in patients with heart failure (Cleland, McGowan et al. 1999)



Furthermore the effect of beta blocker therapy appeared to be additive to that achieved with ACE inhibitors as many patients in the studies analysed were treated with ACE inhibitors prior to beta blockade as shown in Figure 10.

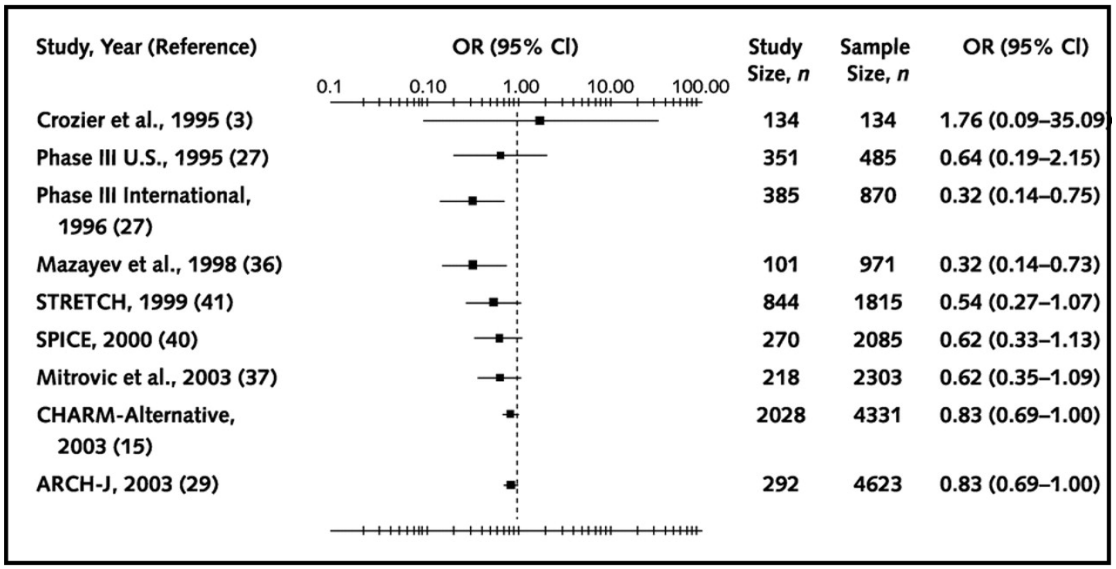
Figure 10: Effect on annual rate of mortality (%) of angiotensin inhibitors alone, with beta blockers added, and with both drugs (Cleland, McGowan et al. 1999)



2 – 6 – 3 Angiotensin Receptor Blocker therapy

Following development and introduction of ACE inhibitor therapy alternative techniques for interrupting the renin-angiotensin-aldosterone cascade were developed leading to trials comparing angiotensin receptor blockers (ARB) with placebo in heart failure, along with studies comparing them with ACE inhibitors. A recent meta-analysis of the major randomised trials of ARB concluded a reduction in all cause mortality in heart failure compared to placebo – odds ratio 0.83 and no difference between angiotensin receptor blockers and ACE inhibitors (Lee, Rhew et al. 2004) as demonstrated in Figure 11.

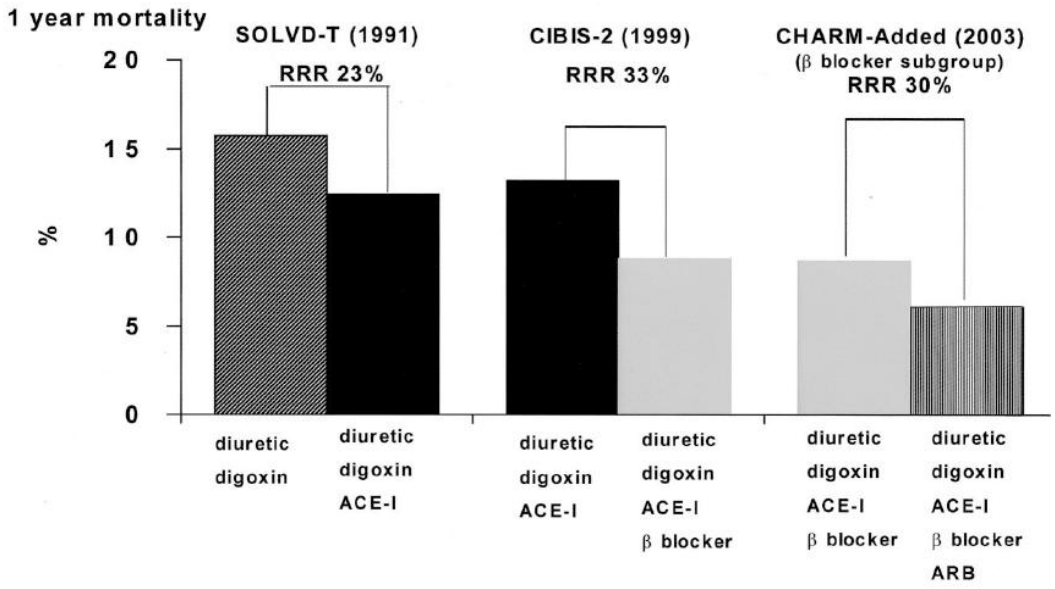
Figure 11: Cumulative meta-analysis for angiotensin-receptor blockers versus placebo comparison all-cause mortality outcome, in patients with chronic heart failure (Lee, Rhew et al. 2004)



2 – 6 – 4 Combined effect

The benefit of these agents in heart failure does not appear to be mutually exclusive – indeed the relative risk reductions of ACE inhibitor, beta blocker and angiotensin receptor blocker therapy are additive as demonstrated in Figure 12 (McMurray, Pfeffer et al. 2004).

Figure 12: Cumulative benefits of incremental neurohormonal inhibition in chronic heart failure (McMurray, Pfeffer et al. 2004)

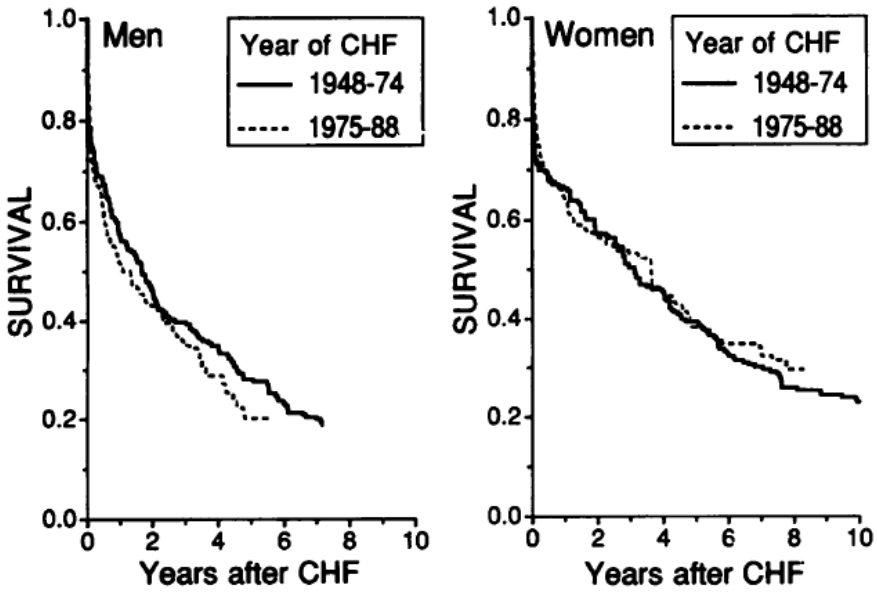


2 – 7 Evidence of improved survival in clinical practice

Given the apparent striking benefit of pharmacotherapy in heart failure it would seem reasonable to expect a large decrease in heart failure mortality since the introduction of ACE inhibitors and beta blockers and more recently angiotensin receptor blockers.

Over 20,000 patients have been randomised into clinical trials of ACE inhibitors and beta blockers alone, and their use in combination has apparently halved the annual mortality (Cleland, Massie et al. 1999). It is clear however that the survival from heart failure remains poor and the benefits seen in clinical trials are not yet apparent in 'real-world' clinical populations. A review of the Framingham cohort with respect to heart failure survival concludes that 'congestive heart failure remains highly lethal…Advances in the treatment of hypertension, myocardial ischaemia, and valvular heart disease during the four decades of observation (1948 – 1988) did not translate into appreciable improvements in overall survival after the onset of congestive heart failure in this large, unselected population' (Ho, Anderson et al. 1993). This is clearly demonstrated in Figure 13.

Figure 13: Age-adjusted survival rates after congestive heart failure by calendar year of first diagnosis of heart failure for men and women during the calendar years 1948-1988 (Ho, Anderson et al. 1993)



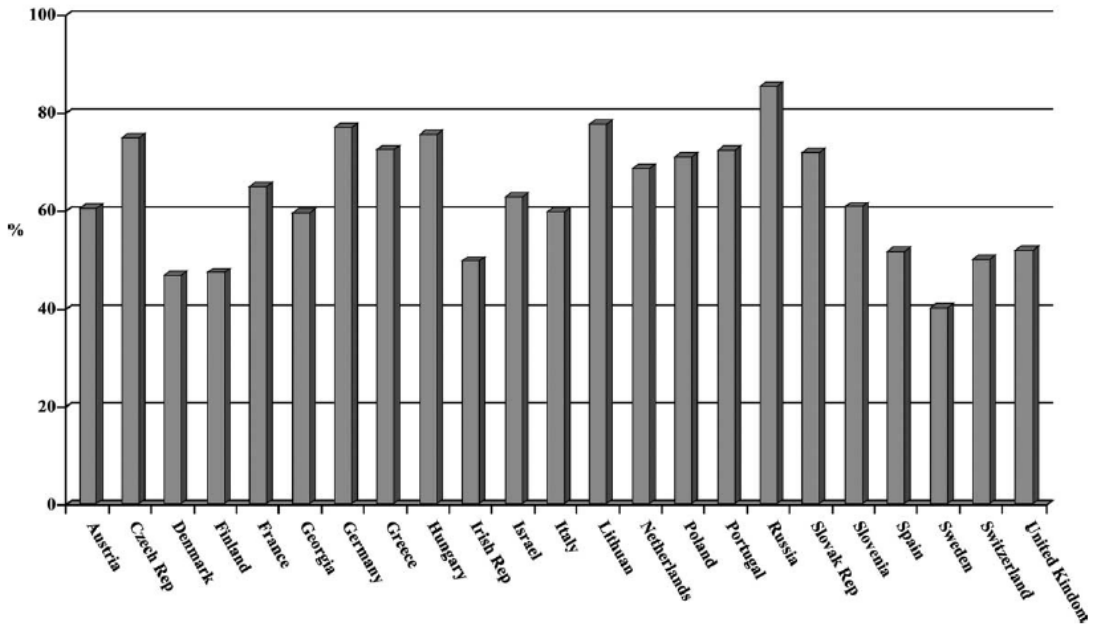
A more recent analysis of survival following incident heart failure diagnosis in patients from west London revealed a mortality of 19% by one month and 36% at one year – strikingly different to patients enrolled in clinical trials, even those treated with placebo (Cowie 1998).

One potential explanation for this is under-use of these proven therapies in heart failure. Comparison of trial populations with all heart failure patients demonstrates that few will meet the exacting enrolment criteria, and out of those who do, not all will receive appropriate therapy (Squire 2005). An alternative explanation is that clinical trials recruit a selected heart failure population – principally patients with stable chronic heart failure who by definition have survived the initial acute decompensation. Cleland and Clark demonstrated that by excluding patients who die within 90 days from community studies the mortality is much more similar to that seen in clinical trials (Cleland and Clark 1999). Compared to patients enrolled in clinical trials the average community heart failure patient is 10 years older with more co-morbidity but likely to have less severe symptoms and degree of left ventricular systolic dysfunction. This variation may also explain their similar outcome when adjusted for 90 day survival.

There is also a clear time lag between the emergence of evidence in favour of a therapeutic agent and subsequent use widespread enough to affect population survival. For example with ACE inhibitors there was an interval of 5 years between their general availability in 1991 and their routine use in hospitals, with an even longer delay before their use by primary care physicians – in 1996 only 33% of patients with heart failure being managed in primary care received an ACE inhibitor (Mair,

Crowley et al. 1996). Analysis of heart failure management in America between 1981 and 1991 demonstrated that a maximum of only 40% of patients diagnosed with heart failure received treatment with an ACE inhibitor (Senni, Tribouilloy et al. 1999). Perhaps more surprisingly a national study from the USA specifically looking at elderly patients with proven left ventricular systolic dysfunction and no contraindication to ACE inhibitor therapy found that only 68% received this treatment (Masoudi, Rathore et al. 2004). Current estimates of the use of heart failure therapy in Europe have been published (Komajda, Follath et al. 2003), demonstrating that only 62% of patients discharged from hospital following an admission with heart failure received an ACE inhibitor. Factors associated with the use of ACE inhibitors included younger age, male gender, ischaemic aetiology, diabetes and ejection fractions under 40%. Rates of beta blocker use were even lower at 37%. There is a wide variation of prescription rates by country as demonstrated in Figure 14 below.

Figure 14: Prescription rate of ACE inhibitors (in %) in the different countries participating in the Euro Heart Failure Survey (Komajda, Follath et al. 2003)



Another striking figure from this survey is that only 13% of the 10,701 patients enrolled across Europe would meet the entry criteria for the three large placebo controlled trials of heart failure (SOLVD Investigators1991; MERIT-HF Study Group1999; Pitt, Zannad et al. 1999) further emphasising the very select nature of clinical trial populations (Lenzen, Boersma et al. 2005). For those who did meet the criteria only 50% and <10% of those eligible for ACE inhibitor and beta blocker respectively achieved target dose level – further reason for differences between trial eligible patients and the general heart failure population.

Why such a large proportion of heart failure patients do not receive recommended therapy is not fully understood but is likely to reflect a combination of factors ranging from lack of awareness of guidelines to economic pressures on prescribing costs (Cabana, Rand et al. 1999). Reluctance to change practice or disagreement with the guidelines are additional elements that can be overcome with education, collaboration, audit and the use of specialist nurses bridging care between primary physicians and the specialist (Khunti, Sorrie et al. 1999; Stewart, Marley et al. 1999).

As well as underuse of proven therapies and differences between clinical trial and community heart failure populations additional reasons for the observed mortality differences include the confounding effect of patients with heart failure with normal ejection fraction – up to 50% of community heart failure patients (Vasan, Larson et al. 1999), and challenges in detecting survival differences in general populations as ACE inhibitors may only prolong survival by a mean of four to six months (Glick, Cook et al. 1995). This is however countered by the fact that clinical trials often

underestimate the true benefit due to employing intention-to-treat analysis whereby crossover patients dilute treatment benefit (Khand, Gemmel et al. 2000). As primary and secondary prevention of cardiovascular disease improves, the population characteristics of heart failure patients may change – coronary artery disease is now the leading aetiology of heart failure, replacing hypertension which may confer higher overall risk (Massie and Shah 1997).

Given these complicated factors affecting survival in the wider heart failure population, prospective studies in the community are required to assess true survival and plot trends. An innovative study looking at differences between heart failure mortality and re-admission between 1984, 1988 and 1992 in Scotland demonstrated an improvement in survival even after adjustment for age, gender, co-morbidity and aetiology (Cleland, Massie et al. 1999). Patients under 65 years had an absolute reduction in mortality at three years of 12%; those over 65 years of age had an absolute reduction of 5% again over three years. While this may suggest improvement it is still well below that seen in clinical trials and repeated studies are needed. Furthermore data on drug use was not available so a link between increased uses of proven therapies is not conclusive.

2 – 8 Ethnicity

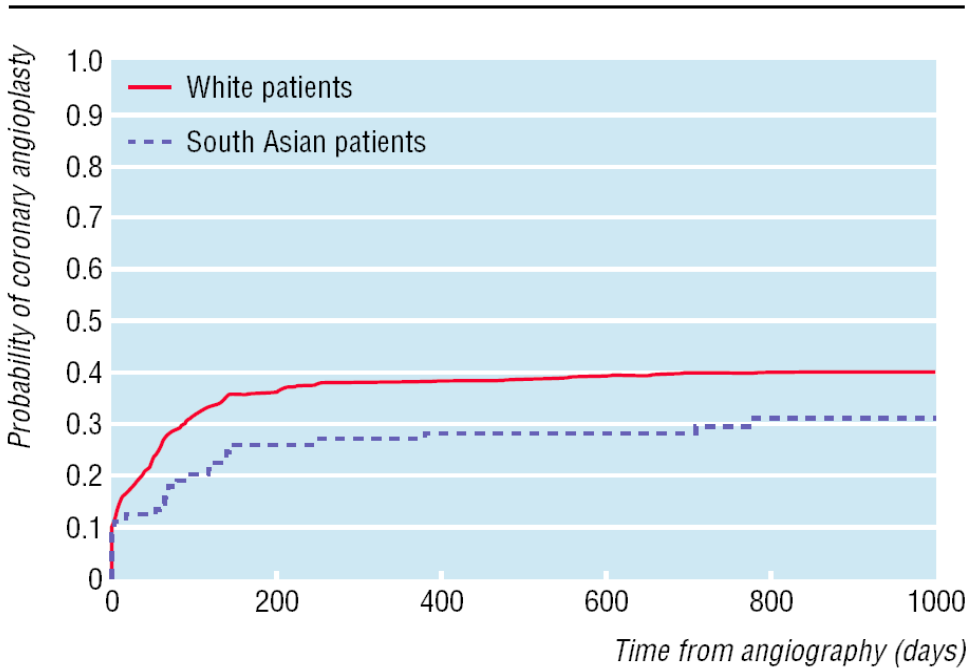
Ethnicity can be defined in various ways but a commonly used definition is 'pertaining to a social group within a culture and social system that claims or is accorded special status on the basis of complex, often variable traits including religious, linguistic, ancestral or physical characteristics' (Ghali 2002). This definition will be used throughout.

2 – 8 – 1 Ethnicity and cardiovascular disease

Given the differences in genes and gene expression along with diet, exercise levels, smoking habits and a multitude of additional factors it is not surprising that disease expression, presentation and progression can vary considerably between ethnic groups (Chaturvedi 2003). The two largest ethnic groups in which cardiovascular disease has been extensively studied include American African Caribbeans and South Asians in the United Kingdom. Cardiovascular disease remains the leading cause of death in both these ethnic groups, but variations between them have been reported, mainly with respect to coronary artery disease. South Asians have elevated risks of ischaemic heart disease but a different risk factor profile to Caucasians. Factors such as smoking and hypertension are common to both; others are more prevalent in South Asians such as glucose intolerance, obesity, unfavourable lipid profiles and diabetes. Identification of unique risk factors in differing ethnic groups has led to focus on elements such as inflammation and endothelial dysfunction as risk factors for all.

As well as different risk factor profiles the pattern of coronary disease also varies with ethnicity. South Asians are more likely to have three-vessel disease with more diffuse coronary atheroma compared to age-matched Caucasians. In contrast African Caribbeans have a risk of heart disease nearly half that of Caucasians, despite initially similar risk factor profiles to South Asians. On closer analysis rates of obesity and patterns of lipid disorders differ markedly. However both South Asians and African Caribbeans demonstrate differences in health care access. South Asians in the UK are more likely to wait longer for specialist review and have longer delays until appropriate diagnostic and interventional procedures – despite being more likely to have more severe coronary disease. Some of this may be related to difficulties in understanding and navigating the health care system – mainly due to language and social strata differences. Despite this, South Asian patients who are diagnosed with coronary artery disease and recommended revascularisation are less likely to receive planned interventions (Feder, Crook et al. 2002) as demonstrated in Figure 15.

Figure 15: Probability of South Asian and Caucasian patients receiving coronary angioplasty after angiography among those deemed appropriate for angioplasty (Feder, Crook et al. 2002)



2 – 8 – 2 Ethnicity and heart failure

Currently available data on heart failure across ethnic groups are sparse; but there does appear to be differences in heart failure risk. Given ischaemic heart disease is the commonest aetiology for heart failure it seems logical that an ethnic group with a higher rate of coronary disease is more likely to develop heart failure. Survival following diagnosis of heart failure is well researched in Caucasians but little data on South Asians are available. Research from Birmingham has demonstrated important differences in the perception of heart failure and its treatment, as well as deficiencies in the information offered to South Asian patients, emphasising the need for focussed intervention with emphasis on education in these high-risk subgroups (Lip, Khan et al. 2004).

A study undertaken in Harrow, London, assessed the ethnic differences in the prevalence and aetiology of left ventricular systolic dysfunction among 1392 patients randomly selected from local primary care practice (Galasko 2005). Of the 734 patients who attended, 71% were white and 29% non-white (mostly South Asian), and 5.5% had probable left ventricular systolic dysfunction and 3.5% definite systolic dysfunction. There was no significant difference in the prevalence between South Asian and white patients, but South Asians had a higher prevalence of coronary artery disease (100% vs. 56%, p=0.04) as assessed by myocardial perfusion scintigraphy and coronary angiography. A higher rate of diabetes in the South Asian cohort was also noted.

A longitudinal study of American Indians has assessed the prevalence of left ventricular systolic dysfunction to be 14% in middle aged to elderly adults, with markedly higher rates in men (17.4% vs. 7.2%) and diabetic patients (12.7% vs. 9.1%). Multivariate analysis identified left ventricular systolic dysfunction to be associated with male sex, coronary artery disease and hypertension, all similar risk factors to those demonstrated in Caucasian patients (Devereux, Roman et al. 2001).

While studies such as those described above have demonstrated associations between traditional risk factors for cardiovascular disease and heart failure in ethnic minorities, others have tried to identify evidence for alternative patho-physiological states between ethnic groups. This has mainly focussed on altered metabolism and insulin resistance, for example homocysteine and leptin.

Homocysteine is an amino acid associated with vascular disease when elevated (Wald, Law et al. 2002). Patients with heart failure from any cause have elevated homocysteine levels; furthermore South Asian patients have higher homocysteine levels with or without cardiovascular disease, suggesting ethnic differences in dietary factors may contribute to the development of heart failure. A study assessing differences in homocysteine levels between South Asian, White European and African Caribbean patients with heart failure demonstrated no significant variation, and without difference in the levels of B_{12} or folate suggesting dietary factors may be important but not dietary deficiency in folate or B_{12} as previously suggested(Sosin, Patel et al. 2008).

A further study from Birmingham assessed the ethnic variations in adipocytokines such as leptin between South Asians and Caucasians. Elevated markers of insulin resistance were found in heart failure patients irrespective of ethnicity but mean leptin concentration were 5.25% (95% CI: 1.50 – 9.02, p=0.007) higher in South Asian patients compared to Caucasians (Patel, Sosin et al.). This data suggests that metabolic deterioration is important in heart failure as already described (Murray 2004), but this in turn may be influenced by ethnicity and provides preliminary evidence for variations in the patho-physiology of heart failure between ethnic groups.

2 – 8 – 3 Ethnicity and response to heart failure therapy

Anti-hypertensive agents and their effects have been studied across ethnic groups (Saunders, Weir et al. 1990; Materson, Reda et al. 1993), and evidence of differences in response to beta blockers has been demonstrated. Additional evidence that the benefit of losartan in reducing stroke rate in hypertensive patients is reduced in Black patients compared to Caucasians (Dahlof 2002) has been shown. Similar to the response to an angiotensin receptor blocker such as losartan, there is evidence that the benefit of ACE inhibitor therapy is attenuated in Black patients. In fact in the V-HeFT II trial Black patients did not sustain a survival advantage with enalapril over combination hydralazine and nitrate therapy (Carson, Ziesche et al. 1999). Interestingly American Asian patients report ACE inhibitor induced cough at a rate as high as 50% - clearly limiting their tolerability but also suggesting altered pharmacology given the link between bradykinin levels and cough (Fox, Lalloo et al. 1996).

Little robust data exists on any difference between beta blocker efficacies across ethnic groups. The trial of bucindolol in heart failure failed to show any improvement in survival and was abandoned after an interim analysis, the authors concluded one explanation for the lack of effect may have been the relatively large proportion of Blacks in the trial – 24% - as there was a suggestion of differences between racial groups and the response to beta blocker therapy (BEST Trial 2001). A review of the US Carvedilol Heart Failure Trials program data which recruited 1,094 patients, 20% of whom were Black, did not demonstrate any significant difference in the magnitude of benefit with carvedilol (Yancy, Fowler et al. 2001).

It appears the aetiology and optimal treatment of heart failure may vary according to ethnicity although this aspect is rarely emphasised in clinical guidelines. A randomised trial of heart failure in Black Americans with at least three months of NYHA class III or IV heart failure assessed the additional benefit of a combination preparation of isosorbide dinitrate and hydralazine to standard heart failure therapy (Taylor, Ziesche et al. 2004). The trial recruited between June 2001 and July 2004; at the time of enrolment 74% were on a beta blocker and 70% on an ACE inhibitor. The addition of the combination specified was associated with a reduced mortality of 6.2% over 18 months compared to 10.2% for placebo ($p=0.02$). Given the high rates of neurohormonal blockade already in place this suggests the existence of an alternative mechanism driving heat failure progression which can be targeted with a combination nitrate and hydralazine preparation. Further trials specifically addressing ethnic variations in response to heart failure therapy are required.

2 – 9 Lack of ethnic variation in trial cohorts

South Asians form the largest ethnic minority group in the United Kingdom at 7%, and have been described to have higher rates of coronary disease, often of a more severe form. Therefore South Asians constitute a large population at risk of heart failure. Despite this South Asians are consistently under-represented in clinical trials. Analysis of six different non-cardiology trials in the United Kingdom found that South Asians constituted only 1.7% of the 12,323 patients enrolled (Mason, Hussain-Gambles et al. 2003). This significant bias towards research in Caucasians has implications given the differences in risk factor profile and possible differences in response to drug therapy. Where data on ethnicity and response to heart failure therapy exists it is often due to the fortuitous inclusion of a significant enough proportion of Black or South Asian patients rather than due to explicit trial design (Taylor and Wright 2005). The differences in disease between ethnic groups can be attributed to differences in genotype, phenotype, social factors, environment, lifestyle, and co-morbidities. Given these differences, trial design must account for the contribution of these factors and how they can be modified or treated. Any therapeutic benefits identified may still be applicable to the whole population.

2 – 10 Summary

In this chapter I have reviewed survival of our local heart failure patients and related this to current evidence based drug therapy. The need to assess prognosis and a review of available methods has been discussed. The impact of ethnicity on outcome as well as the patho-physiology of heart failure and the current lack of data is presented. The hypotheses that survival in patients admitted to hospitals in Leicester with heart failure is similar to national published data and that significant differences in survival between Caucasians and South Asians exist are to be tested in this thesis.

The questions to be answered in this thesis relevant to this chapter can be summarised as follows:

1. What is the crude survival of patients admitted to hospital with a new diagnosis of heart failure?

2. Can simple admission data be used to construct a prognostic model identifying high risk patients?

3. What differences in the epidemiology and aetiology of heart failure exist between South Asian and Caucasian patients?

4. Do South Asian patients receive similar investigation and treatment to Caucasian patients?

5. Do South Asian patients with heart failure have an increased mortality compared to Caucasians?

6. Do factors which predict outcome vary between Caucasians and South Asians?

The answers to questions 1 and 2 are discussed in chapter 5, with the answers to questions 3 to 6 discussed in chapter 6.

Chapter 3 – Methods

3 – 1 Introduction

In order to answer the research questions outlined in chapters 1 and 2 the design of this study focuses on collection of a large amount of data pertaining to the aetiology, demographics, co-morbidity, treatment and outcome of a selection of patients admitted to hospitals in Leicester with heart failure. In order to address the specific effect of ethnicity as discussed in chapter 2, a cohort consisting of both South Asian and Caucasian patients was chosen.

In this chapter I will defend the study design, patient identification methods and describe the data collection techniques used. Following this I will describe the statistical analysis undertaken and the novel technique for analysis of electrocardiogram data developed for use in this study.

3 – 2 Choice of study design

Prior investigations into our local heart failure population have demonstrated improvement in heart failure survival over time, but a persistently high case fatality rate (Blackledge, Newton et al. 2003). Leicestershire's health information service has a comprehensive record linkage system, allowing for accurate (> 95%) follow up of individual patients, in terms of routinely recorded events such as hospitalisations and

mortality. From the late 1990's, these data have contained self-reported ethnicity coding, for which local coverage is thorough. The use of case-registers and record linkage has been used to assess incidence, prevalence, survival and risk factors for outcomes. A major advantage is access to a large data set which improves precision of any analysis, and allows for long follow-up periods. The retrospective nature of registry analysis reduces the phenomenon of recall bias as data have been collected prior to 'follow-up' and without knowledge of any hypotheses being tested (Mortensen 1995). Following identification of a large cohort from a registry it is then feasible to select a smaller cohort in order to conduct a more detailed case-control type analysis (Clayton and Hills 1993). This smaller group can be used to obtain data on risk factors and potential confounders, and also to assess the quality of the data from the registry as a whole.

I wished to explore this dataset and also validate the coding diagnosis, and examine the survival impact of ethnicity. An aim of this study was to compare the clinical characteristics of and the relative prognosis for, South Asian and Caucasian patients hospitalised for the first time with heart failure after correcting for disease severity, access to investigations and pharmacological therapy in the two populations. I also wished to assess possible aetiological factors in these cohorts. In order to directly compare the effect of ethnicity I chose a matched cohort analysis design. As ethnicity was chosen as the main strata and all patients were known to have heart failure, I selected all South Asian patients with heart failure and matched them by age and sex with non-South Asian patients.

3 – 3 Matched cohort analysis

A matched cohort design utilises two patient populations which are matched for one or more variables. The purpose of this matching is to remove the effect of this variable on the outcome assessed – if there is no missing data or loss of subjects the effect of the variable(s) chosen on outcome should be negligible (Greenland and Morgenstern 1990). This choice of study design is not often used which may in part be due to the difficulty in identifying matched patients (Cummings, McKnight et al. 2003). However, with a total patient sample size of 5,790 all South Asian patients admitted with heart failure were matched with patients of the same sex and age. It is usual practice to select the 'unexposed' cohort so that it follows the covariate distribution of the 'exposed' cohort. As our patients were not 'exposed' to any specific intervention given the studies observational and retrospective nature, I nominated the primary cohort as those patients with South Asian ethnicity and matched the secondary cohort with them. In order to minimise matching complexity and impact on the efficiency of the study I chose to match patients by only two variables, namely the patients' age and sex. Give the number of patients to select from I chose the patient with the nearest age by date of birth. The matching process was undertaken with the entire South Asian cohort prior to analysis of case notes to minimise any bias introduced if matching were restricted to those patients with available records.

3 – 4 Cohort identification

Leicestershire Health Authority record linkage system 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.

I 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 1998 and 31 March 2001. I 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 with no previous heart failure related hospitalisation in a minimum of the preceding five years. As a relatively small degree of migration occurs in those aged over 40, I 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 these data may have omitted a small number of residents, it constitutes a large cohort from a demographically varied population. Ethnicity, information recorded routinely, was that reported in the hospital discharge data. A total of 5,788 patients admitted with a new diagnosis of heart failure on discharge coding were indentified, and from these the matched cohort to be studied were identified using a case matching strategy described below.

Formal inclusion and exclusion criteria used in the patient identification process are shown in Table 6 below.

Table 6: Entry criteria during patient identification phase

Inclusion Criteria	Exclusion Criteria
Age over 40 (no upper limit)	Entry into the region within 5 years of the index admission
Heart failure diagnosis in any coding position	Prior admission to hospital with a discharge diagnosis of heart failure within 5 years

3 – 5 Case matching strategy

I matched each South Asian patient with 2 sex- and age-matched Caucasian patients. Figure 16 shows the flowchart of case matching and the generation of the final cohort. Details regarding the patients whose notes were either incomplete or miscoded stratified by ethnicity are shown in Table 7. No significant difference in the rates of miscoded or incomplete records between ethnic groups was observed.

Figure 16: Case-matching process

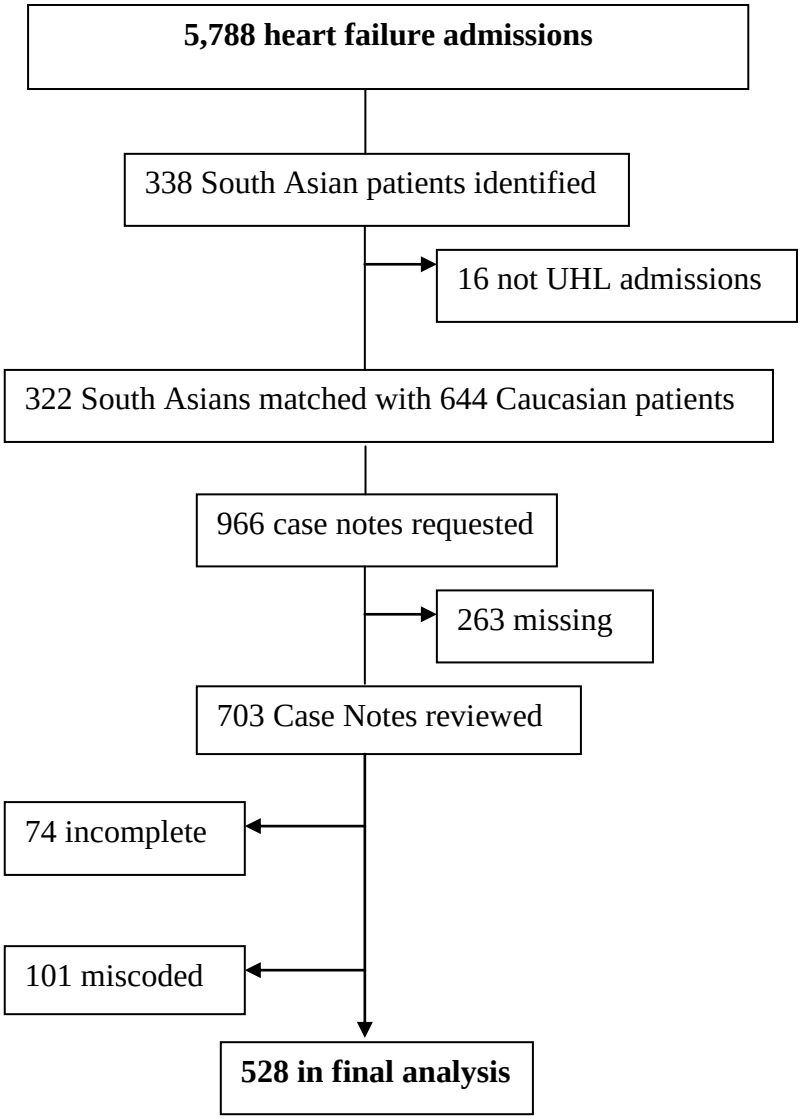


Table 7: Breakdown of incomplete and miscoded notes by ethnicity

	Caucasians (n=466)	South Asians (n=237)
Incomplete	47 (10%)	27 (11%)
Miscoded	67 (14%)	34 (14%)
Correct	352 (76%)	176 (75%)

3 – 6 Final analysis cohort

Further detail on the demographics of the final cohort are given in the initial results section of chapter 4, but in order to demonstrate the effect of matching I will present here the final cohort details. The basic demographic data for the final analysis cohort are shown in Table 8 below.

Table 8: Basic demographic data for the final analysis cohort

	All **n (%)**	**Caucasian** **n (%)**	**South Asian** **n (%)**	**p value**
Admissions	528 (100)	352 (66)	176 (33)	
Male	302 (57)	205 (58)	97 (55)	0.494
Female	226 (43)	147 (42)	79 (45)	0.494
Mean Age	69	70	68	0.106

As can be seen from the table above the age and sex distribution for the two cohorts are identical with no significant difference between mean age and sex distribution noted. As data collection was retrospective and the final analysis based on patients whose case notes were available, no potential confounding by inequitable drop out between cohorts was encountered.

3 – 7 Post-hoc power analysis

The sample size chosen was limited by the number of South Asian patients in the cohort of heart failure admissions identified whose case notes were available. These 176 patients were matched with two Caucasian patients to give a total sample size of 528. To assess whether this sample size provided sufficient power to identify the effect size under assessment a post-hoc power calculation was undertaken as described below.

Using the technique and software described by Faul and Erdfelder (Faul, Erdfelder et al. 2007) an assessment of power was calculated based on the effect size between mean survival in the South Asian and Caucasian cohorts. The full outcome data are described in chapter 5 however the summary data used for the calculation is presented in Table 9 below.

Table 9: Mean survival in days stratified by ethnicity

Variable	Caucasian	South Asian
Mean Survival	805 days	892 days
Standard Deviation	572	540

This generates an effect size of 0.156. Assuming a significance level (α) of 0.05 the actual power to detect such an effect size when assessing the difference between two means using t-testing is 0.95, well over the accepted limit of 0.80 (Cohen 1969).

3 – 8 Validation of diagnosis

The validity of the diagnosis required documentation of appropriate symptoms (shortness of breath, peripheral oedema, fatigue) and physical findings (pulmonary crepitations, peripheral oedema, gallop rhythm, jugular venous distension) in keeping with the definition discussed in Chapter 1. I sought supportive documentation from reports of chest radiography. If doubt remained, an appropriate therapeutic response following diuretic therapy was accepted. Cases for which the diagnosis of heart failure on the index admission could not reliably be confirmed were excluded as false positive cases. Given the patient cohort was derived from those coded as a heart failure admission I am unable to assess the rate of false negative cases – patients who were admitted with heart failure but coded with an alternative diagnosis. Due to the limitations of the study design assessing this potential confounder is not possible.

Reasons for this miscoding were collected on the 101 patients involved and these are summarised in Table 10 below. Overall 86% of discharge diagnoses of heart failure were validated as correct although in 12% of these the record was insufficient for use in the study. This is reassuringly similar to a study undertaken in Sweden analysing the case records of 321 admissions coded with heart failure on discharge, and found that the diagnosis was valid in 82% (Ingelsson, Arnlov et al. 2005).

Table 10: Reasons for miscoding of heart failure in 101 patients excluded

Reason	Number	Example
Alternative diagnosis proven	40	Heart failure considered during admission but alternative diagnosis such as pneumonia more certain
Inappropriate admission event	15	Heart failure listed on discharge coding as part of patients past medical history – index admission was for alternative reason
Coding error	27	No evidence of heart failure in clinical record
Index admission unavailable	10	Notes retrieved but no data on index event available
Other	9	Surgical procedure coded as CCF actually referred to complete circumcision of foreskin

Further analysis of these 101 cases shows that 66% were Caucasian and 33% South Asian demonstrating there was no ethnicity bias to the miscoded notes. Similarly 62% of the case notes recorded as incomplete was Caucasian and 38% South Asian.

3 – 9 Validation of ethnicity coding

The ethnicity code recorded in the central database is based on self-reporting by the patient when admitted to hospital. Methods for assessing the validity of ethnicity based on distinctive naming algorithms such as the South Asian Names and Group Recognition Algorithm exist (Aspinall and Jacobson 2007), however I undertook a more crude validation by assessment of the patients name. This will have reduced any false positive cases of South Asian ethnicity however confirming no Caucasian patients were in fact South Asian on the basis of name was not possible. It is likely however that any bias introduced on the basis of ethnicity coding would be minimal.

3 – 10 Data retrieval techniques

I abstracted baseline clinical characteristics including demographic features, clinical history, physical findings, and biochemical/haematological information relevant to the index heart failure admission onto a pre-designed data collection form (see Appendix 1). Biochemical and haematological data recorded were the first available from the admission episode. If not clearly recorded in the medical notes they were obtained by querying the central hospital pathology database.

A history of coronary heart disease was recorded if there was a prior history of angina, myocardial infarction or coronary revascularisation. Diabetes was recorded in those treated with insulin, oral hypoglycaemic drugs or dietary restriction. Hypertension was recorded for those with a history of treated hypertension or clearly

on anti-hypertensive therapy, the admission blood pressure was not used. Furthermore if doubt about a patients history of hypertension existed (for example on a drug used for both hypertension and angina) they were not recorded as having hypertension.

Details of baseline and discharge drug therapy were abstracted from the notes and a copy of the electrocardiogram on presentation taken. Data from a chest X-ray taken on admission was recorded either from a written entry in the clinical record or a formal report from a radiologist. The echocardiographic results database was searched for any echocardiography data on each patient in the study, and the results and date of study in relation to the hospital admission episode recorded. The admitting physician's speciality was also recorded, and the case record scrutinised for any documented advice or review by a cardiologist.

3 – 11 Database construction

A bespoke database was constructed in Microsoft® Access with a front end identical to the data capture form to allow accurate data entry. A single master table recording all the data was created, with linked sub-tables pertaining to each data section such as demographics, biochemistry etc. to facilitate subsequent data searches. A unique patient record identifier was created to allow tracking of patient data. In compliance with hospital and research department policies all retrieved data was anonymous and recorded under the study number only. A separate spreadsheet linking study numbers to case record numbers was stored separately under secure conditions.

All subsequent searches of the database were logged and recorded to allow review of retrieved data and ease future querying in the event of erroneous data or mis-typed data fields. All data retrieval forms were retained until the end of the data collection period and then cross checked with the database for accuracy of entered data before being confidentially destroyed.

3 – 12 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 (31 March 2003), providing a minimum of twenty four months of follow up for those alive at the end of the study period. For patients who migrated from the area before 31 March 2003, the date of migration was taken as the end of follow up.

3 – 13 Statistical Analysis

All statistical analysis was performed using SPSS© version 14.0 on datasheets exported directly from the main database. Differences between groups were examined using the χ^2 test for categorical variables and Mann-Whitney test for continuous variables. Data are presented as the mean for continuous variables and as proportions for categorical variables. A two sided p-value of <0.05 was considered statistically significant.

Crude survival was estimated using the Kaplan-Meier method and Cox proportional hazards modelling used to assess the influence on outcome of covariates. Covariates assessed for such an influence included age, prior myocardial infarction, hypertension, renal insufficiency, diabetes or stroke, and baseline serological variables including sodium, creatinine, haemoglobin and glucose. To examine for linearity of associations between outcome and continuous variables, these were categorised by quartiles. The methodology used is detailed further in chapter 5 which outlines the development of a prognostic model for predicting survival.

3 – 13 – 1 Missing data

To minimise the effect of absent data values by biasing towards those with data present thereby skewing results and reducing power (Harrell, Lee et al. 1996), all missing continuous variables were imputed using the expectation-maximisation method which is based on the correlation between each variable with absent values and all other variables as estimated from the set of complete subjects (Greenland and

Finkle 1995). This method is based on the assumption that subtype data are missing at random with regard to the true outcome so that, among cases with a given set of covariates, the probability that case sub-classification is missing does not vary across groups (Schroeder and Weinberg 2001). With regards to the continuous variables included in the analysis with missing values Table 11 below details the number and percentage of the whole study cohort with missing data for that variable.

Table 11: Details of missing data imputed prior to analysis

Variable	Number with missing value	Percentage of whole cohort
Pulse rate	40	8%
Blood pressure	58	11%
Sodium	1	< 1%
Potassium	1	< 1%
Creatinine	1	< 1%
Glucose	96	18%
Haemoglobin	2	< 1%
Mean Cell Volume	30	6%
QRS duration	63	12%

Any variables missing in more than 20% of patients were not included in the final analysis to avoid introduction of bias. These include cholesterol (present in only 40%), creatinine kinase and troponin (present in < 30%), pulmonary artery pressure (rarely recorded), left atrial size, and diastolic dysfunction (never recorded).

3 – 13 – 2 Univariate analyses technique

The ontinuous and categorical variables used in the univariate analysis are shown in Table 12. Each variable under review was assessed using the semi-parametric Cox proportional hazards model to test for any influence on the selected outcome, usually survival. This model does not assume any distribution for the baseline hazard and specifies that the hazard ratio is constant over time and independent of all other covariates (Rao and Schoenfeld 2007). Tests on the normality of data were undertaken and where necessary logarithmic adjusted values were used. Crude risk ratios for mortality were calculated for all potential prognostic determinants. Continuous variables were analysed with and without categorisation into either quartiles or grouped around the median.

Table 12: Continuous and categorical variables in the univariate analysis

Continuous variables	Categorical variables
Age	Sex
Duration of admission	Ethnicity
Pulse rate	Smoking status
Systolic blood pressure	Ischaemic heart disease
Diastolic blood pressure	Hypertension
Serum sodium	Stroke
Serum potassium	Diabetes
Serum creatinine	Heart failure history
Serum glucose	Chronic obstructive pulmonary disease
Serum haemoglobin	Pacemaker
Serum mean cell volume	Renal failure
QRS duration	Symptom duration
QRS dispersion	Cardiomegaly on chest X-ray
QT duration	Upper lobe diversion on chest X-ray
QT dispersion	Pulmonary oedema on chest X-ray
QTc duration	Pleural effusion on chest X-ray
QTc dispersion	Echo performed
JTc duration	Systolic function category
JTc dispersion	Valve disease category
	Drugs on admission
	Drugs on discharge

3 – 13 – 3 Multivariate analyses technique

All potential prognostic determinants with a probability value of $p < 0.10$ were included in a multivariate logistic regression analysis using a forward conditional method and then used to develop a prognostic index. To ensure the final model remained simple to use, variables were dichotomised according to the quartile giving the highest hazard ratio on multivariate analysis. The sum of the scores was taken, the highest score being 8, with a lower score corresponding to improved survival. Each possible total score binary cut-off for low and high risk of all-cause mortality was assessed for its sensitivity, specificity, positive predictive and negative predictive values. Receiver operating characteristic (ROC) curves were constructed using these data, by plotting the sensitivity against 1 – specificity for each cut-off point. The area under the curve (AUC) was calculated, with 0.5 taken as indicating the test result is no better than chance, and 1.0 indicating a test with perfect sensitivity and specificity. All statistical analysis was performed using SPSS software (version 14.0, SPSS, Chicago, Ill).

3 – 14 ECG Analysis

The 12-lead electrocardiogram (ECG) can be of diagnostic and prognostic benefit in heart failure (Iuliano, Fisher et al. 2002; Ng, Loke et al. 2003). The first recorded ECG in each patient was copied and analysed. Only 2% of patients had a pacemaker in-situ and these were included in the ECG analysis. Previous studies have used manual measurement of ECG intervals with callipers but with an inherent degree of inaccuracy. In order to ensure optimal accuracy of interval assessment I developed a novel software solution. In order to validate the software I analysed a separate cohort of 100 ECGs obtained at the time of each patient's attendance for echocardiography, recorded at 25mm/s and 1mV/cm standardization with a Hewlett Packard PageWriter machine.

ECGs were then digitised at a resolution of 300 dots per inch using a Canon Canoscan N124OU scanner and stored electronically. Analysis was performed using a bespoke Microsoft® Windows® application (ECG Analyser v1.12) written by myself using Borland® Delphi® software development interface. This software allows precise location of each segment of the QRS complex by zooming it at great resolution to individual QRS complexes. Each ECG was calibrated from the standardised ECG paper - a sequence of five sequential R waves in the rhythm strip was manually identified to allow calculation of the mean R-R interval. Following this, the software automatically selects one QRST complex in each lead and individually magnified them to 600%. The onset of one Q wave, end of an S wave and the end of a T wave were manually identified in each lead. When U waves were present the end of the T wave was taken as the nadir of the curve between the T and U waves. If any part of

the QRST complex was unclear it was flagged and not included in the calculations. The application then calculated the maximum, minimum and mean QRS duration across all leads analysed. Maximum, minimum and mean QT duration were also calculated. The same range of QTc durations were derived using Bazett's formula. Final calculation data for each ECG was logged in a data file as comma separated values for later statistical analysis.

These 100 separate ECGs were recorded on a Hewlett Packard HP708 as this also calculates mean QRS, QT and QTc for each ECG, allowing comparison between the ECG machines derived data and that from the software analysis. The correlation coefficient (r) for QRS duration was 0.982, $p<0.0001$ (Figure 17). QT correlation coefficient (r) was 0.987, $p<0/0001$ (Figure 18) and QTc correlation coefficient (r) 0.951, $p<0.0001$ (Figure 19). Given the high degree of correlation with a standard ECG machine this software allows me to accurately calculate intervals on ECGs not recorded on machines with such capabilities, and also calculate dispersion for the intervals. Screenshots of the software are included in Appendix 2.

Further ECG analysis on the heart failure cohort included assessment of cardiac rhythm and identification of left ventricular hypertrophy using the Cornell product criteria. With this method the sum of the R wave amplitude in lead aVL and the S wave amplitude in lead V3 is multiplied by the mean QRS duration to give a voltage-duration product which enhances detection of increased left ventricular mass [Okin 1995]. These calculations were performed manually on all ECGs.

Figure 17: Correlation between Hewlett Packard HP708 derived and ECG Analyser QRS measurements

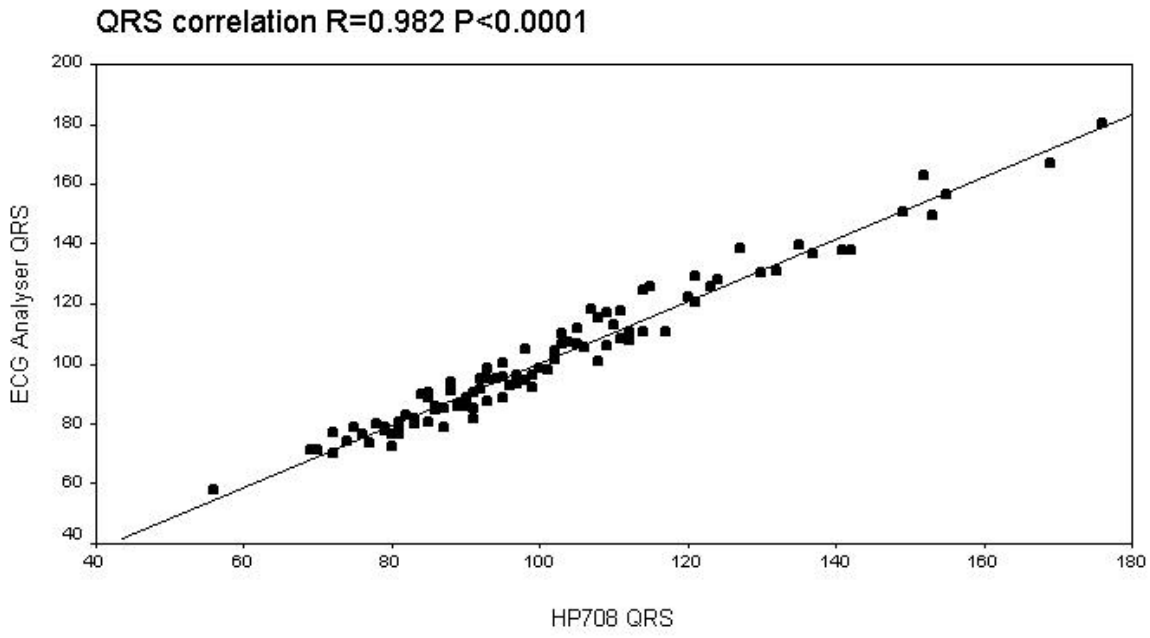


Figure 18: Correlation between Hewlett Packard HP708 derived and ECG Analyser QT measurements

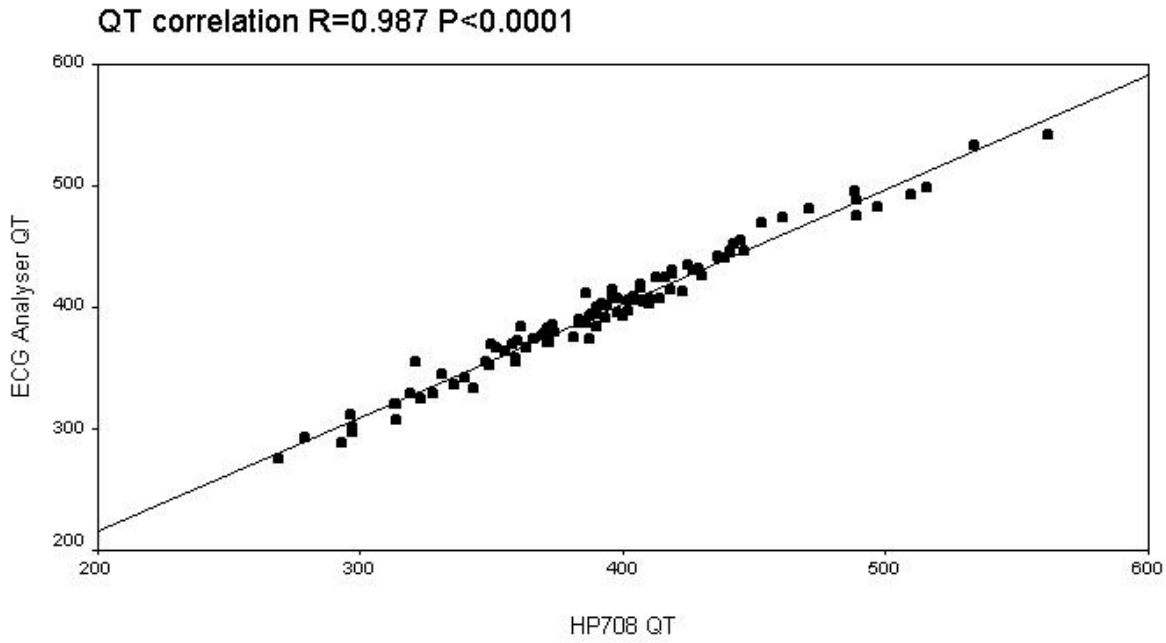
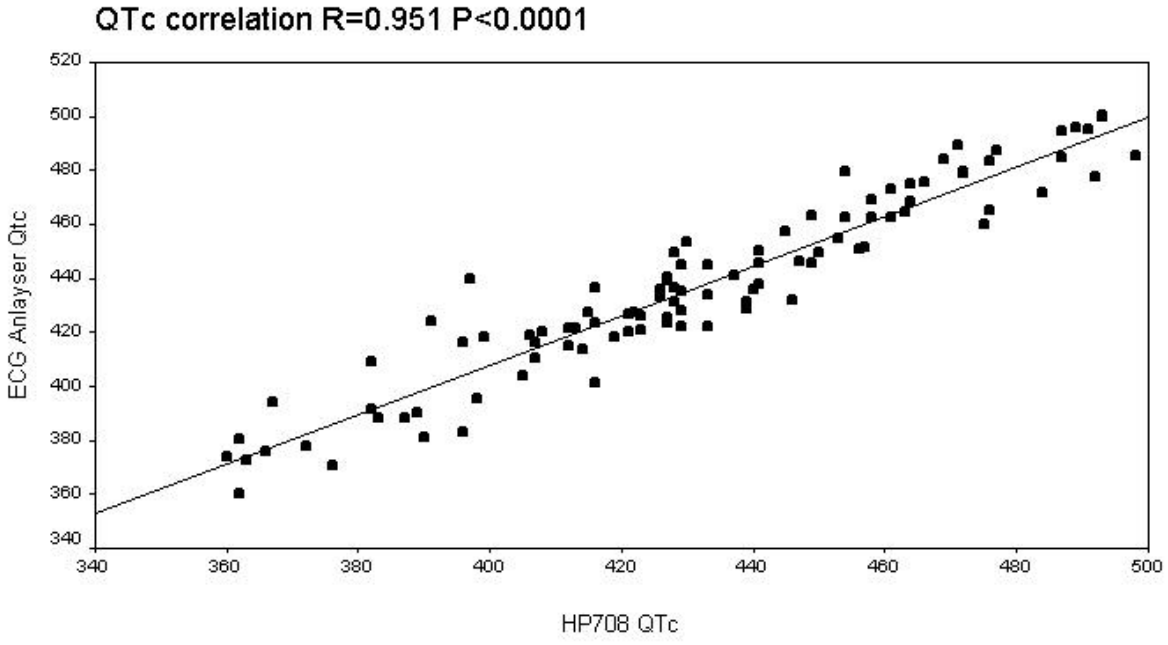


Figure 19: Correlation between Hewlett Packard HP708 derived and ECG Analyser QTc measurements



3 – 15 Summary

In this chapter I have described the methodology for the design of the study, case identification, cohort selection and data collection. I have explained the statistical analysis undertaken and performed a post-hoc power analysis calculation. Handling of missing data is discussed. In addition the technique and software developed to analyse ECG data have been demonstrated.

Chapter 4 – Results

4 – 1 Introduction

In this preliminary results chapter I will present tabulated data showing the demographic characteristics of the whole cohort including age, sex, and admission duration. Further data on symptoms, co-morbidities, clinical findings and biochemistry follow, along with data on electrocardiology and echocardiography. Finally data on admission and discharge drug therapy will be reviewed.

I will then answer the research questions posed in chapter 1 and discuss these data in comparison to published figures, highlighting any differences between this study cohort and the general heart failure population.

4 – 2 Main Study Population

The basic demographics of the heart failure cohort are shown in Table 13. These data show that the mean age of patients studied was 69 years, ranging from 39 years to 102 years. Male patients form 57% of the cohort studied. The mean duration of hospital admission is 14 days, although there is a significant outlier in that one patient was hospitalised for over one year following their index admission. Review of this set of notes confirmed this prolonged admission was a result of multiple medical and surgical comorbidities and complications. The median duration of admission was

only 8days. At the end of follow up 240 (45%) of the total cohort had died, with 56 (11% of the population, 23% of all deaths) of these deaths occurring during the index admission. Of particular interest is that only 41% of patients admitted with heart failure were under direct care of a cardiologist. Although the data retrieval method used will not have captured any informal advice offered by cardiologists it is clear the majority of heart failure admissions are under the care of non-cardiologist physicians.

Table 13: Basic demographics of the heart failure cohort

	Number	**%**
Patients studied	528	100
Male	302	57
Female	226	43
Mean Age	69	
Age range	39 – 102	
Mean duration	14	
Median duration (range)	8 (0 – 380)	
Cardiologist input	218	41
Died	240	45
Died during admission	56	11

4 – 3 Symptoms of heart failure

Given that a diagnosis of heart failure requires identification of symptoms such as breathlessness and fatigue, evidence for these symptoms were sought in the medical record, along with an estimation of duration. The frequency and duration of heart failure symptoms recorded are shown in Table 14.

A clear description of the patients' symptoms was recorded in 83% of admission records studied. The duration of heart failure symptoms varied from less than 24 hours to more than 6 months, with 45% of patients reporting symptom duration between 1 day and 1 month. The commonest reported symptom was dyspnoea – present in just over 60% of all patients, followed by orthopnoea and oedema. Chest pain was reported in 19% of patients. Surprisingly only 4% of patients were documented as reporting fatigue as a symptom in the clinical record.

The patient's NYHA class of heart failure is an important indicator of heart failure severity and also an independent indicator of prognosis. Unfortunately only a very few admissions documented heart failure symptoms with a grading by NYHA class. Although in some cases I may have been able to infer NYHA class from the description, given the low numbers where this may have been feasible and inherent inaccuracy I elected to not record or analyse NYHA class.

Table 14: Frequency and duration of heart failure symptoms recorded

	Number	%
Patients studied	528	100
Data available	437	83
Symptoms duration < 24 hours	118	22
Symptoms duration 24 hours - 1 week	113	21
Symptoms duration 1 week - 1 month	127	24
Symptoms duration 1 – 6 months	55	10
Symptoms duration > 6 months	6	1
Dyspnoea	323	61
Orthopnoea	148	28
Paroxysmal nocturnal dyspnoea	78	15
Oedema	87	16
Chest Pain	99	19
Fatigue	20	4
Cough	48	9

4 – 4 Co-morbidity

Documentation of important co-morbidities in patients with heart failure was recorded and the frequencies of co-morbidities including smoking history are shown in Table 15.

Thirty-six percent of all patients reported either prior or current smoking status. A diagnosis of ischaemic heart disease was reported in 35% of all patients and a diagnosis of hypertension was reported in 37%. Very few patients (6%) reported documented hyperlipidaemia and only 11% had sustained prior cerebrovascular disease. Diabetes – an important risk factor for ischaemic heart disease and heart failure - was recorded at admission in 27% of the total cohort. Chronic obstructive pulmonary disease (COPD) – a common co-morbidity in heart failure and also a diagnostic confounder was recorded in only 9% of all patients. Seventy-six (14%) of patients reported no prior medical history of note.

Table 15: Frequency of co-morbidities including smoking history

	Number	%
Any Smoking	188	36
Current smoker	83	16
Ex smoker	105	20
Family history of ischaemic heart disease	29	5
Angina	122	23
Myocardial infarction	111	21
Any ischaemic heart disease	186	35
Hypertension	197	37
Hyperlipidaemia	30	6
Stroke	57	11
Diabetes	140	27
Renal failure	10	2
Malignancy	15	3
Chronic obstructive pulmonary disease	47	9
No past medical history	76	14

4 – 5 Clinical data

The distribution of pulse and blood pressure recorded at admission with frequencies at the upper and lower quartiles are shown in Table 16. The mean pulse recorded on admission was 94 beats per minute, with 33% of patients having a tachycardia on arrival (pulse greater than 100 beats per minute). The mean blood pressure of the whole cohort was 142 / 81 mmHg with just under 30% of patients having marked hypertension (systolic greater than 180 mmHg). A further 20% of patients presented with hypotension (systolic lower than 100 mmHg).

Table 16: Distribution of pulse and blood pressure recorded at admission with frequencies at the upper and lower quartiles

	Number	%	Units
Mean Pulse	94		bpm
Median Pulse	91		bpm
Pulse > 100	176	33	bpm
Pulse > 120	65	12	bpm
Pulse < 50	7	1	bpm
Mean Systolic	142		mmHg
Median Systolic	140		mmHg
Systolic > 180	152	29	mmHg
Systolic > 140	144	27	mmHg
Systolic < 100	107	20	mmHg
Mean Diastolic	83		mmHg
Median Diastolic	81		mmHg
Diastolic > 94	126	24	mmHg
Diastolic < 70	113	21	mmHg

4 – 6 Biochemistry

The range of sodium, potassium, creatinine, glucose and haemoglobin with frequencies at the upper and lower quartile are shown in Table 17. The mean sodium and potassium recorded for the whole cohort were within normal limits at 137mmol/l and 4.2mmol/l respectively. Twenty-two percent of patients were hyponatraemic on admission (Sodium < 135mmol/l). The mean creatinine for the whole cohort was 123µmol/l on admission with 24% of patients having a creatinine greater than 133µmol/l. As few patients had a weight recorded in the notes on admission I was unable to estimate glomerular filtration rates. The mean glucose for the whole cohort was abnormal – elevated at 8.8mmol/l, with 25% of patients having on admission glucose greater than 10mmol/l. The mean haemoglobin for the whole cohort was normal at 12.9g/dl, and 23% of patients had haemoglobin on admission of under 11.5g/dl.

As the data collection form in Appendix 1 suggests information on Troponin, cholesterol level and CK were also collected where available, However, as fewer than 30% of patients had these measurements available for the index admission they were not included in the final analysis.

Table 17: Sodium, potassium, creatinine, glucose, and haemoglobin with frequencies at the upper and lower quartiles

	Number	%	Units
Mean Sodium	137		mmol/l
Sodium > 140	114	22	mmol/l
Sodium < 135	115	22	mmol/l
Mean Potassium	4.2		mmol/l
Potassium > 4.6	112	21	mmol/l
Potassium < 3.8	130	25	mmol/l
Mean Creatinine	123		µmol/l
Creatinine < 85	126	24	µmol/l
Creatinine > 133	127	24	µmol/l
Mean Glucose	8.8	8.4	mmol/l
Glucose < 5.9	114	22	mmol/l
Glucose > 10	130	25	mmol/l
Mean Haemoglobin	12.9	13.0	g/dl
Haemoglobin > 14.3	123	23	g/dl
Haemoglobin < 11.5	124	23	g/dl

4 – 7 Electrocardiography

The first recorded electrocardiogram (ECG) for each patient on admission was copied and analysed as outlined in the methods chapter. The distribution of heart rhythm, left ventricular hypertrophy and interval duration along with frequencies at the upper and lower quartiles are shown in Table 18. The majority (69%) of patients were in sinus rhythm at the time of the first ECG recording. A total of 26% of patients had left ventricular hypertrophy. The mean QRS duration for the whole cohort was within normal limits at 104ms. A prolonged QRS duration (greater than 120ms) was seen in 22% of the whole cohort, with a further 5% having a QRS duration prolonged beyond 150ms.

Table 18: Distribution of heart rhythm, left ventricular hypertrophy and interval duration along with frequencies at the upper and lower quartiles

	Number	%	Units
ECG available	464	88	
Sinus rhythm	322	69	
Atrial Fibrillation	118	25	
Atrial Flutter	8	2	
PPM	8	2	
Heart block	8	2	
Left ventricular hypertrophy	122	26	
Mean QRS	104		ms
Max QRS	128		ms
Min QRS	80		ms
QRS dispersion	48		ms
QRS > 120	100	22	ms
QRS > 150	21	5	ms
Mean QTc	450		ms
Max QTc	496		ms
Min QTc	406		ms
QTc dispersion	90		ms

4 – 8 Chest X-ray

The findings on admission chest X-ray for the 78% of patients with a reported chest X-ray are shown in Table 19. Half of the whole cohort had chest X-ray evidence of cardiomegaly, and 38% had evidence of frank pulmonary oedema. A further 39% had additional signs suggestive of pulmonary congestion such as upper lobe venous diversion and fluid present in horizontal fissures.

Table 19: Findings on admission chest X-ray for the 78% of patients with a reported chest X-ray

	Number	**%**
Chest X-ray available	410	78
Increased cardiothoracic ratio	205	50
Upper lobe venous diversion	119	29
Fluid in fissure	39	10
Pulmonary Oedema	156	38
Pleural Effusion(s)	60	15

4 – 9 Echocardiography

In total 70% of patients admitted with heart failure underwent assessment with echocardiography, of these 50% were performed during the admission and a further 36% after admission. A smaller proportion (14%) of patients had undergone echocardiography within 1 year of the admission. Figure 20 demonstrates the timing of echocardiographic examination.

With regards to assessment of systolic function, 28% of patients had documented normal left ventricular systolic function. This may imply heart failure with normal ejection fraction but additional supportive data such as analysis of mitral inflow, pulmonary vein flow and tissue Doppler interrogation were not routinely available. For the remaining 72% with impaired left ventricular systolic function, 23%, 24% and 25% had mild, moderate and severe impairment of systolic function respectively. The distributions of echocardiographic findings are shown in Table 20.

Data on valve disease and estimated pulmonary artery systolic pressure were collected from echocardiographic reports where available. However, fewer than 40% of all reports included an estimated measure of pulmonary artery pressure so this was not used in the final analysis. While the majority of echocardiographic reports commented on valve function there was a wide variation in the technique used for valve assessment with only a minority of reports providing robust quantitative data on valve function, hence this also does not appear in the final analysis.

Figure 20: Timing of echocardiographic examination

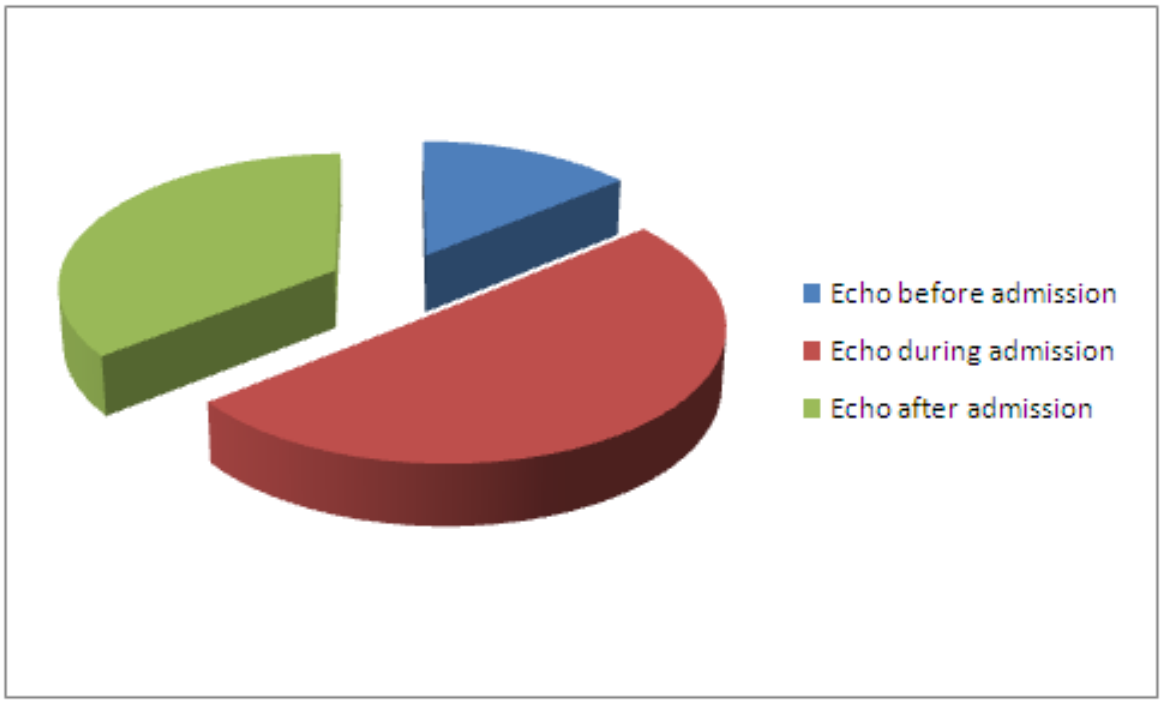


Table 20: Distribution of echocardiographic findings

	Number	%
Normal LV function	102	28
Mild LV dysfunction	85	23
Moderate LV dysfunction	87	24
Severe LV dysfunction	90	25

4 – 10 Admission drug therapy

The frequencies of patients admitted on individual drugs including heart failure therapy are shown in Table 21. A total of 126 (24%) of patients were admitted taking no regular medication, although 40% were taking no heart failure specific medication such as a diuretic, ACE inhibitor or beta blocker. Of the remaining 76% who were on regular medication, a large proportion (46%) were taking a diuretic suggesting prior treatment for suspected heart failure in the absence of a hospital admission. ACE inhibitors were being used by 23% of patients on admission, and beta blockers (any) by 13%. A small proportion of patients were taking other medications such as digoxin, amiodarone and clopidogrel, with a total of 7% receiving formal anticoagulation with warfarin therapy. Aspirin use was restricted to 29% of the total cohort despite 35% of patients reporting a past medical history of ischemic heart disease.

Table 21: Frequency of patients admitted on individual drugs including heart failure therapy

	Number	%
Admission drugs known	518	98
Aspirin	148	29
Diuretic	237	46
ACE inhibitor	119	23
ARB	27	5
Beta blocker	66	13
Digoxin	36	7
Spironolactone	4	1
Calcium channel antagonist	106	20
Statin	35	7
Insulin	64	12
Nitrate	61	12
Warfarin	36	7
Clopidogrel	1	<1
Amiodarone	17	3
No heart failure therapy *	207	40
No drugs	126	24

* = No diuretic, ACE inhibitor, ARB or beta blocker

4 – 11 Discharge drug therapy

The frequency of patients discharged on individual drugs that survived admission with a validated diagnosis of heart failure are shown in Table 22, with the percentage of patients prescribed each heart failure therapy on discharge represented in Figure 21.

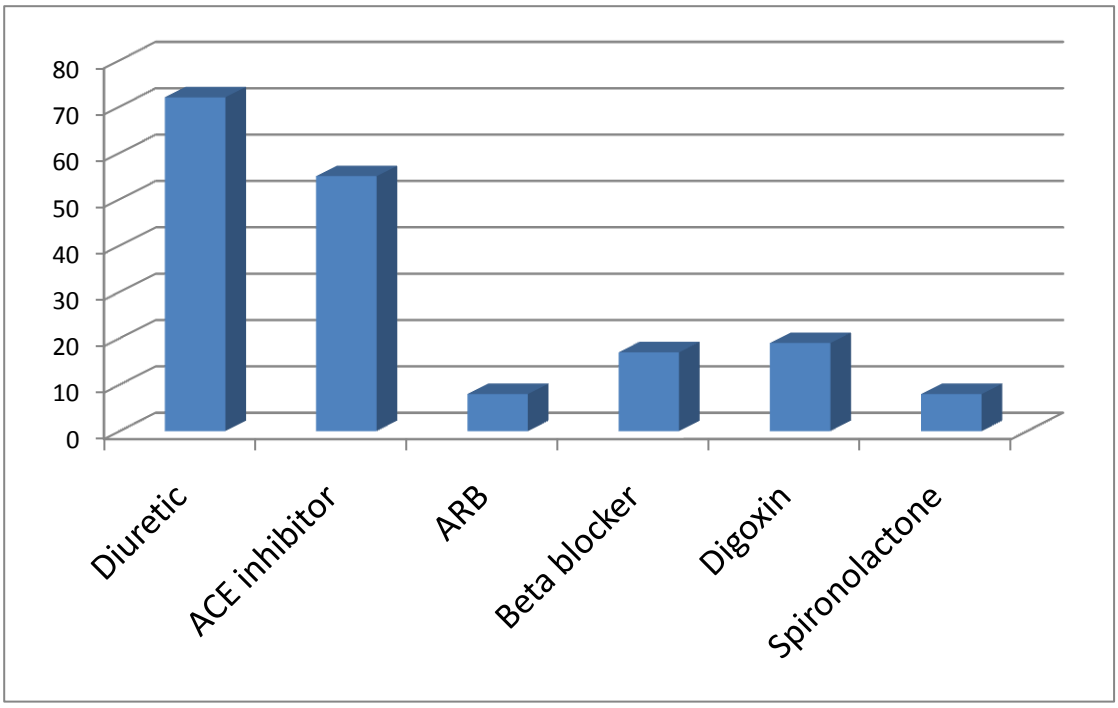
Of the 472 patients surviving the index admission a total of 351 (74%) patients left hospital on a regular diuretic, with 162 (46%) of these taking a dose equivalent to more than 80mg of furosemide per day. Only 285 (60%) of patients left hospital on an ACE inhibitor or ARB, and only 78 (17%) of patients were discharged on a beta blocker. Seventy-six (16%) patients were discharged on digoxin. A total of 77 (16%) of all admissions with heart failure were discharged with no regular prescription for an ACE inhibitor, ARB, beta blocker or a diuretic. Overall 65 (14%) of patients were discharged on no medical therapy at all.

Table 22: Frequency of patients discharged on individual drugs that survived admission with a validated diagnosis of heart failure

	Number	%
Aspirin	210	44
Diuretic	351	74
ACE inhibitor	255	54
ARB	30	6
Beta blocker	78	17
Digoxin	76	16
Spironolactone	29	6
Calcium channel antagonist	65	14
Statin	76	16
Insulin	68	14
Nitrate	75	16
Warfarin	64	14
Clopidogrel	3	<1
Amiodarone	34	7
No heart failure therapy *	77	16
No drugs	65	14
> 80mg furosemide	162	34

* = No diuretic, ACE inhibitor, ARB or beta blocker

Figure 21: Percentage of patients prescribed each heart failure therapy on discharge



ARB = Angiotensin Receptor Blocker

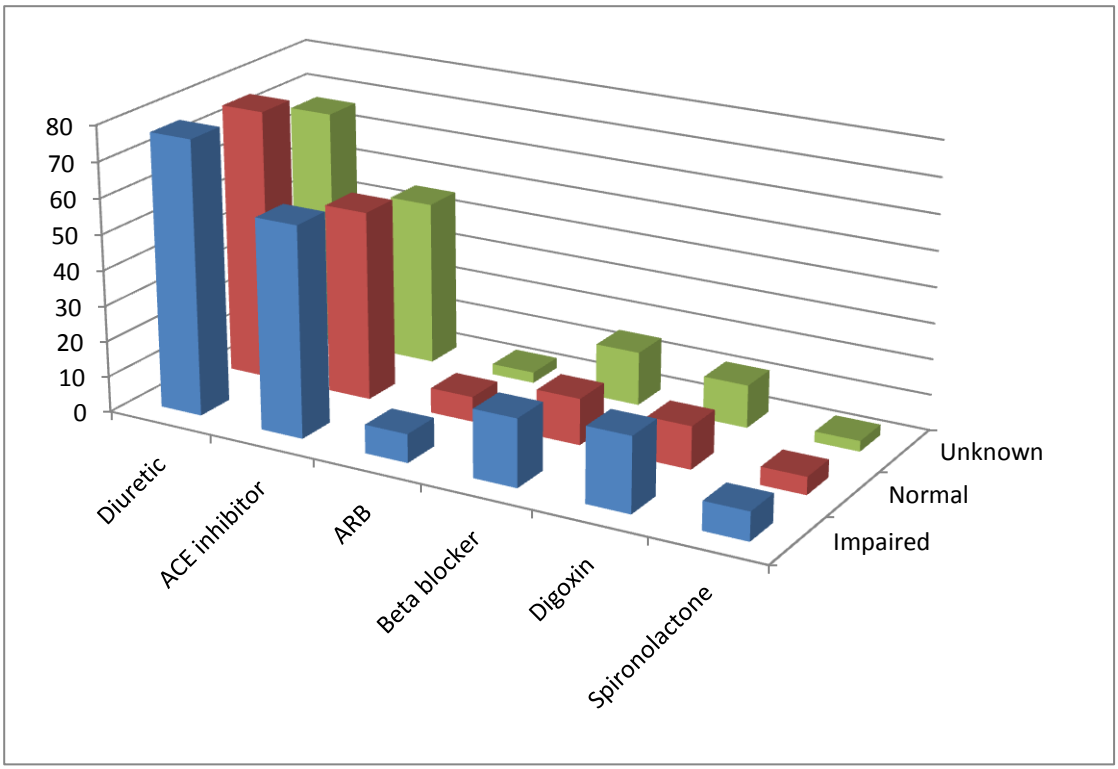
As discussed in chapter 1 drugs such as ACE inhibitors and beta blockers are only licensed in heart failure with systolic dysfunction. As only 243 patients of the 528 (46%) who survived the index admission were documented as having impaired systolic function at echocardiography a further analysis of the discharge drug data was undertaken on these patients only, to assess whether the low rates of ACE inhibitor and beta blocker prescription are driven by the non-prescription of these drugs in patients with preserved systolic function. Patients where data on systolic dysfunction was not available are not included. The frequency of patients discharged on discharged on individual drugs that survived admission with a validated diagnosis of heart failure stratified by systolic function are shown in Table 22, with the percentage

of patients prescribed each heart failure therapy on discharge stratified by systolic function represented in Figure 22.

Table 22: Frequency of patients discharged on individual drugs that survived admission with a validated diagnosis of heart failure segregated by systolic function

	Systolic dysfunction (n=243)		**Normal function (n=96)**		**Unknown function (n=134)**	
	Number	**%**	**Number**	**%**	**Number**	**%**
Diuretic	188	77	73	76	90	67
ACE inhibitor	143	59	51	53	61	46
ARB	19	8	7	7	4	3
Beta blocker	45	19	13	13	20	15
Digoxin	50	21	11	12	15	12
Spironolactone	20	8	5	5	4	3
No drugs	37	15	13	14	26	19

Figure 22: Percentage of patients prescribed each heart failure therapy on discharge stratified by systolic function



4 – 12 Revascularisation data

The available data on the frequencies of patients undergoing revascularisation are shown in Table 23. It is clear that very few patients admitted with heart failure go on to have revascularisation as identified by a relevant entry or letter in the notes at the time of notes retrieval and review. Only 34 (6%) underwent angiography either during the admission or within the follow-up period (minimum 6 months), and only 31 (6%) patients went on to have revascularisation either via percutaneous angioplasty or surgical therapy with bypass grafting. These very low rates of revascularisation are more suggestive of a lack of available data on revascularisation rather than genuinely low rates, particularly as 35% of this cohort had a prior history of angina or myocardial infarction suggesting revascularisation may have been considered or undertaken in many of these patients. This may be due to a patients' admission being undertaken and recorded at one hospital with subsequent angiography and revascularisation at a different centre without the relevant correspondence being held in the former clinical record.

Table 23: Frequencies of patients undergoing revascularisation

	Number	**%**
All admissions	528	100
Angiography	34	6
Angioplasty	21	4
CABG	28	5
CABG or Angioplasty	31	6

4 – 13 Summary

The average patient in this cohort admitted to a hospital in Leicester with a new diagnosis of heart failure is a male aged 69 who has had symptoms of breathlessness for several weeks. He is likely to have a background of hypertension or ischaemic heart disease and be either a current or ex-smoker. Admission blood pressure and pulse will be normal and he is likely to be in sinus rhythm. A chest X-ray will suggest cardiac failure and an echocardiogram will confirm left ventricular systolic dysfunction. If he survives the admission he will be discharged after around 8 days and will not meet a cardiologist. He will leave hospital taking a diuretic and probably an ACE inhibitor but not a beta blocker.

This rather crude 'mock' patient based on the average findings described above does demonstrate that the likely aetiology of heart failure in this cohort is related to hypertension and / or ischaemic heart disease. Unfortunately the rates of prescription of disease altering and life-prolonging heart failure therapy are low but in keeping with European data.

In Chapter 1 I posed 6 research questions to be answered with this preliminary data. I will now answer each of these in turn referring to the results described in this chapter.

4 – 13 – 1 Epidemiology of local heart failure patients

As discussed in Chapter 1 the principle aetiologies of heart failure are ischaemic heart disease and hypertension. In this cohort the commonest co-morbidities declared at the time of admission – a crude marker of aetiology - were ischaemic heart disease and hypertension, present in 35% and 37% of the total cohort respectively. The rate of ischaemic heart disease is lower than published data such as the Framingham heart failure cohort (Levy, Larson et al. 1996) where 59% of men and 48% of women had underlying ischaemic heart disease. It is however similar to the figure of 36% identified in the Hillingdon heart failure study (Cowie, Wood et al. 1999). Hypertension was reported in over 70% of patients in the Framingham cohort but only 14% in the Hillingdon study – this may reflect changing aetiology over time given that the Framingham cohort study followed patients from 1948 onwards. The degree of investigation into heart failure aetiology is also critical – by utilising nuclear perfusion testing and invasive cardiac catheterisation the percentage of patients with heart failure of 'unknown aetiology' fell from 42% to 10% with the percentage of those with heart failure due to ischaemic heart disease rose from 29% to 52% (Fox, Cowie et al. 2001). The mean age of patients admitted was 69 years although this is likely to be skewed given the age matching strategy employed. It is not possible to assess the incidence or prevalence of heart failure given the cohort was selected from known admissions with heart failure.

Only 9% of patients declared a prior diagnosis of chronic obstructive pulmonary disease; this is significantly lower than that in other published series. In a study of 800 patients hospitalised with heart failure in the USA between April 1998 and March

1999 (Havranek, Masoudi et al. 2002) a total of 33% had chronic obstructive pulmonary disease; notably the mean age of admissions in this study was higher at 79 years compared to 69 years in this study. Previous reports have offered lower estimates such as a rate of chronic obstructive pulmonary disease of 23% in patients receiving a new diagnosis of heart failure in 1991 (Senni, Tribouilloy et al. 1998).

This difference may be explained in a number of ways; the mean age of the cohort in this study was lower, the diagnosis of chronic obstructive pulmonary disease was not validated and very few patients had evidence of respiratory function testing to support the diagnosis. As the combination of heart failure with chronic obstructive pulmonary disease carries both a higher mortality and rates of readmission as well as complicating effective heart failure therapy, further studies directed towards this group of patients are required (Rutten, Cramer et al. 2006). Diabetes of any variety was present in 27% of patients in this study, very similar to other published heart failure series including the recent CHARM study which recruited 7,601 patients with symptomatic heart failure into a randomised trial of Candesartan (Pfeffer, Swedberg et al. 2003). Of this population 28% had diabetes on enrolment. As will be discussed later diabetes is a major co-morbidity in heart failure and associated with increased mortality.

4 – 13 – 2 Symptoms of heart failure

The rate of recorded symptoms for heart failure was low. Given the primary symptom of heart failure is dyspnoea, and this is a key criterion for diagnosis, the fact that only 61% of records clearly stated this suggests possible under-reporting. This may be due to limitations of the study method and lack of detail in the clinical record. Similarly the expected rates of oedema and fatigue are much higher than reported here. There is evidence of limited reproducibility of both symptoms and signs in heart failure from a study of 102 patients with myocardial infarction who were sequentially assessed by three physicians (GADSBOLL, HoILUND-CARLSEN et al. 1989). Dyspnoea was documented for between 26% and 35% of the patients suggesting significant inter-observer variability in symptom recording. Similar variation was seen for physical signs, with oedema varying between 1% and 8%, pulmonary crepitations from 8% to 14%.

Detailed studies of patients with proven heart failure demonstrate that round 50% report shortness of breath and 40% report lack of energy (Bekelman, Havranek et al. 2007). Overall patients report a mean of 9 separate symptoms but this varies considerably over time. Other studies have reported 100% occurrence of some symptoms although these are prospective studies where patients are specifically questioned with respect to their functional status in order to derive NYHA class. A proportion of these will be NYHA class I which by definition means they are symptom free and therefore unlikely to spontaneously report dyspnoea.

While it is probable the retrospective nature of this study has lead to under-reporting of both symptoms and signs of heart failure it is unlikely to have influenced the final prognostic model as no clinical variable is included. This is in keeping with many other prognostic models which do not include any symptoms or physical signs with the exception of NYHA class or the presence of an S_3 gallop (Eichhorn 2001).

4 – 13 – 3 Duration of hospital admission

The duration of hospital admission ranged from a minimum of zero – for patients who died on the same day of admission - to a maximum of 380 days with a mean of 14 days and a median of 8 days. This is in keeping with other data from the UK in 1990 suggesting mean admission duration of 20 days, with variation by speciality noted as evidenced by a mean duration of 11.4 days for patients on acute medical wards and 28.5 days for patients on geriatric wards (McMurray, McDonagh et al. 1993). There is considerable variation across Europe with data from a large-scale European study on heart failure admissions (Cleland, Swedberg et al. 2003) showing that duration of hospital therapy varies from a mean of 7 days in Georgia and Israel to 19 days in Russia, with the UK centres reporting a mean duration of 12 days – very similar to the data in this study. Another major problem in heart failure is the high rates of re-admission following discharge, with one third of patients re-admitted within 12 months. Data on re-admission of patients in this cohort were not available.

Given that heart failure hospitalisations represent a disproportionate amount of health care expenditure (McMurray, Petrie et al. 1998) such prolonged hospital admissions

will place significant demands on health care provision. Although there is a suggestion that the mean duration of admission has fallen from 20 days in 1990 to 14 days in this study – albeit in different patient cohorts - it is still a lengthy and costly in-hospital stay, with re-admission within 12 months likely. The current estimate for the cost of a single in-patient day for standard heart failure therapy stands at £198 (The National Collaborating Centre for Chronic Conditions 2003).

4 – 13 – 4 Heart failure and cardiologist care

The data abstracted from the case notes of patients admitted to hospital suggests that only 41% of patients receive care from a cardiologist, the remainder are under the care of general physicians. This may have an impact on access to investigations, prescription of recommended treatment and availability of appropriate follow up. The importance of cardiology input in patients admitted with myocardial infarction has been highlighted in a recent paper from the Myocardial Infarction National Audit Project (MINAP) (Birkhead, Weston et al. 2006). This study of over 88,000 admissions with myocardial infarction between January 2004 and March 2005 demonstrated that only 36% were under the care of a cardiologist, with an adjusted risk of death at 90 days of 0.86 (0.81 – 0.91) compared to those treated by a non-cardiologist. The rates of non-prescription of ACE inhibitors and beta-blockers for patients discharged from hospital were lower in those under the care of a cardiologist with adjusted ratios of 0.98 (0.91 – 1.06) and 0.92 (0.8 – 0.97) respectively.

Differences in the patient populations between the cardiologist and non-cardiologist may explain some of these effects, with patients under the care of a cardiologist likely

to have less co-morbidity, and a higher proportion are less than 75 years of age (32% vs. 45%). This echoes a paper in 1999 from the United States suggesting that differences in the case mix account for the differences in outcome rather than the care given, but commenting that post myocardial infarction secondary preventative therapies are markedly underused regardless of the speciality (Frances, Go et al. 1999). Little data exists on the effect of physician speciality on heart failure care but one study from Scotland in 1996 assessed the proportion of patients with documented left ventricular systolic impairment who were treated with ACE inhibitors (Davie and McMurray 1999). The authors demonstrated that more patients were on an ACE inhibitor if they were under the care of a cardiologist – 77% vs. 53% for non-cardiologist care ($p<0.01$) and were more likely to be on a dose used in a major survival study – 48% vs. 31% for non-cardiologist care ($p<0.05$). They also conclude that ACE inhibitors are underused but that differences between cardiologists' and generalists' care of a heart failure patient do exist.

As with the variation in hospital admission duration there is considerable variation in the proportion of patients under the care of a cardiologist across Europe, ranging from 13% in Israel to 88% in Belgium with UK centres reporting 21% of patients under the care of a cardiologist, 62% under a general physician and 20% under the care of a geriatrician (Cleland, Swedberg et al. 2003). Although less than half of the patients in this cohort were under the care of a cardiologist, this is higher than the average rate in the United Kingdom. When analysed with respect to consultant care, the mean duration of admission for patients under the care of a cardiologist was 12.8 days compared to 13.7 days for patients under the care of a non-cardiologist, a non-significant difference with a p-value of 0.7. There was no difference in the median

admission duration (8 days). This lack of difference in admission duration may imply the rate limiting step is time for investigations such as echocardiography rather than initiation of therapy.

4 – 13 – 5 Investigations in heart failure

Out of the total cohort of 528 patients over two-thirds undergo echocardiographic assessment of left ventricular function – the gold-standard test for defining the severity and aetiology of heart failure. A small proportion (14%) of these patients underwent echocardiography within one year prior to admission and 36% had echocardiographic assessment performed after discharge. The remaining 50% had their echocardiogram undertaken during the index admission. Given that echocardiography forms a key component of all published heart failure guidelines, it would be ideal if all patients could have immediate assessment during the admission. However, given the burden on health care resources and limitations on diagnostic investigations a number of patients are discharged with a clinical diagnosis of heart failure and appropriate therapy commenced pending the definitive investigation.

Published data on the number of patients with heart failure undergoing examination with echocardiography during their index admission suggests wide variations in practice. Data from the OPTIMIZE-HF registry – a performance improvement initiative in place at 91 hospitals in the United States assessed the investigation and treatment of 5,791 patients with heart failure and found that 89% of all admissions had an assessment of left ventricular systolic function, although the absence of assessment of LV systolic function was not associated with mortality at 90 days

(Fonarow, Abraham et al. 2007). This can be contrasted with data from a large-scale European survey on the patient characteristics and diagnosis of 11,327 patients who either died or were discharged with a diagnosis of heart failure (Cleland, Swedberg et al. 2003). The majority of these patients had assessment with electrocardiography, chest X-ray and electrolyte measurement but only 66% ever had an echocardiogram. Rates of echocardiography varied from 40% in the United Kingdom to 93% in Belgium. Further analysis of the Euro Heart Failure survey restricted to patients over the age of 80 years revealed that only 38% had assessment of left ventricular ejection fraction compared to 65% of those under 80 years of age ($p<0.001$).

In conclusion, the rates of echocardiographic assessment of left ventricular systolic function are very similar to published data on European practice. However, among patients discharged alive from the index admission, mortality was highest for those patients without documented echocardiographic examination. This is likely to be a multifactorial phenomenon. Perceived futility in the face of advanced disease, death prior to 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 are factors meriting further study.

4 – 13 – 6 Heart failure therapy on discharge

The data on drug therapy prescribed on discharge suggest that a minority of patients admitted with heart failure receive the optimal medical therapy outlined in chapter 1. The majority of patients receive long term diuretic therapy but there is no evidence this will impact on disease progression or survival, but may improve symptoms in the

short term. Whilst you might expect all patients with heart failure to be discharged on a diuretic as fluid congestion is a major consequence of cardiac dysfunction, the fact that 26% of patients leave hospital with no diuretic is consistent with other studies, for example in Europe the rate of diuretic prescription varies from 64% to 96%. This may be explained by patients only needing short term diuretic treatment to alleviate symptoms before the patho-physiological cascade leading to fluid retention is halted by treatment with ACE inhibitors or beta blockers.

Only 60% of patients receive therapy with either an ACE inhibitor or angiotensin receptor blocker, the majority of these (90%) receive an ACE inhibitor. A large majority of patients – 83% - do not receive treatment with a beta blocker on discharge despite overwhelming evidence for their benefit. Smaller proportions of patients receive second line agents such as digoxin (16%) and Spironolactone (6%).

Such low rates of beta blocker and ACE inhibitor prescription may relate to delays in translation of published clinical evidence into routine clinical use although the patients studied in this cohort were admitted between April 1998 and March 2001, more than five years after publication of major studies of ACE inhibition in heart failure (SOLVD Investigators 1991; Pfeffer, Braunwald et al. 1992; SOLVD Investigators 1992; Acute Infarction Ramipril Efficacy (AIRE) Study Investigators 1993; Kober, Torp-Pedersen et al. 1995). The significantly lower rates of beta blocker prescription may reflect the fact that the major beta blocker studies were published in 1999 and 2001 (CIBIS-II Investigators 1999; MERIT-HF Study Group 1999; Packer, Coats et al. 2001).

These low prescription rates are in keeping with published data from Europe. The Euro Heart Failure Survey published results in 2003 on the treatment of 11,304 patients discharged with a diagnosis of heart failure from European hospitals between 2000 and 2001 (Cleland, Swedberg et al. 2003). They found that ACE inhibitor prescription rates varied from 40% in Sweden to 85% in Russia, with UK centres reporting prescription rates of 52%. Beta blocker prescription rates were significantly lower ranging from 10% in Spain and 65% in Finland, with UK centres reporting rates of around 23%. The overall average prescription rates were 62% for ACE inhibitors and 37% for beta blockers with a further 36% receiving digoxin and 21% Spironolactone. Diuretic prescription rates were high at 87% ranging from 64% to 96%.

There is no apparent effect of knowledge of left ventricular dysfunction on the prescription rates of heart failure therapy – for example ACE inhibitors were used in 59% of patients with known systolic dysfunction and 53% of patients with known normal systolic function ($p=0.46$). Rates of drug use were lower in patients with no assessment of systolic function although the differences did not reach statistical significance ($p=0.081$).

In conclusion the rates of prescription of proven therapy to improve heart failure survival on discharge are low, but are very similar to published data on European practice.

4 – 13 – 7 Cardiac resynchronisation therapy in heart failure

The current guidelines on cardiac resynchronisation therapy for heart failure restrict its use to patients with persistent NYHA class III heart failure symptoms despite optimal medical therapy at maximal tolerated doses, with an ejection fraction under 35%, sinus rhythm and QRS duration on the surface ECG of greater than 150ms. These strict criteria are those used for the enrolment of the recent CARE-HF trial studying the benefit of cardiac resynchronisation in patients with heart failure of more than six weeks duration (Cleland, Daubert et al. 2005).

The data provided in this study can provide a crude measure of how many patients may potentially meet these criteria, although there is no data on the patients' symptom level at discharge to identify those who remain symptomatic despite medical therapy. If I restrict the analysis to patients in sinus rhythm with a QRS duration of greater than 150ms and a proven ejection fraction of under 35% (moderate or severe systolic impairment) then only seven patients of the cohort with echocardiographic assessment (364) meet these criteria – a total of 2%, suggesting a potential maximum number of 11 patients from the entire cohort of 528. If more relaxed criteria of a QRS greater than 120ms, ejection fraction of less than 35% and any rhythm this number climbs to 49 which is 13% of the cohort with data on left ventricular function. This is broadly similar to data published by Grimm in 2003 who assessed a cohort of 566 patients with dilated cardiomyopathy presenting over 10 years from 1991 to a German hospital and found that 14% of patients would meet the more relaxed criteria for resynchronisation therapy and only 7% would meet the strict criteria such as that used in the CARE-HF trial (Grimm, Sharkova et al. 2003).

This crude estimation of the potential maximum number of patients who may be eligible for resynchronisation therapy suggests only a minority of heart failure admission would meet the current criteria for heart failure pacing therapy.

4 – 13 – 8 Revascularisation in heart failure

The very low rate of patients who apparently receive revascularisation suggests a lack of reliable data in this area. Given that as many as half of all patients with heart failure have an underlying aetiology of coronary disease when invasively investigated (Fox, Cowie et al. 2001), and that revascularisation following assessment of hibernating myocardium may improve prognosis (Senior, Kaul et al. 1999) it is surprising that so few patients underwent coronary angiography following their admission with heart failure. As it is likely that this proportion is not a true reflection of local practice further studies directed at this question are required.

The question of whether revascularisation is warranted in all patients with coronary artery disease and heart failure with significant left ventricular dysfunction is not easy to answer with currently available data – principally limited to small scale surgical trials undertaken before the introduction of therapies such as beta blockade and cardiac resynchronisation therapy (Senior 2006). Two ongoing studies are attempting to address this issue, the heart failure revascularisation trial in the United Kingdom (Cleland, Freemantle et al. 2003) and the Surgical Treatment for Ischaemic Heart Failure study in the United States (Doenst, Velazquez et al. 2005). There is evidence that the outcome of patients with heart failure secondary to coronary artery disease is

worse than in patients without coronary disease: A study of 217 patients presenting with acute heart failure in Switzerland found that 71% of patients had coronary disease (defined as more than one significant stenosis on angiography, prior myocardial infarction, or prior revascularisation by angioplasty or bypass grafting) and these patients had a significantly lower survival rate at 720 days, with only 48.7% alive compared to 76.4% of patients without coronary disease (p=0.0004) (Purek, Laule-Kilian et al. 2006). Moreover at initial presentation only 12% of patients with coronary artery disease received revascularisation, and only a further 8% underwent revascularisation during follow up. Similarly data from the United States on 77 patients with heart failure and *proven* large reversible perfusion defects on myocardial perfusion imaging found that only 13% had undergone revascularisation after 5 years of follow-up (Miller, Tointon et al. 2002).

Clearly there is a careful judgement over the benefit of revascularisation in patients with heart failure and poor ventricles versus the potentially high risk of operation in these patients. Evidence of hibernating myocardium – chronically dysfunctional myocardium due to ischaemia with the potential for recovery – may aid in selecting patients suitable for revascularisation. The optimal technique for selecting suitable patients is Dobutamine stress echocardiography or single photon emission computed tomography (SPECT) (Cigarroa, deFilippi et al. 1993; Bax, van Eck-Smit et al. 1998). Importantly there appears to be no survival benefit if revascularisation is undertaken in patients with heart failure and coronary disease without evidence of viable myocardial tissue (Allman, Shaw et al. 2002; Bourque, Hasselblad et al. 2003). At present I have no data on which patients – if any – underwent assessment for myocardial viability.

4 – 14 Conclusion

In this chapter I have presented data on the basic demographics of the heart failure cohort studied along with details on the co-morbidity, symptoms, investigations and discharge drug therapy. Following this I have addressed the six research questions outlined in Chapter 1 and demonstrated that the demographic, aetiology, investigations and management undertaken in this cohort are very similar to published data on European practice. In summary this heart failure cohort demonstrates no significant differences from prior published heart failure patient demographics.

Chapter 5 – Outcome data

5 – 1 Introduction

In this chapter I will review the survival of patients in the cohort studied and use both univariate and multivariate analysis to assess for any interaction between patient variable and survival as outlined in Chapter 3. The format of the chapter follows that of the preliminary results chapter in that I will review the overall survival and then assess for interactions within the basic demographics, co-morbidity, biochemistry, chest X-ray, echocardiographic and drug therapy in turn. Following this, variables associated with survival on multivariate analysis will be used to construct a model to predict outcome.

I will then answer the research questions posed in chapter 2 and discuss these data in comparison to published survival data and known predictors of outcome in heart failure.

5 – 2 Entire cohort - crude survival and in hospital mortality

The crude unadjusted survival rates for in-hospital; 30-day, 12 months and 24 months for the whole heart failure cohort are shown in Table 24. Overall it can be seen that 11% of the whole cohort died during their index admission with heart failure. By 30 days 15% died and this climbed to 27% at one year and 35% at 2 years.

Table 24: Crude unadjusted survival rates for in-hospital, 30-day, 12 and 24 months for the whole heart failure cohort

Survival period	Unadjusted	95% CI
In-hospital	89	86 – 92
30 days	85	82 – 88
12 months	73	69 – 83
24 months	65	61 – 69

5 – 3 Admission demographics

The crude hazard ratios for basic admission demographic variables in all patients are shown in Table 25. Variables demonstrating association with mortality on univariate analysis include increasing age, with a hazard ratio of 1.055 for each additional year over 63, and prolonged hospital admission duration, with a hazard ratio of 1.015 for each day over 5 days. Duration of symptoms had no appreciable association with mortality. Care by a cardiology consultant was not associated with a significant difference in mortality, the hazard ratio being 0.790 but with the 95% confidence interval crossing 1 and consequently a p value of greater than 0.05.

Table 25: Crude hazard ratios for admission demographic variables in all patients

Variable	Hazard ratio	Upper	Lower	P value
South Asian Ethnicity	0.785	0.545	1.132	0.195
Male Sex	0.903	0.639	1.276	0.563
Increasing Age (per one year)	1.055	1.036	1.074	<0.001
Age < 63	1			
Age 63 to 70	2.066	1.234	3.460	0.006
Age 71 to 77	2.954	1.767	4.937	<0.001
Age ≥ 77	4.224	2.497	7.146	<0.001
Increasing duration (per one day)	1.015	1.003	1.026	0.012
Admission < 5 days	1			
Admission 5 to 7 days	0.692	0.398	1.203	0.192
Admission 8 to 14 days	1.983	1.198	3.282	0.008
Admission ≥ 15 days	3.600	2.091	6.197	<0.001
Symptoms < 24 hours	1			
Symptoms 24 hours to 1 week	0.863	0.508	1.465	0.585
Symptoms 1 week to 1 month	1.348	0.813	2.236	0.248
Symptoms 1 to 6 months	1.406	0.739	2.677	0.299
Symptoms > 6 months	0.729	0.128	4.140	0.721
Cardiology consultant care	0.790	1.064	0.587	0.121

5 – 4 Past medical history

The crude hazard ratios for co-morbidities for all patients are shown in Table 26. Variables demonstrating association with mortality on univariate analysis included chronic obstructive pulmonary disease and malignancy. The presence or absence of ischaemic heart disease, hypertension or diabetes showed no significant association with survival. Surprisingly renal failure appears to have no association with outcome although this is past history of proven renal failure which was present in only 10 patients – a very small proportion of the entire cohort at less than 2%.

Table 26: Crude hazard ratios for co-morbidities for all patients

Variable	Hazard ratio	Upper	Lower	P value
Ever smoked	0.779	0.544	1.117	0.174
Ex-smoker	1.013	0.660	1.556	0.952
Current smoker	0.633	0.390	1.029	0.065
Any ischaemic heart disease	1.200	0.839	1.717	0.318
Hypertension	0.862	0.604	1.229	0.412
Stroke	1.381	0.796	2.395	0.251
No diabetes	1			
Insulin treated diabetes	1.224	0.750	1.998	0.419
Diet treated diabetes	2.206	0.786	6.190	0.133
Drug treated diabetes	1.638	0.891	3.013	0.112
No diabetes	1			
Diabetes of any type	1.442	0.978	2.125	0.064
Renal failure	1.821	0.508	6.528	0.358
Malignancy	5.000	1.394	17.931	0.014
Chronic obstructive pulmonary disease	1.870	1.016	3.441	0.044
No past medical history	0.908	0.557	1.482	0.700

5 – 5 Admission clinical data

The crude hazard ratios for admission clinical variables in all patients on univariate analysis are shown in Table 27. For pulse and blood pressure the reference category was chosen as the quartile containing the mean value – for example the mean blood pressure for the cohort was 138mmHg so the other three quartiles were compared to this reference group.

This analysis demonstrates an association between increasing systolic and diastolic blood pressure and improved survival, with a hazard ratio of 0.993 and 0.980 for each mm of mercury over a systolic of 139 and a diastolic of 80 respectively. Overall increasing heart rate had no significant association with survival although patients with a pulse rate between 91 and 108 beats per minute had a hazard ratio of 1.726 (95% confidence intervals 1.059 to 2.813, p=0.029). This may reflect that few patients had heart rates elevated to the higher and lower extremes, for example the mean heart rate was 94 with a median of 90 – in other words the majority of patients had a pulse rate within the range of 90 to 108.

Table 27: Crude hazard ratios for admission clinical variables in all patients

Variable	Hazard ratio	Upper	Lower	P value	Units
Increasing pulse (per 1 bpm)	1.001	0.993	1.008	0.854	bpm
Pulse under 80	1				bpm
Pulse 80 to 90	1.534	0.939	2.503	0.087	bpm
Pulse 91 to 108	1.726	1.059	2.813	0.029	bpm
Pulse ≥ 109	1.102	0.669	1.814	0.703	bpm
Increasing systolic (per 1 mmHg)	0.993	0.987	0.999	0.026	mmHg
Systolic 122 to 139	1				mmHg
Systolic 140 to 158	1.668	1.031	2.696	0.037	mmHg
Systolic ≥ 159	0.794	0.476	1.326	0.378	mmHg
Systolic < 122	1.601	0.971	2.640	0.065	mmHg
Increasing diastolic (per 1 mmHg)	.980	0.970	.990	<0.001	mmHg
Diastolic 70 to 80	1				mmHg
Diastolic 81 to 92	0.654	0.399	1.074	0.093	mmHg
Diastolic ≥ 93	0.388	0.231	.651	<0.001	mmHg
Diastolic < 70	0.824	0.504	1.347	0.440	mmHg

5 – 6 Admission symptoms

The crude hazard ratios for admission symptoms in all patients on univariate analysis are shown in Table 28. No significant association with survival was found.

Table 28: Crude hazard ratio for admission symptoms in all patients

Variable	Hazard ratio	Upper	Lower	P value
Dyspnoea	1.297	0.840	2.003	0.241
Orthopnoea	0.870	0.583	1.298	0.494
Paroxysmal nocturnal dyspnoea	0.912	0.556	1.496	0.716
Oedema	1.096	0.684	1.756	0.704
Fatigue	0.406	0.145	1.138	0.086
Cough	0.981	0.536	1.796	0.951

5 – 7 Chest X-ray and echocardiography data

The crude hazard ratios for chest X-ray and echocardiography data in all patients by univariate analysis are shown in Table 29. The presence of pulmonary oedema on a chest X-ray has a hazard ratio of 1.558 (p=0.030) compared to a chest X-ray without pulmonary oedema. Left ventricular systolic impairment of a moderate degree has a hazard ratio of 1.964 (p=0.024) but severe left ventricular systolic impairment does not appear to be associated with increased mortality. This is despite almost identical

numbers of patients in these two categories, with 24% and 25% respectively of the whole cohort with echocardiography data available.

Table 29: Crude hazard ratios for chest X-ray and echocardiography data in all patients

Variable	Hazard ratio	Upper	Lower	P value
Cardiomegaly	1.061	0.719	1.565	0.766
Upper lobe venous diversion	1.288	0.840	1.975	0.247
Fluid in fissure	0.655	0.330	1.300	0.226
Pulmonary oedema	1.558	1.043	2.327	0.030
Pleural Effusion	1.361	0.786	2.355	0.271
Left ventricular function normal	1			
Mild impairment	1.347	0.745	2.434	0.324
Moderate impairment	1.964	1.095	3.524	0.024
Severe impairment	1.167	0.649	2.098	0.607

5 – 8 Blood results data

The crude hazard ratios for biochemistry and haemoglobin in all patients by univariate analysis are shown are Table 30. A rise in sodium by 1mmol/l over 140mmol/l is associated with a hazard ratio of 0.963 (p=0.048), in other words a lower sodium is associated with increased mortality, demonstrated by a hazard ratio of 1.797 for patients with a sodium under 135mmol/l. An increase in potassium however was associated with increased mortality, with a hazard ratio of 1.485 for every 1mmol/l over 3.8mmol/l (p=0.003). A strong association between creatinine and survival was noted, with each 1µmol/l increase in creatinine above 85 µmol/l having a hazard ratio of 1.008 (p<0.001). Patients with a creatinine greater than 134µmol/l have more than a four-fold chance of mortality compared to patients with a creatinine under 85µmol/l. An inverse relationship between haemoglobin and mortality was noted, with mortality increasing as haemoglobin falls. For every 1g/dl over 14.4g/dl the hazard ratio is 0.837 (p<0.001). Patients with haemoglobin levels under 11.5g/dl have a hazard ratio of 3.013 (p<0.001) compared to patients with haemoglobin levels over 14.4g/dl. Increase in glucose was also associated with increased mortality, a rise in serum glucose by each 1mmol/l over 5.9 has a hazard ratio of 1.056 (p=0.010), and for patients with a glucose greater than 10.1mmol/l the hazard ratio is 2.287 compared to patients with a glucose less than 5.9mol/l (p=0.001).

Table 30: Crude hazard ratios for biochemistry and haemoglobin in all patients

Variable	Hazard ratio	Upper	Lower	P value	Units
Per 1mmol/l in sodium above 140mmol/l	0.963	0.928	1.000	0.048	mmol/l
Sodium 138 to 140	1.222	0.753	1.986	0.417	mmol/l
Sodium 135 to 137	1.430	0.859	2.380	0.169	mmol/l
Sodium < 135	1.797	1.062	3.040	0.029	mmol/l
Per 1mmol/l in potassium above 3.8mmol/l	1.485	1.144	1.485	0.003	mmol/l
Potassium 3.8 to 4.1	1.091	0.658	1.807	0.736	mmol/l
Potassium 4.2 to 4.6	1.323	0.830	2.109	0.240	mmol/l
Potassium ≥ 4.7	1.992	1.192	3.327	0.009	mmol/l
Per 1µmol/l in creatinine above 85µmol/l	1.008	1.004	1.011	<0.001	mmol/l
Creatinine 85 to 104	1.867	1.119	3.117	0.017	µmol/l
Creatinine 105 to 133	1.857	1.117	3.088	0.017	µmol/l
Creatinine ≥ 134	4.537	2.672	7.706	<0.001	µmol/l
Per 1mmol/l in glucose above 5.9mmol/l	1.056	1.013	1.101	0.010	mmol/l
Glucose 6.0 to 7.5	1.208	0.737	1.982	0.453	mmol/l
Glucose 7.6 to 10	1.208	0.737	1.982	0.453	mmol/l
Glucose ≥ 10.1	2.287	1.386	3.774	0.001	mmol/l
Per 1g/dl in haemoglobin above 14.4g/dl	0.837	0.768	.912	<0.001	g/dl
Haemoglobin 13 to 14.3	2.053	1.239	3.401	0.005	g/dl
Haemoglobin 11.5 to 12.9	2.128	1.276	3.549	0.004	g/dl
Haemoglobin < 11.5	3.013	1.784	5.088	<0.001	g/dl

5 – 9 Admission ECG data

The crude hazard ratios for electrocardiographic data in all patients by univariate analysis are shown in Table 31. This extensive analysis of ECG variables demonstrated that no variable has a significant association with mortality.

Table 31: Crude hazard ratios for electrocardiographic data in all patients

Variable	Hazard ratio	Upper	Lower	P value	Units
Sinus	1				
AF	1.416	0.926	2.165	0.108	
Other	1.929	0.849	4.382	0.117	
Sinus	1				
Not sinus	1.456	0.985	2.153	0.060	
Per 1ms increase in QRS	1.005	0.997	1.013	0.197	ms
Per 1ms increase in Max QRS	1.004	0.997	1.011	0.288	ms
Per 1ms increase in Min QRS	1.006	0.997	1.014	0.208	ms
Per 1ms increase in QRS dispersion	1.000	0.990	1.011	0.954	ms
Per 1ms increase in Mean QTc	.999	0.995	1.003	0.661	ms
Per 1ms increase in Max QTc	.999	0.996	1.003	0.756	ms
Per 1ms increase in Min QTc	.999	0.995	1.004	0.798	ms
Per 1ms increase in QTc dispersion	1.000	0.996	1.003	0.899	ms

5 – 10 Admission Drug data

The crude hazard ratios for admission drug therapy in all patients on univariate analysis are shown in Table 32. Admission drugs demonstrating significant association with mortality are diuretics and beta-blockers. The use of a diuretic has a hazard ratio of 1.598 (p=0.009) suggesting increased mortality in patients admitted already on a diuretic. Conversely patients admitted on a beta blocker have a hazard ratio of 0.533 (p=0.025) suggesting increased survival in patients already treated with a beta blocker on admission.

Table 32: Crude hazard ratios for admission drug therapy in all patients

Variable	Hazard ratio	Upper	Lower	P value
Aspirin	0.916	0.624	1.345	0.655
Diuretic	1.598	1.126	2.266	0.009
ACE inhibitor	0.755	0.498	1.146	0.187
ARB	1.578	0.724	3.442	0.251
Beta Blocker	0.533	0.308	0.924	0.025
Digoxin	1.592	0.805	3.147	0.181
Spironolactone	0.408	0.042	3.952	0.439
Nicorandil	0.522	0.134	2.042	0.350
Insulin	1.182	0.700	1.997	0.531
Nitrate	1.222	0.716	2.086	0.463
Warfarin	0.771	0.385	1.542	0.462

5 – 11 Discharge drug data

The crude hazard ratios for discharge drugs commonly used in heart failure therapy in all patients on univariate analysis are show in Table 33. This demonstrates that patients discharged taking ACE inhibitors or beta blockers have increased survival compared to those not taking these drugs. The presence of an ACE inhibitor on discharge has a hazard ratio of 0.490 ($p<0.001$) and for a beta blocker 0.288 ($p<0.001$). In addition the presence of aspirin on discharge has a hazard ratio of 0.578 ($p=0.005$) compared to patients not on aspirin.

Table 33: Crude hazard ratios for discharge drug therapy in all patients

Variable	Hazard ratio	Upper	Lower	P value
Aspirin	0.578	0.394	0.848	0.005
Diuretic	1.085	0.694	1.696	0.720
ACE inhibitor	0.490	0.334	0.717	<0.001
ARB	1.219	0.577	2.575	0.604
Beta Blocker	0.288	0.156	0.532	<0.001
Digoxin	1.101	0.667	1.819	0.706
Spironolactone	0.692	0.308	1.557	0.374

5 – 12 Prognostic model development

An aim of this thesis was to develop a simple, pragmatic model to aid in the identification of patients newly admitted to hospital with a diagnosis of heart failure who are at high risk of death, using information readily available within the first 24 hours of admission.

All variables collected were tested for their association with mortality using initially univariate then multivariate regression analysis. The model was refined using a forward conditional method with a significance of 0.05 for entry into the model. The variables were entered in a pragmatic manner by starting with demographics such as age, sex and ethnicity before adding data pertaining to admission variables such as blood pressure and biochemistry.

At each step the variables added were examined for their additional influence on the models performance. Those not increasing the power of the regression analysis were discarded and replacement variables assessed.

Finally the model selection was also undertaken using a backward conditional method where all possible variables are included and then removed sequentially and the models performance assessed.

5 – 12 – 1 Independent predictors of all cause mortality

On multivariate Cox modelling six variables were found to be independently associated with all cause mortality: age, systolic blood pressure, serum creatinine concentration, serum glucose concentration, serum haemoglobin and history of prior diuretic use. These six variables were used to construct a scoring system.

Initially all continuous variables were modelled as such, however as a final prognostic model is easier to compute with categorical variables all continuous variables were transformed into quartile groups. Independent predictors of all cause mortality with variables categorised by quartile are shown in Table 34.

Table 34: Independent predictors of all cause mortality

Predictor	Predictor	Wald X^2	Hazard Ratio (95% CI)	P value
Age	< 63	14.6	1.00	
(years)	63 – 70	4.026	1.545 (1.101 – 2.364)	0.045
	71 – 77	8.001	1.823 (1.203 – 2.765)	0.005
	> 77	13.831	2.206 (1.454 – 3.348)	0.0002
Systolic blood pressure	> 158	9.756	1.00	
(mmHg)	140 – 158	5.995	1.591 (1.096 – 2.311)	0.015
	122 – 139	0.754	1.199 (0.796 – 1.806)	0.385
	< 122	7.212	1.696 (1.153 – 2.494)	0.007
Serum creatinine	<85	23.530	1.00	
(µmol/l)	85 – 104	3.392	1.485 (0.975 – 2.262)	0.066
	105 to 133	2.741	1.429 (0.937 – 2.180)	0.098
	> 133	19.675	2.502 (1.668 – 3.752)	<0.0001
Serum glucose	< 6.0	15.265	1.00	
mmol/l	6.0 – 7.6	0.742	1.184 (0.806 – 1.738)	0.389
	7.7 – 10.0	0.829	1.193 (0.816 – 1.743)	0.363
	> 10.0	12.916	1.916 (1.344 – 2.732)	<0.0001
Serum haemoglobin	> 14.3	8.341	1.00	
g/dl	13.1 – 14.3	8.329	1.486 (0.984 – 2.244)	0.059
	11.5 – 13.0	3.758	1.510 (0.995 – 2.292)	0.053
	< 11.5	3.553	1.816 (1.211 – 2.723)	0.004
Diuretic on admission		4.919	1.339 (1.035 – 1.734)	0.027

5 – 12 – 2 Age and blood pressure on multivariate analysis

A linear relationship between age and risk of mortality was seen with the adjusted hazard ratio increasing from 1.545 (95% CI 1.101 to 2.364) for patients aged 63 to 70 (when compared to those under 63) to 2.206 (95% CI 1.454 to 3.348) for patients aged over 77 years. Admission systolic blood pressure had the strongest association with mortality when under 122 mmHg with a hazard ratio of 1.696 (95% CI 1.153 to 2.494).

5 – 12 – 3 Creatinine on multivariate analysis

Creatinine on admission was crudely associated with all cause mortality with a hazard ratio of 1.003 (95% CI 1.002 to 1.004). Patients with a serum creatinine in the highest quartile (> 133 µmol/l) had a hazard ratio of 2.502 (95% CI 1.668 to 3.752) compared to those with a serum creatinine in the lowest quartile (< 85 µmol/l). Furthermore the Wald X^2 statistic of 19.675 is the highest for any variable suggesting it is the most powerful predictor of mortality.

5 – 12 – 4 Haemoglobin on multivariate analysis

Multivariate analysis demonstrated that admission haemoglobin remained a significant predictor of all cause mortality with a hazard ratio of 1.486 (95% CI 0.984 to 2.244) for the second highest quartile, and 1.816 (95% CI 1.211 to 2.723) for patients with an admission haemoglobin below 11.5g/L.

5 – 12 – 5 Serum glucose on multivariate analysis

In the overall model, glucose remained an independent predictor of all cause mortality with a hazard ratio of 1.916 (85% CI 1.344 to 2.732) when elevated to the highest quartile. To ensure any new diagnoses of diabetes made during the index admission were not confounding these data, any patient discharged on insulin or oral hypoglycaemia agents was also classified as diabetic for the purposes of this stratification.

5 – 12 – 6 Prognostic index

The prognostic index score was calculated for each patient based on the variables independently associated with increased all cause mortality. Initially a model utilising the calculated Wald chi-square statistic as the score variable was developed (for example a creatinine greater than 133 µmol/l scores 20). As this calculation is cumbersome a simplified scoring system was developed which performed to the same level as the initial mode. This final index gives a potential score ranging from one to eight and the scoring system used for the prognostic index and is shown in Table 35. Systolic blood pressure did not improve the sensitivity or specificity of the final index and was therefore not included.

Table 35: Scoring system used for prognostic index

Variable	Score
Age < 60	1
Age 60 – 69	2
Age 70 – 79	3
Age > 80	4
Creatinine > 133	1
Glucose > 10	1
Female haemoglobin < 11	1
Male haemoglobin < 13.4	1
Diuretic on admission	1

A cut-off of a score of 1 – 3 indicating low risk, versus a score of 4 – 8 indicating high risk has a sensitivity of 78% and a specificity of 57%. The sensitivity and specificity of the prognostic index over possible range of cut-off values are shown in Table 36.

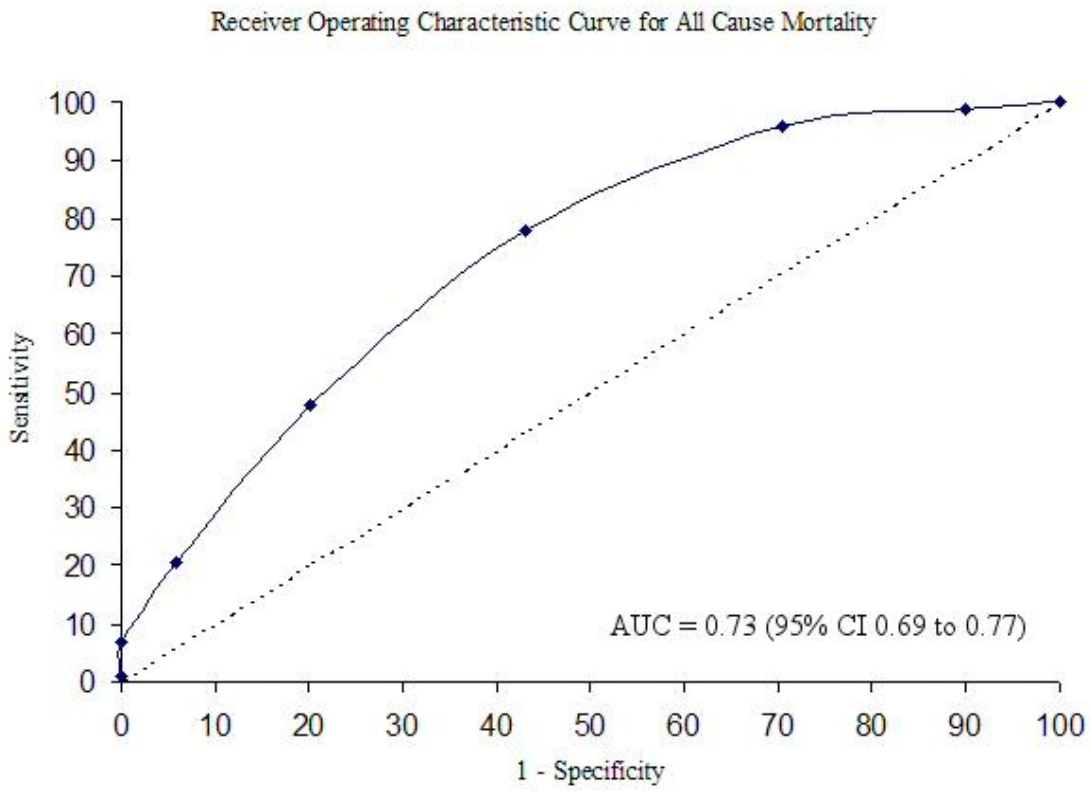
Table 36: Sensitivity and specificity of prognostic index over possible range of cut-off values

Index denoting low/high risk	Patients in high risk group	Deaths in high risk group	Sensitivity	Specificity	PPV	NPV
1/ 2 – 8	496	237	98.8	10.1	47.8	90.6
1 – 2 / 3 – 8	433	230	95.8	29.5	53.1	89.5
1 – 3 / 4 – 8	311	187	77.9	56.9	60.1	75.6
1 – 4 / 5 – 8	172	114	47.5	79.9	66.3	64.6
1 – 5 / 6 – 8	66	49	20.4	94.1	74.2	58.7
1 – 6 / 7 – 8	17	16	6.67	99.7	94.1	56.2
1 – 7 / 8	2	2	0.83	100	100	54.8

PPV = positive predictive value and NPV = negative predictive value

The AUC for the prognostic index with the best sensitivity and specificity was 0.73 (95% CI 0.69 to 0.77) as demonstrated in the receiver operating characteristic curve for the prognostic index shown in Figure 23.

Figure 23: Receiver operating characteristic curve for the prognostic index



Dashed line indicates reference for an AUC of 0.5

Kaplan-Meier survival estimates with patients grouped into low risk (score = 1 – 3) and high risk (score 4 – 8) demonstrate a significant increase in mortality in the high risk group with a log rank statistic of $p < 0.0001$. The Kaplan-Meier curves for population stratified by prognostic score are shown in Figure 24. The percentages of all-cause mortality across scores derived with the prognostic index are shown in Figure 25. Finally the Kaplan-Meier curves for the low risk group (score 1 – 3) and the high risk group (score 4 – 8) is shown in Figure 26.

Figure 24: Kaplan-Meier curves for population stratified by score

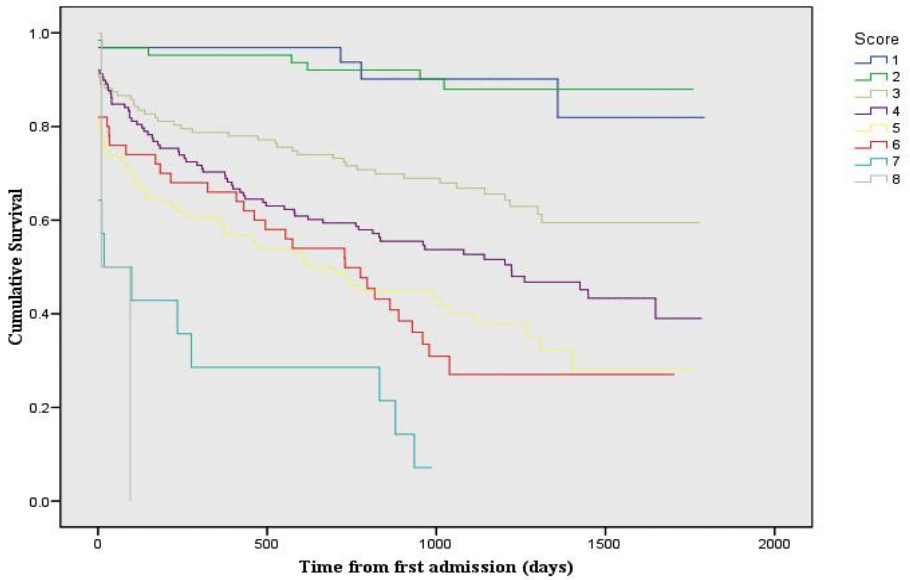
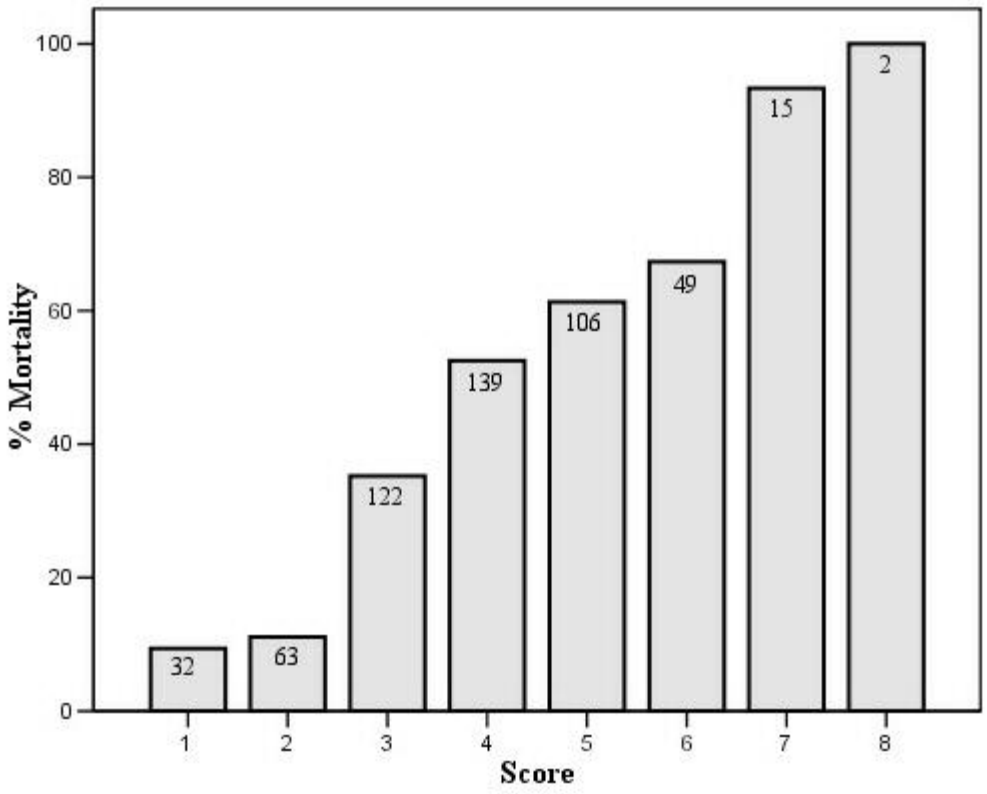
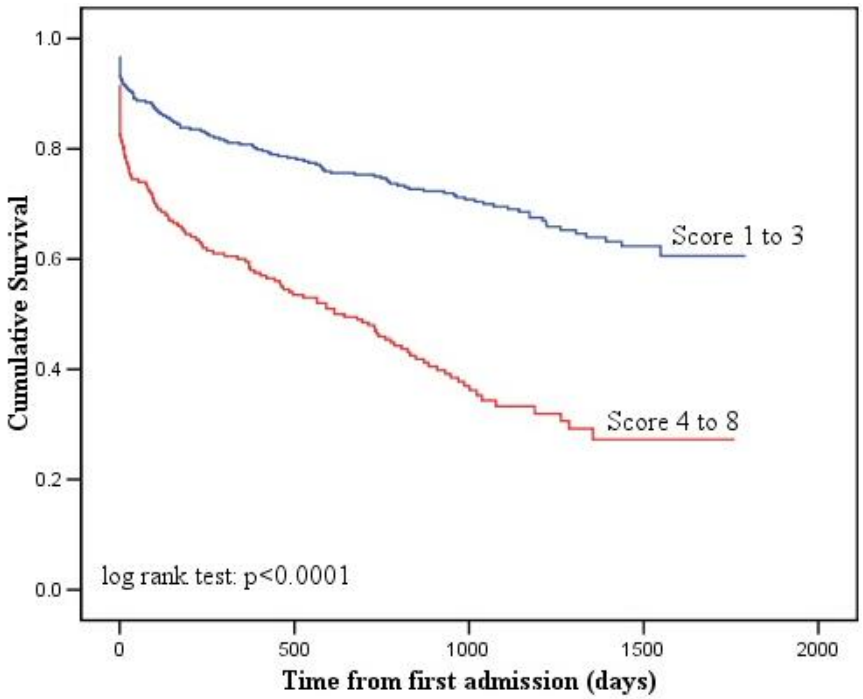


Figure 25: Percentage mortality across scores derived with the prognostic index



Numbers in bars represent number of patients in that group

Figure 26: Kaplan-Meier curves for the low risk group (score 1 – 3) and the high risk group (score 4 – 8)



Survival at 30 days for those in the low risk group is 92% (95% CI 88 to 95), compared to 80% (95% CI 75 to 84) in the high risk group. Similarly 1 year survival is better in the low risk group at 86% (95% CI 81 to 90) vs. 64% (95% CI 58 to 69) and 82% (95% CI 76 to 87) vs. 53% (95% CI 47 to 58) for 2 year survival. The survival at 30 days, 1-year and 2-years stratified by prognostic index score are shown in Table 37.

Table 37: Survival at 30 days, 1-year and 2-years stratified by prognostic index score

	Score 1 – 3	95% CI	Score 4 – 8	95% CI	All	95% CI
30 day	92	88 – 95	80	75 – 84	85	82 – 88
1 year	86	81 – 90	64	58 – 69	73	69 – 83
2 year	82	76 – 87	53	47 – 58	65	61 – 69

5 – 12 – 7 Adjusted survival analysis

In order to account for the simultaneous influence of the variables identified as having a significant interaction with survival on multivariate analysis estimated of the adjusted survival using Cox proportional hazards was performed. Table 38 expands on Table 24 in section 5 -2 and by using the co-variates defined in the prognostic model adjusts the crude survival accordingly. As can be seen the adjusted survival at 30 days is 88% and 68% at two years.

Table 38: Crude unadjusted and adjusted survival for in-hospital, 30 day, 1-year and 2-years for the whole heart failure cohort

Survival period	Unadjusted	95% CI	Adjusted	95% CI
In-hospital	89	86 – 92		
30 days	85	82 – 88	88	85 – 90
1 year	73	69 – 83	77	73 – 81
2 years	65	61 – 69	68	64 - 72

5 – 13 Discussion

These results demonstrate that a number of variables easily obtainable within 24 hours of a first hospital admission for heart failure are independently associated with all cause mortality. The majority of these variables have previously been shown to be predictors of mortality (Jiang, Alexander et al. 2001; Jong, Vowinckel et al. 2002; Bouvy, Heerdink et al. 2003; Brophy, Dagenais et al. 2004), although many of these studies recruited highly selected patients, usually relatively young Caucasian patients with minimal co-morbidity and often in the setting of a randomised clinical trial. This study was undertaken in a community based population admitted to hospital with a validated new diagnosis of heart failure, and no significant exclusion criteria. Unsurprisingly the presence of malignancy was associated with increased mortality on univariate analysis. In addition patients with chronic obstructive pulmonary disease were over 85% more likely to die during the follow up period (hazard ratio of 1.870, 95% CI 1.016 - 3.441, p=0.044). This is similar to data from a cohort of 1,020

patients with heart failure in Italy, where the odds ratio of death in patients with heart failure and chronic obstructive pulmonary disease was 1.50 with 95% confidence intervals of 1.00 to 2.26 (p=0.05) (Macchia, Monte et al. 2007). In that cohort with a mean age of 80, 24% of patients had COPD, compared to only 9% in this study. Such patients are at high risk of readmission – elevated by as much as 35%, and less often receive therapy with beta blockers (Le Jemtel, Padeletti et al. 2007) no doubt due partly to concerns over deleterious effects of beta blockade on respiratory function despite numerous reports to the contrary (McGavin and Williams 1978; Fenster, Hasan et al. 1983; Fogari, Zoppi et al. 1990). Combining alpha-adrenergic blockade with non-selective beta-blockers such as carvedilol may facilitate higher rates of beta blockade in patients with heart failure and chronic obstructive pulmonary disease (Sirak, Jelic et al. 2007).

Many published prognostic factors include variables which are not widely available to the majority of heart failure patients, and are hence impractical for use in a simple model. As with published data, I have shown increasing age, lower systolic blood pressure, higher creatinine and lower haemoglobin levels to be independent predictors of an increased risk of death from all causes. I will discuss each of these factors in turn.

5 – 13 – 1 Age and blood pressure

Advancing age has repeatedly been shown to be a strong predictor of mortality, except perhaps in patients with severe heart failure, where biological age and disease burden are more significant than numerical age (Aaronson, Schwartz et al. 1997). As this population is unselected and encompasses a wide range of heart failure severity, numerical age remains a significant independent predictor of mortality. High systolic blood pressure has been associated with survival and may be a surrogate marker for cardiac reserve (Gheorghiade 2006). Although surprising that a single measurement of blood pressure is predictive of outcome, this presumably reflects cardiac function or the adaptation of the peripheral circulation to maintain adequate perfusion pressure despite a low cardiac output. A low systolic blood pressure on admission may therefore represent more severe systolic impairment or a greater degree of decompensation. However, a low systolic blood pressure did not improve the performance of the prognostic model.

5 – 13 – 2 Renal impairment and heart failure

Alterations in fluid and electrolyte haemostasis are important in the pathophysiology of chronic heart failure (Francis 2001), and impaired renal function has been highlighted as a marker for increased risk of death (Lee and Packer 1986). Patients with heart failure and a raised serum creatinine have high serum renin concentrations, and it has been suggested that serum creatinine may be a marker of reduced cardiac output and renal perfusion leading to increased activation of the renin-angiotensin

system (Cowie, Wood et al. 2000). Renal blood flow is a key determinant of glomerular filtration rate in congestive heart failure (Ljungman, Laragh et al. 1990) and this is affected by both decreased cardiac output and increased venous congestion (Stevenson and Perloff 1989), with evidence that right atrial pressure is related to glomerular filtration rate in patients with heart failure (Damman, Navis et al. 2007). Furthermore, such patients are likely to be clinically decompensated with high levels of circulating catecholamines, and be less able to respond to situations which decrease cardiac output. I have confirmed that elevated serum creatinine at the time of admission is an independent risk factor for all cause mortality.

5 – 13 – 3 Anaemia and heart failure

Anaemia is common in heart failure and has recently been shown to be a powerful independent predictor of poor outcome across a range of heart failure severity (Mozaffarian, Nye et al. 2003; Anand, McMurray et al. 2004). I confirmed the high prevalence of anaemia in heart failure, with 17% of patients having an admission haemoglobin < 11g/dl, with this figure increasing to 31% if a cut-off of 12g/dl is applied. Hence a 1.0 g/dl increase in the haemoglobin threshold leads to a near doubling of the prevalence of 'anaemia' in this cohort. Using the World Health Organisation criteria of anaemia defined as a concentration < 13.0 g/dl in men and < 12.0 g/dl in women gives rates of anaemia of 39% and 43% in men and women respectively.

Whether this association between anaemia and increased mortality is causal, or whether anaemia is a marker of risk, perhaps reflecting disease severity is uncertain. The hormonal and metabolic effects of anaemia (Schrier and Abraham 1999) can lead to myocardial hypertrophy, myocardial toxicity and salt and water retention, all of which could be deleterious in heart failure. Additionally there is some evidence that correction of anaemia with erythropoietin and iron not only improved haemoglobin concentration, but also left ventricular ejection fraction and functional status in patients with severe heart failure (Silverberg, Wexler et al. 2001). It has also been suggested that anaemia may be an epiphenomenon of advanced heart failure representing the haemodilution due to volume overload, malnutrition from cardiac cachexia and renal insufficiency. Patients in this study with admission haemoglobins in the lowest quartile were more likely to be older, female, and have impaired renal function and a trend towards more diuretic use – findings similar to those previously demonstrated (Komajda 2004). This increased rate of diuretic use in the lowest haemoglobin quartile (Q1: 51% vs. Q4: 42%, p=0.081) may support a hypothesis of increased volume overload in the most anaemic patients, but it is most likely that anaemia is due to a combination of factors, and low haemoglobin has been shown to be predictive of mortality independent of pulmonary capillary wedge pressure after guided diuresis, suggesting haemodilution alone cannot account for this (Horwich, Fonarow et al. 2002).

Moreover, heart failure may in part be an inflammatory disease, and an alternative hypothesis is that increased levels of inflammatory mediators such as cytokine and tumour necrosis factor-α in heart failure lead to bone marrow suppression and subsequent anaemia of chronic disease (Vila, Martinez-Sales et al. 2007). A study of

high-sensitivity C-reactive protein (a marker of inflammation) in patients with heart failure found it to be an independent predictor of prognosis, further suggesting immune activation may play an important role in the pathogenesis of heart failure (Yin, Chen et al. 2004).

It is worth emphasising these were patients newly admitted to hospital with heart failure, and it may be that the duration of their heart failure may have been sufficiently short to not directly affect the haemoglobin concentration, suggesting it is a reflection of age, renal function and degree of fluid retention rather than systemic organ dysfunction. A previous study of patients with a short duration of heart failure demonstrated that admission anaemia was not associated with worse survival (Kalra, Collier et al. 2003), and suggested that the prognostic relevance of admission haemoglobin is dependent on the stage of the disease process. However, as 45% of his patients were admitted on a diuretic, it could be argued that these patients may have had a significant duration of heart failure burden. Also of significance is the association of even a mild reduction in haemoglobin with worse survival, even when at levels above those that may be considered significant, or traditionally associated with increased risk. Confounding by aetiology of heart failure in patients with anaemia may be significant, as coronary artery disease impairs the ability of the myocardium to tolerate anaemia, and may predispose to myocardial ischaemia and repetitive myocardial stunning with subsequent apoptosis and necrosis leading to progression of ventricular dysfunction.

The potential impact of chronic differences in disease-altering therapy such as ACE inhibitors and beta blockers between patients with and without anaemia and / or renal impairment is not known and may be significant. Another important factor may be the change in haemoglobin level following heart failure therapy, which may help to adjust for initial volume expansion, although one study assessing haemoglobin levels over 24 weeks (Anand, McMurray et al. 2004) found no significant change in haemoglobin (albeit in stable, treated patients). While this does not change the importance of admission haemoglobin as a risk factor, it emphasises the need for further studies in this area.

As the mean cell volume is significantly lower in patients with haemoglobin levels below (86 vs. 89, p=0.0002) this may suggest a link between iron deficiency and anaemia in heart failure. Gastrointestinal malabsorption, chronic aspirin use and poor nutrition are seen in heart failure and may contribute. In this study twelve (13.3%) of the 90 patients with a mean haemoglobin concentration < 11.0 g/dl had a mean cell volume below 76 fl, and 23 (33%) of the 70 patients with a normocytic anaemia (haemoglobin < 11.0g/dl and mean cell volume 76 - 96fl) had evidence of renal impairment (creatinine > 150 µmol/l), findings comparable to those of a previous study of NYHA Class IV patients (Cromie, Lee et al. 2002), in that haematinic deficiency is uncommon, and the majority of anaemia in heart failure is that of chronic disease, some of which is related to renal impairment. The principal aetiology of anaemia (58%) was found to be anaemia of chronic disease in one recently described cohort (Ezekowitz, McAlister et al. 2003).

These data suggest an increase in risk across quartiles of haemoglobin, with no clear suggestion of a U-shaped relationship of haemoglobin with mortality as has been previously shown (Sharma, Francis et al. 2004). The fact that admission haemoglobin in the lowest quartile does not achieve the same level of significance in women as in men, even after adjustment, may suggest an interaction between sex and haemoglobin as a predictor of mortality. Different cut offs for significance of anaemia may be required between men and women, a fact which will be of importance in planning trials to assess the therapeutic benefit of anaemia correction in heart failure patients.

5 – 13 – 5 Hyperglycaemia and heart failure

An important new finding in this study is the increasing risk of mortality with admission hyperglycaemia in non-diabetic patients. Previous studies have shown that diabetes itself is an independent risk factor for the development of heart failure (He, Ogden et al. 2001), and confers a worse prognosis once heart failure is established (Shindler, Kostis et al. 1996; Haas, Vos et al. 2003). Furthermore elevated fasting plasma glucose is an independent predictor of hospitalisation for congestive heart failure in patients with vascular disease or diabetes with end-organ damage (Held, Gerstein et al. 2007). Admission hyperglycaemia has been shown to have significant association with death after myocardial infarction in non-diabetic but not diabetic patients (Capes, Hunt et al. 2000), and admission plasma glucose has been linked with all cause mortality after myocardial infarction even when corrected for HbA_{1c} (Hadjadj, Coisne et al. 2004). In a study of 1,957 patients admitted with an acute coronary syndrome to hospitals in Sweden, hyperglycaemia (defined as plasma glucose > 9.4mmol/l) was associated with a higher 30-day mortality rate of 20.2% vs.

3.5% for patients without hyperglycaemia ($p<0.0001$) and this was more prominent in patients without diabetes (Petursson, Herlitz et al. 2007). Moderately elevated glucose levels have also been associated with increased short term mortality in non-diabetic patients sustaining an ischaemic stroke (Capes, Hunt et al. 2001). However, another study demonstrated that admission glycaemia could identify patients admitted with acute coronary syndromes at high risk in both non-diabetic and diabetic patients (Foo, Cooper et al. 2003), and a study designed to explore non-invasive predictors of death in non-diabetic patients with chronic heart failure did not demonstrate an association with random blood glucose levels and mortality or cause of death (Kearney, Fox et al. 2002). These findings may imply it is the acute glyco-metabolic state that is an indicator of risk rather than the consequence of a pre-existing metabolic disorder, with hyperglycaemia being proposed as a marker of the degree of post infarction stress and catecholamine release (Karlsberg, Cryer et al. 1981) following increased neuro-hormonal activation.

The traditional cardio-renal model of heart failure has been expanded to emphasise the role of neurohormonal activation in the pathology and progression of heart failure, and variables that reflect the magnitude of neurohormonal dysfunction may help to identify patients with heart failure who are at increased risk of entering a decompensated spiral of declining ventricular function, haemodynamic deterioration, and death due to progressive heart failure. Patients with heart failure have increased muscle sympathetic nerve activity, increased cardiac norepinephrine spill-over (Lambert, Kaye et al. 1995), and increased plasma catecholamines and renin. Additionally, sympathetic activation also leads to β-receptor down-regulation, myocardial remodelling and increased rates of ventricular arrhythmias (Pepper and

Lee 1999). Adrenergic stress has been linked with hyperglycaemia, and the degree of acute phase hyperglycaemia has been correlated with the extent of myocardial injury in acute myocardial infarction. It is interesting to note a trend towards an increase in pulse rate with glucose quartiles albeit not significant at the 5% level (Q1: 92 vs. Q4: 98, p=0.107). One potential explanation is that hyperglycaemia secondary to sympathetic excess is directly damaging, as such patients are relatively insulin deficient which leads to reduced peripheral glucose uptake and increased circulating free fatty acids. Free fatty acids may impair endothelium-dependent vasodilation, and have also been shown to promote calcium overload and arrhythmias (Oliver and Opie 1994). Additionally, acute hyperglycaemia in healthy volunteers has been shown to reduce nitric oxide availability, and also increase both QTc and QTc dispersion, both of which may lead to increased risk of arrhythmias and sudden death (Marfella, Rossi et al. 1999).

An alternative explanation is that hyperglycaemia may be a marker of the extent of cardiac failure and degree of sympathetic system activation. Other markers of cardiac sympathetic activity such as plasma norepinephrine are powerful independent predictors of mortality (Cohn, Levine et al. 1984), and measures of autonomic activity such as heart rate variability have been shown to predict death due to progressive heart failure (Kearney, Fox et al. 2002). The lack of an association of hyperglycaemia with increased mortality in diabetic patients may be due to several reasons. Patients with known diabetes, or diabetes newly diagnosed during admission, are more likely to be treated with glucose-lowering therapy which may limit the metabolic effect of hyperglycaemia. It is also difficult to define stress hyperglycaemia in diabetic

patients as the unstressed baseline is not known, making direct comparison between non-diabetic and diabetic patients difficult.

Data on whether patients with raised admission glucose levels underwent the gold standard method to test for diabetes, namely the oral glucose tolerance test, was not obtainable. I attempted to minimise the misclassification of diabetic patients by assessing their discharge medication for the presence of insulin therapy or oral hypoglycaemia agents. To assess how many of the non-diabetic patients subsequently went on to be diagnosed with diabetes, current prescription data for a random group of 110 patients who were not known to be diabetic on either admission or discharge was obtained by contacting their current primary care physician. Of these, only 6 (5%) patients had subsequently been commenced on either insulin or oral hypoglycaemia therapy. Whilst I will not have captured those patients treated by dietary restriction, it appears the potential confounding by misclassification of diabetic patients as non-diabetic will be minimal.

5 – 13 – 6 Prognostic index

The prognostic model demonstrated was designed to be independent of left ventricular systolic function as this data may not be available within 24 hours of admission. Furthermore, by utilising variables that are easily obtainable, the model is not dependent on specialised tests reducing the problems arising from missing data. This index can stratify patients newly admitted to hospital with heart failure into low and high risk groups. It is easy to calculate a patient's score, and the variables included are significant predictors of mortality. The sensitivity (78%), specificity (57%) and AUC (0.73, 95% CI 0.69 – 0.77)) at a cut off point of 1 to 3 indicating low risk, and 4 to 8 indicating high risk, are comparable to those of the risk model based on prospectively collected data by Kearney et al (Kearney, Nolan et al. 2003) (AUC=0.74, 95% CI 0.70 – 0.78, sensitivity 72%, specificity 63%), and very similar to the performance of the prospectively validated American Heart Failure Survival Score in a cohort of NYHA Class I – III patients, where the AUC was 0.73 (Zugck, Haunstetter et al. 2002). A recently published complex risk prediction model based on data from the CHARM study of Candesartan in heart failure had an AUC of 0.73 – 0.76 for the various arms of the trial and outcome measured (Pocock 2006). Pocock's model uses up to 24 variables and the score is calculated by summating the co-efficient of pertinent variables for each individual patient and includes assessment of left ventricular systolic function. Data on haemoglobin, glucose and creatinine were not assessed; age and diastolic blood pressure were independent predictors of mortality.

The most extensively validated model for estimating heart failure prognosis is the Seattle Heart Failure Model in which data on 1125 patients with systolic dysfunction and heart failure was used to develop a risk score (Levy 2006). This was then validated and refined in a further 9942 patients from 5 other cohorts. The overall receiver operating characteristic AUC was 0.729 (95% CI 0.714 – 0.744). The final model includes 14 parameters and requires use of a web based calculator to derive the prognostic score. Despite the complexity of this model its performance is broadly similar to the model presented here.

The index in this study has several strengths as it is derived from data based on a large contemporary cohort of patients newly admitted to hospital with heart failure including a substantial proportion of women and the diagnosis was validated in each case rather than solely relying on discharge coding data. Although this study was designed to be independent of left ventricular systolic function, because this is rarely available within 24 hours and will allow for broader use in community based heart failure patients, it is of note that echocardiography had been performed in 364 (69%) of the cohort and 28% of these patients had normal left ventricular systolic function suggesting a diagnosis of heart failure with normal ejection fraction, although accurate assessment of diastolic dysfunction was not routinely available. The long follow up period (mean 3.5 years) and an overall mortality of 45% allowed us to estimate the effect of several clinical variables simultaneously.

5 – 13 – 7 Limitations of prognostic model

The limitations of this retrospective study must be emphasised. This study is dependent on the accuracy of recorded data; however, variables such as blood pressure and laboratory data are likely to be accurately documented (Southard and Frankel 1989). At present there are no data on a second cohort of heart failure patients and therefore cannot externally validate the factors shown to predict mortality in this study, nor was I able to reliably obtain data on the patients NYHA class and were therefore unable to adjust for this potential covariate. Additionally, the aetiology of heart failure was not yet known in the majority of the patients, and prognostic variables may vary with heart failure aetiology. In particular the impact of hyperglycaemia may be more significant in heart failure of ischaemic aetiology such as has been demonstrated with diabetes. Heart failure follows a variable clinical course, and up to 50% of patients die suddenly rather than succumb to progressive pump failure (Cleland, Massie et al. 1999). Cause of death is unknown in this cohort and it may be that some of these prognostic variables only apply to particular causes of death, for example haemoglobin has been demonstrated to be a significant predictor of death from progressive heart failure but not sudden death (Poole-Wilson, Uretsky et al. 2003).

Serum creatinine has been used as a surrogate for renal function, as accurate records of body mass index on admission were not regularly available, precluding the calculation of glomerular filtration rate. Beta blockers have now become standard therapy in heart failure, the aim being to attenuate activation of the sympathetic system. Studies have demonstrated a significant influence of beta blocker therapy on

prognostic variables, albeit in a cohort undergoing assessment for cardiac transplantation (Zugck, Haunstetter et al. 2002). As this cohort is from a period when beta blocker use was being routinely introduced, the relatively low use of beta blockers (17% vs. 60% for ACE inhibitors or ARB on discharge) may mean that these variables are less applicable to the modern heart failure patient. The corollary of this is that beta blocker use in the general heart failure population is still limited (Cleland, Cohen-Solal et al. 2002; Komajda, Follath et al. 2003). As the study was retrospective, no control over subsequent treatment after discharge was possible. Consequently the variables associated with increased mortality may have been confounded by differences in drug therapy between patients, though significant confounding would seem unlikely given the similarity of risk predictors I have found compared to previous prospective studies.

5 – 14 QRS duration and prognosis

In order to assess the effect of ECG data such as QRS duration on outcome the admission ECGs of the study cohort were assessed in detail. Based on previous published data demonstrating increased mortality in patients with prolonged QRS duration (Hofmann, Bauer et al. 2005) as well as other ECG parameters it was anticipated I would find a similar result. It is therefore surprising that the ECG parameters assessed had no association with mortality on either univariate or multivariate analysis.

On reviewing published data on QRS duration and mortality, the majority are derived from heart failure cohorts within randomised controlled trials. For example the study cited above by Hofmann et al. (Hofmann, Bauer et al. 2005) is based on 248 patients from a cohort of 5,010 patients with heart failure recruited into the Valsartan Heart Failure Trial (Cohn and Tognoni 2001) assessing the effect of Valsartan in patients with NYHA class II or III heart failure, ejection fractions under 40% and symptoms for more than three months. This sub study cohort had a mean age of 60 years, and at the point of admission to the study the mean QRS duration was 140ms (93 – 270ms). A total of 110 patients – 30% of the original sub study cohort – were excluded as they either had a pacemaker in-situ or were on class I anti-arrhythmic drugs, and the mean observation period for mortality was 25.8 months. They found QRS duration to be the only independent prognostic factor when assessed alongside NYHA class, ejection fraction, atrial fibrillation, age and gender. The authors conclude that QRS duration is a powerful predictor of prognosis in patients with heart failure and reduced ejection fraction.

A study undertaken between 1993 and 1996 identified 364 patients with chronic heart failure under review at the Royal Brompton Hospital (Shamim, Francis et al. 1999). The mean age of this cohort was 60 years, and the mean ejection fraction 28%. After 31 months of follow up, 31% had died. The mean QRS duration for all patients at the time of assessment was 121ms. The authors also conclude that QRS duration is a powerful independent prognostic marker in patients with congestive heart failure.

Similar findings were reported from a study from America which retrospectively assessed 669 patients with heart failure of class NYHA II to IV, ejection fraction under 40% and more than 10 premature ventricular contractions per hour on Holter monitoring (Iuliano, Fisher et al. 2002). After 45 months, a total of 41% of patients had died. They found QRS duration greater than 120ms to be an independent predictor of mortality in this cohort, although noted this was restricted to patients with QRS prolongation and left bundle branch block pattern. There is some preliminary evidence that prolonged QRS duration in the setting of heart failure with preserved ejection fraction is associated with similar readmission rates and mortality to patients with prolonged QRS and reduced ejection fractions (Danciu, Gonzalez et al. 2006). Data from the large-scale CHARM trial series studying Candesartan in a variety of heart failure cohorts show that only 14.4% of patients with heart failure and preserved ejection fraction have a QRS duration greater than 120ms compared to 30.1% of those with reduced ejection fraction (Hawkins, Wang et al. 2007). In the overall cohort a prolonged QRS duration was associated with mortality although the risk in patients with QRS duration over 120ms and preserved ejection fraction did not persist after multivariate analysis.

In the cohort of 528 patients in this study, the mean QRS duration was 104ms and the mean age of the patient 69 years. Furthermore, these were not patients already treated for heart failure and included patients irrespective of left ventricular ejection fraction. QRS duration is potentially affected by numerous factors such as age, gender, left ventricular ejection fraction, aetiology of heart failure and concomitant medication. In fact a lower ejection fraction is predictive of prolonged QRS duration suggesting that the mean QRS in cohorts of patients with significantly reduced ejection fraction will be prolonged compared to the more general heart failure cohort. Similarly patients with a prolonged QRS duration are more likely to have systolic dysfunction, a large study of 3,471 patients with heart failure assessed QRS duration and outcome and demonstrated that 20% of patients with heart failure will have a QRS duration greater than 120ms with the rates of systolic dysfunction climbing from 42% in those with a QRS under 120ms to over 70% for those with a QRS duration over 150ms (Shenkman, Pampati et al. 2002).

What is clear from these data is that QRS duration is an independent prognosticator in selected cohorts of patients with heart failure and reduced ejection fraction, and many of these studies are restricted to patients with significant left ventricular dysfunction and relatively prolonged QRS duration at baseline. Data from this study suggests that assessment of QRS duration in an unselected cohort of patients with a clinical diagnosis of heart failure irrespective of ejection fraction is not associated with mortality and is not a valid prognostic marker. This may have implications on the generalisation of heart failure prognostic models to the heart failure community as a whole.

The potential for difference in the prognostic importance of QRS duration between heart failure cohorts has recently been demonstrated in a study from Denmark (Fosbol, Seibaek et al. 2007). A total of 3,028 patients were enrolled into a randomised trial of the anti-arrhythmic dofetlide vs. placebo between 1993 and 1996, and were derived from two heart failure cohorts with 1,518 patients having chronic heart failure and 1,510 patients heart failure with recent myocardial infarction (within 7 days). All patients had heart failure symptoms and an ejection fraction under 35%; patients with severe renal dysfunction or prolonged QTc interval beyond 460ms were excluded. The mean age of the patients was 71 years in the CHF cohort and 69 years in the myocardial infarction cohort. With respect to baseline drug therapy 10% of those in the CHF cohort and 36% of myocardial infarction patients were receiving treatment with a beta blocker. Rates of ACE inhibitor use were higher at 75% and 56% for the CHF and myocardial infarction cohorts respectively. After 10 years 79% of all patients had died. An increase in the QRS duration of 10ms was associated with an increase in risk of mortality by 11% for patients with a recent myocardial infarction ($p<0.0001$) but only 5% in the CHF cohort ($p<0.0001$). Put another way, the hazard ratio for patients with a QRS over 120ms compared to those with a normal QRS duration was 1.87 (95% CI 1.62 – 2.14) for the post myocardial infarction patients and only 1.30 (95% CI 1.16-1.45) for patients with chronic heart failure and no recent infarction. The authors point out that prolonged QRS duration was associated with reduced left ventricular systolic function in both groups in keeping with previous studies (Kashani 2005) but the association of a independent prognostic power of a prolonged QRS interval was only present in patients with heart failure post

myocardial infarction and postulate that patients with prolonged QRS and heart failure post recent myocardial infarction may benefit from resynchronisation therapy.

Of additional interest is the finding from a large-scale study of heart failure admissions in Sweden which assessed the independent contribution of left bundle branch block in 21,685 cases of symptomatic heart failure requiring hospital admission between 1995 and 2003 (Tabrizi, Englund et al. 2007). They found that 20% of patients had left bundle branch block and this was associated with increased 5-year mortality with an odds ratio of 1.21 (95% CI 1.10 – 1.35, $p<0.001$). However, patients with left bundle branch block were older (76 years vs. 75 years, $p<0.001$) and had a higher prevalence of co-morbid conditions such as prior myocardial infarction (50% vs. 46%, $p<0.001$). When multivariate analysis included ejection fraction the presence of left bundle branch block no longer remained independently associated with 5 year mortality. This large scale analysis suggests left bundle branch block is associated with higher mortality but this is related more to co-morbidities and underlying cardiac function rather than directly to the presence of left bundle branch block.

This is further evidence that the absolute prognostic power of QRS duration depends on the cohort selected and support the hypothesis that QRS duration is less useful as a prognostic marker in an unselected heart failure cohort such as that studied in this thesis, which includes patients with heart failure and normal ejection fraction as well as post myocardial infarction patients.

5 – 15 Summary

Routine clinical variables available within 24 hours of a first admission to hospital with heart failure are associated with increased mortality from all causes. The assessment of these variables in conjunction with standard clinical judgement could aid the physician in predicting the prognosis of an individual patient with heart failure, and facilitate appropriate counselling and initiation of appropriate therapy in those at a higher risk of death. QRS duration is not an independent prognostic marker in an unselected heart failure cohort.

What are the clinical implications of these results? I have confirmed that anaemia on admission is common and is an independent risk factor for all cause mortality, supporting the suggestions that physicians need to identify and treat reversible causes of anaemia where possible. Importantly the risk related to anaemia is independent of renal impairment, which is a potential cause of anaemia and itself an independent prognostic marker. The identification of admission hyperglycaemia in non-diabetic patients as an independent risk factor warrants further investigation. It may be that serum glucose is a marker of increased sympathetic activity and aid in identifying patients at higher risk of disease progression and decompensation. Alternatively it may indicate patients who have increased rates of ischaemic heart disease with ongoing vascular stress who may potentially benefit from revascularisation strategies. Validation of these prognostic factors in another cohort of heart failure patients is required, preferably by a large scale prospective study.

On the initial multivariate analysis a fall in admission systolic blood pressure was associated with increased mortality as has been demonstrated in a number of other studies (Gheorghiade 2006; Lee 2006). However during refinement of the final prognostic model the inclusion of a score based on blood pressure did not add to the models final accuracy and was therefore omitted. This may suggest that the impact of blood pressure on survival is less when other variables such as creatinine are included. Other variables that have been shown in other studies to be of prognostic importance include BNP (Olsson, Swedberg et al. 2007) and troponin level (Perna, Macin et al. 2005; You 2007) – unfortunately these data were not available on this cohort of patients and were therefore not included in the prognostic model. Further studies undertaken to assess the prognosis and risk factors in our local heart failure population should include a detailed assessment of the role of biomarkers in estimating survival.

5 – 15 – 1 Survival of patients admitted with heart failure

This study has reinforced the high mortality associated with heart failure. Of 100 patients admitted to hospital with a new diagnosis of heart failure 11 will die during the index admission, and a total of 27 will be dead at the end of one year and 35 at the end of two years. This is very similar to data from the Framingham heart study which demonstrated 1 year mortality of 26% for those during the study period of 1990 to 1999 with a 5 year mortality of 52% (Mosterd and Hoes 2007). More recent data from the Olmsted county survey of 4,537 patients diagnosed with heart failure between 1979 and 2000 showed a 1 year mortality of 21% in men for those diagnosed between 1996 and 2000, with a 5 year mortality rate of 50%. While these rates have improved from 1 and 5 year mortality rates of 30% and 65% respectively, they remain

high. The mortality of heart failure is improving, albeit slowly, despite the rapidly increasing evidence-base of therapeutic strategies including pharmacotherapy and device therapy. As discussed earlier this may reflect the inherent delay between publishing effective strategies and their use in routine clinical practice.

Given the high mortality in the cohort studied, and the very low rates of proven heart failure therapy prescriptions such as beta blockers on discharge from hospital, clearly a priority for local practice will be to improve the use of proven heart failure therapies in an effort to reduce mortality.

5 – 15 – 2 Prognostication in heart failure

As demonstrated it is feasible to construct a prognostic model using variables widely available within the first few hours of a hospital admission. Scoring a patient based on their age, creatinine, haemoglobin, glucose and prior diuretic use can stratify patients into high and low risk with a degree of sensitivity and specificity comparable to previously published prognostic models. More complex prognostic models such as the Seattle survival score (Levy 2006) can also be used to estimate the additional benefit of medical or device therapy, however in this more simple prognostic score the aim is to identify patients at greater risk of mortality to ensure they receive appropriate intensive treatment and monitoring. Given that it does not require invasive assessment of cardiac function or specialised tests, it is easier to apply to a general heart failure population than models using parameters such as assessment of peak VO_2 (Aaronson, Schwartz et al. 1997) or norepinephrine spill-over measurements (Kaye, Lefkovits et al. 1995).

This pragmatic approach to assessment of prognosis in heart failure is similar to the model developed by Bouvy et al. who assessed prognosis in 152 patients admitted to hospital with heart failure who were enrolled in a clinical trial of drug compliance (Bouvy, Heerdink et al. 2003). The authors derived a model based on 7 factors which could predict mortality with a sensitivity of 84%, specificity of 69% and an area under the receiver-operator characteristic (ROC) curve of 0.77. The variables in this model included age, male sex, history of diabetes, history of renal impairment, ankle oedema, weight and blood pressure. This is broadly similar to the model described

here which performs with a sensitivity of 78%, specificity of 57% and an area under the ROC curve of 0.73.

It is important to note significant differences in both the size and composition of the cohorts used. The 528 patients in this cohort were unselected heart failure admissions compared to 152 patients enrolled in a clinical trial designed to assess the impact of pharmacist-led intervention on drug compliance in heart failure. Other notable factors are an identical mean age of 69 years in both cohorts, but very different rates of drug use at baseline. In the cohort studied by Bouvy et al, 66% of patents were taking ACE inhibitors at the time of admission and 49% were taking a beta blocker. This is no doubt due to the fact these were established heart failure patients enrolled into the trial by their cardiologist as opposed to patients admitted to hospital with a first ever diagnosis of heart failure.

This study does demonstrate the feasibility of developing a simple, pragmatic prognostic model which can identify high risk patients at the point of admission with a new diagnosis of heart failure. Attempts to validate the apparent accuracy of this model using cross-validation or bootstrap statistical techniques based on the inherent dataset are appealing but not very useful; the ideal strategy is validation in a separate cohort of similar patients (Harrell, Lee et al. 1996).

5 – 16 Conclusion

In this chapter I have reviewed the variables associated with mortality on both univariate and multivariate analysis and then developed a simple and pragmatic prognostic model. This has then been compared with previously published data on heart failure prognostication. In addition the neutral effect of prolonged QRS duration on outcome has been discussed.

Chapter 6 – Ethnicity data

6 – 1 Introduction

In this chapter I will review the demographics of the South Asian cohort compared to the Caucasian cohort, highlighting any significant differences. This will be followed by a comparison of investigational data such as ECG and echocardiographic parameters. Drug therapy both on admission and discharge will be compared between South Asian and Caucasian patients. The survival differences between the ethnic groups will be discussed; finally an assessment of any differences in the prognostic factors associated with mortality between ethnic groups will be presented. I will then answer the research questions posed in chapter 2 and compare data in this study with published data on the effect of ethnicity on heart failure treatment and survival.

6 – 2 – 1 Comparison of demographics between ethnic groups

The basic admission demographics stratified by ethnicity are shown in Table 39.
It can be seen that there were no significant differences in the age, sex distribution or mean admission duration between the Caucasian and South Asian cohorts. There was a significant difference in the proportion of patients dying during the index admission - 13% of Caucasians compared to 7% of South Asians (p=0.046).

Table 39: Basic admission demographics stratified by ethnicity

	Caucasian	%	South Asian	%	p value
Admissions	352	66	176	33	
Male	205	58	97	55	0.494
Female	147	42	79	45	0.494
Mean Age	70		68		0.106
Age range	39 – 102		42 – 90		
Mean duration	15		13		0.281
Median duration (range)	9 (0 – 380)		7 (0 – 162)		0.319
Died	167	47	73	41	0.194
Died during admission	44	13	12	7	0.046

6 – 2 – 2 Comparison admission variables between ethnic groups

The baseline co-morbidity, examination and biochemistry stratified by ethnicity are shown in Table 40. The significant differences in co-morbidity are that South Asian patients are more likely to have a diagnosis of diabetes – 46% of the cohort compared to 18% of Caucasian patients ($p<0.0001$) – and more likely to have a diagnosis of hypertension (45% vs. 33%, $p=0.006$). More Caucasians have a diagnosis of chronic obstructive pulmonary disease – 11% vs. 5% for South Asians ($p=0.031$). This would be in keeping with higher rates of smoking in Caucasian patients whereby 42% of Caucasians were either current or ex-smokers compared to 22% of South Asian patients ($p<0.0001$).

No significant differences in the admission pulse and blood pressure were detected between ethnic groups, however 31% of Caucasians were in atrial fibrillation on presentation compared to only 24% of South Asians (p=0.0002). Admission renal biochemistry was broadly similar between ethnic groups, with no significant differences in sodium, potassium or creatinine levels. The mean glucose in South Asians was significantly higher at 9.6mmol/l compared to 8.4mmol/l (p=0.019) clearly following the higher rate of diabetes in this group. Admission haemoglobin was lower in South Asians compared to Caucasians although this difference was only statistically significant in females (11.7g/dl vs. 12.6g/dl, p=0.001).

Table 40: Baseline admission co-morbidity, examination, biochemistry stratified by ethnicity

	Caucasian	South Asian	p value
Current or ex-smoker	149 (42%)	39 (22%)	<0.0001
Heart failure	44 (13%)	18 (10%)	0.444
Angina	75 (21%)	47 (27%)	0.165
Myocardial infarction	75 (21%)	36 (20%)	0.821
Coronary revascularisation	20 (6%)	10 (6%)	1.0
Hypertension	117 (33%)	80 (45%)	0.006
Stroke	37 (11%)	20 (11%)	0.766
Diabetes	62 (18%)	81 (46%)	<0.0001
Chronic obstructive pulmonary disease	38 (11%)	9 (5%)	0.031
Mean pulse rate (/min)	95 (24.7)	92 (20.8)	0.115
Mean systolic blood pressure (mmHg)	140 (27.5)	145 (28.4)	0.063
Mean diastolic blood pressure (mmHg)	83 (17.9)	83 (18.0)	0.559
Atrial fibrillation	94 (31) *	24 (15) *	0.0002
Mean sodium (mmol/L)	137 (4.6)	137 (4.6)	0.149
Mean potassium (mmol/L)	4.2 (0.71)	4.2 (0.64)	0.438
Mean creatinine (μmol/L)	121 (75.8)	128 (86.3)	0.657
Mean serum glucose (mmol/L)	8.4 (5.2)	9.6 (3.7)	0.019
Mean haemoglobin (g/dL) – All	13.1 (2.0)	12.5 (2.2)	0.002
–Males	13.4 (1.8)	13.1 (2.2)	0.235
–Females	12.6 (2.1)	11.7 (2.0)	0.001

6 – 2 – 3 Comparison of ECG and echo data between ethnic groups

The differences in the ECG and echocardiographic data stratified by ethnicity are shown in Table 41. This demonstrates some interesting observations. Caucasian patients are admitted with a mean QRS duration significantly longer compared to South Asians (107ms vs. 99ms, p=0.0001) and a higher proportion have documented severe left ventricular systolic impairment on echocardiography (28% vs. 18%, p=0.025) suggesting South Asians present to hospital with less severe ventricular dysfunction. Furthermore the proportion of patients admitted with heart failure but normal left ventricular systolic function is higher in South Asians at 38% compared to 23% of Caucasians (p=0.002).

With regards to echocardiographic assessment being undertaken, an equal proportion of South Asian and Caucasian patients underwent echocardiography although there was a suggestion that South Asians are less likely to have an echocardiogram during the admission with only 40% having in-patient assessment compared to 54% of Caucasians (p=0.063) and a significantly higher proportion having an echocardiogram after discharge (46% vs. 31%, p=0.005). More Caucasians have left ventricular hypertrophy as assessed by the Cornell-voltage product than in South Asians (30% vs. 19%, p=0.037).

Table 41: ECG and echocardiographic data obtained stratified by ethnicity

	Caucasian	South Asian	p value
Left ventricular hypertrophy	92 (30%)	30 (19%)	0.037
Mean QRS duration (ms)	107	99	0.0001
QRS > 120ms	76 (25%)	24 (15%)	0.021
Echo performed	244 (69%)	120 (68%)	0.790
Echo before admission	38 (16%)	13 (11%)	0.221
Echo during admission	131 (54%)	52 (40%)	0.063
Echo after admission	75 (31%)	55 (46%)	0.005
Normal left ventricular function	56 (23%)	46 (38%)	0.002
Mild left ventricular systolic dysfunction	60 (25%)	25 (21%)	0.426
Moderate left ventricular systolic dysfunction	59 (24%)	28 (23%)	0.859
Severe left ventricular systolic dysfunction	69 (28%)	21 (18%)	0.025

6 – 2 – 4 Comparison of drug therapy between ethnic groups

The rates of admission and discharge drug therapy stratified by ethnicity are shown in Table 42. Rates of diuretic use on admission vary between ethnic groups, with 48% of Caucasians admitted taking a diuretic compared to 39% of South Asians (p=0.041) perhaps suggesting more severe heart failure. A non-significant difference in the use of ACE inhibitors on admission was noted, but 19% of South Asians were admitted

on a beta blocker compared to only 9% of Caucasians (p=0.001). Additional differences include a higher rate of calcium channel blocker use in South Asians and a higher rate of digoxin use in Caucasian patients. The latter is likely to be linked with the higher rate of atrial fibrillation in Caucasians on admission.

With regards to therapy on discharge there were no significant differences in the use of diuretics, ACE inhibitors (or ARB) and beta blockers, but a higher proportion of Caucasians were discharged on digoxin (22% vs. 7%, $p<0.0001$) again most likely related to atrial fibrillation but possibly indicating more severe disease. The rates of Spironolactone use were low in both groups with no significant difference detectable.

Table 42: Admission and discharge drug therapy stratified by ethnicity

	Caucasian (n=352)	South Asian (n=176)	p
Admission			
Aspirin	98 (28%)	50 (28%)	0.891
ACE inhibitor or ARB	91 (26%)	54 (31%)	0.241
Diuretic	169 (48%)	68 (39%)	0.041
Beta blocker	32 (9%)	34 (19%)	0.001
Calcium channel blocker	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
Discharge			
Aspirin	131 (43%)	79(51%)	0.139
ACE inhibitor or ARB	183 (61%)	101 (65%)	0.386
Diuretic	237 (78%)	115 (74%)	0.289
Beta blocker	46 (15%)	32 (21%)	0.154
Calcium channel blocker	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

6 – 3 Survival differences between ethnic groups

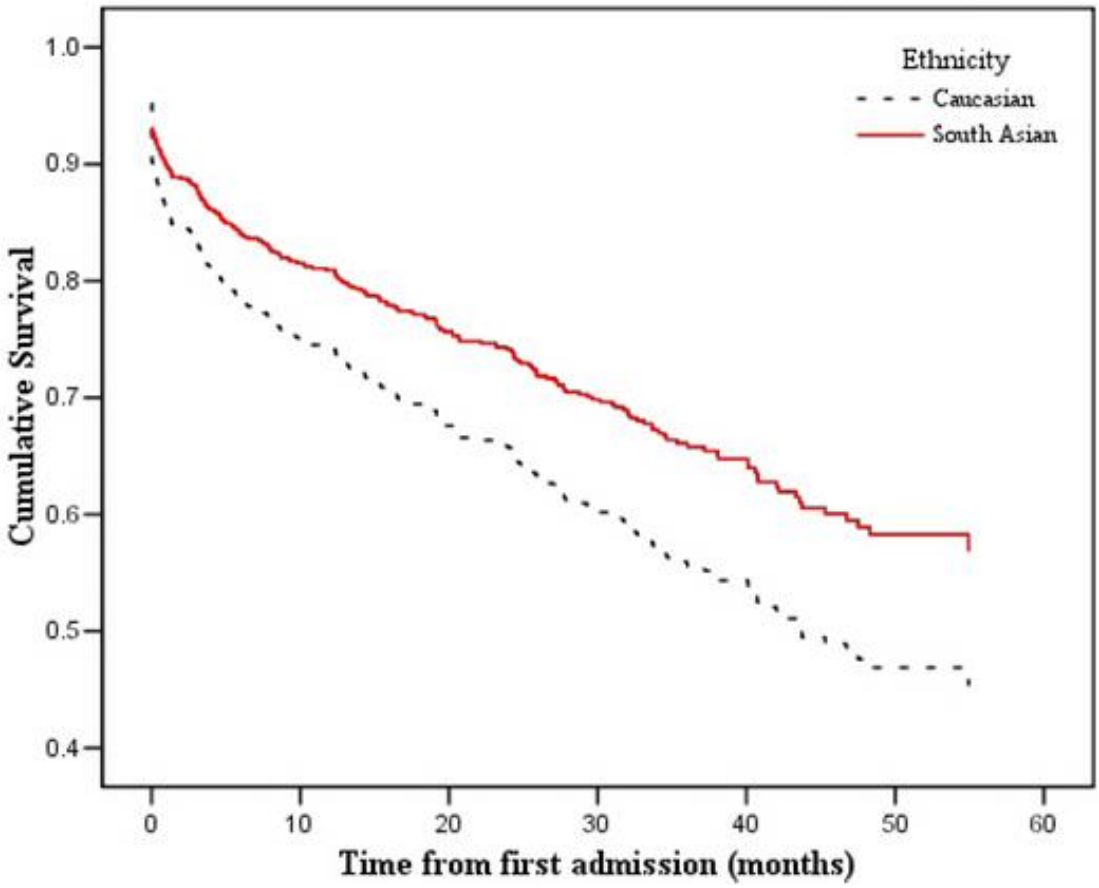
The crude unadjusted and adjusted survival rates for in-hospital, 30-day, 12 and 24 months survival stratified by ethnicity are shown in Table 43. These data clearly demonstrate that even when adjusted for age, blood pressure, glucose, haemoglobin, creatinine and prior diuretic use the survival in South Asians is better than in Caucasians. Contrast an adjusted 2 year survival of 75% in South Asians compared to 64% in Caucasians. The better survival in South Asians is apparent early on, with a 30-day survival of 91% compared to 85% in Caucasians. This difference in survival is represented graphically in Figure 27, which is an adjusted survival analysis for all patients stratified by ethnicity.

Table 43: Crude unadjusted and adjusted survival rates for in-hospital, 30-day, 12 and 24 month survival stratified by ethnicity

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

Values are percentage (95% Confidence Interval)

Figure 27: Adjusted survival analysis for all patients stratified by ethnicity



6 – 4 Differences in prognostic factors between ethnic groups

The assessment of univariate and multivariate factors associated with mortality as described in Chapter 5 was undertaken for the cohort as a whole, and also for the Caucasian and South Asian groups within the whole study cohort. This demonstrated there was no difference in the factors that remained significant on multivariate analysis in either ethnic group. The ability of the prognostic model described in chapter 5 to identify high risk patients worked equally well in both ethnic groups. The crude hazard ratios for independent prognostic factors stratified by ethnicity are

shown in Table 44. However there are some differences in the hazard ratios between ethnic groups, for example a serum creatinine in the highest quartile has a hazard ratio of 4.129 (95% CI 2.447 – 6.967) in Caucasians compared to a hazard ratio of 1.158 (95% CI 0.570 – 2.351) in South Asians. Similarly the hazard ratio for elevated serum glucose and reduced haemoglobin were relatively lower in the South Asian patients.

Table 44: Crude hazard ratio for independent prognostic factors stratified by ethnicity

	Predictor	Caucasians	South Asians
Age	< 63	1.00	1.00
(years)	63 – 70	1.917 (1.133 – 3.245)	1.039 (0.472 – 2.288)
	71 – 77	1.604 (0.951 – 2.703)	1.992 (0.942 – 4.212)
	> 77	1.972 (1.170 – 3.323)	2.251 (1.067 – 4.748)
Systolic blood pressure	> 158	1.00	1.00
mmHg	140 – 158	1.709 (1.065 – 2.743)	1.738 (0.907 – 3.329)
	122 – 139	1.369 (0.820 – 2.285)	1.371 (0.650 – 2.890)
	< 122	1.633 (1.023 – 2.605)	1.527 (0.695 – 3.354)
Serum creatinine	<85	1.00	1.00
µmol/l	85 – 104	2.020 (1.191 – 3.427)	0.850 (0.405 – 1.784)
	105 to 133	1.695 (0.991 – 2.900)	1.093 (0.537 – 2.224)
	> 133	4.129 (2.447 – 6.967)	1.158 (0.570 – 2.351)
Serum glucose	< 6.0	1.00	1.00
mmol/l	6.0 – 7.6	1.373 (0.866 – 2.179)	0.881 (0.417 – 1.860)
	7.7 – 10.0	1.174 (0.750 – 1.838)	1.572 (0.732 – 3.374)
	> 10.0	2.474 (1.603 – 3.821)	1.569 (0.789 – 3.118)
Serum haemoglobin	> 14.3	1.00	1.00
g/dl	13.1 – 14.3	1.467 (0.902 – 2.387)	1.499 (0.641 – 3.506)
	11.6 – 13.0	1.909 (1.160 – 3.139)	0.964 (0.425 – 2.184)
	≤ 11.5	2.111 (1.288 – 3.462)	1.666 (0.769 – 3.612)
Diuretic on admission		1.173 (0.856 – 1.609)	1.616 (0.981 – 2.664)

6 – 5 Discussion

This study extends the knowledge of the demographic features and outcomes for South Asian and Caucasian patients following first hospitalisation for heart failure (Blackledge, Newton et al. 2003). After correcting for differences in population ages, survival is better for South Asians compared to Caucasians. Heart failure appears to be more advanced in Caucasian patients at the point of first hospitalisation, at which point few patients have a prior diagnosis of heart failure.

6 – 5 –1 Ethnicity and prognosis

Previous reports suggested ethnicity may influence the aetiology, prognosis and natural history of heart failure (Dries, Exner et al. 1999; Exner, Dries et al. 2001; Dries, Strong et al. 2002; Rathore, Foody et al. 2003; Sosin, Bhatia et al. 2004). While this study indicates differing coronary heart disease risk factor profiles between South Asian and Caucasians with heart failure, the markers of poor prognosis were virtually the same in each cohort. As expected, increasing age, lower systolic blood pressure and renal impairment were associated with higher case fatality rate. However I also observed an influence on prognosis of ethnicity itself, of plasma glucose and of anaemia.

6 – 5 – 2 Heart failure – influence of ethnicity

A number of observations suggest the better prognosis for South Asian patients at hospitalisation is not due to the younger age of these patients, but may reflect less advanced heart failure. Normal left ventricular systolic function was recorded in 38% of South Asians and 23% of Caucasian patients. Using the broader definition of preserved left ventricular systolic function applied in Euro Heart Failure survey (Lenzen, Scholte op Reimer et al. 2004), namely normal or mildly reduced systolic function, this proportion remained higher in South Asian (59%) compared to Caucasian (48%) patients. Echocardiography indicated much lower prevalence of severe left ventricular dysfunction in South Asians, and surrogate indicators of disease severity also suggest less advanced disease in South Asians; symptom duration of less than 24 hours was more common, mean QRS duration shorter, and diuretic use at admission, a probable indicator of more established disease, was less prevalent.

Studies from the USA suggest delays in treatment seeking among black American patients with heart failure (Evangelista, Dracup et al. 2002). However heart failure admission rates were lower in Asian patients than in Caucasians in California (Alexander, Grumbach et al. 1999; Goldsmith, Lip et al. 1999). A number of small UK studies suggested coronary heart disease may be treated less aggressively among South Asians (Goldsmith, Lip et al. 1999; Feder, Crook et al. 2002). More recent UK prospective studies indicate higher use of cardiac procedures among South Asians, even after allowing for co-morbidity (Britton, Shipley et al. 2004). These observations suggest South Asian patients in Leicestershire may access secondary health care earlier in the course of heart failure than do Caucasian patients, as has been suggested

for angina (Chaturvedi, Rai et al. 1997). Such a phenomenon may contribute to better survival.

Alternatively, or additionally, improved survival for South Asians may be due to greater prevalence of heart failure with normal ejection fraction. The greater prevalence among South Asians of hypertension and diabetes, perceived aetiological factors for heart failure with normal ejection fraction and the echocardiographic data are in keeping with this. Indeed preserved function on echocardiography was associated with better survival. Interestingly Caucasian patients had higher rates of left ventricular hypertrophy by electrocardiographic criteria (30% vs. 19% in South Asians, p=0.037) despite lower rates of a prior diagnosis of hypertension (33% vs. 45% in South Asians, p=0.006). Ethnic differences in the electrocardiographic criteria required to diagnose hypertension has been demonstrated with respect to African Americans and Caucasians (Okin, Wright et al. 2002). African Americans have higher average lead voltages thereby reducing the specificity of the electrocardiogram in correctly identifying hypertension unless ethnic-specific thresholds are used. A recent systematic review of the accuracy of electrocardiography in screening for left ventricular hypertrophy concluded that voltage criteria should not be used to rule out left ventricular hypertrophy in hypertension casting doubt on the correlation between electrocardiographic changes and left ventricular mass. Data on the electrocardiographic changes in hypertensive South Asian patients are sparse although one study assessing 380 patients, 32 of whom were of South Asian ethnicity found no difference in mean electrocardiographic voltage between South Asian and Caucasians (Spencer, Beevers et al. 2004).

What is not clear is whether, in the patients in the current study, preserved and impaired systolic function on echo represents different disease states or simply different stages of the same process. Serial assessment of left ventricular systolic function would be needed to address this issue.

6 – 6 Summary

Following first hospital admission with heart failure, survival is better for South Asian compared to Caucasian patients. The predictors of adverse prognosis are similar in South Asian and Caucasian patients. At the time of first admission to hospital South Asian patients are more likely to have preserved left ventricular systolic function, and less likely to have advanced heart failure than their Caucasian counterparts.

I will now go on to address the research questions posed in chapter 2.

6 – 6 – 1 Ethnicity and heart failure epidemiology

As discussed above this study has identified significant differences in the epidemiology of heart failure between South Asians and Caucasian patients. Patients of South Asian ethnicity are more likely to have diabetes and hypertension and less likely to have atrial fibrillation and chronic obstructive pulmonary disease. The rates of ischaemic heart disease are similar between the ethnic groups, although in the Harrow heart failure watch South Asian patients had higher rates of coronary artery disease compared to Caucasian patients (100% vs. 56%) and lower rates of alcoholic cardiomyopathy (Galasko 2005). As the rates of proven coronary disease were low in both groups studied here the true prevalence of coronary disease may have been

underestimated. A study undertaken in Canada assessing 887 patients admitted with heart failure between 1997 and 1999 where 12% of patients were of South Asian ethnicity demonstrated that South Asians were more likely to be diabetic, less likely to have atrial fibrillation and more likely to have an elevated creatinine level (Singh and Gupta 2005), findings broadly similar to this study with the exception of renal function.

These data suggest that heart failure in South Asians is not an identical disease to that in Caucasians and this is further borne out by the differences in survival and degrees of left ventricular dysfunction observed. Whether this finding is because South Asian patients present sooner than Caucasian patients rather than a difference in underlying pathophysiology is not clear, although further analysis of the data demonstrated that only 24% of South Asian patients reported a symptom duration of 1 week to 1 month compared to 33% of Caucasians, with even fewer reporting symptoms for more than one month (10% vs. 14%). As discussed in Chapter 2 there are important variations in the risk factor profile of South Asian patients, with higher rates of glucose intolerance and diabetes and unfavourable lipid profiles. The pattern of coronary disease is also different, with South Asians more likely to have three-vessel disease. Given the prime aetiology of heart failure in the modern era is ischaemic heart disease, one might expect South Asians to have more severe heart failure as a result of higher rates of premature and more severe coronary disease. Furthermore South Asian patients sustaining a myocardial infarction are more likely to have anterior wall infarction compared to Caucasians (Gupta, Doobay et al. 2002).

Recent work on assessing the underlying pathophysiology of heart failure across ethnic groups has identified significantly raised leptin levels in South Asian patients with heart failure despite no difference in insulin levels, suggesting altered adipocyte metabolism in this ethnic group (Patel, Sosin et al.). An additional study by the same group has shown no significant differences in homocysteine levels among different ethnic groups (Sosin, Patel et al.). It is known that South Asians have higher levels of visceral fat and greater resistance to insulin at similar levels of body mass index to Caucasians; this may relate to differences in levels of pro-inflammatory adipokines such as leptin and tumour necrosis factor-α (Gupta, Singh et al. 2006).

The data presented here raise the possibility that ethnicity impacts on the presentation and type of heart failure – it may be that South Asians are more likely to demonstrate heart failure with normal ejection fraction given the higher rates of hypertension observed, as this is a typical aetiological factor for heart failure with normal ejection fraction (Vasan and Levy 1996; Gandhi, Powers et al. 2001). A counter argument to this is that atrial fibrillation is more common in heart failure patients with normal ejection fraction (Masoudi, Havranek et al. 2003) and coronary artery disease less common (Vasan, Larson et al. 1999). A single study has suggested that diabetes is a risk factor for heart failure with normal ejection fraction (Redfield, Jacobsen et al. 2003).

It is clear that the profile of South Asian patients presenting with new onset heart failure is different to that in Caucasians and this can be only partly explained by differences in ischaemic heart disease risk factors such as hypertension and diabetes.

6 – 6 – 2 Ethnicity and heart failure investigation and treatment

The proportion of patients undergoing the gold-standard investigation for heart failure, namely echocardiography, was no different with respect to ethnicity. There was a suggestion that South Asian patients may be more likely to have an echocardiographic assessment of ventricular function following discharge rather than during the index admission although with borderline statistical significance. This suggests that the use of investigations for heart failure is not related to ethnicity, similar to findings of investigations into ethnic differences in coronary heart disease. A study undertaken in 2004 analysed the use of exercise electrocardiography, coronary angiography, and revascularisation procedures in 10,308 civil servants aged between 35 and 55 years (Britton, Shipley et al. 2004). The authors found no association between South Asian ethnicity and reduced use of cardiological investigation or treatments and comment that differences in access to medical care are unlikely to account for the ethnic differences in coronary heart disease. In fact South Asian patients had higher rates of exercise electrocardiograms or coronary angiography even after adjustment for metabolic dysfunction or diabetes. This may reflect earlier referral by physicians aware of increased risk of coronary disease in South Asians, or early treatment-seeking behaviour in South Asians (Chaturvedi, Rai et al. 1997). Furthermore, when assessing the number of primary care consultations in the year before coronary angiography, a significantly higher rate was found in South Asian patients with chest pain, suggesting early symptom reporting (Feder, Crook et al. 2002). The situation with heart failure in South Asians may be similar to that of coronary heart disease – they present earlier in the course of the illness (as evidenced by shorter symptoms duration and less severe left ventricular systolic function) and go

on to receive the same level of investigation and treatment as for non-South Asian patients.

With respect to heart failure therapies with proven efficacy such as ACE inhibitors and beta blockers there were no significant differences in prescription rates between ethnic groups. More South Asian patients received treatment with calcium channel blockers than Caucasians, perhaps due to lower rates of severe left ventricular systolic impairment where traditional calcium channel blockers are contraindicated or higher rates of persistent hypertension. Digoxin use was much higher in Caucasians although this is more likely to reflect the higher rates of atrial fibrillation in Caucasians rather than its use as second-line therapy in significant left ventricular systolic dysfunction.

6 – 6 – 3 Ethnicity and heart failure survival

When conceiving this study it was anticipated that higher rates of coronary disease and diabetes in South Asians would lead to more severe heart failure and increased mortality. The data produced in this study convincingly demonstrate that survival in South Asian patients with heart failure is better than that of age matched Caucasian patients. Even on multivariate analysis South Asian ethnicity is associated with a hazard ratio of 0.71 (95% CI 0.53 – 0.96) compared to Caucasian patients. This finding is compatible with earlier data produced from this patient population and builds on this research (Blackledge, Newton et al. 2003). At 2 years after the first hospitalisation with heart failure 36% of Caucasians will have died compared to only 25% of South Asians – even when adjusted for all other prognostic factors.

Little data currently exist on the survival of South Asians with heart failure. A study undertaken in 233 patients admitted with heart failure to hospitals in Birmingham in 1994 demonstrated that after 8 years of follow up 91% of patients of European origin had died compared to 87% of non-European origin patients (Sosin 2004). This difference has a log-rank test for difference of 0.0705. While this may imply better survival for non-European patients the study included only small numbers of non-European patients, specifically 15 African-Caribbean and 31 Indo-Asian patients forming 19% of the total cohort. Furthermore a significant difference in the age of the patients existed between the European and non-European groups, with 60% of European patients over 75.6 years of age compared to only 17% of non-Europeans ($p<0.001$).

As previously mentioned, a potential explanation for the observed improved survival in South Asians with heart failure is that they present earlier and with less severe left ventricular dysfunction than their Caucasian counterparts. Given there is no evidence of differences in the investigations and treatment following admission, this hypothesis is reasonable. Data on the duration of symptoms prior to admission demonstrate South Asian patients present after 1 week compared to several weeks for Caucasians, and have lower rates of severe left ventricular dysfunction. The data on symptoms were abstracted from the case records and their accuracy is hard to define. Further studies specifically addressing pre-hospital primary care attendances, investigations and treatment along with semi-quantitative assessment of symptom type and duration would be required to prove this hypothesis. Additional supportive evidence to suggest pre-hospital treatment may in part explain the improved survival is that more South

Asian patients were admitted on a beta blocker or an ACE inhibitor than Caucasian patients.

6 – 6 – 4 Ethnicity and heart failure prognosis

The variables associated with mortality on multivariate analysis did not vary between the ethnic groups although the relative strengths of the risk factors were different, for example significant renal impairment has a much higher hazard ratio in Caucasians than in South Asians. Given that the risk factors chosen for use in the predictive model – namely age, creatinine, haemoglobin, glucose, systolic blood pressure and prior diuretic use - are relatively simple characteristics of patients with heart failure no difference with respect to ethnicity was anticipated. This is the first report to analyse prognostic markers in heart failure with respect to ethnicity and further research in this field is warranted. It is anticipated that the prognostic impact of variables associated with the altered pathophysiology of heart failure in South Asians such as c-reactive protein and tumour necrosis factor-α may be different to that in Caucasians. Evidence that the role of these factors in the prognosis of coronary artery disease varies with ethnicity already exists (Fichtlscherer, Heeschen et al. 2004) including the distribution and degree of calcification of coronary atheroma (Nasir, Shaw et al. 2007).

6 – 7 Conclusion

In this chapter I have assessed the impact of ethnicity on the presentation, investigation and treatment of heart failure followed by a discussion on the association of ethnicity on heart failure survival. The similarity of factors predictive of heart failure mortality across ethnic groups is reviewed and finally I have addressed the relevant research questions in chapter 2 and proposed new hypotheses for future research.

Chapter 7 - Conclusion

7 – 1 Introduction

This thesis studied a large cohort of patients from two ethnic groups to determine the demographic, aetiology, investigation, treatment and survival of patients admitted to hospital with a new diagnosis of heart failure, and assess the impact of ethnicity on these factors. By detailed review of the case record for each admission, the diagnosis was validated and data on heart failure symptoms, clinical findings and baseline therapy recorded. Additional data on biochemistry, ECG and echocardiographic findings, along with medication at the point of discharge from hospital, were included in a multivariate analysis undertaken to develop a pragmatic risk prediction model.

Before highlighting the key findings of this thesis I will briefly summarise the findings of the literature review in Chapters 1 and 2, and then go on to assess the strengths and limitations of the methodology used. Finally, I will describe how the data presented here lead on to a variety of further research studies in heart failure.

7 – 2 Outcomes of literature review

In this thesis the literature on heart failure epidemiology, survival and the impact of ethnicity was reviewed. A large number of studies have described the epidemiology and survival of many cohorts of heart failure patients, although frequently these are not 'real world' patients with heart failure but those selected for entry into clinical trials requiring strict inclusion and exclusion criteria. A minority of studies have assessed the more general heart failure population. Consequently a great deal is known about the epidemiology of heart failure in Caucasian patients, predominantly males under the age of 75 years, as they form the bulk of heart failure trial patients. Another effect of this bias is that patients from ethnic minorities are under-represented in both studies of the epidemiology and therapy for heart failure – generalisations regarding the applicability of standard therapy to patients of differing ethnicity are frequently made without definitive evidence.

There is consensus in the literature that the survival of patients with heart failure has improved in recent years, but only by relatively small amounts and overall the prognosis remains bleak, and worse than that for many common malignancies such as breast cancer. Data from both clinical trials and population studies have been reviewed. At present there is limited data on the survival of patients with heart failure in Leicestershire and this has been derived from databases based on non-validated discharge diagnosis coding – a potential cause for error.

This persistent poor survival is evident despite the ever increasing evidence base for a variety of therapeutic strategies in heart failure. The rationale and potential benefit of

standard heart failure therapies have been discussed, followed by potential reasons for this apparent paradox – better heart failure treatments, but limited evidence of significant improvement despite their use.

A number of patients with heart failure and certain additional features are at high risk of further hospital admissions or decompensation and death. The literature supporting the use of a variety of prognostic models have been discussed and limitations of their applicability in the general heart failure population made clear.

On the basis of the overall literature review it was concluded that heart failure survival in the current era remains poor and little is known regarding the epidemiology and survival of the local heart failure population as compared to published cohorts. Furthermore there is a significant lack of knowledge of the variation in epidemiology, diagnosis, investigation and therapy of heart failure among ethnic minority groups such as South Asians.

From this twelve questions to be addressed by this thesis were proposed:

1. How does the epidemiology of local heart failure patients compare with published data?

2. How long are patients admitted to hospital and what is the impact on service provision?

3. What proportion of patients admitted with heart failure receives specialist input from a cardiologist?

4. What proportion of patients admitted with heart failure undergoes appropriate investigations such as echocardiography?
5. Do patients admitted to hospitals in Leicester with heart failure receive optimal medical therapy on discharge?

6. What proportion of patients admitted with heart failure would be eligible for treatment with cardiac resynchronisation therapy?

7. What is the crude survival of patients admitted to hospital with a new diagnosis of heart failure?

8. Can simple admission data be used to construct a prognostic model identifying high risk patients?

9. What differences in the epidemiology and aetiology of heart failure exist between South Asian and Caucasian patients?

10. Do South Asian patients receive similar investigation and treatment to Caucasian patients?

11. Do South Asian patients with heart failure have an increased mortality compared to Caucasians?

12. Do factors which predict outcome vary between Caucasians and South Asians?

7 – 3 Major findings of thesis

By analysing the case records of a large cohort of unselected heart failure admissions to local hospitals I have demonstrated that the epidemiology of patients presenting to hospital with a new diagnosis of heart failure is very similar to published data on heart failure cohorts from the United Kingdom, Europe and the USA. The aetiology, admission duration, in-hospital treatment and survival are in keeping with other centres suggesting there are no major differences in our heart failure population. It is vital to emphasise that the prognosis of heart failure remains very poor – by 1 year 27% have died and this climbs to 35% at two years, with 11% having died during their first admission with heart failure.

The majority of patients admitted to local hospitals with heart failure undergo appropriate assessment with echocardiography – a vital diagnostic step – and the overall rate of 70% is in keeping with overall reports from both the United Kingdom and Europe.

With regards to instituting evidence-based heart failure therapy it is clear that at the time of collection of the data for this thesis, current practice was poor – only two thirds of patients were discharged on an ACE inhibitor and less than 20% on a beta blocker. This finding is no different to published data on European wide prescription rates and emphasises drug therapy as a vital area for novel strategies to be developed and introduced.

As highlighted in the literature review, estimating a patient's prognosis is an important step in directing appropriate care. By utilising simple clinical variables routinely available within 24 hours of admission, it is feasible to stratify patients into low and high-risk groups with a degree of accuracy comparable to many other prognostic models, which usually include more complex variables or those which require specialised investigations. This simple, pragmatic and easy to calculate model can be easily applied to the generic heart failure population at the point of admission to highlight patients who require more intensive or specialist treatment.

The importance of haemoglobin levels and anaemia has been reinforced, with additional new data on the association between hyperglycaemia and increased mortality - particularly the interesting observation that this is a more prominent association in patients without a formal diagnosis of diabetes. These data build on a body of evidence demonstrating the increased mortality in patients with hyperglycaemia across a wide range of acute medical conditions including myocardial infarction and stroke. Although this is only an observed association with a number of possible explanations, the presence of hyperglycaemia may reflect more severe disease or higher physiological stress as well as impaired metabolism and altered cell functions.

Novel data on the epidemiology of heart failure in South Asians have been presented in this thesis. South Asians are more likely to have a preceding diagnosis of hypertension and diabetes, and less likely to have atrial fibrillation or concomitant pulmonary disease. Rates of underlying ischaemic heart disease are similar - a surprising finding given the evidence for higher rates of more severe coronary artery

disease in South Asians. Furthermore, the mode of presentation is different – South Asians appear to present earlier in the course of their heart failure episode, and are more likely to have heart failure with a normal ejection fraction. Given these clear differences in the pattern and presentation of heart failure in South Asians, it is not unsurprising that their survival is different to that of Caucasians. The observation that South Asians have a better survival than their age and sex-matched Caucasian counterparts is a novel one. Potential reasons for this important observation in heart failure outcomes may be the differences in the underlying aetiology and manifestation of heart failure in South Asians, since there are no significant differences in the therapy given to either ethnic group or indeed the prognostic factors highlighting high-risk patients.

Finally, a number of other important data have been presented in this thesis. Changes in the pattern of ventricular activation on the ECG have frequently been cited as markers of more severe disease and worse prognosis. However, in this unselected cohort of heart failure patients, no ECG factors were associated with adverse outcomes suggesting this may be a manifestation of the inherent bias in heart failure clinical trials towards enrolling the younger heart failure patient with less co-morbidity. An important follow on from this is that the proportion of patients admitted to hospital with heart failure that qualify for emerging device based heart failure therapy, such as cardiac resynchronisation pacing is very low – this again casts doubt over the generalisation of indication criteria derived from focussed clinical trials.

7 – 4 Strengths and limitations

The major strength of this thesis is the unselected nature of the heart failure cohort studied. The data presented and discussed are derived from a large cohort of patients admitted to hospital with a validated diagnosis of heart failure irrespective of age, sex, degree of left ventricular dysfunction, co-morbidities and baseline therapy. By validating the diagnosis against European guidelines, the survival data are that for the 'real world' heart failure population and not the minority who may meet trial enrolment criteria. Unlike the previous report from this patient population (Blackledge, Newton et al. 2003) this thesis also has the advantage of careful verification of the admission diagnosis, and prior medical history, through review of hospital records. It is therefore feasible to extrapolate the results presented here to the wider heart failure community.

The second major feature is that this thesis presents 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. Given the high proportion of patients dying by the end of follow up, the study is sufficiently powered to detect differences between ethnic groups, albeit on a post-hoc analysis.

The retrospective nature of the data collection restrains the quality of data retrieved to that available in the clinical record. Without a structured method to capture qualitative data such as the description of patient's symptoms and clinical signs, it is difficult to know how accurate the clinical record is. However few of these factors feature in the final analysis and none in the prognostic model. The lack of data on

NYHA class of heart failure severity may be limiting, as this has consistently been shown to be a useful prognostic marker – whether NYHA class would add to the multivariate analysis and subsequent prognostic model presented here is not known.

By its very design a matched cohort study restricts the patients chosen for analysis, although by matching on only two features, namely patient age and sex, the introduction of a significant bias is unlikely. Given that South Asian patients are the minority ethnic group, matching each South Asian to two Caucasian patients allows for a larger cohort and increases the power of the study.

A significant limiting factor in the final data collection was the availability of the clinical records. As can be seen from the methodology section 26% of the original cohort matched for analysis could not be included as their clinical record was not available. It is not known whether this group of patients is significantly different to that studied in terms of demographics and survival. Omission of these may have biased towards survivors who perhaps are more likely to have a continuing clinical record available for review although the rate of 11% in-hospital mortality suggests this is unlikely. A total of 10% of the records analysed were incorrectly coded as heart failure – either an alternative diagnosis was proven or no clear evidence for heart failure was found on review. This overall rate of 90% of hospital discharges being coded correctly for heart failure is reassuring, and is very similar to other studies of the validity of hospital discharge register coding (Ingelsson, Arnlov et al. 2005). This information supports prior analyses from this register (Blackledge, Tomlinson et al. 2003) and safe identification of heart failure cohorts from the discharge coding details in further research studies.

Furthermore while the methodology allowed me to exclude false positive cases of heart failure, I was unable to assess for false negative cases given the study design limiting me to cases already coded as heart failure admissions. While it would be ideal to be able to also assess and understand cases of heart failure mistakenly identified as an alternative diagnosis this would require an alternative strategy such as a prospectively enrolled study of patients with dyspnoea.

A retrospective review of case records also limits analysis to data available and coping with missing data is an important aspect. By using advanced statistical techniques to estimate missing variables the analyses are more robust than if restricted to recorded values. Overall the majority of variables had few missing, although 18% of patients did not have a glucose level recorded in the record. Given that glucose is used in the final prognostic model it would be important to validate the observed association of hyperglycaemia and worse outcomes in an alternative cohort of patients to ensure no bias has been introduced.

Another currently unaddressed issue is over the validation of the ethnicity coding used in the patient identification process. While a crude check of the patients name was performed and is likely to have ensured no South Asian patients were miscoded as Caucasian or vice-versa, the fact that ethnicity relies on self reporting and cross linkage of clinical records there is potential for ethnicity coding errors. This is more likely to be a major issue if several ethnic groups are being assessed rather than just two as in this study. Again, the only practical way to address this would be during a prospective study where ethnicity can be directly assessed and validated.

The prognostic model developed in this thesis has the major advantage of being simple to use – both in collection of the variables included and calculation of the risk score. It is important to emphasise that the model presented is only valid in this cohort and in order for it to be used in clinical practice it needs to be validated in a separate selection of patients admitted with a new diagnosis of heart failure. While it may be possible to assess the model's robustness using statistical techniques such as bootstrapping, it is more appropriate and accurate to apply the risk score to a separate population and measure its accuracy at identifying high risk patients.

Two significant variables regarding each patient admitted to hospital with heart failure in this thesis are not known – what treatment the patient received after discharge and how many were re-admitted with decompensated heart failure. A significant proportion of the expenditure in heart failure health care is in-hospital care of patients during decompensation episodes and patients with more severe heart failure are more likely to be re-admitted. Furthermore, identification of patients at significant risk of early re-admission may allow direction of more intensive and specialist therapy to try and prevent further hospital episodes. It is possible re-admission rates vary between the ethnic groups given the differences in disease pattern and survival demonstrated here. The therapy a patient receives following discharge is also a significant factor not covered in this thesis, with respect to both drug prescribed and dose level obtained. Achieving the recommended target dose in patients with heart failure is difficult and time consuming. An absolute minority of patients are discharged on fully appropriate therapy, and while it is hopeful those without will receive treatment with beta blockers via their primary care physician, this cannot be assumed. If data on

both re-admission rates and out of hospital therapy were known, this may add to the ability to predict high risk patients and strategies to reduce heart failure expenditure.

Finally there is considerable discussion and debate around the epidemiology, treatment and outcome of patients with heart failure and preserved systolic function. Given that the enrolment criteria established a-priori did not include knowledge of systolic function then this cohort of patients with heart failure includes both those with proven systolic dysfunction and those without. As the analysis of prognosis and development of the model were on the entire cohort it cannot be held as a valid model in only patients with systolic dysfunction. Given that there are considerable differences between patients with and without systolic dysfunction it is possible that by analysing these two groups together the prognostic impact of some of the variables discussed has been modified. Alternatively it may be true that the model developed includes prognostic variables common to both cohorts of heart failure patients and is therefore independent of systolic function. A more detailed and again ideally prospective study with detailed echocardiographic criteria would be required to allow the performance of this prognostic model to be addressed in all types of heart failure patient.

7 – 5 Future research questions

As discussed above the strength of the data presented in this thesis could be improved with the additional collection of details of subsequent re-admissions and heart failure therapy received in primary care. A repeat query of the discharge register to assess for subsequent admissions with heart failure will provide crude assessment of re-admission rates, although repeated case record analysis and liaison with primary care would be required to assess for changes in therapy between admissions.

The prognostic model presented here may be useful in clinical practice in order to easily identify high risk patients, but requires validation in a separate selection of patients from the cohort obtained from the discharge register. It may be possible to perform this validation without review of further case records – the patients age will be available from the discharge register and the haemoglobin, creatinine and glucose can be obtained from the hospital pathology database. The final factor in the prognostic model is the presence or absence of a diuretic on admission – information that may be obtainable via a telephone discussion with the primary care team. Given the high rate of heart failure admission episodes validating correctly (90%) it would not be vital to review the admission records for a second cohort.

The data presented here strongly suggests South Asians with heart failure present earlier to hospital with heart failure and have a different pattern of disease – more hypertension and heart failure with normal ejection fraction – compared to Caucasians. An initial interesting study would be to undertake detailed echocardiographic analysis of a cohort of South Asians presenting to hospital with

heart failure and assess if markers of subclinical systolic dysfunction are present. This could then be compared to age-matched Caucasians, and may support the hypothesis that heart failure in South Asians follows a different progression to that in Caucasians, and provide further explanations for the observed differences in survival. It is noteworthy that there are no significant differences in the heart failure therapy prescribed to either Caucasians or South Asians despite the minimal evidence base for their efficacy in all ethnic groups. It is vital that large-scale studies of heart failure therapy in ethnic groups such as South Asians are performed to ensure they do derive at least similar benefits from ACE inhibitors and beta blockers.

Along with a large number of recent studies the overall low rates of ACE inhibitor and beta blocker use – irrespective of ethnicity – are of concern and merit further investigation. Why do only two thirds of patients receive and ACE inhibitor and less than one quarter a beta blocker? While tentative association between clinical factors such as dyspnoea, renal function, age and sex can be made from the data presented here, it would require a formal detailed analysis of prescription practices via a prospective study to identify reasons for non-prescription. This will be critically important to aiding development of multi-disciplinary strategies to increase the use of proven heart failure therapy and improve survival, thereby potentially reducing hospital episodes and costs.

The clear association between hyperglycaemia at the point of admission in non-diabetic patients with increased mortality is important and warrants further analysis. It is not known whether hyperglycaemia is an epiphenomenon of more severe heart failure, or implicated directly in the disease process. Elucidation of the effects of

hyperglycaemia on cardiac cell physiology and function, disease progression, response to therapy, and benefits of intensive glucose lowering therapy during admission will require a combination of small-scale cellular analysis and larger-scale studies of the effect of both hyperglycaemia and its treatment on outcomes.

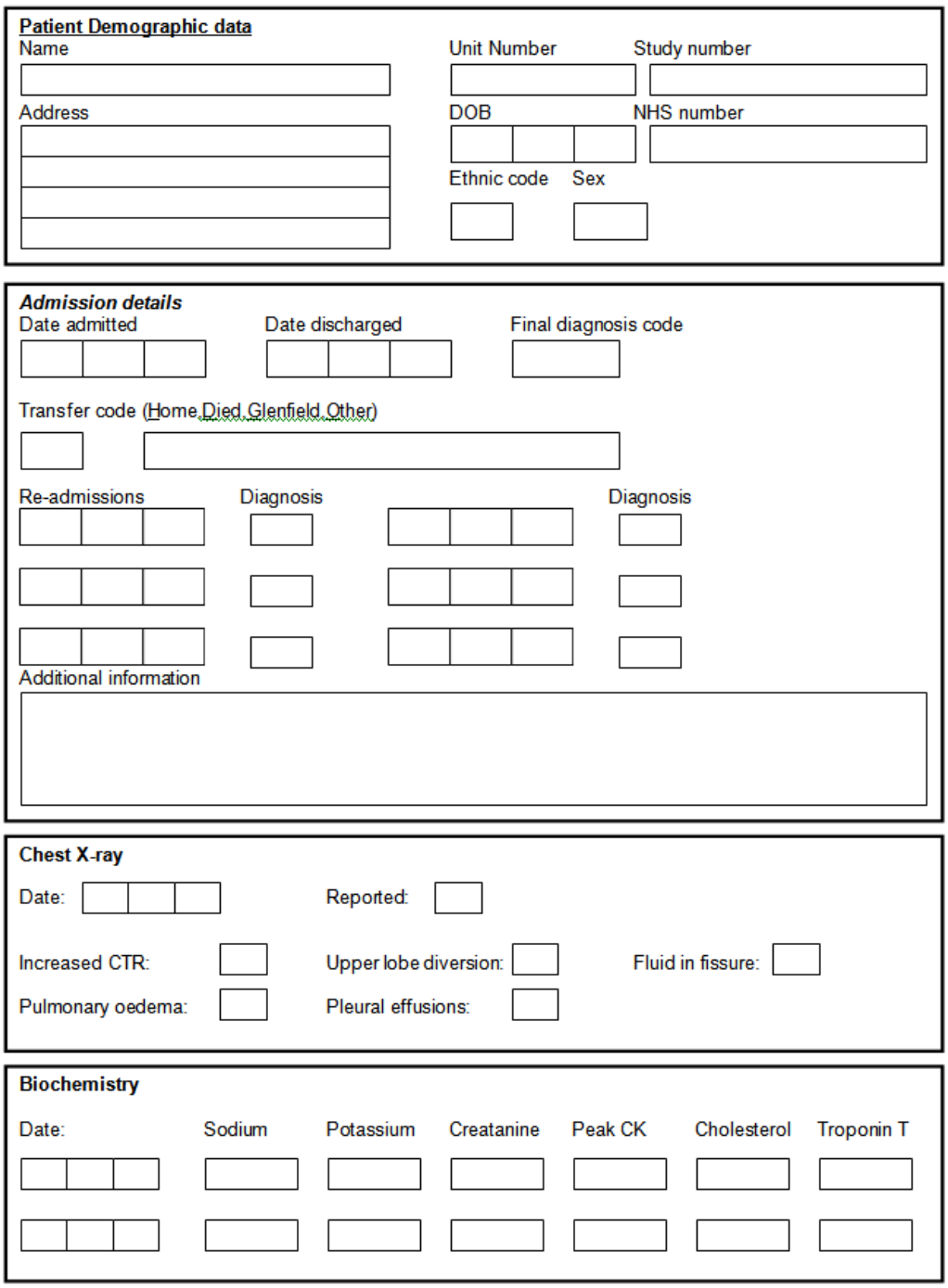
The prognostic model could also be developed further by utilising additional variables such as natriuretic peptides – these may already be available for some of the patients in this cohort given that other studies assessing BNP in heart failure were running for the period of this study, and additional demographics such as socio-economic status. Previous studies undertaken in Leicestershire have used the patients postcode as a proxy marker for social deprivation (Blackledge, Tomlinson et al. 2003). The postcode for all the patients in this study was collected so the additional effect of social deprivation on outcomes could be added to the multivariate analysis.

7 – 6 Conclusion

In this chapter I have summarised the findings of the literature review and how the findings of this thesis add to the current knowledge on the epidemiology and prognosis of patients hospitalised with heart failure. Novel and important data on the significance of ethnicity on heart failure outcomes has been reviewed. Finally I have suggested areas requiring further research and how this may be undertaken.

Appendices

Appendix 1 Data collection form



Risk factors / co morbidity

		Date / Severity / Value
Smoker		
Family history		
Angina		
MI		
Hypertension		
Hyperlipidaemia		
CVA		
Diabetes		
Renal failure		
Malignancy		

ECG information

Date: Copy no:

PR QT QRS QRSd Qtc JT JTc LVH Std

Ste A.Fib A.Flut VT NSVT 2nd HB CHB

Date: Copy no:

PR QT QRS Qtc JT JTc LVH Std

Ste A.Fib A.Flut VT NSVT 2nd HB CHB

Drug therapy

Drug	Trial of drug?	Admission	Review 1	Review2	Details
Aspirin					
Diuretic					
ACEI					
AIIA					
B-Blocker					
Digoxin					
Spironolactone					
Ca antagonist					
Statin					
Fibrate					
K activator					
Alpha blocker					
Insulin					
Nitrates					
Warfarin					
NSAID's					
OHA					
Clopidogrel					

Drug information

Failed beta-blocker trial	
Failed ACEI trial	
Failed ATII trial	
Other complications	

Revascularisation data

Angiogram Date: ☐☐☐ LV impairment: None ☐ Mild ☐ Moderate ☐ Severe ☐

EF: ☐

	LMS	LAD	Cx	RCA	Other
Disease					
Angioplasty Date: ☐☐☐ To:					
Stent					
Date: ☐☐☐ To:					
Stent					
CABG Date: ☐☐☐ To:					
Valve surgery Date: ☐☐☐					

Complications / other information

Echo information

Date: ☐☐☐ Time from diagnosis to echo: ☐ Never had echo? ☐

LV function: Normal ☐ Systolic dysfuntion: ☐ Diastolic dysfunction: ☐

Impaired ☐ Mild ☐ Moderate ☐ Severe ☐

EF: ☐ PAP: ☐ LA size: ☐

VALVES:

Aortic	Normal ☐	Regurgitant ☐	Stenotic ☐	Severity / Gradient ☐
Mitral	Normal ☐	Regurgitant ☐	Stenotic ☐	Severity / Gradient ☐
Pulmonary	Normal ☐	Regurgitant ☐	Stenotic ☐	Severity / Gradient ☐
Tricuspid	Normal ☐	Regurgitant ☐	Stenotic ☐	Severity / Gradient ☐

Other information

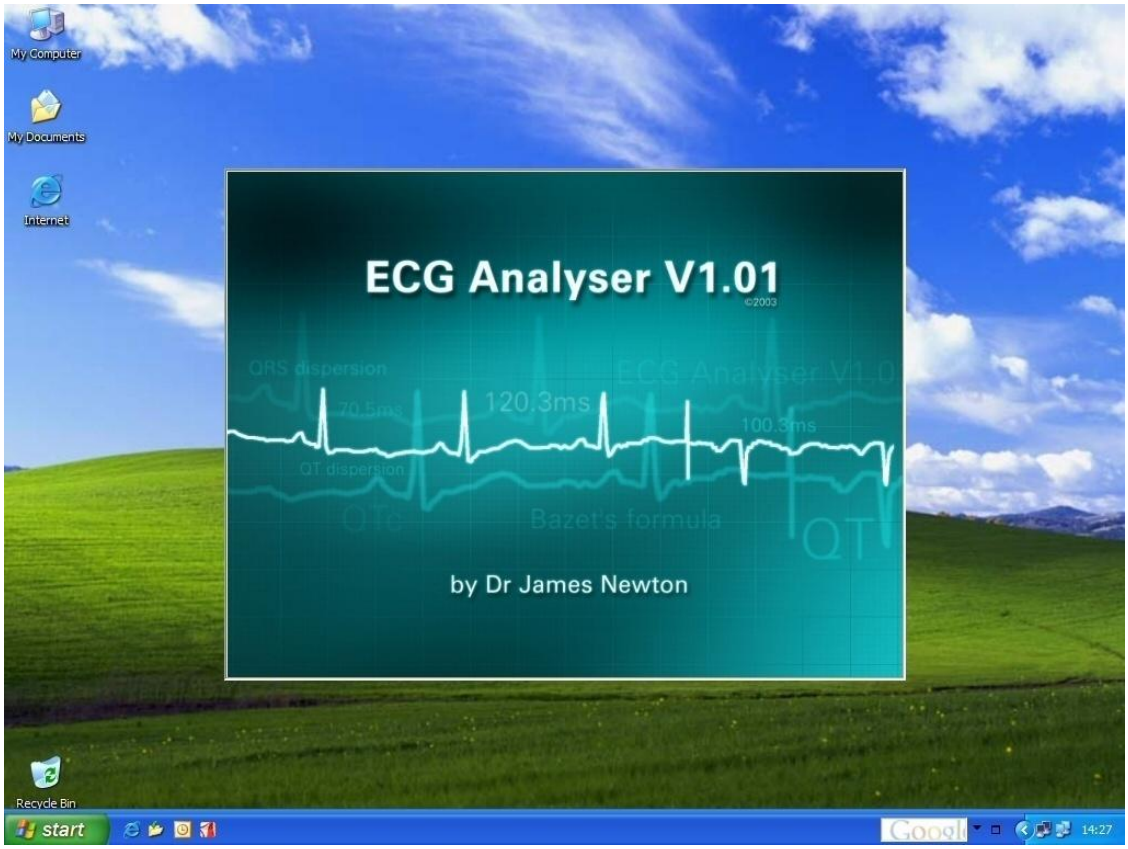
Clinical information

Duration of symptoms ☐

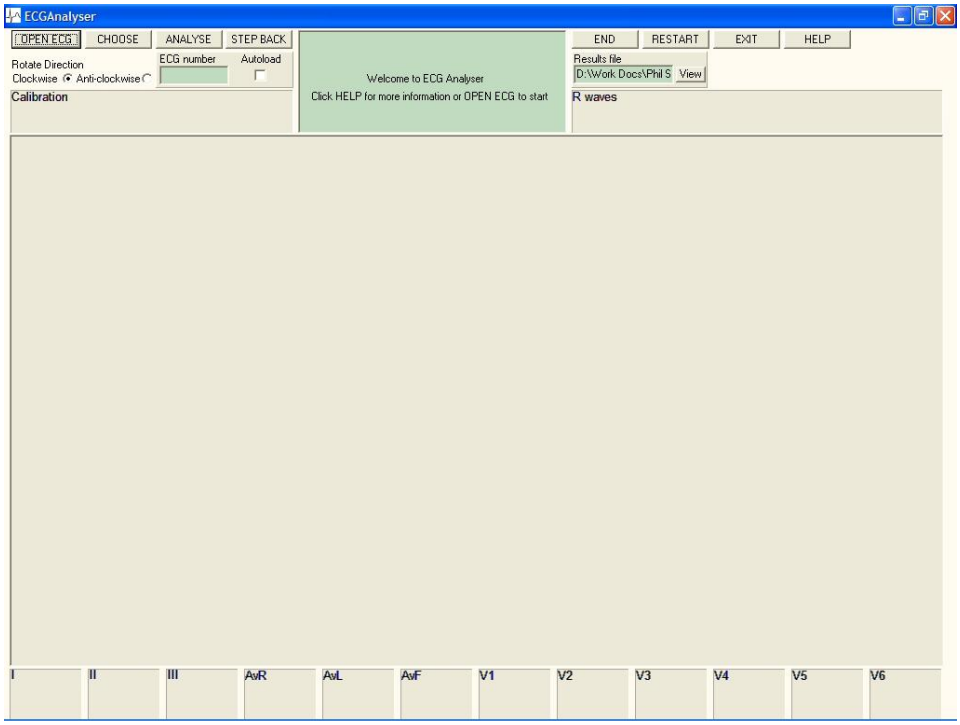
		Referred	Examined			Referred	Examined
Symptoms:	Dyspnoea	☐	☐	**Signs:**	Oedema	☐	☐
	Orthopnoea	☐	☐		Crackles	☐	☐
	PND	☐	☐		Added sounds	☐	☐
	Oedema	☐	☐		Tachycardia	☐	☐
	Angina	☐	☐		Cardiomegaly	☐	☐
	Fatigue	☐	☐		Alternans	☐	☐
	Weight gain	☐	☐		Wheeze	☐	☐
	Wheeze	☐	☐		Cyanosis	☐	☐
	Cough	☐	☐		Hypotension	☐	☐

Other

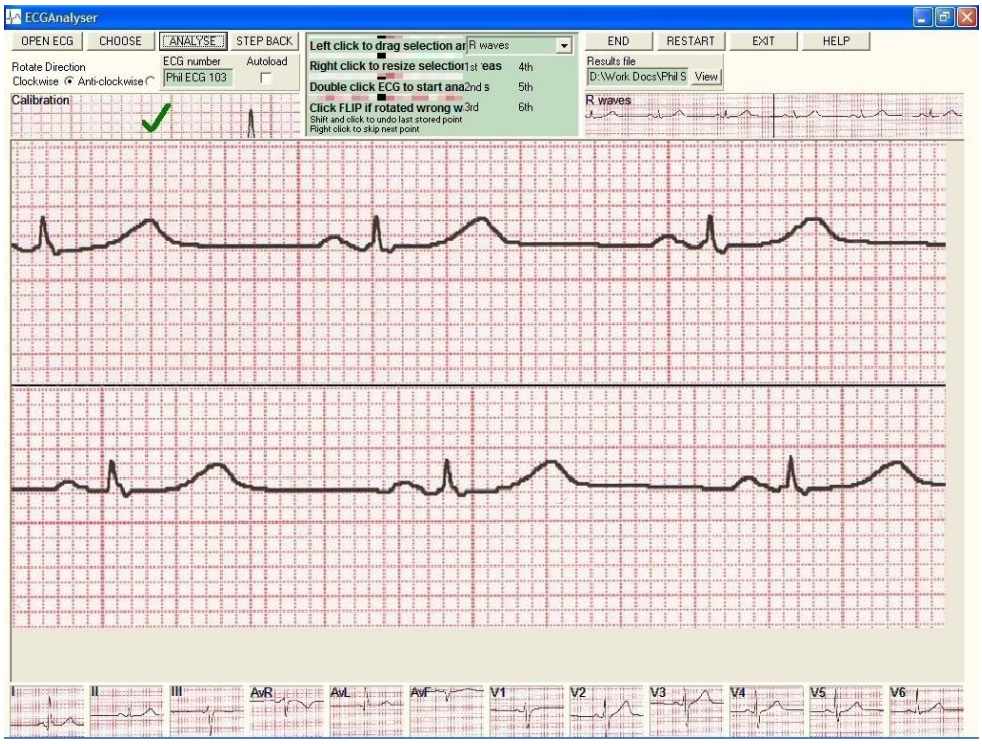
Appendix 2 ECG Analyser software



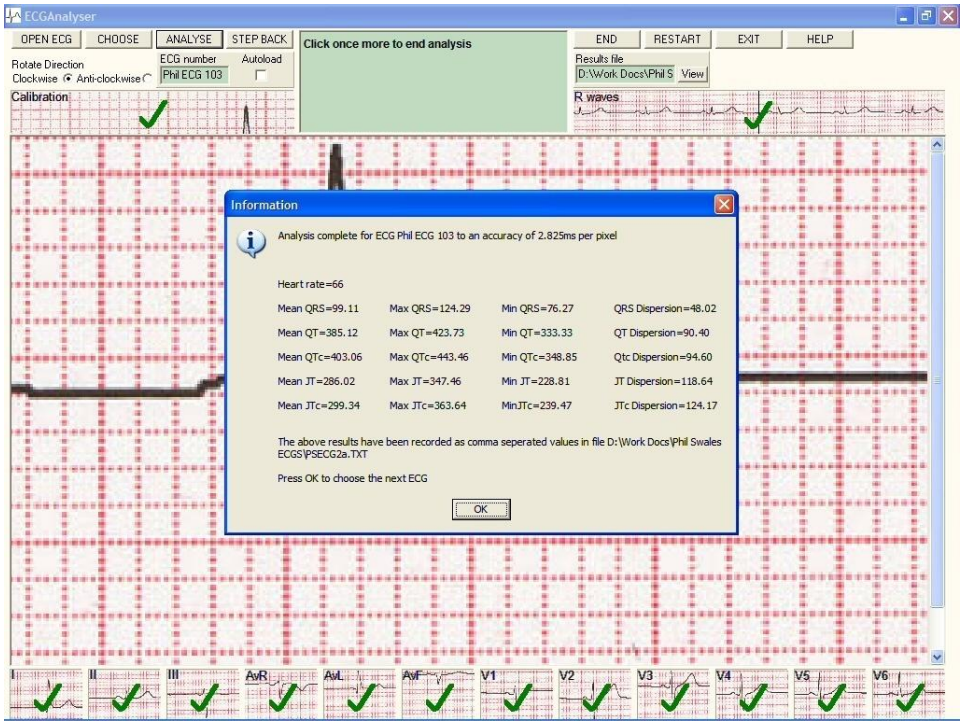
ECG Analyser software loading screen



ECG Analyser software main screen before ECG loaded



ECG Analyser software in action – high resolution ECG analysis demonstrated



ECG analysis completed and results displayed on screen as well as passed to results file

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