Long term outcomes in patients with heart failure The Darlington Retrospective Out Patient Study (DROPSY)

SINGH, RAJENDER

Long term outcomes in patients with heart failure

The Darlington Retrospective Out Patient Study (DROPSY)

Dr Rajender Singh

Submitted for the degree of Doctor of Philosophy

2013

Durham University

Summary

The Darlington Retrospective Outpatient Study (DROPSY) was carried out at the Darlington Memorial Hospital Darlington. From Jan 2002 to Dec 2007, 1041 patients were seen in the heart failure (HF) clinic. Of these 270 (26%) were diagnosed as having left ventricular systolic dysfunction (LVSD). Of the 771 patients who did not have systolic dysfunction, we identified 243 patients who fulfilled the study criteria for heart failure with preserved ejection fraction (HFpEF). The remaining 528 patients formed the non heart failure (Other) group.

Patients with HFpEF were older and more likely to have hypertension and diabetes than the other two groups. The LVSD group had more men plus ischemic heart disease patients while the third group of non HF also had more females and a high number with COPD.

Over the mean follow up of 7 years, the number of admissions to hospital per patient was similar in both the LVSD and HFpEF groups, but HFpEF patients had a significantly longer length of stay. In the HFpEF group, the use of beta blockers, ACE inhibitors, and a lower median resting HR of < 78 / min predicted better survival. All cause mortality was high in both LVSD and HFpEF groups, with strikingly different cause of death. Patients with LVSD had more cardiovascular deaths whereas HFpEF patients were more likely to die of non-cardiovascular causes. Patients in the third group diagnosed as not having HF (Other group) also had high five year mortality.

Conclusion

Patients with LVSD and HFpEF have high mortality but different causes of death. The use of beta blockers, ACE inhibitors, and a lower resting heart rate in the HFpEF group was associated with better survival. Patients who were reassured as not having HF do badly as well.

Declaration

The research contained in this thesis was carried out by the author whilst a postgraduate student in the School of Medicine and Health at Durham University. None of the work in this thesis has been submitted in candidature for any other degree.

Statement of copyright

Dr Rajender Singh

Acknowledgement

This thesis work would not have been possible without the patience, guidance, enthusiastic encouragement and useful critiques by my supervisors Professor J.J Murphy and Professor A.P.S Hungin. They demanded a high standard and a work ethic that elevated my abilities; gave me the academic freedom to pursue new ideas and provided valuable support and guidance to make this research possible.

I am also much obliged to Professor D.W Wilson, who has guided me through the maze of statistical formulas and SPSS software used for analysing reams of data.

I wish to thank Prof A Fuat, for his valuable and constructive suggestions during the planning and development of this research, and help with data collection from the one stop heart failure clinic.

I am deeply grateful to Gill Brennan, for her support with daily issues of data collection and her valuable help for accessing clinical records and performing the double data entry.

Finally, I would like to thank my parents (Dalip singh, Satya Devi) and family (Shweta, Pari, Aayush) for their love and affection. They have always been there to cheer me, encourage me with enthusiasm and words of wisdom.

Contents

Abbreviations used

AAA = Abdominal aortic aneurysm

ACC = American College of Cardiology

ACEi = Angiotensin converting enzyme inhibitors

AHA = American Heart Association

ARB = Angiotensin receptor blockers

AR = Aortic regurgitation

AS = Aortic stenosis

AT 1= Angiotensin receptor 1

AT 2 = Angiotensin receptor 2

B blockers = Beta-blockers

BP = Blood pressure

b.p.m = beats per minute

BSC = British Society of Cardiology

BSE = British Society of Echocardiography

CCF = Congestive cardiac failure

CHD = Congestive heart disease

CHF = Congestive heart failure

CI = Confidence interval

COPD = Chronic obstructive pulmonary disease

CVS = Cardiovascular

DHF = Diastolic heart failure

E/A ratio = Early and atrial filling phase of the left ventricle

ECG = Electrocardiography

ECHO = Echocardiography

eGFR = Estimated glomerular filtration rate

EF = Ejection fraction

ESC = European Society of Cardiology

GP = General Practitioners

Hb = Haemoglobin

HF = Heart failure

HR = Heart rate

HFNEF = Heart failure with normal ejection fraction

HFpEF = Heart failure with preserved ejection fraction

HFrEF = Heart failure with reduced ejection fraction

ICD = International Classification of Disease

IHD = Ischemic heart disease

JVP = Jugular venous pressure

IVSDs = Interventricular septal diameter in systole

LBBB = Left bundle branch block

LVIDd = Left ventricle internal diameter in diastole

LVSD = Left ventricular systolic dysfunction

MI = Myocardial infarction

Mg/dl = Milligrams per deci litre

Mmol/l = Milli moles per litre

µmols/l = Micro moles per litre

MR = Mitral regurgitation

MS = Mitral stenosis

NICE = National Institute for Health and Care Excellence

NSF = National Service Framework

NSR = Normal sinus rhythm

NYHA = New York Heart Association

OMT = Optimal medical therapy

ONS = Office for National Statistics

OR = Odds ratio

PCT = Primary Care Trust

PH = Proportional hazard

PR = Pulmonary regurgitation

PS = Pulmonary stenosis

RAS = Renin angiotensin system

SOA = Swelling of ankles

SOB = Shortness of breath

SPSS = Statistical Package for Social Sciences

TR = Tricuspid regurgitation

TTE = Trans thoracic echocardiography

WHO = World Health Organisation

Introduction

Heart failure (HF) is a common condition responsible for significant morbidity and mortality, placing a substantial burden on the health care system (1). Even for those with mild heart failure five-year mortality approaches 50%, which is worse than for most forms of cancer (2, 3). In terms of morbidity, heart failure impairs quality of life more than any other common chronic condition (including hypertension, diabetes, arthritis, chronic lung disease and angina) (4, 5).

The preceding three decades have seen an improved appreciation of the pathophysiology of HF and its management. Whereas in the past diuretics and digoxin were the principal treatment, the outcome of several randomised controlled clinical trials have brought about a paradigm shift, changing the focal point to the use of angiotensin converting enzyme inhibitors (ACEi), beta blockers, aldosterone antagonist, and angiotensin receptor blockers (ARBs) as the indispensable first line treatment for the management of HF patients. The role of diuretics and digoxin has become supportive.

The identification of HF, which until the 1980s had relied to a great deal on the clinical expertise of the physician, saw wider utilization of echocardiography for verifying the diagnosis. Additionally clinical guidelines were published by the European Society of Cardiology (ESC), the American Heart Association (AHA), and the American College of Cardiology (ACC), streamlining the diagnosis and management of HF.

Enhanced appreciation of the pathophysiology of HF has also led to the acknowledgement that there may be two distinct types of HF. Firstly, where there are symptoms (breathlessness and / or fatigue) and signs of fluid retention, with objective evidence of left ventricular systolic dysfunction (LVSD), principally by echocardiography. Secondly, where the symptoms and clinical features of HF are

present but echocardiography shows a normal or preserved systolic function, so-called diastolic HF or HF with preserved systolic function, or HF with preserved ejection fraction (HFpEF).

Despite the recent advances, diagnosis and management of HF remains a problem with over diagnosis and under treatment (6), such that patients do not gain the full benefits of clinical research.

This could be due to a number of reasons. HF is mainly diagnosed and managed by the general practitioners (GPs) who have traditionally had limited access to echocardiography. Other factors include diagnostic uncertainty, amplified by limited access to diagnostic services, lack of awareness of research evidence and guidelines, concerns about adverse effects, perceived problems with ACE inhibitors, beta-blockers, and poor communication between primary and secondary care (7, 8).

There is also uncertainty as to how evidence based management can be best delivered to patients. Should it occur in primary care where GPs have open access to echocardiography, the so called “open-access model” (9, 10)? Alternatively, is it best delivered by a specialist HF clinic in secondary care (11)?

In 2002, a weekly one-stop diagnostic HF clinic was established in Darlington Memorial Hospital. This was led by a GP with a special interest in cardiology and a HF nurse. This clinic runs in parallel to a consultant cardiologist clinic. Patients are referred from primary care. All have clinical assessment, blood tests, chest- X ray, electrocardiogram (ECG), and trans-thoracic echocardiography (TTE). Other investigations are performed as required. The left ventricular systolic function is assessed by “eye ball” assessment, with Simpson’s rule and measuring wall motion index when possible. Patients in whom HF or LVSD is not confirmed are discharged back to the general practitioners, or if necessary, to another physician. For those with

HF due to LVSD, a management plan is formulated which includes patient education, initiation of evidence-based treatment and follow up in a nurse-led titration clinic.

A retrospective cohort study of the records of all the patients presenting to the one stop HF clinic at Darlington Memorial Hospital from Jan 2002 to Dec 2007 was performed to ascertain patient characteristics and their clinical outcomes.

I reviewed the case notes of all these patients referred to the one stop HF clinic. Subjects found to have clinical signs and symptoms of the HF were identified. They were further studied and categorised based on their echocardiography (TTE) results in two groups:

1) Those with impaired contraction (systolic) function of their left ventricle (LVSD).

2) Those with preserved contraction (systolic) function of the left ventricle (HFpEF).

I followed up the management and outcome of this cohort of patients, utilising their hospital and general practice records, and data from the Medical Research Information Service (MRIS), to answer the primary research question, “What is the long term outcome in patients with heart failure who are managed as per clinical guidelines?”

Chapter 1

The Definition of Heart failure

Although the diagnosis and management of heart failure is one of the largest tasks for the physicians, it has been a challenge to provide an all-encompassing definition for this syndrome (12). In 1933 Thomas Lewis in his book, *Disease of the Heart,* stated that “the very essence of cardiovascular practice is the recognition of early heart failure” (13).

Advances in the understanding of the cardiac physiology have rendered earlier definitions inadequate. Physicians have used the term in a practical way to convey information about an individual patient, but the work of the clinical scientist and epidemiologist necessitate a more rigorous approach to the definition of HF (14). Also, as no single measurement reliably discriminates between the normal and failing heart, no definition is universally accepted (12).

Over a period, different authors have variously defined HF. Lewis, in 1930, defined HF as a condition in which the heart fails to discharge its contents adequately (13). In 1950, Wood defined HF as a state in which the heart fails to maintain an adequate circulation for the needs of the body despite adequate filling pressure (15). In 1977 Wagner et al defined HF “as a state that exists when either the systolic or diastolic operation of the ventricle is impaired to a degree that, despite compensatory mechanisms, the demands of the peripheral organs are not satisfied, the peripheral muscle shortens inadequately, and / or the pulmonary and systemic venous system becomes congested from high filling pressures” (16). And in 1980 Braunwald defined HF as “a pathophysiological 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” (17).

This highlights the difficulty in defining HF, as these definitions emphasise one or several features of this complex syndrome, such as hemodynamic, oxygen consumption, or exercise capacity (18).

More recently the European Society of Cardiology (ESC) published guidelines for the diagnosis of HF in 1995 (19), 2001 (20), 2005 (21), 2008 (18), and in 2012 (22). In all these documents, the task force members acknowledge, “a simple objective definition of the heart failure is currently impossible as there is no cut off value of cardiac or ventricular dysfunction or change in flow, pressure, dimension, or volume that can be used reliably to identify patients with heart failure”.

ESC guidelines, for practical purposes, consider the essential component of HF to be “a syndrome in which the patient should have the following features: symptoms of heart failure, typically breathlessness or fatigue, either at rest or during exertion, or ankle swelling and objective evidence of cardiac dysfunction at rest”.

1.1 Role of echocardiography

Echocardiography remains the gold standard for evaluation of left ventricular function as in clinical practice it is widely available and easily reproducible. Assessment of the left ventricular systolic function is of paramount importance as it not only provides prognostic information but also helps guide appropriate therapy to be instituted (22). Left ventricular systolic function can be assessed in great detail. This can be analysed and quantified using a number of methods.

These are qualitative, semi quantitative and quantitative assessments. “Eye ball” assessment of the global left ventricular (LV) function is the qualitative method. Semi quantitative assessment is performed using a wall motion score / index. For quantitative assessment measurements include fractional shortening, ejection fraction, LV volumes in systole and diastole, and the myocardial performance index.

Ejection fraction, which is most commonly used, is the stroke volume [calculated as (end diastolic volume – end systolic volume] divided by end diastolic volume.

For the present study evaluation of the systolic function was done using ejection fraction where possible or the “eye ball” assessment. Both approaches are validated for use in clinical practise (23).

1.2 ESC definition of heart failure (22)

HF is a clinical syndrome in which patients have the following features:

Symptoms typical of HF (breathlessness at rest or exertion, fatigue, tiredness, ankle swelling); Signs typical of HF (tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly); Objective evidence of a structural or functional abnormality of the heart at rest (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration)

Similarly, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) (24) in 2009 defined HF as a “complex clinical syndrome that can result from structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood”. Here the authors have also emphasised that HF is largely a clinical diagnosis, which is based on a careful clinical history and a thorough physical examination.

1.3 Grading of severity of HF

HF patients are usually classified according the severity of their symptoms and exercise capacity. The most commonly used classification system is the New York Heart Association (NYHA) functional classification system (25).

Table 1.4 NYHA classification

Class 1 (mild): No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, or dyspnoea.

Class 2 (mild): Some limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitations, or dyspnoea.

Class 3 (moderate): Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitations or dyspnoea.

Class 4 (severe): Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency present at rest. If any physical activity is undertaken discomfort is increased.

Chapter 2

Literature review

"The longer you look back, the further you can look forward." Sir Winston Churchill.

Historical perspective

Writings from the times of the Greek and the Egyptian civilizations tell us that HF was a fairly well recognised condition. Narratives of HF exist from ancient Egypt, Greece, and India, and foxglove was used as a medicine by the Romans (26). Understanding the nature of HF improved after William Harvey described the circulation in 1628. Wilhelm Conrad Röntgen discovered X rays in the 1890's (27). His discovery has arguably had the greatest impact on the way we view ourselves. His report of the accidental discovery of a new form of radiation that penetrates through almost everything was revolutionary at that time. The value of being able to see inside a body without having to perform surgery was immediately obvious, and scientists and physicians rushed to find bigger and better uses for X-rays.

Around the same time a Dutch physician and physiologist, William Einthoven developed the first Electro Cardiograph (ECG) Machine, using a simple string – galvanometer, which led to improvements in the investigation of HF (28).

The Italian naturalist Lazzaro Spallanzani (1729-1799) first demonstrated the importance of echo reflection, the principle behind echocardiography. With his extensive experiments on the navigation by bats in complete darkness, he concluded that they use sound and their ears for navigation, called echo reflection. Pierre and Jacques Currie in 1880, discovered the piezo-electric effect, a peculiar phenomenon in certain quartz crystals which were the basis of early ultrasound systems (29).

The first experiments using ultrasonic echo reflection for examining the heart were initiated by a cardiologist Inge Edler and a physicist Carl Hellmuth Hertz in Lund, Sweden in 1953 and produced the first echocardiogram of the heart (30). For his

pioneering work Inge Edler has also been called the father of echocardiography (31). Cardiac ultrasound has been the most important advancement in diagnostic cardiology since the discovery of X-rays. In the past 25 to 30 years, echocardiography has become a basic examination in clinical cardiology. Echocardiography provides information regarding cardiac morphology, function and hemodynamics non-invasively. It is the most frequently performed cardiovascular examination after electrocardiography and chest X-ray (31). In less than half a century, this technique has evolved to a mainstay of cardiovascular medicine. Among the many forms of echocardiography are M-mode, two-dimensional, Doppler, stress, trans oesophageal, intraoperative, contrast, digital, three-dimensional and intracardiac echocardiography (32). The evolution of echocardiography has been dramatic, and its ultimate capabilities are still unrealized.

The evolution of cardiac catheterization has occurred over the last four centuries. Stephen Hales (1677-1761), a botanist and physiologist, performed the earliest known cardiac catheterization. In 1711 he inserted brass cannulae through the venous and arterial system into the ventricles of a horse by route of the jugular vein and carotid artery (33).

In 1929, Dr Werner Forssman (1904 – 1979), a 25 year old surgical trainee in a German town near Berlin, explored methods for a more direct access to the cardiac chambers, initially experimenting on himself and thus performing the first right heart catheterization in a human (34). The advent of cardiac catheterization represents a major medical and scientific achievement. It has revolutionised the diagnosis and treatment of cardiovascular disease and played a critical role in the advancement of the scientific knowledge (29).

The advent of echocardiography, cardiac catheterisation, and nuclear medicine have improved the diagnosis and investigation of patients with suspected HF thus helping provide evidence based management and improve survival.

2.1 Treatment

For 2000 years, HF had been treated with bloodletting and leeches. Bloodletting dates at least from the Hippocratic days. It was avidly pursued in the 17th and 18th centuries, particularly in France and Italy and the practice became highly specialised in the hands of the barber surgeons (35). Many families had their own equipment for catching blood. Bloodletting and leeching went out of vogue in the late 18th century (35). For centuries Ayurveda, the traditional Indian medical system, has used Arjuna bark (Terminalia Arjuna) for treatment of HF (36). In the 19th and early 20th centuries, HF associated with fluid retention was treated with Southey's tubes, which were inserted into oedematous peripheries, allowing some drainage of fluid (26). In the 17th -19th century "dropsy" was the word associated with fluid overload. This was considered a primary disease, as physicians were not able to distinguish between the cardiac and renal dropsy.

Dropsy was treated with herbal medications. Medicinal properties of the digitalis (foxglove) plant were well recognised and have been used in medicine for centuries. Leonard Fuchus (1501-1566), a German physician and humanist, named the plant Digitalis in his book *Historia Stripium* (1542), and recommended it for "the scattering of dropsy" (37). William Withering (1741-1799), who was aware of the work of Fuchus, encountered the plant again when he met a "wise woman" who used foxglove as one of the components of her medicine for dropsy.

Withering's specific contribution was to place digitalis on a proper scientific footing, and thereby eliminate much of its folklore and superstition. He established that the dried powdered leaf of the plant was five times as effective as the fresh leaf. The

powder was also better than a decoction, as boiling seemed to destroy some of the active principle. He then went on to study 163 patients with dropsy, and recorded his results carefully (38). Withering's recognition of the foxglove as the active principle of the various witches' brews that had been used to treat dropsy (oedema) was primed by his extensive botanical studies and investigations (37). Withering published his major work on the foxglove (digitalis) - *"An account of the Foxglove and some of its Medical Uses" in* 1785 (39).

2.1.1 Dawn of the diuretics

Diuretics were the most important medications for treating dropsy in the late 19th and early 20th century. Many agents were used including the bitartrate, acetate, nitrate of potash, digitalis, and squill, spirit of nitrous ether, scoparium, juniper, copaiba, turpentine, cantharides, and gin. These diuretics were predominantly useful in cardiac and renal dropsy; they had no effect upon portal dropsy (40). Digitalis was acknowledged as a medication of astonishing efficacy in many cases of cardiac dropsy, and principally in cases where the heart's action was irregular (40).

In the 19th century mercury and its compounds began to be used as diuretics. Mercury had been used in industry and medicine for many centuries, but the pharmacological properties of mercury were not well understood. Despite the obvious utility of these compounds in the past, their toxicity overshadowed their usefulness. Rediscovery of the diuretic effects of mercurous chloride by Wood in 1849 and by Jendrassick in 1886 contributed to the development of their place in the treatment of the oedema (41).

Working in Vienna in 1919, Arnold Vogl a third year medical student, made the chance discovery that the parenteral administration of an organic mercurial compound, Marbaphen (Novasurol), when used to treat a girl with congenital syphilis, produced unexpected diuresis (42). This initiated a new phase and led to the

development of less toxic organomercurial diuretics which were regarded as the “most reliable and powerful diuretic agents” (43). Organomercuial diuretics were the main stay of therapy for congestive symptoms till the 1950s (42).

Digitalis and mercury were extensively used for the management of patients with signs and symptoms of congestive HF both for inpatient and out patients (44). Guy’s Pill :- [a mixture of mercurial pill (Blue Pill), digitalis leaves in powder, squill in powder, extract of gentian, - one thrice daily] was well known and widely prescribed for cardiac dropsy (45).

In 1932, a German bacteriologist Gerhard Domagk proclaimed the discovery of a red dye prontosil that was active against streptococcal infections in mice and humans. Soon after it was shown that the active ingredient of this antimicrobial agent was sulphanilamide (46). Around the same time Meldrum and Roughton described the enzyme carbonic anhydrase in 1932 (47). It was noted by Pitt that sulphanilamide alkalinized the urine and this process and bicarbonate reabsorption were dependent on the enzyme carbonic anhydrase (48). Schwartz was the first to connect hydrogen secretion and sodium reabsorption in this context and gave sulphanilamide to treat congestive HF. This ushered in a new diuretic age and Roblin synthesized the new and more powerful carbonic anhydrase inhibitor acetazolamide (48). These compounds block hydration of carbon dioxide in tubular cells so that the bicarbonate ion cannot be reabsorbed and thus carries sodium, water and potassium with it. These were the first orally effective diuretics (49). Unfortunately, they had low potency and became ineffective if used for a prolonged duration.

In 1957 Novello and Sprague, while studying the aromatic sulphonamides, observed unexpectedly high activity with benzenedisulfonamides. These compounds exhibited an order of inhibition of carbonic anhydrase observed previously with heterocyclic sulphonamides. In addition, they also produced a marked increase in chloride

excretion and caused diuresis not unlike that observed with the organic mercurials (50). Thiazides were effective orally even in those patients who had become resistant to mercurial diuretics and were less toxic (51, 52). These drugs exert their effect primarily by inhibiting reabsorption in the early segment of the distal tubule of the nephron (49). Thiazides were not without side effects and the commonest were hypokalemia, and sensitizing the heart to actions of digitalis (53).

For years it was believed that secondary hyperaldosteronism was mainly responsible for the salt and water retention in congestive cardiac failure and much research was concentrated on this (54, 55). Spironolactone (a specific aldosterone antagonist) was not very effective in cardiac oedema. It was shown that aldosterone levels were slightly raised in untreated HF and fell to normal as body weight went down with diuretics, and only rose as the body was depleted of salt (56). Spironolactone competitively inhibits the effects of aldosterone on the distal tubule, and is more effective when used with a diuretic that increases the load of sodium presented to the distal tubule. (57)

Further exploration of the sulphonamide structure and substituting the existing thiazides with a sulfamyl-benzene group produced a dramatic change in the qualitative nature of the renal response. This new potent compound named furosemide was developed in 1963 (42). These sulphamoylbenzoate diuretics interact with a Na, K, 2CI-cotransporter within the luminal membrane of the ascending limb of the loop of Henle (58). Furosemide proved more effective than comparable standard doses of other diuretics. Higher doses were successfully used in resistant oedema and intravenous furosemide was of particular value in acute pulmonary oedema (59). These new and powerful diuretics made it possible for the physician to control the symptoms in most patients with cardiac oedema.

Other drugs, which have been used in the past for treatment of congestive cardiac failure, are xanthines, glucocorticoids, mannitol, alcohol and serum albumin. These are rarely used now (49).

Up till the 1970s complete immobilisation was advocated and shown to reduce cardiac size and improve symptoms for patients with HF (60). However it was seen that symptoms re appeared after mobilisation and also patients had a high incidence of thromboembolic complications.

2.1.2 Emergence of angiotensin converting enzyme inhibitors (ACEi)

The emergence of angiotensin converting enzyme inhibitors (ACEi) ranks amongst one of the major therapeutic advances of the 20th century. Their discovery, like that of the diuretics, was essentially by chance. Our understanding of the renin-angiotensin system (RAS) can be traced back to the 19th century when Tigerstedt and Bergman published an article on renin in 1889 (61). Angiotensin converting enzymes (ACE), like carbonic anhydrase, is also a zinc-metalloproteinase belonging to a large group of related enzymes that include carboxypeptidase A and alkaline phosphatise (62). A scientific group in London was working on the mechanisms whereby the venom of the Brazilian snake *Bothrops jaracopa* caused circulatory collapse. The venom was found to contain peptides that inhibited ACE and potentiated bradykinin (63). Subsequently these peptides were also shown to inhibit the conversion of angiotensin I to angiotensin II by canine pulmonary tissue (64).

The first ACEi studied in man was a synthetic nonapetide, teprotide which in patients with elevated renin activity, was able to block the pressor response to infused angiotensin I and lower blood pressure (42). In 1980 a systematic enquiry by Cushman and Ondetti (65) into the snake venom led them to develop the first orally active ACEi, captopril. It was soon realised that the mercapto group in the captopril caused side effects like rash, taste disturbance and proteinuria. This heralded the

search to synthesise an ACEi lacking the mercapto group and Enalapril was developed by Patchett in 1984 (66). Enalapril is an esterified pro-drug that yields the free acid, enalaprilat, an active ACEi. By changing the amino acid backbone from proline to lysine, the orally active lisinopril has been produced.

Over the years, various other ACEi agents have been developed and many randomised controlled trials have proved their efficacy in improving symptoms, reducing hospitalisation, and improving survival in patients with heart failure.

2.1.3 Beta-blockers

In the 1940s and 50s nitro-glycerine was well known as a vasodilator agent and widely used for angina treatment. It was assumed that as nitrates dilated peripheral blood vessels they would also dilate blood vessels in the heart, increasing blood flow and thus oxygen delivery to the myocardium. So the main thrust of research was on the development of vasodilators for increasing the oxygen supply to the heart in patients with angina (67).

At the same time in 1948, Raymond P Ahlquist proposed that there were two distinct types of adrenotrophic receptors which he tentatively named as alpha and beta receptors (68). He also demonstrated that it was the beta receptor which caused myocardial stimulation (68).

Sir James Black was impressed by Ahlquist's theory of beta-receptors in the heart. He was aware that systemic blood pressure and heart rate determined myocardial demand for oxygen (69). Unlike others who were working on ways to increase the oxygen supply to the myocardium, Sir James Black started to work on ways to reduce myocardial demand for oxygen in hearts whose oxygen supply was restricted due to arterial narrowing.

Ahlquist's alpha and beta-receptors gave him the starting point. He wanted to find a beta-receptor antagonist to slow the heart rate and thus reduce the myocardial demand for oxygen. He first produced pronethalol (which never came into widespread clinical use) and then propranolol in 1965. Propranolol, and subsequently other beta blockers, have changed the face of cardiovascular medicine (70). Initially they were used to treat hypertension, angina and arrhythmias. But over the last 25 years beta-blocker therapy has also proved the most effective treatment for chronic HF.

2.2 Evidence based treatment for LVSD

In the recent past many guidelines and systematic reviews have been published on the management of chronic HF. These provide recommendations for the diagnosis and use of evidence based treatment.

2.2.1 Angiotensin converting enzyme inhibitors

The majority of trials in HF failure have involved ACE inhibitors. In 1983 the **Captopril-Multicentre study** (71), was one of the first randomized, double blind, placebo controlled trials in heart failure refractory to digitalis and diuretic therapy. Patients treated with captopril showed improvement in exercise tolerance and New York Heart Association (NYHA) functional class compared to those on placebo. This also heralded the era of HF trials.

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) group (72) in 1987, randomized 253 patients with NYHA class 4 HF on conventional therapy to either enalapril (2.5 to 40 mg per day) or placebo. At 6 months, mortality was 26 percent in the enalapril group and 44% in the placebo group- a reduction of 40% ($p = 0.002$). Mortality was reduced by 31% at one year ($p = 0.001$). In addition, a significant improvement in NYHA class was observed with enalapril, together with a reduction in heart size and a need for other medication for HF. This was the first trial to show improved survival with an ACEi.

Studies of Left Ventricular Dysfunction (SOLVD) Trial (1991)

In the **SOLVD – Treatment trial** (73), one of the largest trials with enalapril, 2569 patients with congestive HF NYHA class 2 and 3, and an EF of 35% or less who were already taking conventional therapy other than ACE inhibitors were randomised to receive 2.5 mg to 20 mg twice daily enalapril or placebo. Patients were followed up for an average of 41 months. There were 510 (39.7%) deaths in the placebo group as compared with 452 in the enalapril group (35.2%). There was 16% reduction in risk in total mortality, and fewer patients were hospitalised for worsening HF. This was the first large scale trial in HF which showed that the mortality benefit shown in CONSENSUS could be applied to milder forms of HF.

SOLVD - prevention (74) trial examined the effect of enalapril on asymptomatic left ventricular dysfunction. 4228 patients with an ejection fraction of 35% or less, who were not receiving diuretics, digoxin, or vasodilators for treatment of HF, were identified. Patients were randomised to receive either 2.5 mg to 20 mg twice-daily enalapril or placebo. Patients were followed up for average of 37 months. There was reduced incidence of HF and related hospitalizations, with a trend toward fewer cardiovascular deaths.

2.2.2 Angiotensin converting enzymes inhibitors post Myocardial Infarction

Survival and Ventricular Enlargement (SAVE) Trial (75) enrolled 2231 patients 3 to 16 days after an acute myocardial infarction with a left ventricular ejection fraction of 40% or less but without overt HF or symptoms of myocardial ischemia. Patients were randomly assigned to receive either placebo or captopril 50 mg three times daily, and followed up for an average of 42 months. There was 19% risk reduction in all-cause mortality and incidence of both fatal and non-fatal major cardiovascular events was consistently reduced in the captopril group. These benefits were observed in patients

who received thrombolytic therapy, aspirin, or beta-blockers as well as those who did not. This was the first trial to show prevention of congestive HF.

The Acute Infarction Ramipril Efficacy (AIRE) study (76) recruited 2006 patients, 3 – 10 days post myocardial infarction who had shown clinical evidence of either transient or ongoing HF. They were randomly allocated to placebo or ramipril 5 mg twice daily. Follow up was continued for a minimum of 6 months and an average of 15 months. There was a 27% risk reduction in all-cause mortality in the ramipril group. This benefit was evident as early as 30 days and was consistent across a range of subgroups.

Trandolapril Cardiac Evaluation (TRACE) study (77) recruited 1749 patients, 3 – 7 days post myocardial infarction with an ejection fraction of 35% or less with or without symptomatic HF. Patients were randomly assigned to receive placebo or trandolapril 4 mg once daily. Follow up was for 24 to 50 months. There was a 22% relative reduction for overall mortality with trandolapril. There was a reduction in deaths from cardiovascular causes, sudden deaths, and the development of severe HF.

Dose ranging trials with Angiotensin converting enzyme inhibitors

In Assessment of Treatment with Lisinopril And Survival (ATLAS) trial (78) 3164 patients with NYHA class 2 to 4 and an ejection fraction ≤ 30% were randomly assigned to either low doses (2.5 – 5 mg daily) or high doses (32.5 to 35 mg daily) of lisinopril. The study population was followed up for 46 months. When compared with the low dose group, patients in the high-dose group had a significant (12%) lower risk of death or hospitalisation for any reason ($p = 0.002$) and 24% fewer hospitalisations for HF ($p = 0.002$). This highlighted that even therapy that exerts positive effects in clinical trials may not be effective in clinical practice if the doses in the study are not used.

Conclusion: The NICE HF guidelines of 2010 (79) recommended ACE inhibitors, titrated to the target doses obtained from clinical trials, as the first line therapy in patients with LVSD.

2.2.3 Angiotensin – II receptor blockers

Angiotensin - II type 1 - receptor blockers (ARBs) act by a different mechanism from ACE inhibitors, although both reduce the stimulation of angiotensin II receptors. ACE inhibitors block the formation of angiotensin II, a potent vasoconstrictor agent, thereby decreasing the amount of angiotensin available to both angiotensin type 1 (AT1) and angiotensin type 2 (AT2) receptors. ARBs selectively block the binding of angiotensin II to the AT1 receptors, but do not affect the AT2 receptors. In the management of hypertension, ARBs were found to be an effective alternative to ACE inhibitors, particularly when side effects such as cough are encountered. A potential role in the management of HF was also postulated.

Major trials with Angiotensin - II type receptor blockers (ARBs) are broadly divided into three groups. 1) Patients intolerant to ACE inhibitors (CHARM Alternative) 2) ACEi vs. ARB (ELITE I / II, OPTIMAL, VALLIANT) and 3) ACEi added with ARB (CHARM added, Vel-HEFT)

Group 1

Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Alternative (80) enrolled 2028 adult patients (≥ 18 years) with symptomatic congestive HF (NYHA class 2-4) for at least 4 weeks. The ejection fraction must have been ≤ 40% and determined within six months. They were not receiving ACEi because they were previously intolerant of them. 740 patients experienced the primary outcome of cardiovascular death or hospitalisation for CHF: 334 (33%) in the candesartan group and 406 (40%) in the placebo group [(unadjusted hazard ratio 0.77), 95% CI 0.67 - 0.89: p = 0.004]. The average annual event rates

were 13.8% in the candesartan group and 18.2% in the placebo group. The absolute risk reduction of 7 major events per 100 patients corresponds to treating 14 patients with candesartan for 1 year to prevent one cardiovascular death or hospitalisation for CHF. Candesartan was generally well tolerated and reduced cardiovascular mortality and morbidity in patients with symptomatic HF and intolerant to ACE inhibitors.

Group 2

Evaluation of Losartan in the Elderly (ELITE) study (81) was designed to determine the safety and efficacy of AT1 receptor blockade with losartan in the treatment of HF in elderly (65 years or more) compared to the ACE inhibitor captopril.

Seven hundred and twenty two ACE inhibitor naive patients with NYHA class 2-4 HF and EF of 40 percent or less were randomised to losartan 50 mg once daily or captopril 50 mg three times daily. There was no difference in renal dysfunction in the two groups, losartan was better tolerated than captopril and fewer patients discontinued losartan therapy. Unexpectedly in this study of the elderly, treatment with losartan was associated with lower mortality than the captopril group (4.8 % vs. 8.7 %; risk reduction 46%; 95% CI 5-69%: p = 0.035)

The Losartan Heart Failure Survival study ELITE II (82) was designed to confirm whether losartan is superior to captopril in improving survival and is better tolerated. There were 3152 patients aged 60 years or older with NYHA class 2-4 heart failure and ejection fraction of 40% or less. Patients, stratified for beta blocker use, were randomly assigned to losartan 50 mg once daily or captopril 50 mg three times daily. The primary and secondary end was all cause mortality. Median follow up was 1.5 years. There was no difference in all-cause mortality in the losartan group (17.7%) vs. 15.9% in the captopril group (hazard ratio 1.13% [95.7% CI 0.095 – 1.35] p = 0.16). Losartan was not superior to captopril in improving survival in the elderly HF patients, but significantly better tolerated.

Optimal trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) (83) was designed to compare the effects of losartan 50 mg once daily with those of captopril 50 mg three times daily on mortality and morbidity in patients with acute myocardial infarction and evidence of HF or left- ventricular dysfunction. All cause mortality was not significantly different in the two groups with 499 (18%) deaths in the losartan group vs. 447 (16%) in the captopril group, over an average follow up of 2.7 years (range 0-9). This trial also did not show superiority or non-inferiority of losartan relative to captopril, though it was better tolerated.

Valsartan in Acute Myocardial Infarction (VALIANT) (84) was a prospective, multicentre, double blind, randomised, active control trial with three parallel treatment groups. Post myocardial infarction patients with signs and symptoms of HF or LVSD (ejection fraction ≤35% on echocardiography) and receiving conventional therapy were randomly assigned to additional therapy with valsartan 160 mg alone, valsartan 80 mg twice daily plus captopril 50 mg three times daily, or captopril 50 mg three times daily. The primary end point was death from any cause.

After a median follow up of 24.7 months, 979 patients in valsartan group died, as did 941 patients in the valsartan and the captopril group and 958 in the captopril group. Mortality from any cause and cause specific mortality were similar in the three treatment groups.

Group 3

Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)- Added trial (85) enrolled 2548 patients with NYHA class 2-4 and an ejection fraction of 40% or less who were being treated with ACEi. Patients were randomly assigned to candesartan (n = 1276, target dose 32 mg once daily) or placebo (n = 1272). 55% of the patients were receiving beta blockers and 17% spironolactone at baseline. The primary outcome was a composite of cardiovascular

death or hospital admission for CHF and the median follow up period was 41 months. 483 (38%) patients in the candesartan group and 538 (42%) in the placebo group experienced the primary outcome of cardiovascular death or admission to hospital for CHF (HR 0.85, 95% CI 0.75 - 0.96, p = .011). This was equivalent to an absolute reduction of 4.4 patients with events per 100 patients treated corresponding to a number to treat of 23 to prevent one event of cardiovascular death or CHF admission. All cause mortality did not differ in both groups.

Valsartan-Heart Failure Trial (Val-HeFT) (86) investigated the effect of valsartan when added to an ACE inhibitor. Patients receiving background therapy for heart failure were eligible if they had NYHA class 2-4 symptoms, ejection fraction of 40% or less and a left ventricular internal diameter in diastole (LVIDd) of more than 2.9 $cm/m^{2.}$

3034 patients receiving an ACE inhibitor but not beta-blocker at baseline were randomly assigned to receive placebo or valsartan 160 mg twice daily. Mortality was not affected by valsartan but morbidity endpoints were significantly reduced (36.3% in placebo, 31.0% in valsartan; p= 0.002) in patients receiving an ACEi but no beta-blocker. Valsartan also reduced HF hospitalisation and slowed remodelling in patients treated with an ACEi in the absence of beta- blockade, particularly in those on lower dose of ACEi. Interestingly in the subgroup analysis, patients receiving triple therapy with ACEi, beta blockers, and valsartan there was a significant increase in mortality [129 (17%) vs. 97 (13%) deaths], hazard ratio (HR) 1.42, 95% CI 1.09-1.85, p = 0.009, compared with those on ACE inhibitors, beta blockers, and placebo.

Conclusion: In August 2010 NICE (79) looking at all the evidence regarding the ARBs in management of chronic HF recommended that clinicians:

a) Consider an ARB licensed for HF as an alternative to ACEi in patients with HF due to LVSD who have intolerable side effects with ACEi.

b) Monitor serum urea, electrolytes, creatinine and eGFR for signs of renal impairment and hyperkalaemia.

2.2.4 Evidence for beta blockers in heart failure

For a long time beta blockers have been considered to be contraindicated in HF due to their negative inotropic effect and thus their use in HF may seem counterintuitive. In 1975, Waagstein et al used a beta blocker in seven patients. All patients had resting tachycardia, and advanced congestive HF. Over a period of 2 to 12 months these patients had improvement in symptoms, echocardiography measurements, and X-ray appearances (60).

In 1980 Karl Swedberg et al (87), gave twenty eight patients with HF, beta blockade for six to 62 months. There was improvement in the ejection fraction on echocardiography, functional class, and reduced mortality in this severely ill group.

This initial work supported the hypothesis that excessive catecholamine cardiac stimulation was important in the pathophysiology of congestive cardiac failure and this could be reduced by chronic beta blockade. These studies also suggested that beta receptor blockers should be added to conventional treatment with digitalis and diuretics in all patients with severe congestive cardiomyopathy.

The Metoprolol in Dilated Cardiomyopathy (MDC) (88) was a multi centred randomised, placebo controlled parallel group trial of metoprolol on mortality and need for heart transplantation in patients with symptomatic idiopathic dilated cardiomyopathy. 383 patients with HF and an EF of < 40% were randomised to receive 100 – 150 mg metoprolol daily or placebo over the background treatment. Metoprolol was well-tolerated, improved symptoms and cardiac function, prevented clinical deterioration but had no significant effect on the all-cause mortality.

The Cardiac Insufficiency Bisoprolol study (CIBIS) (89) was a placebo controlled, randomised, double blind study that recruited 641 patients with chronic HF and an EF of <40% in NYHA class 3 (95%) or 4 (5%). All patients received diuretics and 90% were receiving ACEi. 320 patients were randomised to bisoprolol 5 mg/day and 321 to placebo. Mean follow up was 1.9 years. Primary end point was total mortality.

There were 67 (20%) deaths in the placebo group compared to 53 (16.6%) in the bisoprolol group (p = 0.22). Relative risk of death was 0.80 with 95% CI of 0.56 to 1.15. The observed difference in mortality between the two groups did not reach statistical significance, but the increasing doses of beta blocker in severe HF conferred functional benefit. The authors postulated that the reason for statistical non-significance was probably because only half the patients were titrated to the target dose of 5 mg bisoprolol, in patients who were already on standard therapy for HF (diuretics and ACEi)

Carvedilol Heart Failure Study Group (90) enrolled 1094 patients with chronic HF in a double blind, placebo controlled, stratified programme. Patients were assigned to one of the four treatment protocols based on their exercise capacity. Within each of the four protocols patients with mild, moderate, or severe HF with left ventricular ejection fraction of ≤ 0.35 were randomly assigned to receive either placebo (n = 398) or carvedilol (n = 696). Patients were already receiving conventional therapy for HF. The primary end point was death or hospitalisation for cardiovascular reasons.

There were 31 (7.8%) deaths in the placebo group and 22 (3.2%) deaths in the carvedilol group after a median follow up of 6.5 months. This represented a 65% reduction in the risk of death (95% CI 39 to 80%; p<0.001) in patients receiving carvedilol. As compared to placebo, there was also a 27% reduction in the risk of hospitalisation for cardiovascular causes in the carvedilol group (19.6% vs. 14.1% p = 0.036) as well as a 38% reduction in the combined risk of hospitalisation or death

(24.6% vs. 15.8%, p<0.001). The study was stopped before schedule due to a significant reduction in mortality in the carvedilol group.

Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)

The Cardiac insufficiency bisoprolol study (CIBIS) had shown a non-significant trend towards lower mortality and 30% fewer admissions to hospital for worsening heart failure (89). CIBIS II was designed to test this evidence further. 2647 symptomatic patients in NYHA 3 or 4, with an left ventricular ejection fraction of ≤ 35%, on diuretics and ACEi were randomly assigned to bisoprolol (n = 1327), starting dose at 1.25 mg increased to maximum of 10 mg per day or placebo (n = 1320). Mean follow up was 1.3 years. All-cause mortality in the bisoprolol group was 156 (11.8%) vs. 228 (17.3%) in the placebo group, with a hazard ratio of 0.66 (95% CI 0.54-0.81, p < 0.001) at the second interim review. There were also fewer sudden deaths in the bisoprolol group. The study was stopped early after these results.

Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) (91) enrolled 3991 patients with chronic HF and NYHA class 2 - 4 with an ejection fraction ≤ 40%, stabilised with standard therapy. A total of 1990 patients were randomised to metoprolol CR/XL 12.5 mg (NYHA 3-4) or 25 mg once daily (NYHA 2) and 2001 patients were randomised to placebo. The target dose was 200 mg once day. Primary end point was all cause mortality.

145 patients in the metoprolol group and 217 in the placebo group died (p = 0.009, p = 0.062 after adjustment for the first and second interim analysis). This was a 34% reduction in all-cause mortality in clinically stable patients with symptomatic HF and thus requiring 27 patients to be treated for one year to prevent one death with metoprolol CR / XL.

2.2.5 Beta - blockers in advanced heart failure

Carvedilol Prospective Randomised Cumulative Survival (COPERNICUS) study (92). 2289 patients with symptoms of HF at rest and an EF <25% (but not volume overloaded) were randomised to receive carvedilol (n = 1156) or placebo (n = 1133) for an average of 10.4 months. Carvedilol was started at 3.125 mg twice daily, and thereafter titrated to a target dose of 25 mg twice daily. The annual mortality rate in the placebo group was 19.7%, which was reduced to 12.8% in the carvedilol group: a 35% risk reduction of death (p = 0.001). Carvedilol also reduced the risk of death or any hospitalisation by 24% (p = 0.004) prompting early termination of the study.

Carvedilol or Metoprolol European Trial (COMET) (93)

COMET included 3029 patients with chronic HF, NYHA class 2-4, an EF <35%, and a previous admission for cardiovascular reasons who were on optimum treatment with diuretics and an ACEi. 1511 patients were randomised to receive carvedilol 25 mg twice daily, and 1518 to metoprolol 50 mg twice daily. The primary end point was all cause mortality. Patients had a mean age of 63 years and mean follow up of 58 months. 512 (34%) patients died in the carvedilol group and 600 (40%) in the metoprolol group. The hazard ratio 0.83 (95% CI 0.74-0.93, p = 0.0017), suggesting that carvedilol extends survival compared with metoprolol.

This is the only major clinical trial comparing two beta blockers in HF. There was a 17% reduction in mortality with carvedilol as compared to metoprolol. This has raised the question whether one particular beta blocker is better than another for patients with HF.

The results of this trial have been partly explained by the fact that the preparation of metoprolol used was short acting and that possibly carvedilol provided additional benefit other than just beta blockade to account for better survival in this group.

The Beta-Blocker Evaluation Of Survival trial (BEST) (94).

2708 patients with an EF of 35% or lower, and NYHA class 3 (92%) and 4 (8%) were randomly assigned to double blind treatment with either bucindolol (1354 patients) or placebo (1354 patients) and followed for the primary end point of death from any cause. The study was stopped after the seventh interim analysis. At that time, there was no significant difference in the mortality between the two groups. There were a total of 449 (33%) deaths in the placebo group as compared to 411 (30%) in the bucindolol group (adjusted p = 0.13). Thus in patients with advanced HF there was no significant overall survival benefit. This is the only large study that did not show survival benefit with beta blockers in patients with HF. This could be because of different pharmacological properties of bucindolol. Bucindolol is a non selective beta blocking agent with intrinsic sympathomimetic activity. It has mild vasodilator properties with strong β2-adrenergic blockade and only weak α1- blocking properties which makes bucindolol uniquely sympatholytic among the beta blockers evaluated in HF (95). This sympatholysis can produce an irreversible loss of adrenergic support that can be deleterious to the failing heart

2.2.6 Beta-Blockers in post Myocardial Infarction LV dysfunction

Carvedilol Post Infarct Survival Control in LV Dysfunction (CAPRICORN) (96). One thousand nine hundred and fifty nine patients with a proven acute myocardial infarction and left ventricular EF of ≤40% were randomly assigned to 6.25 mg carvedilol (975 patients), titrated to a maximum of 25 mg twice daily, or placebo (984 patients). For the primary end point of all-cause mortality or cardiovascular hospitalisation there was no difference between the carvedilol and the placebo groups [340 (35%) vs. 367 (37%), hazard ratio 0.92 (p = 0.296, 95% CI 0.80 - 1.07)]. However all-cause mortality alone was significantly lower in the carvedilol group than in the placebo group [(116 (12%) vs. 151 (15%), hazard ratio 0.77 (p = 0.03, 95% CI

0.60 – 0.98)]. Carvedilol also reduced cardiovascular mortality and the rate of non-fatal myocardial infarction.

Cardiac Insufficiency Bisoprolol Study (CIBIS) III (97) tested whether beta blockers as initial therapy may be as useful as adding beta blockers to a regimen containing an ACE inhibitor. 1010 patients with mild to moderate HF and an EF ≤ 35%, who were not receiving ACE inhibitor, beta blocker, or ARBs were randomised to open label mono therapy with either bisoprolol (target dose10 mg daily; n = 505) or enalapril (target dose 10 mg twice daily; n = 505) for 6 months, followed by their combination for 6 to 24 months. The combined primary end point was all cause mortality or hospitalisation.

Bisoprolol first treatment was non-inferior to enalapril-first treatment in the intention to treat analysis but not in the pre specified statistical criterion for non-inferiority. There was no difference in terms of safety and efficacy.

Conclusion: NICE (79) recommends that all patients with HF should be offered ACEi and beta blockers licensed for HF, using clinical judgement when deciding which drug to start first. NICE also recommends that licensed beta-blockers should be offered to patients who are older adults, with peripheral vascular disease, erectile dysfunction, diabetes mellitus, interstitial pulmonary disease and chronic obstructive pulmonary disease (COPD) without reversibility.

2.2.7 Aldosterone Antagonist in heart failure

Rationale: Aldosterone has an important role in the pathophysiology of HF. Angiotensin stimulates the release of aldosterone from the adrenal cortex which plays an important role in blood pressure regulation and fluid balance. Aldosterone not only causes reabsorption of sodium and water in to the blood, but also promotes loss of potassium and magnesium, sympathetic activation, parasympathetic inhibition,

myocardial fibrosis, baro receptor dysfunction, vascular damage, and impairs arterial compliance (98).

Many physicians have assumed that inhibition of the RAAS by an ACE inhibitor will suppress the formation of aldosterone, but even when the highest tolerated doses of ACEi are used they may not completely suppress the RAAS and aldosterone production may only be transiently suppressed.

Even if angiotensin 2 production is completely suppressed there is evidence that aldosterone production may not be completely inhibited (99). Also there is evidence to suggest that angiotensin 2 may be produced by non-ACE dependent mechanisms (100). So it was hypothesised that blocking the aldosterone receptors would significantly reduce the risk of death from all causes among patients who had severe HF, regardless of ACEi / ARB usage.(101)

Randomised Aldactone Evaluation Study (RALES) (101) enrolled 1663 patients who had symptomatic severe HF (NYHA 3-4) and left ventricular EF ≤ 35%, who were being treated with an ACE inhibitor, a loop diuretic, and in most cases digoxin. 822 were randomly assigned to receive spironolactone 25 mg daily and 841 to receive placebo. The primary end point was all cause mortality.

There were 386 (46%) deaths in the placebo group and 284 (35%) in the spironolactone group (Relative risk of death 0.70; 95% CI .60 to 0.82; $P < 0.001$). This 30 percent reduction in the risk of death with spironolactone was attributed to both lower risk of death from progressive HF and sudden death from cardiac causes. There was also improvement in symptoms of HF as assessed by the NYHA class. 10% patients had gynecomastia or breast pain with spironolactone as compared to 1% with placebo. This trial was stopped early after a mean follow up of 24 months as interim analysis determined that spironolactone was more efficacious.

Eplerenone Post-Acute Myocardial Infarction Heart Failure and Survival study (EPHESUS) (102)

Following the results of the RALES trial (101), the role of aldosterone blockade in reducing mortality and the rate of hospitalisation among patients with acute myocardial infarction complicated by HF and left ventricular systolic dysfunction (EF <40%) was investigated using eplerenone an aldosterone blocker that selectively blocks the mineralocorticoid receptor and not glucocorticoid, progesterone, or androgen receptors.

3313 patients were randomly assigned to receive eplerenone (25 mg initially titrated to 50 mg per day) and 3319 patients to receive placebo in addition to optimal medical therapy.

During the mean follow up period of 16 months there were 478 (14.5%) deaths in the eplerenone group and 554 (16.7%) in the placebo group (relative risk, 0.85; 95% CI 0.72 to 0.94; p = 0.005). eplerenone also reduced the risk of hospitalisation. The rate of serious hyperkalemia was 5.5% in the eplerenone group and 3.9% in the placebo group (p = 0.002), while the rate of hypokalemia was 8.4% in the eplerenone group and 13.1% in the placebo group (p < 0.001).

Eplerenone in Mild Patients Hospitalisation and Survival Study in Heart Failure (EMPHASIS-HF) trial (103)

This was a randomised, double blind, placebo controlled trial that recruited 2737 patients with NYHA class 2 HF and EF < 35%. Patients who were on recommended therapy were randomised to eplerenone (up to 50 mg daily) or placebo, with a median follow up of 21 months when the trial was stopped because of significant benefit in the eplerenone group. The results showed a 37% reduction in the primary end point of the composite of cardiovascular death or hospitalisation for HF [18.3% vs. 25.9%,

hazard ratio 0.63, (95% CI 0.54 – 0.74), p = <0.001]. There was a 24% reduction in cardiovascular deaths and a 42% reduction in hospitalisation for HF. The main side effect was hyperkalemia with eplerenone (11.8% vs. 7.2%).

These results were consistent with the findings from the RALES trial (in more severe HF), and EPHESUS trial (post myocardial infarction with LV dysfunction) and provided compelling evidence for use of aldosterone blockade in patients with mild HF.

2.2.8 Digoxin in heart failure

Digitalis Investigation group (DIG) (104) recruited patients with left ventricular EF <45%, who were receiving diuretics and ACEi and were in sinus rhythm. They were randomly assigned to digoxin (n=3397) or placebo (n=3403). Patients were followed up for an average of 37 months. Overall mortality was not affected as there were 1181 (34.8%) deaths in the digoxin and 1194 (35.1%) in the placebo group (relative risk, 0.99; 95% CI 0.91 to 1.07; p = 0.08). However there was a trend to reduced deaths attributed to HF (relative risk 0.88: 95% CI 0.77 to 1.01; p = 0.06). Hospitalisation due to HF or other cardiovascular causes was substantially reduced.

NICE (79) recommends use of digoxin for worsening or severe HF due to left ventricular dysfunction despite first and second line treatment for HF.

2.2.9 Role of Ivabradine

Ivabradine is drug that inhibits the $\mathbf{I_f}$ channel in the sinus node. Its only pharmacological effect is to slow the heart rate in patients with sinus rhythm.

Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) (105). This study enrolled 6588 patients in NYHA class 2-4, sinus rhythm with a rate of ≥ 70 / minute, an EF < 35% and, hospitalization in the previous 12 months.

Patients on optimal medical therapy (OMT) were randomized to ivabradine (up-titrated to a maximal dosage of 7.5 mg twice daily) or placebo. The median follow-up was 23 months. The primary composite outcome of cardiovascular death or HF hospitalisation in the Ivabradine group was 793 (24%) vs. 937 (29%) in the placebo group [hazard ratio 0.82 (p = 0.0001 95% CI 0.75 – 0.90)]. There was no difference in all-cause mortality. The absolute risk reduction (ARR) in the primary composite mortality–morbidity endpoint was 4.2%, equating to an NNT (for an average of 23 months to postpone one event) of 24. Ivabradine also improved LV function and quality of life.

Morbidity - mortality evaluation of the I_f inhibitor Ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) trial (106) was a randomised placebo controlled trial that enrolled 10917 patients with coronary artery disease and an EF of less than 40%. Ivabradine did not improve cardiac outcomes but it was well tolerated.

2.2.10 Device therapy in heart failure

Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) (107) This trial hypothesised that in patients with prior myocardial infarction and reduced left ventricular function, the scarred myocardium would trigger malignant ventricular arrhythmias and sudden death.

The MADIT II trial was designed to evaluate the potential survival benefit of a prophylactically implanted defibrillator in patients with prior myocardial infarction and a left ventricular ejection fraction of 30% or less. 1232 patients were recruited and randomly assigned in a 3:2 ratio to receive implantable defibrillator (n=742) or conventional therapy (n=490). The primary end point was all cause mortality.

During an average follow up period of 20 months, there were 105 (14.2%) deaths in the ICD group and 97 (19.8%) in the conventional group. Hazard ratio 0.69 (95% CI, 0.51 to 0.93; p = 0.016). As compared to the conventional therapy, defibrillator therapy was associated with a 31% reduction in the risk of death.

Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (108)

2521 patients with NYHA class 2 or 3 and a left ventricular EF of 35% or less were randomised to conventional therapy for HF (847 patients), conventional therapy plus amiodarone (845 patients), or conventional therapy plus a conservatively programmed shock only, single lead ICD (829 patients). Median follow up was 45.5 months. There were 244 (29%) deaths in the conventional therapy group, 240 (28%) in the amiodarone group, and 182 (22%) in the ICD group. As compared to placebo amiodarone was associated with a similar risk of death (hazard ratio- 1.06, 97.5% CI, 0.86 to 1.30; p = 0.53) and ICD therapy was associated with a decreased risk of death of 23% (hazard ratio 0.77; 97.5% CI, 0.62 to 0.96; p = 0.007) and an absolute reduction of 7% in mortality, equating to an NNT (for 45.5 months to postpone one death) of 14.

Up to 50% patients with systolic HF have an intraventricular conduction defect such as left bundle branch block which results in abnormal electrical depolarisation and dyssynchrony. Prolonged QRS duration results in abnormal intraventricular septal motion, reduced contractility and diastolic filling time and prolonged duration of mitral regurgitation. This places the failing heart under considerable stress and mechanical disadvantage. In many patients this is reversed with complex cardiac pacing known as cardiac resynchronisation therapy (CRT).

Multicentre In Sync Randomised Clinical Evaluation (MIRACLE) (109) 453 patients with moderate to severe symptoms of HF associated with an ejection fraction of ≤ 35% and a QRS interval 130 msec or more were randomised to receive cardiac

resynchronisation (n = 228) or to a control group (n = 225) for six months while conventional therapy was maintained. The primary end point was NYHA functional class, quality of life, and distance walked in six minutes.

As compared with the control group, patients assigned to the cardiac resynchronisation group experienced an improvement in the distance walked in six minutes (+39 vs. +10m, p = 0.005), functional class (p < 0.001), quality of life (-18.0 vs. -9.0 points, p = 0.001) and ejection fraction (+4.6% vs. -0.2%, P < 0.001). Thus there was significant clinical improvement with cardiac resynchronisation for a subgroup of patients with QRS morphology.

Comparison of Medical Therapy, Pacing and Defibrillation in heart failure (COMPANION) (110)

1520 patients with advanced HF (NYHA 3 or 4), with QRS duration of at least 120 msec or more, were assigned in a 1:2:2 ratios to OMT, optimal therapy plus cardiac resynchronisation therapy with pacemaker (CRT-P) or CRT with defibrillator (CRT-D). The primary end point was composite of death and all cause hospitalisation.

The risk of the combined end point of death or hospitalisation for HF was reduced by 34% in the pacemaker group (p < 0.002) and by 40% in the CRT-D group (p < 0.001 for the comparison with the pharmacologic-therapy group). A pacemaker reduced the secondary end point of death from any cause by 24 % (p = 0.059), and a CRT-D reduced the risk by 36% (p = 0.003). In patients with advanced HR, and prolonged QRS interval, CRT decreased the combined risk of death from any cause or first hospitalisation and, when combined with an implantable defibrillator, significantly reduced mortality.

Cardiac Resynchronization- Heart Failure (CARE-HF) Study (111)

Patients with NYHA 3-4, HF symptoms due to LVSD and cardiac dyssynchrony, who were on standard pharmacological therapy, were randomly assigned to receive medical therapy alone or with cardiac resynchronisation. The primary end point was all cause mortality or unplanned hospitalisation.

A total of 813 patients were enrolled and followed up for a mean of 29 months. There were 82 (20%) deaths in the CRT group as compared to 120 (30%) in the medical therapy only group (Hazard ratio 0.64, 95% CI: 0.48 - 0.85, p=0.002). cardiac resynchronisation also reduced the Interventricular mechanical delay, the end systolic index, and the area of the mitral regurgitant jet.

The authors concluded that CRT provided benefits in addition to the standard pharmacologic therapy by improving symptoms, quality of life and reduced complications and risk of death.

NICE (112) in May 2007 recommended cardiac resynchronisation therapy with a pacing device as a treatment option for people with HF who are:-

Currently experiencing NYHA class 3-4 symptoms; are in sinus rhythm with either QRS duration of 150 msec or longer, or with QRS duration of 120- 149 msec on ECG and mechanical dyssynchrony that is confirmed by echocardiography; have an EF of 35% or less and on optimal medical therapy.

Since the publication of the NICE guidance there have been further trials designed to evaluate expanded indications for CRT in HF patients. The major targets for expansion have been advanced HF with narrow QRS complex (<120msec) and patients with mild HF (NYHA class 1 and 2)

The REVERSE (113) and the MADIT-CRT (114) trials used hospitalisation for HF and all cause mortality as primary end points. The REVERSE study included 610 patients with an EF less than of 40%, QRS duration of more than 120 ms, and NYHA class 1 or 2. All patients were implanted with a CRT device with or without ICD and then were randomised to CRT-ON and CRT-OFF. In the European cohort, 19% of patients with CRT-ON had a worsened clinical composite response vs. 34% in CRT-OFF ($p = 0.01$). In the MADIT-CRT study 17.2% of patients in the CRT-D group experienced death or a HF event, whereas 25.3% reached a primary end point in the ICD-only group ($p < 0.001$).

Thus CRT improves quality of life, enhances reverse LV remodelling, and reduces HF hospitalisation regardless of the severity of symptoms. These changes are reflected in the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF 2012 (22). They recommended CRT for NYHA class 3-4 patients in sinus rhythm with a QRS duration of 120ms, LBBB QRS morphology, and EF ≤ 35% with good functional status and expected to survive > 1 year. CRT has also been recommended for NYHA class 2 patients in sinus rhythm on optimal medical therapy with a QRS duration of >130 sec, LBBB QRS morphology, and EF of ≤30% who are expected to survive for > 1 year with good functional status.

2.2.11 Current treatment guidelines for LV systolic dysfunction

According to the ESC HF guidelines (22) patients with systolic HF should receive, a beta blocker, an ACE inhibitor, and in most cases a diuretic which should be started soon after diagnosis. This is because ACEi have a positive remodelling effect on the LV and have been shown to improve survival and reduce rehospitalisation. Beta blockers also lead to a substantial improvement in EF and in certain subsets of patients their anti-ischemic and anti-arrhythmic effects may be beneficial. Angiotensin receptor blockers are recommended in patients unable to tolerate ACEi.

Mineralocorticoid / aldosterone receptor antagonists (spironolactone / eplerenone) are recommended for all patients with persisting symptoms despite treatment with an ACEi and beta blocker to reduce the risk of HF hospitalisation and the risk of premature death.

Ivabradine should be considered for patients who are in sinus rhythm with a resting pulse rate > 70 bpm despite being on an ACEi and a beta blocker. Ivabradine should also be offered to patients who have a high resting pulse rate but are intolerant to beta blockers. This reduces the risk of hospitalisation.

Digoxin may be considered for symptomatic patients in sinus rhythm intolerant of beta blockers and receiving ACE inhibitor and mineralocorticoid / aldosterone receptor antagonists.

2.3 Literature review of heart failure with preserved ejection fraction (HFpEF)

The EF is important not only for its prognostic importance but most clinical trials have used it for patient selection. As a result the vast majority of the major trials have selected patients with EF less than 35%. This has immensely benefited patients with HF and reduced EF (HF-REF); effective evidence exists for reducing both morbidity and mortality.

An EF of > 50% is generally considered to be normal (22). Some of the trials have enrolled HF patients with an EF of more than 40-45% and no other cardiac abnormality especially of the systolic function. To describe this cohort of patients who have clinical signs and symptoms of HF but preserved or mildly reduced ejection fraction the term heart failure with preserved ejection fraction (HFpEF) was created.

Assuming that patients with LV systolic dysfunction and HFpEF have the same underlying pathophysiological process, attempts have been made to extrapolate evidence from the HF trials with LV systolic dysfunction to the HFpEF patients.

This has led to the designing of few randomised trials with ACEi, ARBs and beta blockers in patients with HFpEF.

Candesartan in Heart Failure: Assessment of reduction in Mortality and Morbidity (CHARM) – Preserved (115) trial enrolled 3023 patients with NYHA class 2-4 and an EF of >40%. Primary outcome was cardiovascular death or admission to hospital for CHF with a median follow up of 36.6 months. There was no difference in the patients experiencing the primary outcome with 333 (22%) in the candesartan group and 366 (24%) in the placebo group [hazard ratio 0.89 (p = 0.118, 95% CI .077 – 1.03)]. It only had moderate effect in reducing hospitalisation.

The perindopril in elderly people with chronic heart failure (PEP-CHF) study (116) This trial randomized 850 HF patients who were at least 70 years of age, EF of 45% or more, and evidence of diastolic dysfunction on echocardiography. The primary endpoint was a composite of all-cause mortality and HF related hospitalisation. Patients were followed up for minimum of one year and median follow up was 2.1 years. Poor recruitment, large numbers of withdrawals and the open label prescription of ACEi reduced the power of the study. There were 107 deaths in the perindopril group vs. 100 in the placebo group [hazard ratio = 0.92. (p = 0.545, 95% CI 0.70 – 1.21)]. Perindopril was associated with a reduction in heart failure hospitalisation as well as an improvement in symptoms and 6 minute walk test. However uncertainty remains about these conclusions as the study had insufficient power for its primary end point.

Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I - PRESERVE) (117) was the third major trial to examine the role of the renin-angiotensin-aldosterone system in HFpEF patients. This trial randomised 4128 patients aged ≥ 60 years with NYHA class 2-4, and an EF of ≥45% to receive Irbesartan or placebo. The primary end point was all cause mortality and patients

were followed up for 4 years. 742 (36%) patients with irbesartan and 763 (37%) patients in the placebo group reached the primary end point [hazard ratio 0.95 (p = 0.35, CI (0.86 – 1.05)].

The SENIORS Study (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) (118) was the first major trial with beta blockers in patients with HFpEF. It randomised 2128 HF patients, 70 years or older with a history of HF. 1359 (64%) had impaired EF≤35% and 752 (36%) had an EF > 35%. There was no difference in the effect of Nebivolol vs. placebo between the reduced (EF ≤ 35%) [HR 0.86; 95%CI: 0.72-1.04, p=0.117) and preserved (EF> 35%) [HR 0.81; 95% CI: 0.63-1.04, p=0.720) groups.

These trials have failed to show any significant benefit an ACEi / ARB or beta blockers. The present ESC guidelines (22) acknowledge that at present there are no proven treatments for HFpEF patients. The main emphasis of managing these patients is to use diuretics for HF symptoms, achieve adequate control of blood pressure and manage myocardial ischemia appropriately.

2.4 Prognosis in heart failure

Cardiovascular diseases are a leading cause of death in the population. Over the last few decades with improvement in diet, cholesterol, blood pressure control and early diagnosis and management of coronary heart disease there has been a decline in overall IHD mortality (119). Equally survival after the onset of HF has improved in recent decades. This improvement is likely a consequence of changes in relative contribution of hypertension, coronary heart disease, valve disease and also the increasing use of evidence based pharmacologic therapies (73). However the death rate remains high as ≈ 50% of people diagnosed with HF will die within 5 years. (120)

2.4.1 Prognosis in LVSD

The prevalence of HF with LVSD is high and continues to increase. This is because ischemic heart disease, the major precursor of LVSD, is being managed more efficiently and effectively leading to an ageing population with a high prevalence of HF (121). In a population based study Redfield et al (122) found the prevalence of HF to be 2.2%, which increased from 0.7% in persons aged 45 years to 8.4% in those aged 75 and over. Along with the increasing prevalence the incidence is also higher in the older population (123).

Heart failure mortality is higher than that associated with the most other chronic conditions. One study comparing survival of heart failure and cancer patients (124) showed that , with the exception of the lung cancer, HF carried the poorest 5 year survival rate (approximately 25% for both sexes) compared to breast, large bowel, and ovarian cancer. In the Framingham heart study (125) the overall 1 year and 5 year survival rates for men were 57% and 25% and 64% and 38% for women. By comparison, 5 year survival for all cancers among men and women in the US during the same period was approximately 50%.

Even in the population based study reports HF continues to have poor survival. In the ECHOES (Echocardiographic Heart of England Screening Study) (126) the 5 year survival rate in patients with HF and LVSD was 53%. In another community based study Danielle et al (127) found a 5 year survival rate of 45% in HF patients with reduced ejection fraction. In a population based study of incident (new) HF by Cowie et al (128) survival was found to be 81% at one month, 75% at three months, 70% at six months, 62% at 12 months, and 57% at 18 months. Thus one third of the new HF patients had died at one year.

Patients who have LVSD and are on optimal medical therapy (an ACEi or an ARB, plus a beta blocker) continue to have poor prognosis. Allen-LaPointe and colleagues

(129) evaluated the survival pattern in patients who were on long term beta blockers and ACEi / ARBs for LVSD. After a mean follow up of 4.9 years 46.5% of the patients had died. Interestingly in this study they found that only beta blocker use in the long term provided survival benefit.

Survival in the elderly population is equally dismal. In a study of elderly (>75 years) patients, the first year mortality was 28% (130) Thus in spite of the advances made in treating patients with LVSD prognosis remains poor.

2.4.2 Prognosis in HFpEF

There have been conflicting reports of mortality in patients with HFpEF. Initial studies of HFpEF epidemiology showed that the survival was similar to the LVSD patients. In a population based study Bhatia et al (131) found that the mortality rate in patients with reduced ejection was similar to the preserved ejection fraction patients. Owan and colleagues (132) studied all consecutive patients hospitalised with decompensated HF from 1987 through 2001. This study showed that there was no improvement in the HFpEF mortality trends over each successive 4 year time period.

However, other studies have suggested that mortality in the HFpEF group was better than the LVSD patients. The Euro Heart Failure Survey (133) followed up patients for 12 weeks. All-cause mortality although high in both groups was higher in patients with LVSD than those without (12% vs. 10% OR 1.35, 95% CI: 1.13-1.62).

In a literature based meta analysis Somaratne et al (134) reviewed 24501 patients with HFpEF and LVSD. After a mean follow up of 47 months mortality in the HFpEF group was 32% compared to 40% in the LVSD group.

A more recent meta analysis [Meta-analysis Global Group in Chronic Heart Failure (MAGGIC)] by Doughty et al (135) compared survival in patients with HFpEF and those with LVSD using individual patient data. They included 31 studies comprising

41972 patients. HFpEF was present in 10347 patients and LVSD in 31625. Patients with HFpEF had a lower mortality than the LVSD group [hazard ratio 0.68, 95 CI: 0.64, 0.71). In an adjusted Cox proportional hazards model, patients with HFpEF had a lower risk of cardiovascular death than those with the LVSD [hazard ratio 0.55 (95% CI: 0.49, 0.61)]

Despite the results of the studies mortality in both HFpEF and LVSD patients continues to be high.

Chapter 3

Heart Failure: Nationally and in the North East

3.1 The North East region

The North East of England is a mixed urban and rural region extending from the Scottish border to Yorkshire and from the Pennine Hills to the North Sea. It is the smallest of the English regions in both area and population. As per the office of the national statistics, 2,607,000 people live in the north east region (136).

Darlington is one of the five unitary authorities, along with Hartlepool, Middlesbrough, Redcar & Cleveland, and Stockton on Tees. It has a population of more than 100,000.

Life expectancy in the North East is lower than the national average, reflecting higher levels of illness and of smoking. In county Durham, life expectancy is 76.9 years for men and 80.7 years for women, compared with England as a whole (78.3 and 82.3 years respectively). In Darlington life expectancy at birth is 76.6 years for men and 80.8 years for women, average for the north east region (137).

In common with the national picture, Darlington has an ageing population. There are increasing numbers of elderly, fewer young people, with a fall in the number of working age adults (138). This changing demography will present a considerable challenge for the region.

A detailed report on demographic change in the region (139) forecasts the population structure up to 2041, and states that population change in the North East of England (due to outward migration, better life expectancy and falling fertility rates) is likely to be more pronounced than any other region in England. The implications of the ageing population are likely to be felt in almost every aspect of life.

3.2 The burden of coronary heart disease:

Coronary heart disease (CHD), stroke and related diseases are responsible for over one third of all deaths and a significant burden of ill health in the population (140).

In the last ten years death rates in the UK have been falling. Despite the decline in death rates from cardiovascular disease in the UK, rates are still high compared to other Western European countries, at 350 per 100,000 CHD deaths in men in 2003 (140).

Death rates from CHD are highest in Scotland and the North of England, lowest in the south of England (140). The North East has the highest premature death rate (158/100,000 in the under 75 years) from circulatory disease, in the country. This is significantly higher than that of England as a whole (128/100,000) and than the other government office regions (139).

Within the region there are significant variations. Middlesbrough, Easington, and Wansbeck have significantly higher mortality rates from circulatory disease than the North East region as a whole. North Tyneside, Berwick upon Tweed, Castel, Morpeth and Tyndale have significantly lower mortality rates. For Darlington the age standardised death rates from CHD for men and women under the age of 75 years for years 2006/08 were 73.54/100,000, and 21.90/100,000 respectively (140).

The overall health of the populations of County Durham and Darlington is poor compared with the national picture and inequalities in health remain persistent and pervasive

The standardised mortality ratio (SMR) for all causes of death for County Durham is 114 and for Darlington 111 (significantly worse than England). The SMR for all circulatory disease in county Durham was 117 and in Darlington 113 (2004-2006), significantly worse than England (141).

In Darlington, over the last ten years, the death rate from all causes has gradually declined for both men and women, but remains worse than the England average.

Early deaths from heart disease and stroke have decreased markedly, especially over the last four years (142).

3.3 Heart failure

Heart failure occurs in around 1% of the adult population rising to 7% in those aged over 75 years and 15% for those aged 85 and over (143). Most cases of HF are due to coronary heart disease (approximately 70%) and most cases have or have had hypertension. Although there has been an overall decline in mortality from coronary heart disease (CHD), the number of patients with HF is increasing (144). This is due to an ageing population combined with improved survival rates after a heart attack in patients with left ventricular dysfunction. The majority of patients admitted to hospital are over 60 and fall within two age groups: 60–74 (24.6%) and over 75 (68.3%) (145).

HF has a significant impact on patient outcomes. Survival rates are worse than for breast and prostate cancer, with annual mortality ranging from 10% to 50% depending on severity, and a high risk of sudden death. Newly diagnosed patients have a 40% risk of dying within a year of diagnosis (128). Patients with HF experience a poor quality of life, with over a third experiencing severe and prolonged depressive illness.

Providing services to patients with HF costs the NHS an estimated £625 million per year (145). HF places a significant demand on hospital facilities and resources through emergency admissions and readmissions. Almost 90% of HF admissions are emergency admissions (146), and it accounts for 5% of all medical admissions. The readmission rate for HF has been estimated to be as high as 50% over 3 months (147-149).

There is good evidence that appropriate diagnosis, treatment and ongoing support can improve quality of life and help reduce admissions and readmissions, morbidity and mortality. The National Service Framework (NSF) for Coronary Heart Disease

(CHD) (150) emphasises the need to develop a systematic approach to the diagnosis, investigation, treatment and ongoing support of people with heart failure throughout the NHS.

In a national review of CHD services, the Healthcare Commission found that despite significant progress in implementing the NSF, progress in meeting the HF standards had been slow (151).

A subsequent review of HF services in 2007 (152), showed that substantial progress had been made in the two years after the NSF review. However, there was still variation across the country in relation to the confirmation of diagnosis, access to evidence based treatment and HF specialist staff.

The second piece of work (153) focused on the inpatient admission routes and used patients with HF to examine access to diagnostics and key treatment. The results indicated that many patients admitted to acute hospitals in England, Wales and Northern Ireland are not managed fully in accordance with international evidence-based guidelines. Only a minority of patients with HF are seen, or followed up, by a specialist service. Whilst most trusts (86.5%) have a lead consultant for the care of patients with HF, only 22.3% of patients admitted to hospital with HF were referred to the lead clinician or a cardiologist (145).

Access to specialist HF teams was also shown to be extremely variable with averages for trusts varying from 0% to 74%. There are also differences in access to evidence-based clinical treatment between different groups of patients. Women appear to be less well managed against recommended guidelines and are less likely to be prescribed anti-failure medication, except diuretics, on discharge. This may reflect differences in age (women are older) and the greater prevalence of HF with a preserved ejection fraction, for which guidelines provide little advice on treatment (145).

2008-2009 QOF data for Darlington PCT has 846 patients on the HF register from a population of 105402 giving a prevalence rate of 0.8%. Since April 2006 there were 218 patients with echo or specialist proven diagnosis and 397 of the eligible 430 (92.3%) on an ACE inhibitor (154).

3.4 Access to Health care

NHS Darlington is one of the 12 primary care trusts (PCTs) which are managed by the NHS Northeast - the Strategic Health Authority for the North East. Working in partnership with NHS County Durham, NHS Darlington is responsible for commissioning health service on behalf of around 600,000 people living in County Durham and Darlington. Around 100,000 of these live in Darlington.

There are 11 GP practices in Darlington providing primary care services. Darlington Memorial Hospital at Darlington provides secondary level care.

Chapter 4

Models for providing heart failure service

Traditionally HF patients have been managed in the community by general practitioners. In the UK , where the general practitioner (GP) act as the gate keeper to health care, not all patients are referred on to specialist, or for secondary care assessment (155).

Previous studies have highlighted the fact that in the community less than 50% patients have HF correctly diagnosed, as compared to a standard of specialist clinical assessment based on a clinical scoring system (156). In another study only 53% of the patients receiving loop diuretics had left ventricular systolic dysfunction on their echocardiogram. This was more so in female patients (157). These studies have highlighted that left ventricular systolic dysfunction is difficult to diagnose solely on the basis of signs and symptoms in the community, resulting in frequent misdiagnosis and inappropriate management (158). In the National Service Framework (NSF) for CHD published in 2000, it stated that “doctors should arrange for people with suspected HF appropriate investigations (electrocardiography, echocardiography) to confirm or refute the diagnosis of HF”. The authors detail various service models, whereby echocardiography by trained operators with competent interpretation could be made available to suspected HF patients by one of the following means:

- Open access echocardiography from primary care
- Specialist heart failure clinic
- Cardiology out- patients

4.1 Open access echocardiography

The simplest confirmation of left ventricular systolic dysfunction is provided by the echocardiogram, which remains the gold standard. Previously access to

echocardiography had not been directly available to the general practitioners. With the advent of open access echocardiography (OAE), defined as echocardiography requested by a GP without prior clinical assessment by a cardiologist (159), more and more centres have been providing this service to their local GPs (160). The rationale is that HF is a common condition, especially affecting the elderly, carrying a poor prognosis but which can be effectively treated with ACEi, reducing mortality by 23% (161). The estimated annual economic burden of treating HF patients has been estimated at £360 million on hospital services (162). Timely diagnosis and management of HF has the potential to reduce the burden on hospital services.

Francis et al (9) reviewed 259 OAE referrals with suspected HF over five months. Of the 119 patients being treated for suspected HF, only 26% (31/119) of these had serious left ventricular systolic dysfunction. Twelve percent were inappropriate referrals and 69% had their medications changed. This service was not truly an OAE service as the echocardiograms were reported by a cardiologist who also recommended further management regarding medications and other investigations as appropriate. How many of the recommendations made were implemented was not known. Also only 17% (93 / 550) of the GPs took part in the referral process suggesting low uptake for the service.

In Darlington, Murphy and colleagues (163) reported an OAE service made available to five GP practices covering a population of 48,000. In 23 months 250 patients were referred. Forty nine (20%) were found to have significant left ventricular systolic dysfunction (EF < 40%). Twenty (8%) were found to have significant valve disease. Echo reports were sent back to the GPs with no specific recommendations regarding further management other than current NICE guidelines.

Case records of these patients were reviewed at the practices two months after the OAE. ACE inhibitor treatment had been started in 78% (38 / 49) of patient with

significant left ventricular systolic dysfunction. Of the patients with haemodynamically significant valvular disease 14 of the 20 had been referred to the hospital for further cardiology opinion. Thus appropriate management decision had been reached in the majority of the patients by providing GPs with the echo report and broad management guidelines (as published by NICE).

Similar UK experience was reported from Newport and Edinburgh in a systemic review of OAE observational studies reported by Khunti (10).

Open access services are less well established in continental Europe (164). An open access echocardiography service was started in the Netherlands in 2002. They looked at 625 consecutive patients from Dec 2002 to March 2007. GPs could refer patients with dyspnoea, heart murmurs or peripheral oedema. Results of the echo were returned to the GPs with recommendation on management of the patients. OAE was popular with GPs as 81% utilised the service and the majority of the patients were referred appropriately.

Thus it seems that OAE is well received by the general practitioners and utilised in an appropriate way. Also initial fears that GPs would use the service indiscriminately and cause an unmanageable burden on the echocardiographic services (165), have not proved true (166).

For the future OAE will continue to be available to the GPs in various forms as it has proved to be an efficient way of investigating patients with suspected HF, and also it reduces the burden on the outpatient service in hospital.

However, as shown in Chapter 3, HF management has become increasingly complex. In a qualitative study published in 2003, Fuat et al explored barriers to the diagnosis and management of HF in primary care. Clinical uncertainty and the complexity of

care were major issues and they have supported the establishment of specialist heart failure services.

4.2 Variation among HF clinics

There is lack of uniformity in the published data to describe which patients are offered treatment and follow up in the HF clinics. Also there is great variability in the setup of these clinics. Patients are either referred from primary care or they are followed up in the community after discharge from the hospital. The aims of and the interventions provided by these clinics and programmes are also quite variable. In some clinics patients are not only investigated and started on evidence based management but also followed up by a nurse to titrate up their medication either in the community or at the hospital. Others provide information, education and self care for the HF patients. Most of the studies aimed to assess the impact of these interventions on hospital readmissions but very few reported impact on survival.

Broadly these can be categorised as nurse led disease management programmes, primarily community based intervention programmes, and the specialist HF clinics in the hospital.

4.2.1 Nurse led intervention programmes

One of the earliest studies in 1997 by Rich et al (167) examined the effect of nurse led multidisciplinary intervention in the community on patients 70 years or more, discharged from the hospital after being treated for congestive HF. Primary outcome for survival at 90 days without admission was achieved in 91 of 142 patients in the treatment group as compared with 75 of the 140 patients in the control group who received conventional care ($p = 0.09$). Also, the number of readmissions in the intervention group was lower than that of the control group (risk ratio - 0.56; $p = 0.02$).

In another study Fonarow and colleagues (168) over a 3 year period provided adjustment to medications and intensive patient education to 214 patients with

advanced HF (NYHA 3-4), accepted for heart transplant after discharge. Comprehensive HF management led to improved functional status and an 85% decrease in the hospital admission rate for patients with advanced HF.

In another study using a MULTIFIT model that emphasises the development of a cognitive, executive, and organisational infrastructure to promote optimal chronic disease management, West et al (169) evaluated a physician supervised, nurse mediated, home based system for HF, implementing clinical guidelines for pharmacologic and dietary therapy. Fifty one patients with a clinical diagnosis of HF were followed for 138 days by nurse managers for promotion of optimal doses of ACE inhibitor or isosorbide dinatrate / hydralazine therapy, promotion of daily sodium intake of < 2 g; and surveillance for symptoms, signs, and laboratory evidence of worsening HF. Compared with the 6 month before enrolment and normalised for variable follow up, the frequency of general medical and cardiology visits declined by 23% and 31% respectively (both $p < 0.03$). Hospitalisation rates for HF and all causes declined by 87% and 74% respectively ($p = 0.001$), compared to a year before.

In another study Ekman et al (170) examined the feasibility of a nurse monitored, out - patient care programme for patients hospitalised with chronic HF. Of the 158 patients who met the eligibility criteria 79 patients were randomised to structured care. There was no difference between the two groups regarding the number of hospitalisations and the days spent in the hospital. This study did not provide evidence of benefit of the nurse led HF programme with advanced heart failure. In another study Strömberg and colleagues (171) randomised 106 patients to either follow up at the nurse led HF clinic or to usual care. After 12 months there were fewer events (death or admission) in the intervention group compared to the control group (29 vs. 40, $p=0.03$). Overall most disease management programmes found

beneficial effects on patient readmission to hospital and some showed improved survival (171-177)

4.3 Specialist Heart Failure Clinics

Although open access echocardiography service can be provided to the primary care physicians, echocardiography can be difficult to do and even more difficult to interpret, and primary care physicians may have difficulty in understanding the technical reports. Even when OAE is provided, HF patients may not be optimally treated as per clinical guidelines (7). For some patients with suspected heart failure a shared plan between the cardiologist and the GP may be warranted (160). Sensing the need for an integrated diagnostic and therapeutic service it was proposed to set up multidisciplinary HF clinics (178).This has led to the development of specialist HF clinics in secondary care hospitals.

The set up and design of the specialist HF clinics reported in the literature varies widely. Some clinics accept patients who have been discharged from hospital (167, 171) whereas in other patients are referred by GPs or other hospital physicians.

One of the earliest reports on specialist HF clinics was by Fox and colleagues (155). They established a “walk in” HF clinic in 1996 and reported the results for the first 15 months. The clinic ran from 1200 to 1600 hrs each weekday. A doctor took the clinical history, examined the patient and then performed echocardiography. Patients had blood samples taken and were informed of the clinical diagnosis, management and follow up plans. An ACEi was prescribed in patients diagnosed with HF. Three hundred and eighty three patients were seen in the clinic with a median age of 75 years, and 44% were males. Though 101 (26%) were diagnosed as having definite HF, only 78 had systolic dysfunction. Six had primary valve disease and 17 had normal systolic function. There was very little further follow up of these patients by the clinic after diagnosis.

In Sweden HF clinics are run by HF nurses. In a descriptive survey of HF services in Sweden 66% (57/86) of hospitals had nurse led HF clinics (175). The clinics provide patient education, telephone counselling and drug titration apart from follow up after hospitalisation. In 40 of the 57 hospitals nurses also made protocol led changes to medications of these patients. These nurse led HF clinics only see patients diagnosed and treated for HF from the hospital. There is no mention about the role of the cardiologist in clinic.

A HF clinic based upon an integrated approach to diagnosis and therapeutic management of HF patients was reported from Copenhagen by Galatius et al (179). The service is provided by physicians with training in cardiology, who take the history, conduct the physical examination, and perform transthoracic echocardiography in the diagnostic unit. This is an open access service to patients with suspected HF from primary and secondary care. Patients confirmed as having LVSD by echocardiography (EF<45%) are referred to the therapeutic clinic for optimisation of medical therapy. Over 21 months 460 patients were seen in the clinic. Three hundred and twenty patients (70%) were found to have clinical evidence of HF. Of these 283 (88%) had LVSD. LVSD patients had a mean age of 73 years, and 70% were male. At base line 55% patients were on ACEi therapy and 29% were taking beta-blockers. The authors observed a 23% decline of HF related hospital admissions during the 21 months of study period.

This study provides a description of the HF clinic but no information is given of the impact of the HF clinic on the increase in the number of prescription for ACEi therapy or beta-blockers. Also there are no published data on the outcome of these patients.

Another descriptive study of the specialist HF clinic in Birmingham is by Shah et al (180). GPs referred patients if they clinically suspected HF. This was a weekly diagnostic clinic but later on patients were also followed up for treatment optimisation.

Over eight years 963 patients were seen. All patients had their history taken, and physical examination, ECG, chest X-ray and echocardiography performed. Only 30% of the patients were diagnosed with LVSD (EF < 55%). At the time of clinic review only 21% patients were taking an ACEi and 10% were on a beta blocker. A further 16% were initiated on an ACEi and then up-titrated, 15% on a beta blocker after being diagnosed with LVSD.

Azevedo and colleagues (181) assessed 339 patients discharged after being admitted for decompensated HF. Patients were either seen in the HF clinic (n = 157) or discharged back to their primary care physicians (n = 182), in non random fashion. The HF clinic was run by cardiology specialists. Patients in the HF clinic group were older (69 yrs vs. 65 yrs), and had more males (60% vs. 45%) than the usual care group whereas there were more patients with atrial fibrillation in the usual care group (46% vs. 30%). Patients seen in the HF clinic had their medications adjusted and 93% were on an ACE inhibitor although only 37% received a beta blocker. After a mean follow up of 373 ± 196 days there were significantly fewer deaths in the HF clinic group 39 (25%) as compared to 63 (35%) in the GP group (adjusted hazard ratio 0.52; 95% CI 0.34 – 0.81).

This study provided some data on the long term outcome of HF patients discharged after hospital. Although a high proportion of the patients seen in the HF clinic were on an ACEi, very little is known about the management of the patients discharged back to the primary care other than the mortality data. Also the study was not randomised which limits any meaningful conclusions about its applicability to the wider patient population.

Thus there is marked variability in the set up, design, referral criteria, and staffing of and intervention provided by the specialist HF clinics reported in the literature.

4.4 History of Heart Failure clinic in Darlington

The one-stop diagnostic HF clinic was established in January 2002 as a joint venture between Darlington PCT and South Durham NHS Trust, and the British Heart Foundation which funded a specialist nurse. Whilst there have been other reports of rapid access clinics in the UK (155, 180, 182, 183), this was probably the first GP specialist led diagnostic and management clinic.

The one-stop HF clinic is run by a GP specialist and a HF nurse. This service is based upon local HF guidelines and protocols. The weekly clinic runs in parallel to a consultant cardiologist's clinic and is sited within the general medical outpatient department of Darlington Memorial Hospital. The clinic template allows for six new and five follow up patients to be seen.

4.4.1 Rational for one stop diagnostic heart failure clinic

(This has been discussed in detail by Dr A Fuat in his PhD thesis "The Diagnosis and Management of heart failure across primary and secondary care", 2006 Durham University) (184). Much of the data in this section is reproduced from Dr Fuat's thesis work with his consent.

Even when facilities for the accurate diagnosis of HF exist (open-access or consultant screened echocardiography) the initiation of evidence based treatment remains an issue in primary care (7, 185, 186). For low rates of usage of ACEi, beta-blockers and spironolactone, the plausible causes can be related to wide-ranging factors, e.g., difficulties in interpretation of echocardiography results, lack of awareness of treatment regimens, concerns with possible side effects, and workload pressures (7, 187). Moreover, target doses of these agents are often not achieved (185, 188-191). The rate of "over-diagnosis" remains around 40% (192, 193), with less than 40% of patients receiving an ACEi (188).

Fuat's study pointed out that there needs to be equity of access for patients with heart failure to the most effective and cost-effective treatment available. General Practitioners should be in a position to be able to offer or arrange optimal management. Evidence based guidelines (194-197) have established the need for an accurate diagnosis of HF, essentially with echocardiography, but doubts remain about the effective use of echocardiography services, and many secondary care clinicians favour referral to hospital (11, 198).

There is increasing pressure within the NHS towards the implementation of evidence-based clinical guidelines (194-197). PCTs need to collaborate with secondary care for the provision of services. The advent of clinical governance is a further imperative towards streamlining the provision of care in this field.

The National Service Framework for Coronary Heart Disease (NSF for CHD) (178) recommendations include echocardiography for all patients with suspected heart failure, the development of a consistent and systematic approach to identify patients with HF or at high risk of developing it, and delivery of appropriate care to those diagnosed with HF, together with regular review.

Hence, possible factors for change in the management of HF due to LVSD include the extensive evidence base and the various national guidelines (197, 199, 200). In addition to the NSF for CHD (201), the new General Medical Services contract (202) and the CHD and Primary Care Collaborative (including MINAP, the Myocardial Infarction National Audit Project) are policy-based strategies that are helping to close the evidence-treatment gap.

The NSF for CHD proposes development of newer models of care for diagnosis and management of LVSD (201). Coinciding with a government call for more GPs with a specialist interest, a GP specialist led one-stop diagnostic clinic was established, to

enable expedient diagnosis and appropriate initiation of evidence-based therapy if LVSD is confirmed.

The primary aim of the service was to identify patients with LVSD and offer evidence based treatment. Given the debate concerning the existence of HFpEF, the lack of accepted diagnostic criteria, and the absence of treatments, the clinicians involved generally avoided making the diagnosis of HFpEF.

4.4.2 Aims of the heart failure clinic service:

The aims of the heart failure diagnosis clinic are:

- To provide rapid access to diagnostic facilities for patients with HF symptoms
- To provide a consistent approach to the diagnosis of HF
- To maximise evidence-based treatment for patients with confirmed LVSD.

4.5 Clinic structure

4.5.1 Referral criteria

Patients access the clinic via:

- GP referral for patients with suspected HF
- GP or HF specialist nurse may refer patients with confirmed HF who require symptomatic assessment
- Referral from other physicians for assessing patient's symptoms.

For GP referrals, there is a standard one-page referral form. Referral forms for the HF diagnostic clinic are received and processed by the central appointments patient office; appointment letters are then sent via post. All patients are sent an information leaflet regarding the diagnostic clinic and which has been produced by the HF team. The GP is asked to undertake baseline blood tests, ECG and chest X-ray. At the clinic

all patients have clinical assessment, relevant blood tests, chest X-ray (if not done by the GP), ECG, echocardiography and selected patients undergo pulmonary function tests. British Society of Echocardiography accredited cardiac physiologists perform the echocardiogram. Left ventricular function is assessed by “eyeball” assessment, with Simpson’s rule and wall motion index measurements when possible. The patient brings the report back to the clinic in a sealed envelope. The cardio-respiratory laboratory provides six dedicated echocardiography slots for use by the clinic.

Patients in whom HF or LVSD is not confirmed are discharged back to the GP or, if necessary, to another physician (e.g. respiratory physician or general cardiologist). If LVSD is confirmed, a management plan is formulated which includes patient education and initiation of evidence-based treatment.

4.6 Staffing of the clinic

4.6.1 Role of the GP specialist in cardiology

The GP specialist in cardiology provides the main clinical leadership to the HF team.

The role of the GP specialist includes:

- Clinical assessment, and organise baseline investigations (blood test, chest X-ray, ECG and echocardiogram) of all referred patients
- Establish a working diagnosis, and formulate a management plan for patients with confirmed LVSD.
- Refer to other specialist services as appropriate.
- Decision to discharge or follow up patients in the clinic

4.6.2 Role of the specialist heart failure and auxiliary nurse

The specialist nurses see patients in clinic after they have received the appropriate diagnostic tests and HF is confirmed by the medical practitioner at the clinic.

The specialist and auxiliary nurses provide the link between the diagnosing clinician, the patient and the organisation of community based care. They collate the results, counsel the patients and carers and ensure follow-up in the clinic, GP or domiciliary setting. They are also responsible for effecting the day-to-day management of the HF patient in relation to specific items such as daily weighing to evaluate fluid overload and exercise regimens.

4.6.3 Role of the consultant cardiologist

The main roles include:

- Overall clinical responsibility for patient care and
- Advice to GP specialist and specialist nurses

4.6.4 Heart failure review clinic

Workload pressure of follow up patients, especially those needing beta-blocker titration, led to the development of a nurse led review clinic. The review clinic provides an integrated and consistent approach to the optimisation of medications. This nurse led review clinic runs parallel the HF clinic, who can seek advice from a clinician if need be.

Chapter 5

Methodology

5.1 Introduction

The interest for the present study arose from the work I had previously undertaken for a project that had involved collection of data from the HF clinic at Darlington Memorial Hospital during 2008.

Patients were referred to this clinic if their doctor suspected HF. At the clinic, all patients had a clinical assessment, relevant blood tests, a chest X-ray, an electrocardiogram (ECG), and an echocardiogram. A British Society of Echocardiography accredited cardiac physiologist performed the echocardiogram. Left ventricular function was assessed by “eyeball” assessment, with Simpson’s rule and wall motion index measurement when possible.

Based on the results of the echocardiogram and other investigations, patients were given a diagnosis of HF due to left ventricular systolic dysfunction (LVSD) or “No HF”. Patients who were confirmed as having LVSD were then started on evidence-based treatment and followed up in the HF clinic until they were titrated to the maximal tolerated doses of the medications. Patients in whom LVSD was not confirmed were discharged back to the care of their GPs, or if necessary, to another physician.

This study had looked at the patients who had been referred to the clinic from its inception in Jan 2002 up to Dec 2007. Data were collected on the total number of patients seen in the clinic in these six years; how many had been diagnosed with LVSD on the basis of an echocardiogram; what proportion were on evidence based treatment (ACEi, beta blockers); and how many had died in this group.

Of the 1041 new patients who were seen in the HF clinic from Jan 2002-Dec 2007, only 270 had been diagnosed as having HF based on reduced ejection fraction. Seven hundred and seventy one patients were diagnosed not to have HF based on

the echocardiogram result and were discharged back to their own doctors or referred to other specialists to find other cause for their breathlessness.

I was interested to know what had happened to the 771 patients suspected to have HF by their doctors, but where the echocardiogram result had shown them to have normal ejection fraction. How many of those discharged might have had HF with preserved ejection fraction (HFpEF)? Was the HFpEF group different from the LVSD group in terms of age, gender, co morbidities, management, hospitalisation and outcome? Did the HFpEF group fare differently than the LVSD group? And what was the cause of death in patients of both groups; did they die of HF or some other cause?

The present study was therefore designed as a more comprehensive follow up of the whole cohort referred to HF clinic. In addition to the long-term outcome of patients diagnosed with HF due to LVSD, I also categorised those with preserved systolic function (in to HFpEF and non-HF) and obtained long term follow up of the whole cohort.

5.2 Development of the study protocol

Patients who attended the HF clinic from Jan 2002 to Dec 2007 were identified from the hospital database electronic system. From this a master list was prepared. The master list was initially divided into two groups of LVSD and “others”. The “others” list was separated into HFpEF and non HF groups (the operational definitions for these groups will be discussed later). These three groups were each given a unique alphanumeric code. The unique alphanumeric code began with the group identifier “LVSD”, “HFpEF”, and “OT” for each group. The beginning of the unique number code was “2066” for the LVSD and HFpEF and the non HF or “other” group was identified using “OT” followed by number “2067”.

The unique alphanumeric code for the study patients enabled the separation of the master list and the lists based on the unique study codes, which were used for data collection. The master list linking patients to the unique study code was in an electronic format, kept on an encrypted and password protected Trust computer with limited access in the research office. This study was conducted in two phases.

In an addition to the initial protocol we added Phase 3 to the study whilst completing the phase 1. This was for obtaining data from the medical research information service (MRIS). Details for this are presented below. For Phase 3 we obtained ethical committee approval separately.

5.2.1 Phase 1 (Hospital Phase)

The case notes of all the patients who were referred to the one stop diagnostic HF clinic during the period (Jan 2002-Dec 2007) were reviewed, and subjects who were clinically found to have signs and symptoms of HF were identified. This cohort of patients were further studied and categorised, based on echocardiography results into two groups

- Patients having impaired systolic contraction and thus having a reduced ejection fraction of their left ventricle (LVSD)
- Patients with normal systolic function and thus having preserved ejection fraction (HFpEF).

The case notes of these two groups of patients were studied in detail regarding their initial presentation, clinical examination, electrocardiogram, and chest X - ray report. These were then correlated with the findings and the report of the echocardiogram.

Once the diagnosis of LVSD was established, the uptake of evidence based medications (beta blockers, ACEis, and spironolactone), and their titration up to the

target dose at subsequent follow up visits in the HF clinic was ascertained for each patient.

5.2.2 Phase 2 (General practice phase)

This part of the study was conducted at the GP surgery of the identified patients. This involved accessing patient data held at the practice to answer the following questions:

- Was HF treatment continued after discharge from the hospital clinic?
- For how long were the HF medications continued?
- Why and by whom were medications changed or discontinued? (Hospital /GP)
- Current medications and their doses
- If the patients were admitted to the hospital, then for how long and how many times?
- Any other co morbidities developed since discharge from the HF clinic
- Vital status and cause of mortality?

5.2.3 Phase 3 (Medical Research Information Service phase)

At the end of Phase 1 of the study, there was an addition to the study protocol: Phase 3 was added. This part of the study was to obtain mortality data from the Medical Research Information Service (MRIS). MRIS is an organisation forming part of the NHS information service. MRIS holds data for patient events (death) and the cause of death as put on the death certificates of these patients.

The initial protocol did not specifically have ethics committee approval for obtaining data from the MRIS. For this we went back to the ethics committee and obtained Chairman's approval. MRIS was provided with a list of study subjects in the three groups.

5.3 Ethics Committee Approval

As this study included National Health Service (NHS) staff and patients, study approval was obtained from my NHS trust (County Durham & Darlington Foundation NHS Trust) research governance committee **(Appendix 1).** They suggested that a consultant be made the chief investigator (Professor J.J. Murphy), who would also act as the data custodian. This change was duly made.

Then I obtained ethical approval from my host university, Durham University **(Appendix 2).** Finally, the study was submitted to the National Research Ethics Service (Newcastle & North Tyneside 2 Research Ethics Committee) **(Appendix 3)**.

Two ethical issues were raised during the review. The first was as to whether this study would classify as research or audit.

There were three questions in this study:

Are we treating patients with heart failure in accordance with evidence based national guidelines? To answer this question we were reviewing the current clinical practice at Darlington Memorial Hospital, against a set standard of evidence based treatment guidelines, and this would technically constitute an audit (203).

Does treating HF according to evidence based guidelines have an impact on patient outcomes in terms of mortality and morbidity? There is a paucity of data on the long term benefit of evidence based treatment in HF patients, even more so in the “real world”. By answering this question we hoped to generate new knowledge (203), outside the selective recruitment of large multicentre controlled trials.

What is the outcome of patients with HF and preserved left ventricular systolic function (HFpEF) or diastolic HF? Again, very little is known about the natural history of HFpEF patients. Is the natural history of HFpEF and LVSD groups similar or different? What do these patients die from? We hoped to generate new knowledge by

answering the above question with regard to the diagnosis, management and outcome of HFpEF patients and this would constitute research (203).

Thus, the study would combine features of both audit and research.

The second ethical issue raised was access to patient records without consent of the patient.

The database, which was developed from the hospital records, identified these patients only by their unique alphanumeric code. This part of the project was effectively an audit. As Prof Murphy and I were both part of the clinical care team looking after these patients, for this part of the project we did not require patient consent.

a) Phase 2 of the study provided information on subsequent management and outcome following discharge back to primary care. The research team anticipated ethical issues regarding access to GP patient records so we contacted the National Information Governance Board (NIGB) for clarification.

General practices were given a list of the patients registered with their practices. This included the patient's name, date of birth and the unique alphanumeric code for the study, drawn from the hospital master list. The practices were asked to provide a computer printout with information regarding medication, doses, co-morbidities, number of hospitalisations, and outcome in the form of mortality.

The practices printed out data sheets without patient identifiable data by selecting the page to be printed from a menu of print options.

These data were entered on to the research database after which any link with the master list was broken. There was no patient identifiable information on the database. I quote the specific guidance that we had from NIGB in this regard:

“As long as no identifiable information will be available to the researcher at the GP surgery and the printouts only contain anonymised information along with the study number, i.e. not name, demographic data, NHS number, date of birth or death etc, and the GP information will remain pseudo-anonymised then this is fine”.

b) The issue of obtaining patient consent was debated at length within the research team.

As Phase 1 of the study involved auditing clinical practice at Darlington Memorial Hospital, this part of the study was discussed with the trust Caldecott Guardian, who gave his approval for the study process. Thus, for accessing patient data from the hospital information system and notes, individual patient consent was not required.

For phase 2, the issue of consent was debated within the research team. This was a retrospective review of an opportunistic cohort of patients who attended the heart failure clinic from 2002 - 2007. Obtaining consent would be fraught with difficulties and in many cases impossible. If we assumed 50% mortality in 5 years, there would be a large number of patients in this cohort who would no longer be alive or who might have lost capacity to consent. Guidance was sought from the NIGB in this regard and their advice was clear: as long the researcher has no access to any patient identifiable data (such as name, demographic data, NHS number, date of birth or death etc), access to pseudo-anonymised data from the general practice did not require individual patient consent.

5.4 The sample size calculation

Patients with HF fell in two groups, those with LVSD and those with HFpEF. The principal long term outcome was mortality. Based upon the published series, I estimated that those with LVSD were likely to have a 5-year mortality of 50% (204). The research team decided that an absolute difference in mortality between the two groups at 5 years of 15% (i.e. a 3% annual difference) would be clinically significant.

Two hundred and forty patients in each group (LVSD and HFpEF) would provide a 90% probability of detecting an absolute difference of 15% (50% to 35% or 65%) in mortality over an average follow-up period of 5 years (i.e. 3% annual difference), using two tailed statistics at the 5% significance level.

5.5 The database

Having previously worked and collected data on Microsoft Office Excel 2007, I used the same software to set up data for this project. Three separate excel spreadsheets were generated and titled LVSD, HFpEF, and Others. Auto fill function was used to generate the unique alpha numeric code to identify the study subjects in all three sheets. The unique alpha numeric code linked the data set to the master list. Data sheets were set up using a hospital computer that was pass-word protected and stored data in an encrypted form.

The following broad categories (in bold) were used to record data for each patient on the data sheet. Also some of the subheadings in these categories are presented here.

Table 5.5 Headings used for data collection

First review in the clinic
Alpha numeric code
Patient demographics
Past medical history
Symptoms on presentation
Clinical assessment on presentation
Investigation results- CXR, ECG, ECHO, blood tests
Medications on presentation
Presentation and clinical assessment
1st admission to the hospital
Results of investigation

Medications and their doses on admission

Medication changed in hospital

Discharge diagnosis

No of total admission and days spent in hospital

Date of start and stop of medications and dose achieved

Date, place and cause of death

BNP and NTproBNP value (where available)

For each patient this resulted in 203 data items under which data were collected. Data items were built over a period of few weeks through an iterative process.

Data were entered by the researcher from the case notes. This was done for the LVSD group first followed by the HFpEF group. For quality assurance and rule out systematic errors, double data entry was done for 10% of the patients. This was done by a research nurse (G Brennan). She would randomly select and order case notes for the patients who had already been reviewed by the researcher. Double data entry by the research nurse was performed using the same headings as the researcher and data were entered using the similar alphanumeric code as used by the researcher on MS excel spreadsheet. The research nurse checked these entries against the original data sheet to check for any inconsistencies. In a few of the records, minor variations e.g. data missed was found in some the data entries. These were corrected by referring to the case notes. No systematic errors were discovered.

5.6 Transfer of data to SPSS

Data were collected on the Microsoft Excel spread sheet. For the purpose of the analysis data were transferred to SPSS statistics 19.0.

5.7 Case records

The research nurse was provided with a printout of the hospital numbers and date of birth of the patients. She requested the case notes of the patients on the list from the

records library in the hospital. This was done using the hospital tracking system. The request tracked these records to be delivered to the cardiac research office at Darlington Memorial Hospital. The records were requested in batches of ten. Delivered case notes were stored in a safe cabinet in the research office with limited access.

The next sets of notes were only requested once the data from the initial sets had been entered on the database. This usually resulted in requesting notes once a week and coincided with the working day of the research nurse. Once the data had been entered on the database, the case records were returned by the research nurse to the records library.

Some of the case notes had to be requested repeatedly. This was especially the case where patients either had frequent visits to various outpatient clinics or had frequent admissions. Case notes for four patients were not available during the study period. These were two patients in the LVSD group and two in the HFpEF groups. Data for these four patients were not used in some of the analysis.

After finishing the data collection from the case notes fifty patients were identified who did not have their prescribing history data complete. The research nurse contacted their general practices requesting them to fax the last prescription of the patient after removing any identifiable information. All practices responded except in four cases where the patients had changed their practices and had been lost to the follow up.

5.8 Heart failure with preserved ejection fraction (HFpEF)

After the data collection for the LVSD group, I reviewed the major clinical trials in heart failure with preserved ejection fraction (HFpEF). These were: Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-preserved study (115), Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction study (I-PRESERVE) (117), and The Perindopril in Elderly People

with Chronic Heart Failure study (PEP-CHF) (116). A working definition of HFpEF was thus established after the review of these clinical trials (see Chapter 6).

Clinical letters from the HF clinic were reviewed against the criteria for HFpEF and a master list was prepared. This had the details of the patients who fulfilled the inclusion criteria. All patients were given a unique trial number. The master list was kept in a secured locker in the research office at Darlington Memorial Hospital with limited access. The research nurse requested the case notes of these patients from the records library through the hospital records tracking system.

A separate workbook of "Microsoft Excel 2007" was established to enter the data of HFpEF patients on to the hospital computer in an anonymised form. All except three case notes for the patients who fulfilled the criteria for HFpEF were available.

5.9 The third group "Others"

For patients who did not fall into either of the two groups, a separate list was created. They were given an alphanumeric code that began with the code of "OT" followed by the numeric code. The data for this group were recorded on a separate Microsoft Excel 2007 data sheet. Data for this group were collected from the clinical letters only and detailed case notes were not reviewed. Mortality data were obtained from the MRIS.

5.10 Cause of death in Heart Failure Patients

Mortality in HF is high. Why and how patients with HF die remains of keen interest and is the subject of much on-going debate and research (205-207). This interest arises due to no clear appreciation of the impact of interventions that are provided as part of the treatment, and for a better understanding of the natural history and the pathophysiology of HF.

One way to appreciate how these patients died is to ascertain the mode of death or factors listed as leading to it. This was planned to be studied from the death certificate of these patients. The Medical Research Information Service (MRIS), part of the NHS Information Centre, holds this information. MRIS was approached with a request to release data for the cohort of patients in the study.

An application form was filled and sent to the MRIS. After scrutinising the application, MRIS specifically queried whether the study has Ethics Committee approval for accessing patient data from the MRIS as part of the protocol?

The initial application to the Ethics Committee had specifically not mentioned access to patient data from the MRIS. We therefore applied for and received Chairman's approval for obtaining cause of death from the MRIS.

The revised application was returned to MRIS with the above clarification. On further review of the application, MRIS felt that, as we will be accessing confidential patient data (cause of death) without patient consent we ought to have Section 251 of the NHS Act 2006 support from the National Information Governance Board (NIGB) for Health and Social Care (*an independent statutory body established to improve and monitor information governance in health and adult social care).* This act allows the common law duty of confidentiality to be set aside in specific circumstances where anonymised information is not sufficient and where patient consent is not practicable. The full committee for NIGB discussed and reviewed our application for section 251 support. In a major policy decision, the NIGB board decided that where the clinical care team looking after the patient wants to access patient death data from the MRIS, it would not be necessary for section 251 support from the NIGB. This change in policy by the NIGB board will help other research teams by saving a lot of time.

Subsequently, an application was sent to the MRIS for access to patient data regarding the cause of death as recorded on the patient's death certificate. A data

sharing agreement was signed with the MRIS and they set up a project team to liaise with us. Patient data were sent in a secure encrypted format using the NHS.net email on a Windows 2007 excel spread sheet. A separate excel sheet was used to send data. Mortality data were returned to us over a secure connection on two separate occasions, with a downloadable link that was password protected. The data file could only be downloaded once before it would automatically be erased. The data file thus received was stored on an encrypted and password protected computer that could only be assessed by the researcher. It was linked to the master list by the unique study alphanumeric number present on the data file. The cause of death was copied to the working data file thus breaking any link with the master list and patient identifiable information.

5.11 Methods

Data were collected on a separate Microsoft excel spread sheet for each of the three groups. Data were transferred to the SPSS 19 sheets separately.

Data analysis was done using descriptive statistics first. Prognostic factors for the model were analysed using the Cox proportional hazard regression method.

5.11.1 The Cox proportional hazard model

The Cox proportional hazards (PH) regression model is a semi-parametric model (it imposes no assumption about the distribution of the time) is commonly used. This model assumes that the ratio between the hazards (instantaneous risk of death) of the two patient groups remains constant over the complete follow-up period. This builds a predictive model for time to event data and produces a survival function that predicts the probability that the event of interest has occurred at a given time *t* for given values of predictor variable (208).

Censored data: survival times are calculated from some baseline date that reflects a natural “starting point” for the study until the patients reach the endpoint of interest

(e.g. death). However we may not know when a patient reached the endpoint, but only that they remained free of the end point at the end of the study. If the event has not occurred, the case is said to be censored. These patients were known not to have reached the end point when they were last under follow up (right censored). In the Cox proportional hazard model censored cases are not used in the computation of the regression coefficients, but are used to compute the baseline hazard (209).

Stratification: The Cox proportional hazard model provides a way to adjust for confounding factors by stratification. Here data are grouped into strata that are defined by different levels stratification variables. Stratification can be used for model checking, if for a variable non-proportional hazards are detected.

Explanatory terms used in the Cox regression model are presented here.

B -This is the coefficient for the constant (also called the "intercept") in the null model. Cox regression coefficient signs are relative to death, not survival. So a positive sign means that larger values of the independent variable have higher death rates. And negative signs mean that larger values of the independent variable have lower death rates.

SE -This is the standard error around the coefficient for the constant.

Wald and P - This is the Wald chi-square test that tests the null hypothesis that the constant equals 0. The Null hypothesis is rejected if the p-value (listed in the column called “p") is smaller than the critical p-value of 0.05 or less

df -This is the degrees of freedom for the Wald chi-square test. There is only one degree of freedom because there is only one predictor in the model, namely the constant**.**

Odds ratio - is a measure of the association between two variables, and indicates the effect of other variables on their relationship.

5.11.2 Paired samples T test

The paired samples T test was used to compare the means of the variables from the clinic appointment and the admission data. This computes the differences between values of the two variables for each case and tests whether the average differs from 0.

5.11.3 Median follow up time

The median follow up time for this study was calculated using the method suggested by Schemper and Smith (210). This method has been described as the Kaplan-Meier estimate of potential follow up (KM-PF) also termed “reverse Kaplan Meier”. It is calculated in the same way as the Kaplan-Meier (211) estimate of the survival function but with the meaning of the status indicator reversed. Thus death (s = 1) censors the true but unknown observation time of an individual, and censoring (s = 0) is an end point. This creates a Kaplan Meier curve where loss of follow up is the event being followed, and death is treated as the censoring data.

Chapter 6

Diastolic Heart Failure: A working definition

6.1 What is Diastolic Heart Failure?

Systolic HF is characterised by reduced left ventricular (LV) ejection fraction often accompanied with progressive chamber dilation and eccentric (increased size and volume) remodelling. On the other hand, diastolic dysfunction can be defined as the condition whereby increased filling pressure is required in order to maintain a normal cardiac output. This is characterised by a normal left ventricle volume, concentric (increased thickness and reduced volume) remodelling, normal LV chamber systolic properties, and abnormalities of diastolic relaxation, filling, or distensibility of the LV. When these diastolic mechanical alterations are associated with signs and symptoms of exertional dyspnoea it is termed diastolic HF (DHF)

6.2 Background

Many physicians imagine that the typical patient with congestive heart failure (CHF) has a low ejection fraction. The usual response of clinicians to an echocardiogram report that suggests normal or preserved LVEF is to look for an alternative diagnosis for patient's symptoms. This focus on the systolic dysfunction is well seen in the large multicentre trials over the years which have defined the management of CHF as they have excluded patients with LVEF > 35% or >40% (212). This has certainly benefited patients with left ventricular systolic dysfunction (LVSD), leading to substantial advantage for the patients, with advances in the appreciation of pathophysiology and natural history, and has provided the consequent strong evidence for effectual treatment strategies (72, 213, 214) .

As the prime focus has been on systolic dysfunction, there is paucity of data in patients with HFpEF. However, since the 1970s, reports have appeared in the literature suggesting that half of all patients with clinical features of CHF have a normal (or near normal) ejection fraction (EF) (123, 215). These patients have been

labelled as “heart failure with normal ejection fraction” (HFNEF), “heart failure with preserved ejection fraction (HFpEF) or “diastolic heart failure” (DHF). All terms are frequently used interchangeably. For the purpose of this thesis I have used the term “heart failure with preserved ejection fraction” as it is the most accurate label and does not imply a mechanism.

The true incidence, prevalence and prognosis of the HFpEF remain debatable. Early studies which primarily looked at patients referred for HF into the hospital reported prevalence rates of HFpEF from 13% to 74% (215). Later community based studies found prevalence rates of 40 to 71 percent (216, 217). Using the European Study group (218) definition of diastolic HF Fischer et al found a prevalence rate of 11.1 % (219).

Incident rates also vary. In the Olmsted County study, 59 of the 139 (43%) patients had a preserved EF (ejection fraction ≥50 %). Of these 5 also had a predominant valvular lesion, so 54 (39%) had HFpEF or DHF (220). In another study 49 of 310 (16%) newly diagnosed patients with HF had a normal qualitative assessment of the left ventricle (221).

Predisposing conditions for HFpEF are older age, female gender, obesity, diabetes, arterial hypertension, and left ventricular hypertrophy (LVH) (219, 222). Patients who are diagnosed to have HFpEF also have rates of recurrent admissions to hospital as high as those with HF with LVSD (223), and marked all cause mortality (224, 225). There have been reports of a steady increase in the incidence and prevalence of HFpEF in the past decade, likely related to changing population demographics and associated cardiovascular disease in the population (132).

6.3 Definition of Diastolic heart failure: Current perspective

The reported wide variation in the incidence and prevalence of HFpEF highlights the fact that studies have not used a uniform definition to identify patients. The gold

standard for defining HFpEF is left heart catheterisation with angiography and simultaneous evaluation of pressure, volume and geometry throughout the cardiac cycle (226). This procedure is not only invasive and impractical for the routine assessment of HF patients but is also expensive and time consuming.

In a consensus statement on diastolic HF, the HF and Echocardiography Association of the European Society of Cardiology (ESC) proposed the presence of three obligatory conditions for the diagnosis of diastolic HF (227). These are (i) the presence of signs or symptoms of congestive HF (ii) presence of normal or mildly abnormal LV systolic function, and (iii) evidence of diastolic LV dysfunction. Signs and symptoms of congestive HF include lung crepitation, pulmonary oedema, ankle swelling, hepatomegaly, dyspnoea on exertion and fatigue.

The presence of normal or mildly abnormal LV function is the second criterion in the ESC guidelines for the diagnosis of HFpEF. They propose a left ventricular (LV) ejection fraction (EF) of > 50 % consistent with the presence of normal or mildly abnormal LV systolic function. However, the choice of a specific cut- off for LVEF remains arbitrary. Major randomised control trials in patients with HFpEF have used different definition to define their patient cohort. The trial “Effects of candesartan in patients with chronic heart failure and preserved left ventricular ejection fraction (CHARM preserved)” (228), defined eligible patients as 18 years or older with a New York Heart Association functional (NYHA) class II-IV of at least 4 weeks duration, who had a history of hospital admission for a cardiac reason, and had a EF ≥ 40 %.

The “Irbesartan in patients with heart failure and preserved ejection fraction (I-PRESERVE)” trial (117), had patients of at least 60 years of age who had HF symptoms and a EF ≥ 45%.

Cleland et al, in the “Perindopril in elderly people with chronic heart failure study (PEP-CHF)”(116), defined their cohort of patients as aged ≥ 70 years and treated with

diuretics for a clinical diagnosis of CHF due to LV diastolic dysfunction. They excluded patients with a wall motion index of <1.4 roughly equivalent to an EF of 40%. (Table 6 shows comparative inclusion and exclusion criteria of these trials.)

In the SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation of Seniors with HF) trial, an EF >35% was used as inclusion criteria (229).

In the Hong Kong diastolic HF study the inclusion was age >18 years, clinical history of HF within 2 months prior to screening, including a chest X ray demonstrating pulmonary congestion, NYHA class II – IV, LVEF >45% by 2D echocardiography or a radionuclide technique (230) .

Beta blockers in heart failure with normal left ventricular ejection fraction (β-PRESERVE) is a study that is currently recruiting and the inclusion criteria include an LVEF ≥ 50% (231).

6.4 Developing a working definition for HFpEF to be adopted in DROPSY

For the present study patients were required to have ongoing NYHA class II-IV symptoms, ± signs of fluid retention and a LVEF > 40% by Simpsons rule, or normal function on “eye balling” as the essential inclusion criteria. Further evidence to indicate a cardiac cause for the symptoms, based on the echocardiogram, ECG or chest X-ray was also necessary (qv).

In the present study cardiac function was assessed by EF was assessed by Simpson’s rule, regional wall motion index where possible, or by a semi quantitative “eye balling” method. Detailed clinical methods used to calculate EF are often not applicable in clinical practice. Thus, a visual estimate, which is a validated technique of assessing LVEF, was used (232, 233) .

Patients who fulfilled the above criteria also needed to have a chest X-ray showing cardiomegaly or pulmonary congestion and / or an electrocardiogram (ECG) that showed left bundle branch block (LBBB) or left ventricular hypertrophy (LVH) by Sokolow-Lyon criteria.

6.5 Evidence of ventricular diastolic dysfunction

The need to obtain positive evidence of LV diastolic dysfunction remains controversial. The ESC lists this as the third obligatory condition for the diagnosis of DHF (227). It has been argued that this clinical definition lacks sensitivity and specificity especially in women, the elderly and in the obese (234). Equally, others have argued that measurement of LV relaxation rates is of doubtful diagnostic value (235). Also there is no single index of diastolic function that is as useful and widely applicable as ejection fraction in patients with systolic dysfunction (236)

In one study, 92% of patients with a history of HF, EF >50 %, and evidence LV concentric remodelling had an elevated LV end diastolic pressure and all had at least one hemodynamic or Doppler echocardiographic index of abnormal LV relaxation, filling, or diastolic stiffness. This study questioned the need for formal assessment of LV diastolic dysfunction (236). For the present study left ventricular hypertrophy (LV septum or posterior wall > 12 mm), left atrial diameter of >40 mm, and E/A ratio of < 0.5 on echocardiography will be used as surrogate markers of diastolic dysfunction.

6.6 Early (E) / Atrial (A) filling ratio of the Left ventricle

During ventricular diastole, blood flows from the atrium to fill the ventricular chamber. This occurs in two phases. The first phase starts with the opening of the mitral valve when there is a rapid movement of blood into the LV cavity in early diastole due to the pressure gradient from the left atrium to the apex. This is called the early (E) phase. As the LV fills up the pressure gradient from left atrium to the LV decreases and then transiently reverses. This brief period in diastole is called diastasis. Late in diastole,

atrial contraction augments LV filling. This is due to atrial systole and called the atrial (A) phase (237).

In hearts with normal filling pressures the E/A ratio is usually more than 1. A reversal of this ratio is indicative of abnormal filling and impaired relaxation of the left ventricle, a marker of diastolic dysfunction.

6.7 Atrial fibrillation

Patients with atrial fibrillation (AF) are inadequately assessed using Doppler–Echocardiographic techniques (238). This is because of the altered left atrial pressure and loss of synchronized atrial contraction (239). Both the ESC guidelines on diagnosis of DHF (227) and PEP-CHF (116) have included AF as a marker of diastolic dysfunction and for the present study AF is included as evidence of diastolic dysfunction.

The main exclusion criteria for the present study were patients with significant valvular heart disease and those with a pulmonary cause of shortness of breath.

As there continues to be disagreement and debate about the best method for diagnosis of diastolic heart failure, the present study used a practical, realistic, and workable definition of identifying patients with DHF in clinical practice without the constraint of having to follow complex diagnostic algorithms. The working definition of heart failure with preserved ejection fraction (HFpEF) for the present study is presented in section 6.8.

Table 6.7 Inclusion criteria for three major trials in HFpEF

Criteria	CHARM preserved	I PRESERVE	PEP-CHF
Age	> 18 years	60years	≥ 70 & on diuretics for clinical CHF
NYHA	2-4	2-4	
Duration of symptoms	≥ 4 weeks		
ECHO- EF%	>40%	≥ 45%	Wall motion index <1.4. EF- > 40%
History of hospitalisation for cardiac cause	Yes	Yes, in the previous 6 months	Yes in the previous 6 months
If not hospitalised		NYHA 2-4, corroborative evidence	
Other			Walk 6 min unaided(r/o-frail)

Corroborative evidence: - Pulmonary congestion on CXR, LVH or LA enlargement on echocardiography, or LVH or LBBB on ECG

PEP-CHF: - 3 of 9 clinical and at least 2 of 4 Echo criteria

Clinical criteria	ECHO criteria
1) Exertion SOB, 2) Orthopnoea or PND; 3) Ankle swelling; 4) Improved breathlessness with diuretic 5) Increased JVP; 6) Prior episode of clinical pulmonary oedema; 7) Prior MI; 8) Cardiothoracic ratio .0.55; 9) Previous radiological pulmonary oedema.	i) LVEF fraction between 40 and 50%, (since abnormal diastolic dysfunction is often associated with some impairment of systolic function) ii) LA diameter >25 mm/m2 body surface area or >40 mm iii) IV septum or posterior LV wall thickness ≥12 mm iv) Evidence of impaired LV filling by at least one of the criteria recommended by the ESC:- a) E/A ratio<0.5 or deceleration time of 280 ms Isovolumic relaxation time of 105ms b) Atrial Fibrillation

6.8 HFpEF- working definition adapted in DROPSY

Inclusion criteria

1) **Hospital admission for cardiac cause in the last 6 months**

With – NYHA class 2-4

± Signs of fluid retention

2) **If not hospitalised –**

Ongoing NYHA 2-4 HF symptoms ± signs of fluid retention
+ (any two of the following)

a) CXR - Pulmonary congestion/ oedema, or Cardiomegaly

Or

b) ECHO - LVH (LV septum or posterior wall > 12mm)
Left atrial diameter > 40 mm
E/A ratio < 0.5

Or

c) ECG – LBBB or LVH (Sokolow-Lyon criteria)
Or Atrial Fibrillation

Essential criteria on 2D echocardiography

EF fraction > 40% (Simpsons rule)

Normal LV systolic function by semi quantitative assessment, or on “eye balling”

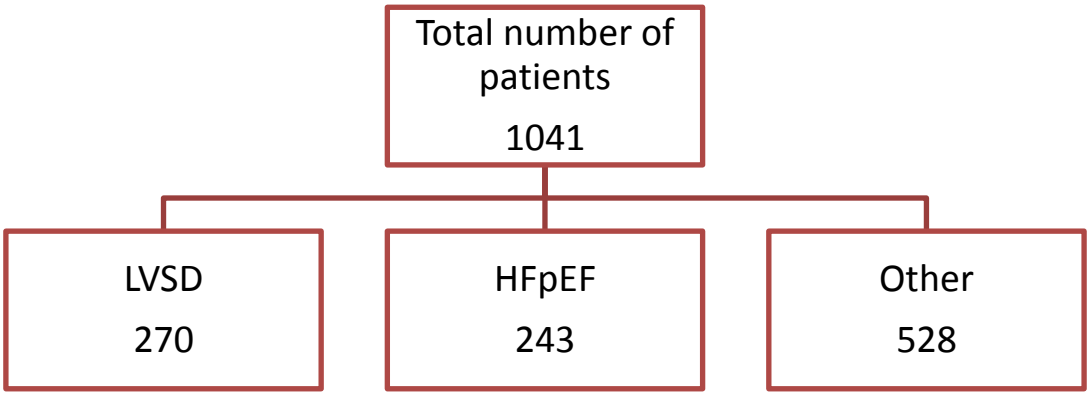
Exclusion criteria

Pulmonary cause of shortness of breath

Significant valvular heart disease

Results

The Darlington Retrospective Outpatient Study (DROPSY) was carried out at the Darlington Memorial Hospital Darlington. From Jan 2002 to Dec 2007, 1041 patients were reviewed in the HF clinic. Of these 270 (26%) were diagnosed as having LVSD. Of the 771 patients who did not have systolic dysfunction, we identified 243 patients who fulfilled the study criteria for heart failure with preserved ejection fraction (HFpEF). The remaining 528 patients formed the non heart failure (Other) group.



Case records of two patients in the LVSD group and two patients in the HFpEF group were not available for review. For these four patients we only had the demographic and outcome data. Final analysis of the data was performed without taking these four patients into account. Six patients from the Non HF (Other) group had no data available and the analyses were confined to 522 patients only.

Demographics

Comparative analysis of the three groups shows that the HFpEF group patients were older; more had hypertension and diabetes than the other two groups. The LVSD group had more male and diabetic patients while the third group of non HF had more

COPD. The subsequent chapters will look at the patients with LVSD, HFpEF and non HF in more detail.

Table: Demographics for all three groups

	LVSD	HFpEF	Non HF (Other)	p value
Total number of patients	268	241	522	
Average age years (range)	74 (60)	78 (52)	75 (61)	0.01
Males	164 (61%)	84 (35%)	183 (35%)	0.00
Females	104 (39%)	157 (65%)	339 (65%)	0.00
Hypertension	114 (43%)	202 (84%)	253 (49%)	0.01
Atrial fibrillation	66 (25%)	86 (36%)	74 (14%)	0.01
Ischemic heart disease	140 (52%)	101 (42%)	138 (26%)	0.00
Diabetes	42 (16%)	55 (23%)	63 (12%)	0.01
Stroke	34 (13%)	10 (4%)	No data	0.00
COPD/ Asthma	58 (22%)	11 (5%)	144 (28%)	0.00

Results for individual group and a combined analysis are provided in subsequent chapters.

Chapter 7

Heart failure with preserved ejection fraction (HFpEF) - Results

Two hundred and forty three (243) patients fulfilled the study inclusion criteria for HFpEF. Case notes for review were available for all except two patients. These two patients were not included in the final analysis leaving 241 patients in this cohort.

7.1 Descriptive analysis of first clinic review

HFpEF patients were older, comprised more females and more had atrial fibrillation than the LVSD and Non HF groups. Although history of COPD was an exclusion criterion, 11 patients who had history of mild asthma (not any regular medications) were also found eligible and included in the study. The demographics and past medical history are presented in the table below.

7.1.1 Demographics and past medical history

Total number of patients	241
Males	84 (35%)
Females	157 (65%)
Average age, years (range)	78 (52)
Past medical history	
Hypertension	202 (84%)
Diabetes mellitus	55 (23%)
Atrial fibrillation	40(17%)
Ischemic heart disease	101(42%)
Stroke	10 (4%)
Mild Asthma	11 (5%)

7.1.2 Smokers

One hundred and fifteen people had never smoked, 117 were ex smokers (stopped smoking before the clinic review). Only a small number were current smokers.

Smoking history	Frequency	Percent
Never	115	47.7
Current	9	3.7
Ex	117	48.5
Total	241	100.0

7.1.3 Presenting symptoms

The majority of the patients seen in the clinic were referred because of either shortness of breath or swollen ankles. One hundred and eighty eight (78%) patients were referred to the clinic due to swollen ankles, but on clinic examination only 102 (42%) had swollen ankles. Table 7.1.3

Table 7.1.3 Presenting symptoms

Shortness of breath (SOB)	231 (96%)
Swelling of the ankles (SOA)	102 (42%)
Orthopnoea	47 (20%)
Paroxysmal nocturnal dyspnoea (PND)	13 (5%)
Fatigue	7 (3%)
Palpitations	7 (3%)

7.1.4 NYHA class

On average patients had been symptomatic for 5.6 months (median 6 months) before being referred to the HF clinic. At the time of review in the clinic patients were most likely to have NHYA class 2 symptoms. A small number of patients were in class 1 & 4. (Table 7.1.4)

Table 7.1.4 NYHA class in clinic

NYHA class	Frequency	Percent
Class 1	6	2.5
Class 2	157	65
Class 3	75	31
Class 4	3	1.5
Total	241	100

7.1.5 Clinical examination findings

Jugular venous pressure (JVP) was raised in 27 (11%) and normal in 214 (89%) patients. The mean systolic and diastolic blood pressure was 153 and 84 (median 150 and 80 and range 115 and 95) mmHg respectively. The average weight of the HFpEF group was 80 (median 77 / range 136) kg. [Body mass index (BMI) was not calculated as the data for height was not routinely recorded]. A systolic murmur was present in 78 (32%) patients and 7 patients had a diastolic murmur. The majority of the patients had clear lung fields on auscultation but 30 (12%) had crepitation.

7.1.6 Chest X-ray findings

Two hundred and seventeen patients had cardiomegaly on their chest X-ray when reviewed in the clinic. This was one of the inclusion criteria for patients with HFpEF.

Table 7.1.6 Chest X-ray findings

Normal	18 (8%)
Cardiomegaly	217 (90%)
Upper lobe diversion	61 (25%)
Pulmonary oedema	12 (5%)
Pleural effusion	9 (4%)
Other findings	1

7.1.6 ECG findings

All the 241 patients at the clinic appointment had an ECG recorded. This was reviewed by the clinician at the time of their consultation. Forty seven new patients were diagnosed with atrial fibrillation after the clinic review. Table 7.1.6

Table 7.1.6 ECG findings

Normal	71 (30%)
Left axis deviation	11 (5%)
Left bundle branch block	15 (6%)
Left ventricular hypertrophy	34 (14%)
Bradycardia	11 (5%)
Atrial fibrillation	87 (36%)
Right bundle branch block	14 (6%)
T wave inversion	12 (5%)

7.2 Echocardiographic findings

Echocardiographic assessment of the heart is the gold standard for measurement of both systolic and diastolic function. This not only helps to classify patients into reduced or preserved EF but also guides management. Of the 241 patients in this cohort only 53 (22%) patients had their LV ejection fraction assessed by Simpson's rule on echocardiography. Average EF was 63% (median and mode of 63%). The remainder had semi quantitative "eye ball" assessment of their global systolic function which was reported as "good / normal LV systolic function".

7.2.1 E/A ratio and Left atrial diameter

One hundred and twelve (47%) patients had the E/A ratio measured at echocardiography. Eighty six (36%) of these had reversal of the E/A ratio suggestive of a stiff ventricle and impaired diastolic filling. The left atrial diameter was measured in 195 patients. The mean (and median) diameter was 45 mm (range 47).

7.2.2 Left ventricular hypertrophy

Interventricular septal diameter in diastole (IVSDd) and posterior wall (PW) thickness of more than 12mm is considered suggestive of left ventricular hypertrophy (LVH). In the HFpEF patients the mean IVSDd was 14mm and the mean PW thickness was 12mm. IVSDd in 139 (58%) patients and PW thickness in 100 (41%) patients was ≥ 12 mm, suggestive of left ventricular hypertrophy. (Table 7.2.2)

Table 7.2.2 Left ventricular hypertrophy

	Interventricular septal diameter in diastole (IVSDd)	Posterior wall thickness
Data available, n (%)	175 (73)	165 (68)
Not available, n (%)	66 (27)	76 (32)
Thickness ≥ 12 mm, n (%)	139 (79)	100 (61)
Mean (mm)	14	12
Median (mm)	14	12
Mode (mm)	13	10
Range	18	14

7.2.3 Valvular heart disease

Significant valvular heart disease was not present in any of the patients. Moderate mitral regurgitation (MR) was present in 52 (21%), moderate tricuspid regurgitation (TR) in 27 (11%), severe TR in 7 (3%), moderate aortic regurgitation (AR) was present in 6 (2.5%), and moderate aortic stenosis (AS) in 3 (1%) of the patients.

7.3 Blood tests

All the patients had blood tests done either on the day of the appointment or previously by the referring physician. These were reviewed at the time of consultation. All patients had serum sodium, potassium, urea, creatinine and full blood count

checked. The results were then available to guide further management with respect to the drug therapy. (Table 7.3)

Table 7.3 Blood tests in the clinic

	Mean	Median	Minimum	Maximum
Sodium (mmol/L)	140	140	127	147
Potassium (mmol/L)	4.2	4.2	3	6
Urea (mmol/L)	8	7	3	24
Creatinine (µmol/L)	109	98	62	657
Haemoglobin (mg/dl)	13	13	9	16
MCV (Fl)	90	90	73	109

7.4 Medications on presentation

7.4.1 Diuretics

One hundred and ninety two (80%) of the patients had been prescribed a diuretic by their physician before being referred to the HF clinic. This was to help patients with shortness of breath and swollen ankles. The majority of patients were taking only one loop diuretic, but 9 (4%) were taking an aldosterone antagonist (Spironolactone) as well.

7.4.2 ACE inhibitors / ARBs

The majority (55%) of patients were not taking an ACEi or ARB (None of the patients were on both the ACEi and ARB together). The frequency of specific ACEi and ARB usage is presented in the table below. Table 7.4.2

Table 7.4.2 Type and frequency of ACE inhibitors / ARBs in the clinic

Type of ACEi / ARBs	Frequency (N= 109)	Percent
Perindopril	32	29
Ramipril	23	21
Lisinopril	19	17
Enalapril	10	9
Trandolapril	1	1
Losartan	10	9
Valsartan	5	5
Candesartan	5	5
Irbesartan	3	3
Olmesartan	1	1
Total	109	

7.4.3 Beta blockers

Eighty three (34%) of the patients were taking a beta blocker on presentation and the majority were on Atenolol. Table 7.4.3

Table 7.4.3 Patients taking beta blockers

Type of beta blocker	Frequency (n=83)	Percent
Atenolol	64	77
Bisoprolol	11	13
Carvedilol	3	4
Metoprolol	1	1
Nebivolol	3	4
Timolol	1	1

7.4.4 Other medications

Digoxin	39 (16%)
Aspirin	118 (49%)
Warfarin	38 (16%)
Calcium channel blockers	83 (34%)
Statins	90 (37%)

7.5 Medications changed in the clinic

Only a minority of patients had their treatment changed in the clinic. In 20 (8%) patients an ACEi was started, and in another 20 patients, the dose of medication was adjusted. The adjustments to medications were mainly for optimising blood pressure control. Five patients had their loop diuretics stopped.

Twenty six (11%) patients were also started on a beta blocker. In the majority of patients this was done to optimise heart rate control in atrial fibrillation. Calcium channel blockers were started in 6 patients. Warfarin was initiated in 23 (10%) patients. Table 7.5.1

Table 7.5.1 Dose changed in clinic

	Started	Dose change	Stopped
ACE inhibitors	20 (8%)	20 (8%)	
Beta blockers	26 (11%)		2
Loop diuretics	7 (3%)		5 (2%)
Aldosterone antagonist	7 (3%)		
Digoxin	5 (2%)		
Warfarin	23 (10%)		
Calcium channel blockers			6(3%)

7.6 Cause of shortness of breath (ascribed in the HF clinic)

At the time that most of these patients were evaluated, it was not normal practice to make a diagnosis of HFpEF. The reviewing clinician therefore attempted to identify a

cause for their shortness of breath and / or oedema. Atrial fibrillation, hypertension, and left ventricular hypertrophy were the commonest reason ascribed for their symptoms. Table 7.6

Table 7.6 Cause of shortness of breath

	(n = 241)
HFpEF	30
Atrial Fibrillation	44
Obesity	17
Hypertension	38
Calcium channel blockers	5
COPD/ Asthma	9
Dependent oedema	20
Old age	4
LVH	18
IHD	21
Other *	9
No cause ascribed	26

* Lack of fitness, kyphoscoliosis, and anaemia.

7.7 Follow up

After clinic attendance the majority of patients were discharged back to the referring doctor. Only 57 (24%) patients were invited back for a further review in the HF clinic. Table 7.7

Table 7.7 Frequency of follow up visits by patients to the HF clinic

Number of patients	Frequency of visits
1	19
2	14
3	9
4	7
5	3
7	2
11	1
13	1
15	1

7.7.1 Other procedures performed

Other procedures and investigations were requested as appropriate to help manage the patients. Table 7.7.1

Table 7.7.1 Other procedures and tests requested

Tests	Frequency
DCCV	3
ETT	4
PFT	1
24 hr monitor	2
PPM	1

(DCCV= DC cardioversion; ETT= exercise tolerance test; PFT= pulmonary function test; PPM= permanent pacemaker implantation)

7.8 First admission to hospital

Following the HF clinic appointment, the first episode of admission to the hospital was recorded. One hundred and fifty eight (65%) of the patients had least one admission to the hospital during the follow up period and 83 (35%) had no admissions.

The median time to first admission following the clinic appointment was 29.4 months (127.90 weeks). Of the 158 patients, 134 (85%) were managed by general physicians, 17 (11%) by the cardiologists, and the remainder were looked after by other specialists. Table 7.8.1 & 2

7.8.1 Presenting complaints on admission

	Frequency (n = 158)
Shortness of breath	36
Chest pain	24
Fall	15
Collapse	21
Stroke	8
Cancer	2
Confusion	10
Diarrhoea	8
Generally unwell	11
Acute renal failure	2
Cardiac arrest	1
Other	20

7.8.2 Patient characteristics on admission

Males	50 (32%)
Females	108 (68%)
Age (mean) years	79
Mean systolic BP	140 mmHg
Mean diastolic BP	73 mmHg
Mean heart rate	82/min

Patients who were admitted to the hospital had a significantly lower mean systolic and diastolic BP as compared to their BP at the time of the clinic assessment. The mean heart rate, on the other hand was significantly higher on admission as compared with the time of the initial clinic assessment. The lower mean BP on admission could have a number of explanations, including a consequence of the cause of admission or the effect of drug modification since the initial clinic visit. Table 7.8.2.a & b

Table 7.8.2a [Blood pressure (BP) and Heart rate (HR) (Paired Samples T test)]

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	BP (systolic) on admission	140	155	28.9	2.3
	BP (systolic) in clinic	153	155	21.3	1.7
Pair 2	BP (diastolic) on admission	73	157	14.3	1.1
	BP (diastolic) in clinic	83	157	13.1	1.0
Pair 3	HR on admission	82	158	19.4	1.5
	HR in clinic	77	158	18.6	1.4

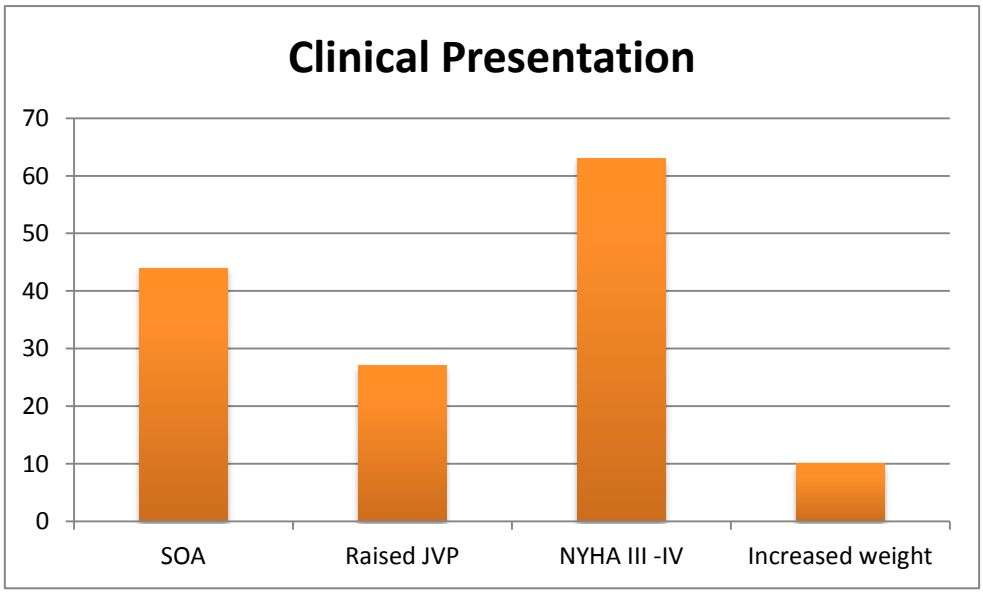
Table 7.8.2b [Blood pressure (BP) and Heart rate (HR) (Paired Samples Test)] on admission and clinic

		Paired Differences					t	df	P
		Mean	Std. Deviation	Std. Error Mean	95% CI of the Difference				
					Lower	Upper			
Pair 1	Systolic BP (admis) - Systolic BP (clinic)	-12.9	32.8	2.6	-18.1	-7.6	-4.8	154	.01
Pair 2	Diastolic BP (admis) - Diastolic BP (clinic)	-9.5	18.3	1.4	-12.4	-6.6	-6.5	156	.01
Pair 3	HR admission - HR in clinic	5.6	23.2	1.8	2.0	9.3	3.0	157	.00

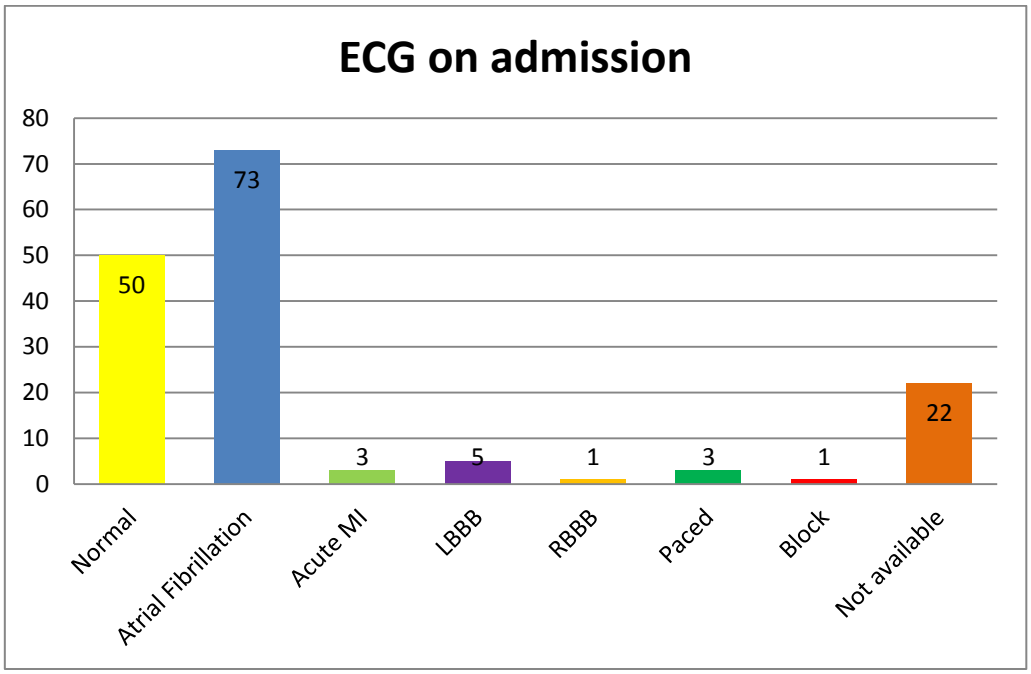
7.8.3 Clinical examination findings on admission

Of the one hundred and fifty eight patients who had an admission to hospital, 70 (44%) had swollen ankles, 27 (17%) had raised JVP, 63 (43%) were in NYHA class 3-4, and 10 (4%) presented with increased weight. Chart 7.8.3

Chart 7.8.3



7.8.4 ECG and Chest X-ray on admission



On admission 17 patients had a normal chest X-ray. Of the 113 patients who had cardiomegaly, 20 also had concomitant pulmonary oedema. Eleven patients had other findings and 18 patients did not have a chest X-ray done on admission.

7.8.5 Blood tests

As compared to the clinic, bloods tests on admission showed a significant increase in urea and creatinine level. At admission, 36 (23%) patients had a significant rise (≥ 50% increase) in creatinine values, 65 (41%) had significantly (> 8 mmol/l) elevated urea levels, 11 (7%) had hyperkalemia (potassium ≥ 6mmol/l), and 30 (19%) of patients had hyponatremia (sodium < 135mmol/l) as compared to the clinic assessment values. Table 7.8.5a

Table 7.8.5a Blood test results on admission

	Sodium (mmol/l)	Potassium (mmol/l)	Urea (mmol/l)	Creatinine (µmol/l)
Mean	138	4.3	12	138
Median	139	4.2	9	105
Std. Deviation	4.5	0.7	10	96
Minimum	123	3	3	7
Maximum	149	8	70	691

A paired samples 2 tail test showed a significant difference in the mean value of blood results at the time of clinical review and at the time of the first hospital admission. Only the mean value for sodium was significantly lower at the time of admission whereas the mean values were significantly higher for potassium, urea, and creatinine. Table 7.8.5b & c

Table 7.8.5b Blood tests on admission and in clinic (Paired samples statistics)

		Mean	N	Std. Deviation	Std. Error of Mean
Pair 1	Sodium (admission)	138	158	4.5	0.4
	sodium (clinic)	140	158	3.3	0.3
Pair 2	Potassium admission	4.3	158	0.7	0.1
	Potassium in clinic	4.2	158	0.1	0.1
Pair 3	Urea on admission	12	158	10	1
	Urea in clinic	8	158	3.2	0.3
Pair 4	Creatinine admission	138	158	96	8
	Creatinine in clinic	114	158	64	5

Table 7.8.5c Blood tests on admission and in the clinic (Paired samples t test)

		Paired Differences					t	df	p
		Mean	Std. Dev	Std. Error Mean	95% CI of the Difference				
					Lower	Upper			
Pair 1	Sodium (admis) – sodium (clinic)	-1.9	4.6	0.4	-2.6	-1.2	-5.2	157	.01
Pair 2	Potassium (admis) - Potassium (clinic)	1	0.7	0.1	-.1	0.2	1.8	157	.07
Pair 3	Urea (admission) - Urea (clinic)	4.4	10	0.8	2.9	5.9	5.8	157	.01
Pair 4	Creatinine (admis) - Creatinine (clinic)	24	86	7	10.5	37.5	3.5	157	.01

7.9 Medications on admission

Table 7.9 Medications on admission

Medications	Frequency [n=158]
ACEi / ARBs	92 (58%)
Beta blockers	58 (37%)
Diuretics	113 (76%)
Aldosterone antagonist	16 (10%)
Digoxin	34 (26%)

7.9.1 Medications changed in hospital

Only a minority of the patients had any alteration to their medications in the hospital. An ACEi was started in 5, and stopped in 13 patients. A beta blocker was started in 4, and stopped in 3 patients. Diuretics dosage was reduced (including discontinued) in 10 patients and increased in 2. Only 2 patients had spironolactone and digoxin started.

7.10 Frequency of admission to hospital

Admission to the hospital for any reason is a marker of a sicker and higher risk population. These patients are likely to fare worse than the comparative group not managed as inpatients.

We studied the HFpEF patients who were admitted to the hospital for any reason. The first episode of admission for any reason was studied in detail. For subsequent admissions frequency data was only collected for the total number of admissions and the total number of days spent as an inpatient. Table 7.10

Table 7.10 Duration and number of inpatient episodes

	First admission (total days)	Total number of admissions (per patient)	Total inpatient stay (days)
Admitted	158		
Not admitted	83		
Mean	12	2	26.
Median	6	2	17
Mode	2	1	2
Std. Deviation	15	2	25
Minimum	1	0	1
Maximum	90	9	123
Sum	1856	367	4164

One hundred and fifty eight (66%) patients were admitted during the follow up period. Sixty seven (42%) patients had a single episode, and 91 (58%) patients had more than one episode of admission. Patients spent an average of 11.75 days as inpatients on their first admission. On an average patients had 2.32 episodes of admission. The cumulative sum of all days spent in the hospital for any reason was 4164. Thus on average each patient spent 26.35 days in hospital.

7.11 Other co-morbidities developed

Over the follow up period patients also developed significant other co-morbidities. Cancer (n = 26), stroke (n = 22), chronic kidney disease (n = 17), and dementia (n = 15) were the leading new diagnoses made. Seven patients were diagnosed with COPD, 5 of whom had mild and 2 had severe symptoms needing home oxygen. Table 7.11

Table 7.11 Other co morbidities developed

	Frequency	Percent
AF	9	4
Bleeding	8	3
Cancer	26	11
Cardiac arrest	2	1
CCF	6	3
CKD	17	7
COPD	7	3
Dementia	15	6
Diabetes	4	2
Fall	7	3
IHD	7	3
Pulmonary fibrosis	1	0.4
Stroke	22	9

7.12 Exposure to medications

In a subset analysis, patients who had been exposed to any of the four medications were selected. The data for the total duration that patients had been prescribed an ACEi / ARB, beta blocker, aldosterone antagonist (spironolactone, eplerenone) and digoxin was collected from the hospital case records and general practice records. In the final analysis 161 (67%) patients had been prescribed an ACE inhibitor, 122 (50%) had been prescribed a beta blocker. Table 7.12

Table 7.12 Duration of medicine exposure

Medications	Number of patients	Mean duration of exposure (months)
ACEi / ARB	161 (67%)	73
Beta blockers	121 (50%)	77
Aldosterone antagonist	29 (12%)	31
Digoxin	57 (24%)	71

The mean duration of exposure was calculated from the actual date of start of the prescription to the stop date. Where patients were continuing on the medications at the end of the study follow up period, 31/08/2011 was taken as the study stop date.

7.12.1 Survival analysis for total drug duration

Univariate and multivariate survival analysis for all-cause mortality using drug duration as a co variant was done using a Cox regression model for ACEi / ARBs, beta blockers, aldosterone antagonists, and digoxin.

7.12.2 Univariate analysis for total drug duration

Table 7.12.2 Univariate analysis for total duration of drug usage

	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
ACEi / ARB	-.01	.00	27.5	1	.01	.9	.97	.98
Beta blockers	-.11	.03	8.9	1	.00	.8	.83	.96
Digoxin	-.00	.00	4.3	1	.03	.9	.98	.99
Aldosterone antagonist	-.01	.01	1.8	1	.17	.9	.96	1

In the univariate model ACEi / ARBs, beta blockers, and digoxin were statistically significant, as determined by the p value and the 95% CI for the odds ratio.

The magnitude of this effect is likely to be small as the odds ratio for ACEi / ARBs, and digoxin is very close to unity. This would suggest that though the results are statistically significant the clinical effect is likely to be small, although it is showing a favourable trend. The magnitude of effect for beta blockers is slightly more. Table 7.12.2

7.12.3 Multivariate analysis for total drug duration

In the multivariate analysis of the above when all the four medications were put in the model the event rate was too small to give any meaningful information. Subsequently

data for both digoxin and aldosterone antagonists were removed from the model for the analysis purposes.

Use of ACEi / ARBs, and beta blockers were significantly related to the all-cause mortality. These results suggest that patients taking ACEi / ARBs and beta blockers have a favourable prognosis compared with patients who were not taking them. Table 7.12.3

Table 7.12.3 Multivariate analysis for drug duration

								95% CI for OR	
		B	SE	Wald	df	p	Odds ratio	Lower	Upper
Step 1	ACE i total exposure	-.01	.05	8.4	1	.00	.98	.97	.99
Step 2	ACE i total exposure	-.01	.05	7.3	1	.00	.98	.97	.99
	Beta blocker exposure	-.11	.05	4.4	1	.03	.89	.80	.99

7.13 Repeat Echocardiogram

One hundred and five (44%) persons had a repeat echocardiogram during the follow up period. Seventy three (70%) of the patients had good LV systolic function with either left ventricular hypertrophy (LVH) or an enlarged left atrium (LA). Eighteen (17%) of the patients were diagnosed with HFpEF using the E/E' ratio. A new diagnosis of LVSD was made in 12 patients. Of these 8 had mild, 2 had moderate, and 2 had severe LVSD. Table 7.13

Table 7.13 Repeat echocardiogram findings

	[n=105]
Good LV systolic function	34
Good LV systolic function with LVH	39
Heart failure with preserved EF	18
Mild LV systolic dysfunction	8
Moderate LV systolic dysfunction	2
Severe LV systolic dysfunction	2
Severe valve disease	2

7.14 Mortality and place of death

Over the median follow up of 6.9 years there were 118 deaths. The location of each patient's death gives us important information about their management in the last few days of their existence. For the present study, the number of patients dying in and out of the hospital was similar. Of the 118 patients who died during the follow up period, 54 (46%) died at home, and 50 (42%) died in the hospital. For 14(12%) patients the place of death could not be ascertained. Of all the deaths 2 patients suffered cardiac arrest at home and were brought to hospital while 1 person had an in-hospital cardiac arrest.

7.15 All cause mortality

The factors that predict poor prognosis in HFpEF patients is not entirely clear. In clinical practice the poor prognostic factors for this group have been extrapolated from the studies done with LVSD patients. For the present study prognostic factors for HFpEF were examined using Cox regression analysis.

7.15.1 Univariate analysis

Cox univariate analysis was performed to identify risk factors as predictors of poor outcome in the HFpEF group. Table 7.15.1

Table 7.15.1 Univariate analysis for all-cause mortality

	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
Age	.06	.01	21.2	1	.01	1	1	1.1
Gender	-.22	.19	1.4	1	.24	0.7	0.5	1.2
Smoker	.09	.09	.87	1	.35	1	0.9	1.3
Hypertension	-.55	.22	6.2	1	.01	0.5	0.4	0.8
AF	.39	.18	4.3	1	.03	1.4	1	2
Diabetes	.28	.21	1.8	1	.17	1.3	0.9	2
IHD	-.00	.20	.00	1	.99	0.9	0.6	1.5
MI	.14	.25	.32	1	.57	1.1	0.7	1.9
COPD	.54	.37	2.2	1	.14	1.7	0.8	3.5
Stroke	.52	.42	1.5	1	.21	1.6	0.7	3.9
NYHA	.63	.17	14.2	1	.01	1.8	1.3	2.6
Hospital admission	1.13	.25	21.1	1	.01	3.0	1.9	5

Using this model age, hypertension, atrial fibrillation, NYHA class, and admission to hospital were the risk factors that were significant predictors of poor outcome. (Hospitalisation was defined as patients admitted once during follow up).

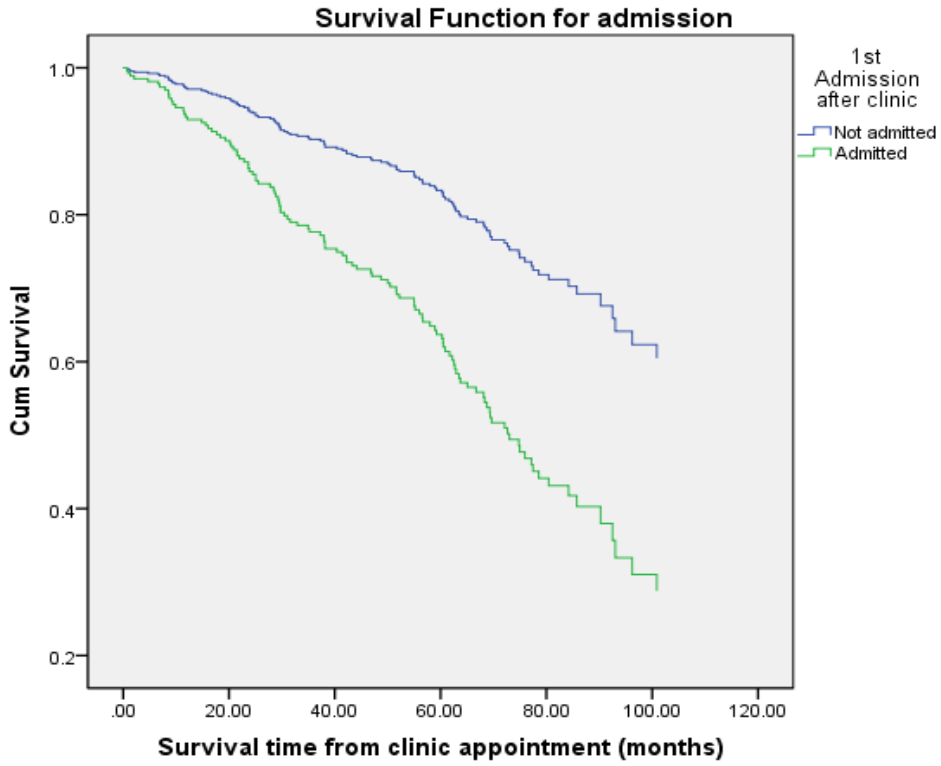
7.15.2 Multivariate analysis

With multivariate analysis age, hypertension, admission to the hospital, and NYHA class continued to be significant predictors of poor prognosis, while atrial fibrillation was not significant. Table 7.15.2

Table 7.15.2 Multivariate analysis for all-cause mortality

	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
Age	.04	.01	12	1	.01	1	1	1.1
Hypertension	-.51	.23	5	1	.02	0.6	0.4	0.9
Atrial Fibrillation	.08	.19	0.2	1	.7	1	0.8	1.6
Admission to hospital	.85	.25	11	1	.01	2.	1.4	3.9
NYHA class	.58	.17	12	1	.01	1.8	1.3	2.5

Graph 7.15.2a Survival function for admission to hospital



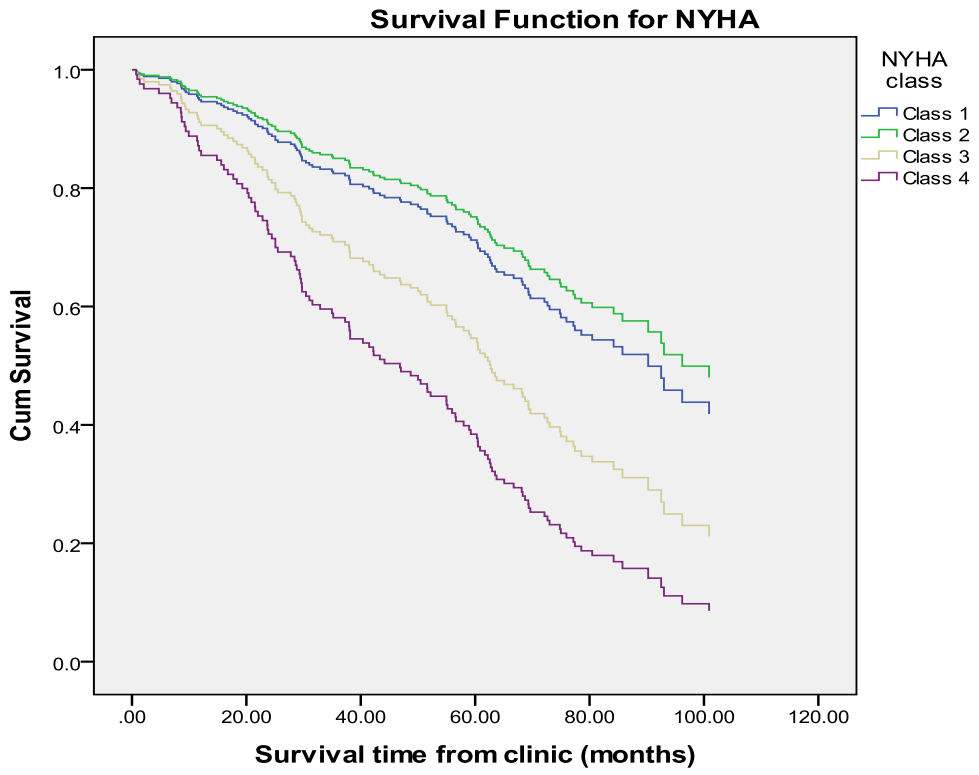
7.15.3 Cox forward conditional regression analysis

Variables found to be significant in multivariate analysis were further assessed using Cox proportional hazard forward conditional regression analysis. Age, hypertension, admission to hospital, and NYHA class continued to be significantly related to survival. Table 7.15.3

Table 7.15.3 Cox forward conditional regression analysis for all-cause mortality

		B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
								Lower	Upper
Step 1	Admission	1	.24	20.2	1	.00	3	1.8	5
Step 2	Age	0.05	.01	13.5	1	.00	1	1	1
	Admission	0.9	.25	13.4	1	.00	2.5	1.5	4
Step 3	Age	0.05	.01	13.7	1	.00	1.0	1	1
	Admission	0.8	.25	11.3	1	.01	2.3	1.4	4
	NYHA class			13	3	.05			
Step 4	Age	0.05	.01	13	1	.00	1.05	1	1.1
	Hypertension	-0.52	.22	5.3	1	.02	.6	0.4	1
	Admission	0.84	.25	11	1	.00	2.3	1.4	3.8
	NYHA class			14	3	.00			

Graph 7.15.3 survival function for NYHA class



Patients in NYHA class 3 and 4 had a poorer prognosis than NYHA class 1 and 2.

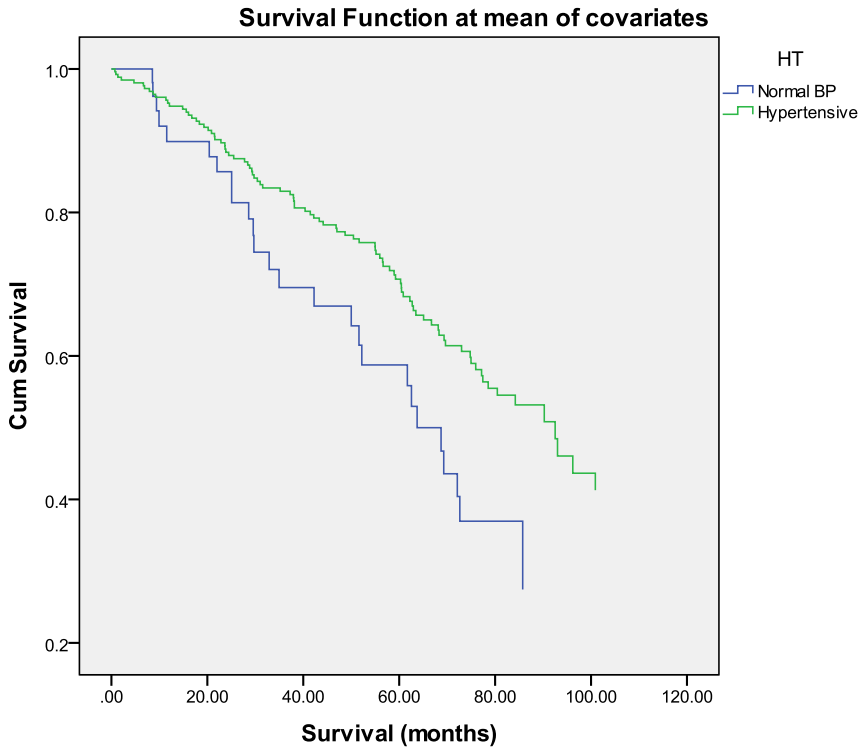
Graph 7.15.3

7.16 Analysis of survival function using stratification

The categorical co variants (hypertension, admission to hospital, and NYHA class) found to be significant in the forward conditional regression for all-cause mortality were analysed for model checking using individual variable stratification. In stratified proportional hazards model separate baseline hazards are computed for each level of the stratification variable, while regression coefficients for the remaining covariates are equal across the strata.

7.16.1 Hypertension

Of the 118 events, 92 (78%) patients had a history of hypertension, and 26 (22%) had normal blood pressure. Data were censored for 110 hypertensive and 13 normal blood pressure patients. When hypertension as a risk factor is factorised, patients with a history of hypertension had a better outcome as compared to the patients with no history of hypertension. This apparent paradox could possibly be due to the effect of medications for hypertension, but was also affected by the large number of censored patient data in the hypertensive group. Graph 7.16.1

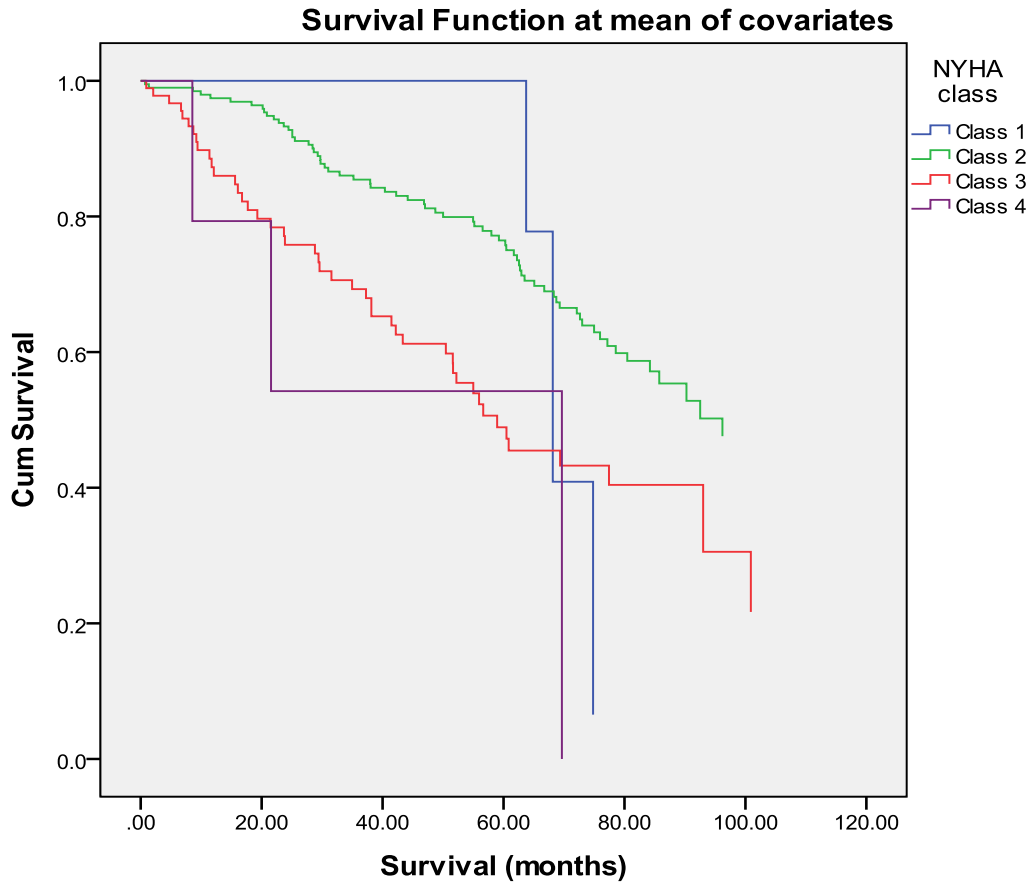


Note: - [Survival function at mean of the covariates shows the survival curves adjusted for the covariates in a regression model]

7.16.2 NYHA class

Stratification of the data by NYHA classification for model checking showed that there were 67 events in NYHA class 2 and 45 events in NYHA class 3. NYHA class 2 had a better prognosis than NYHA class 3. Graph 7.16.2

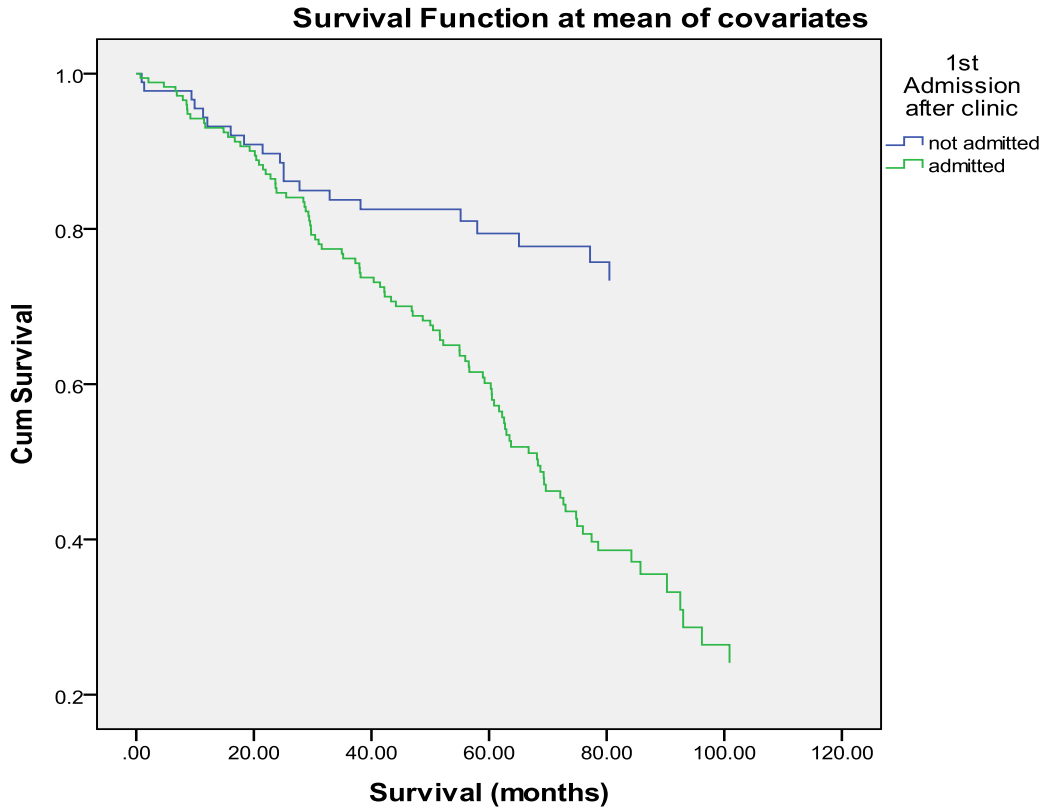
Graph 7.16.2 Survival function for NYHA class



7.16.3 Admission to the hospital

Of the 118 patients who died, 98 (83%) had at least one admission to the hospital. Admission to the hospital for any reason was a predictor of poor outcome. Graph 7.16.3

Graph 7.16.3 Survival after admission to hospital



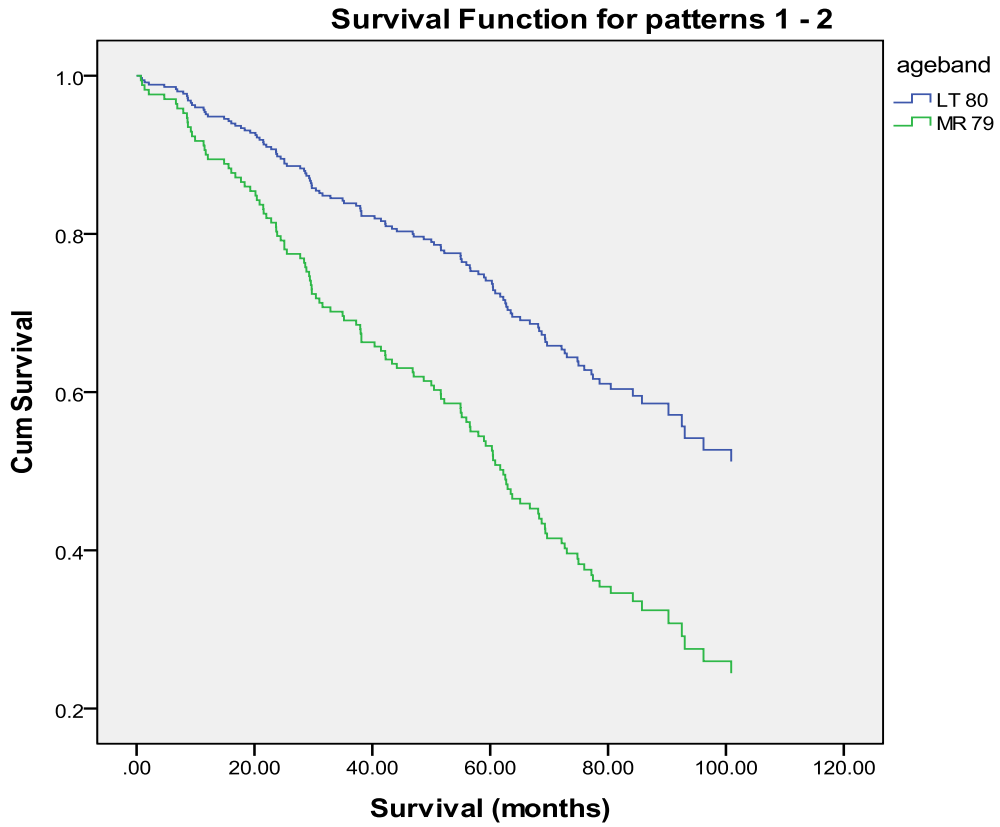
7.17 Age band analysis

The raw data suggested a difference in mortality at the higher end of the age range. To analyse the affect of age on all-cause mortality, we converted age into a categorical variable and divided patients according to the median age in two groups (> 79 years and < 80 years). One hundred and thirty eight patients were less than 80 years old, of which 53 died, and 103 patients were more than 79 years old of whom 65 died. The higher age group had a worse prognosis. Table7.17 & Graph 7.17a & b

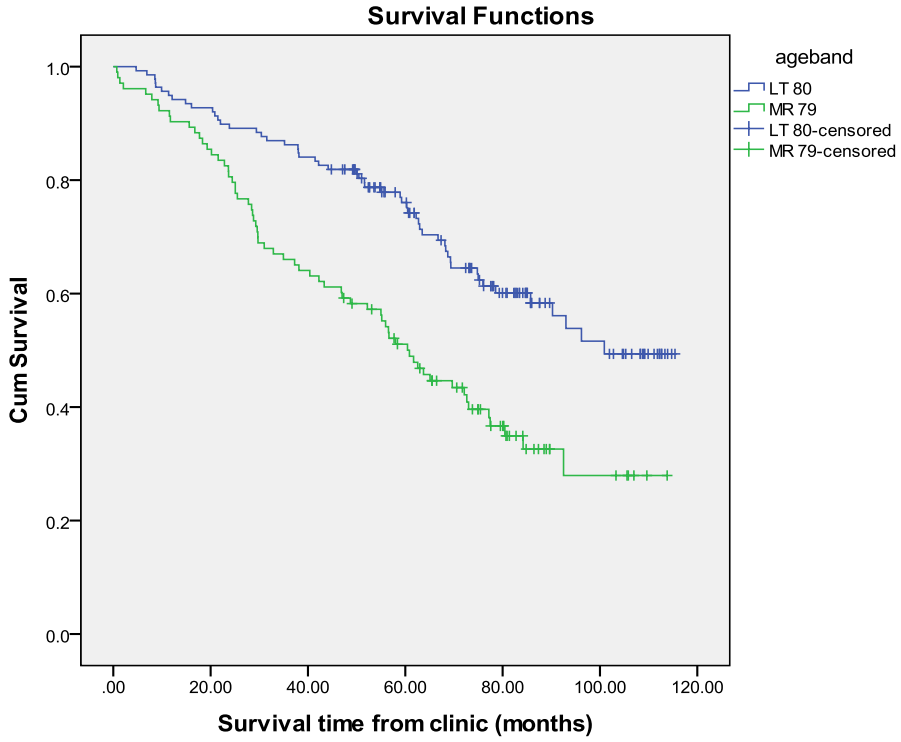
Table 7.17 Age band analysis

	B	SE	Wald	Df	P	Odds ratio	95.0% CI for OR	
							Lower	Upper
Age band	.74	.18	15.9	1	.00	2.1	1.4	3

Graph 7.17a Survival function for age band.



Graph 7.17b Kaplan Meier survival curve for age band.



7.17.1 Multivariate and regression analysis using age band

When data were analysed using ageband instead of “age” as a variable in the Cox multivariable proportional hazard model, gender, hypertension, ageband, and NYHA class were significantly related to poor survival. COPD was not significant. When these variables were further analysed using forward stepwise (conditional logistic regression) the four variables continued to be significantly related to poor survival. Table 7.17.1

Table 7.17.1 Cox forward conditional regression analysis for age band

		B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
								Lower	Upper
Step 1	Age band	.74	.18	15.9	1	.00	2.1	1.4	3
Step 2	Age band	.71	.18	14.1	1	.00	2.0	1.4	2.9
	NYHA class			14.1	3	.00			
Step 3	Gender	-.46	.20	5.3	1	.02	.6	.4	.9
	Age band	.79	.19	17.1	1	.00	2.2	1.5	3.2
	NYHA class			15.2	3	.00			
Step 4	Gender	-.49	.20	5.8	1	.01	.6	.4	.9
	HT	-.52	.22	5.4	1	.02	.5	.3	.9
	Age band	.76	.19	15.7	1	.00	2.1	1.4	3.1
	NYHA class			16.1	3	.00			

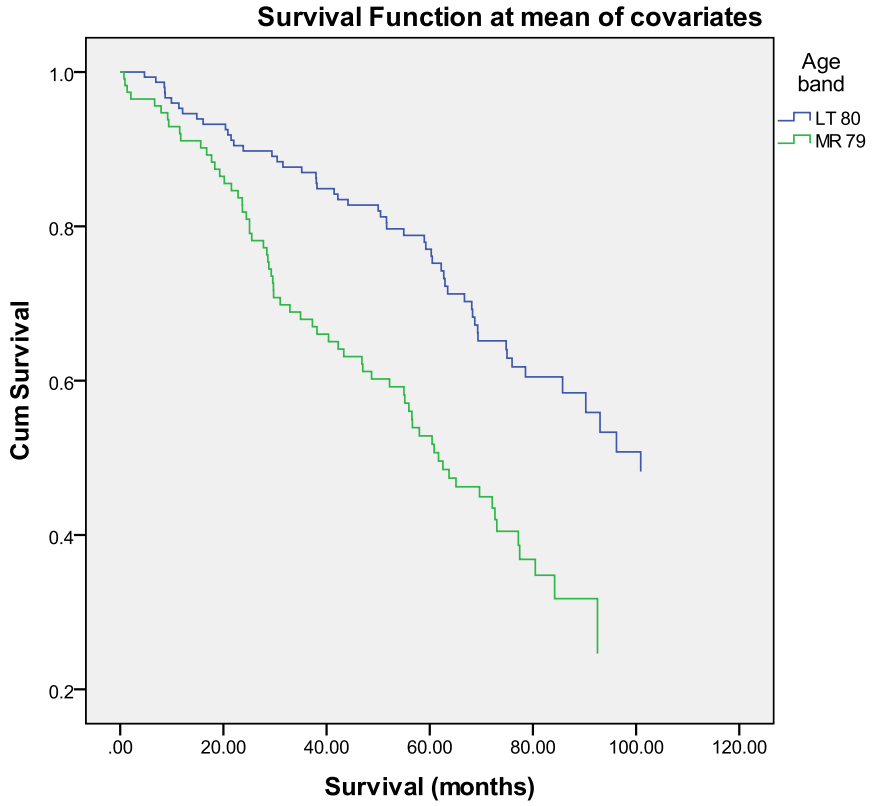
7.17.2 Stratification with age band

When data were analysed by stratifying ageband, the curves were parallel with no substantial difference as compared to when the age variable was used for stratification. Table and graph 7.17.2

Table 7.17.2 Multivariable analysis with age band as stratification

	B	SE	Wald	Df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
Gender	-0.5	0.2	5.9	1	.01	0.6	0.4	0.9
Hypertension	-0.5	0.2	5	1	.02	0.6	0.4	0.9
NYHA class			16.2	3	.01			

Graph 7.17.2 survival for age band stratification



When ageband variable data are analysed using stratification for gender, hypertension, and NYHA class, the survival curves cross over suggesting non significance.

7.17.3 Ageband and gender interaction

The possibility of interaction between ageband and gender was explored. When we analyse for interaction between ageband and gender variables, ageband continues to be statistically significant but gender and ageband*gender interaction are not

significant and there is no interaction between ageband and gender. This is a different model as it attempts to seek an interaction where there is none. In summary all modelling, where appropriate, has legitimately not included ageband and gender interaction. Table 7.17.3

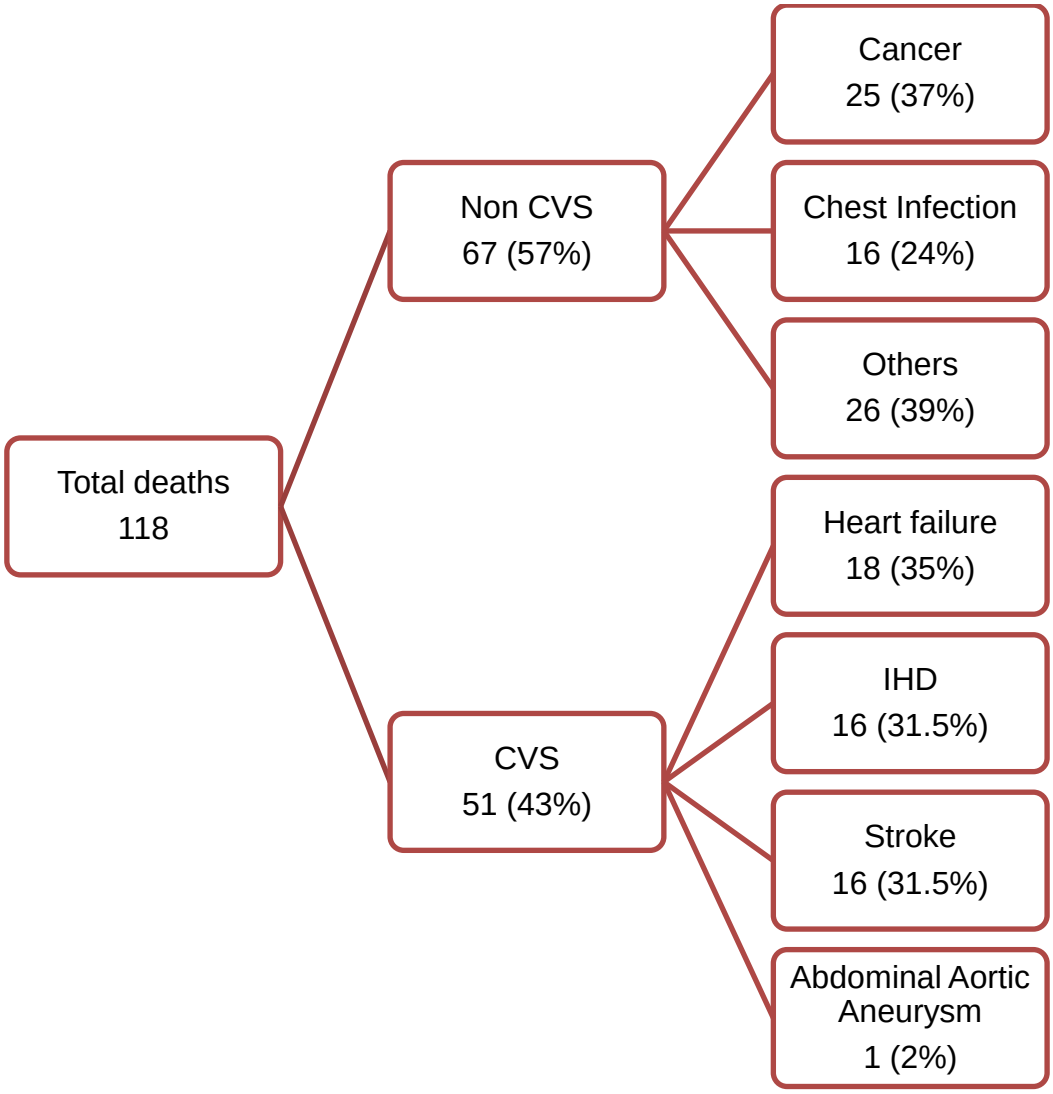
Table 7.17.3 Ageband and gender interaction

	B	SE	Wald	Df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
Gender	.50	.27	3.2	1	.07	1.6	1	2.8
Ageband	.90	.25	13.4	1	.00	2.4	1.5	4
Ageband*gender	-.22	.39	0.31	1	.57	.8	0.4	1.7

7.18 Cause of death

Patients with HFpEF had more non cardiovascular deaths (57%) than cardiovascular (43%) deaths. Heart failure was more common in the cardiovascular category and cancer in the non-cardiovascular category. Flow diagram 7.18

Flow diagram 7.18 Cause of death



7.19 Prognostic factors for cardiovascular deaths

7.19.1 Univariate and multivariate risk factor analysis

In the univariate model for cardiovascular deaths age, gender, atrial fibrillation, diabetes, and admission to hospital were associated with a poor outcome. Table 7.19

In the multivariable analysis age, gender, atrial fibrillation and diabetes continued to be significantly associated with poor prognosis. As in the analysis of all-cause mortality, females had a better prognosis than the males for the cardiovascular deaths. Admission to the hospital was not a significant risk factor for cardiovascular deaths. Table 7.19.1

Table 7.19 Univariate analysis for cardiovascular deaths

	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
Age	.07	.02	11	1	.01	1	1	1.1
Gender	-.72	.28	6.3	1	.01	.48	0.3	0.9
Hypertension	-.42	.35	1.4	1	.23	.65	0.3	1
Atrial fibrillation	1.02	.29	12.6	1	.00	2.7	1.6	4.8
Diabetes	.68	.3	5.2	1	.02	1.9	1.1	3.5
IHD	.54	.28	3.6	1	.05	1.7	.98	3
MI	.45	.34	1.7	1	.18	1.6	0.8	3.1
COPD	-.01	.72	.0	1	.98	1	.23	4
Stroke	.67	.59	1.3	1	.25	2	0.6	6.3
Admission	1.04	.36	8	1	.00	3	1.4	5.8

Table17.9.1 Multivariate analysis for cardiovascular deaths

	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
Age	.10	.02	17.4	1	.00	1.1	1	1.1
Gender	-.97	.35	7.4	1	.00	0.3	.2	.7
Smoker			1.1	2	.56			
Smoker (1)	-.12	1.05	.0	1	.90	0.8	.1	6.9
Smoker (2)	.34	.33	1	1	.30	1.5	.7	2.7
Hypertension	-.41	.37	1.2	1	.27	0.6	.3	1.3
Atrial fibrillation	.78	.32	5.9	1	.01	2.2	1.2	4.1
Diabetes	.85	.34	6.2	1	.01	2.3	1.2	4.5
IHD	.22	.32	.4	1	.48	1.2	.6	2.3
MI	.53	.42	1.6	1	.20	1.7	.7	3.9
COPD/ asthma	-.76	.80	.9	1	.34	.5	.09	2.2
Stroke	-1.20	.82	2.1	1	.14	.3	.06	1.5
NYHA class			4.4	3	.21			
Admission	.59	.38	2.3	1	.12	1.8	.8	3.8

7.19.2 Forward conditional regression analysis

Using forward conditional regression analysis for cardiovascular risk factors, age, gender, atrial fibrillation, and diabetes were significantly related to poor outcome. Data presented in appendix 4 as Table 7.19.2.

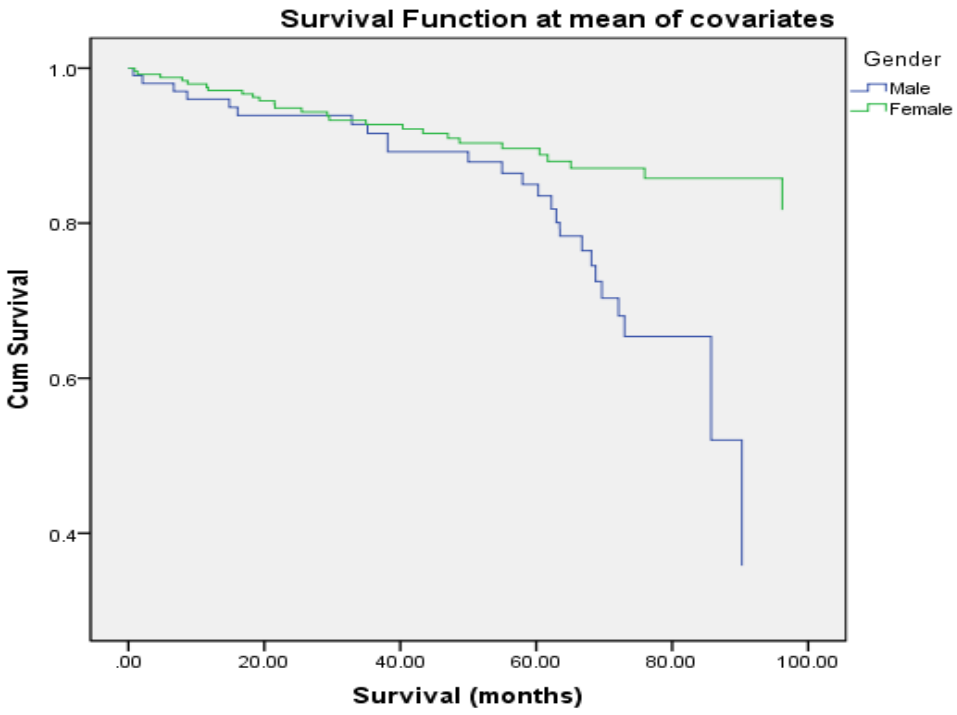
7.20 Stratification for cardiovascular risk factors

The categorical co variants (gender, diabetes, and atrial fibrillation) found to be significant in the forward conditional regression analysis for cardiovascular mortality were analysed for model checking using individual variable stratification.

7.20.1 Gender

When data are stratified according to gender, of the 51 cardiovascular deaths there were 25 male deaths with 39 censored, and 26 female deaths with 131 censored. The survival curves are parallel until up to five years of follow up, when as with the all-cause mortality stratification, there is drop in male survival. Graph 7.20.1

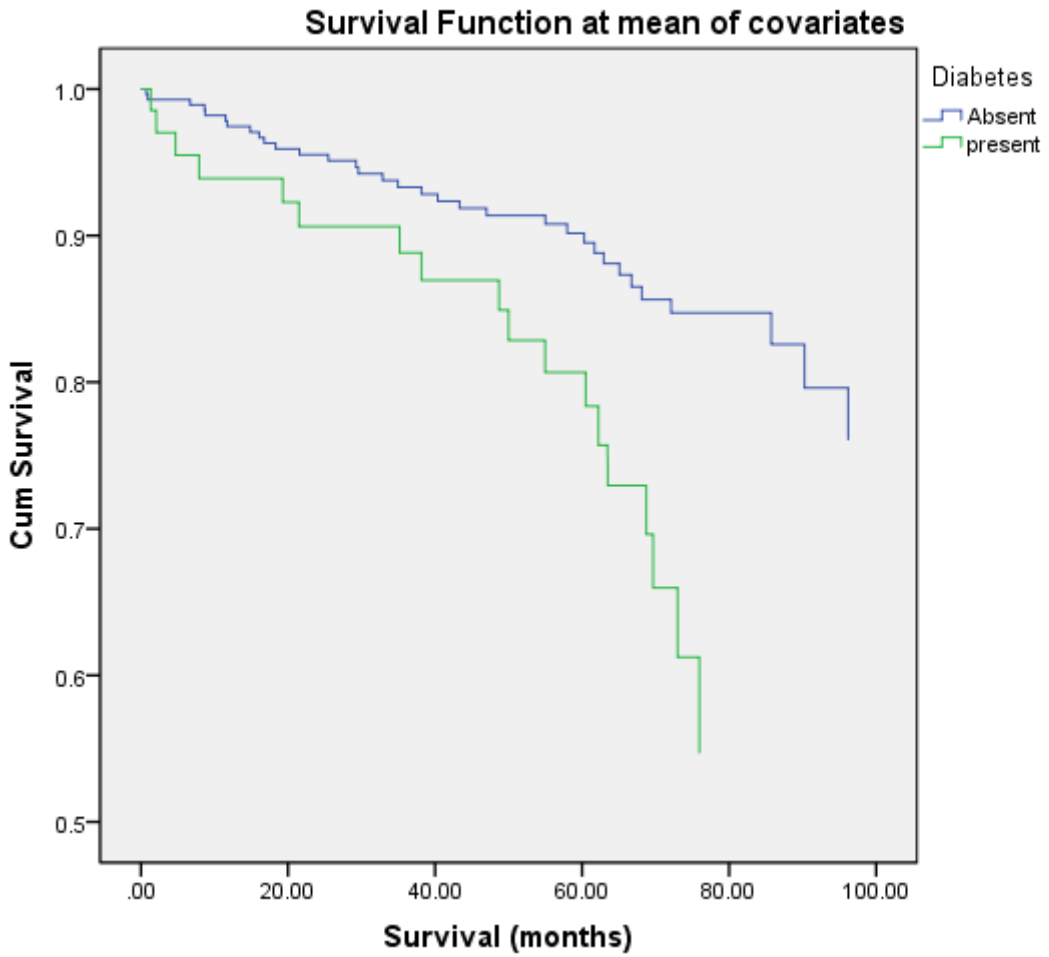
Graph 7.20.1 Survival function for gender stratification



7.20.2 Diabetes

Of the 51 patients with cardiovascular deaths 18 had diabetes. Patients with diabetes had a poorer outcome. Graph 7.20.2

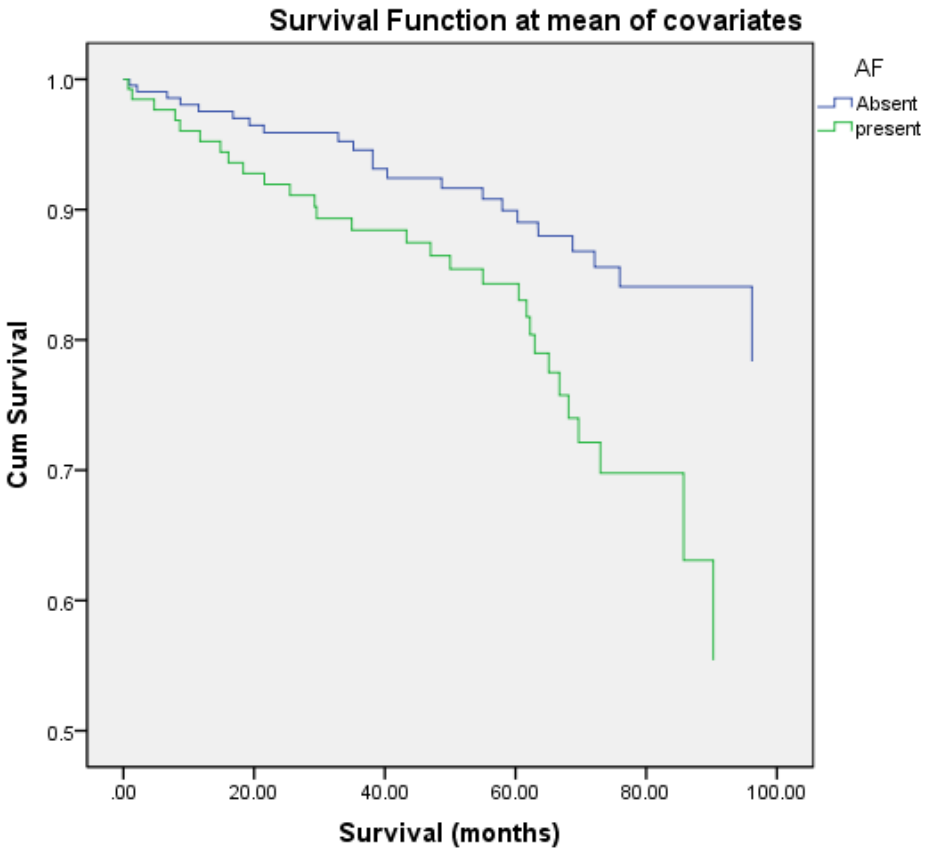
Graph 7.20.2 Stratification for diabetes



7.20.3 Atrial fibrillation

Survival function shows that the curves diverge early on, thus suggesting that patients who had atrial fibrillation were more likely to die of cardiovascular cause. Graph 7.20.3

Graph 7.20.3 Survival function for atrial fibrillation



7.21 Conclusions and discussion

7.21.1 Descriptive analysis

- In our study HFpEF patients were more likely to be females, and to have hypertension and atrial fibrillation as risk factors. These findings are consistent with other published studies in the literature (117, 225).

- At the clinic appointment, patients had symptoms for 6 months on average, and most commonly had NYHA class 2 symptoms.

- Cardiomegaly and atrial fibrillation were the commonest findings on the chest X-ray and ECG respectively.

- Though the mean values of blood test results for serum urea, creatinine, sodium, potassium and haemoglobin were within the normal limits, abnormal

results, above the normal range for urea and creatinine were present in for 4 and 31 percent patients respectively. Serum sodium <135 mmols/l in 4% and potassium ≥ 6 mmols/l in 1% of the patients was also present.

- At the clinic appointment 45% of the patients were already on an ACE inhibitor / ARB and 34% on a beta blocker. Following the clinic appointment another 8% were started on an ACEi / ARBs and 11% on a beta blocker.

- In the absence of a firm diagnosis, the commonest reasons ascribed for shortness of breath were atrial fibrillation and hypertension in this group.

- Only small numbers (24%) were reviewed in the follow up clinic.

7.21.2 Admission data analysis

- The majority (65%) of patients had at least one admission to hospital. The average time from the clinic appointment to first admission was 29.4 months. Patients were mostly admitted with shortness of breath and chest pain.

- The mean systolic and diastolic blood pressures on admission were significantly lower than the clinic readings. This could be due to the effects of the medications patients were taking or a marker of general ill health.

- The blood tests on admission showed a significant increase in urea and creatinine level compared to the previous clinic results.

- On admission 7% of the patients had significant hyperkalemia and 19% had significant hyponateremia compared to the results from the clinic.

- Admission to the hospital was a significant risk factor for all cause mortality but not cardiovascular deaths. Patients needing admission to the hospital are generally sicker than the general population and have a worse prognosis.

- Cancer, stroke, and chronic kidney disease were the leading co-morbidities that developed during the follow up period in the HFpEF group.

7.21.3 Drug data analysis

- There was a trend towards better prognosis for patients who were taking an ACEi and beta blockers in the HFpEF group. This was also true for the duration they had been taking these medications, with patients who had been taking drugs for a longer duration having better outcome. The survival benefit of taking an ACEi is at variance with the major randomised clinical trials in HFpEF patients (PEP-CHF, CHARM preserved, I-Preserved) which had not shown any survival benefit with ACEi / ARBs.

  The possible explanation for the apparent survival benefit of taking an ACEi is likely because the sicker patients may not be able to take all the protector drugs and thus have a poor outcome. Also unlike the clinical trials ours is a real world cohort of patients and thus the populations studied were different giving different results.

  The criteria used to enrol patients for the CHARM (115) trial were less rigorous. Patients had to be in NYHA class 2-4, with a history of hospitalisation for a cardiac cause, and an LVEF >40%. There was no prerequisite for any objective evidence of diastolic dysfunction or signs of HF. For PEP-CHF (116) study patients were > 70 years old, treated with diuretics for a clinical diagnosis of CHF due to LV diastolic dysfunction, hospitalised for a cardiovascular cause within 6 months, and able to walk unaided. This study excluded a large number of patients who were less than 70 years. Also, the clinical diagnosis of HF was only partially supported by patient characteristics and the patients with mild symptoms could have had other conditions than HF.

While in the I-PRESERVE (117) study many of the patients may not have had HF. Also the blood pressure lowering effect of the ACEi / ABR's could be responsible for the beneficial effect seen.

- Similar to the SENIORS (118) trial our cohort of patients who were taking beta blockers showed improved outcome for all cause mortality.

7.21.4 All-cause mortality data analysis

- Co variants age, hypertension, NYHA class, and admission to hospital were significantly related to poor outcome in all-cause mortality.

- Though the number of females in the HFpEF group was significantly more, the all-cause mortality was not significantly different between males and females.

- When data were analysed using age as a categorical variable by banding, those patients who are older than 80 years had a poorer prognosis as compared with those less than 80 year old.

- There was no statistical interaction demonstrated between ageband and gender when these were analysed separately.

7.21.5 Cardiovascular mortality data analysis

- In our study HFpEF patients had more non cardiovascular deaths than cardiovascular deaths. This result is in contrast to the data from the prospective trial but consistent with other population based cohort studies. In the I-PRESERVE (117) trial 70% of patients had cardiovascular deaths. In the population based study of Henkel and colleagues (127) 49% had a non cardiovascular death. The reasons for this could be the retrospective cohort study design, which unlike the prospective trials, includes patients with other serious illnesses and co morbidities which also affect survival.

- Cancer (37%), followed by chest infection (24%), was the leading cause of non cardiovascular deaths in this group. These results are similar to data from other trials. Henkel et al (127) found cancer (23%) and pulmonary disease (29%) as the leading cause of non cardiovascular deaths.

- Heart failure was the leading cause of cardiovascular mortality, followed by equal numbers of stroke and deaths secondary to ischemic heart disease.

- Age, gender, atrial fibrillation, and diabetes were predictors of a poor outcome for cardiovascular deaths. Those in the younger age group and females had a better outcome as compared to older patients and males. Advanced age, male sex, and diabetes mellitus have been found to be predictors of a poor outcome in other studies (127, 240).

- In conclusion HFpEF patients were more likely to be females, older, and had a poor overall survival with more non cardiovascular deaths than cardiovascular deaths. In patients who were taking ACEi /ARBs and beta blockers there was a trend towards improved survival.

Chapter 8

Left ventricular systolic dysfunction (LVSD) - Results

Left ventricular systolic dysfunction was diagnosed in 270 (26%) of the 1041 patients. Case notes for two patients were not available for review and the analysis is done using the data for 268 patients.

8.1 Demographics

Mean Age, years (range)	74 (60)
Males	164 (61%)
Females	104 (39%)
Hypertension	114 (43%)
Atrial fibrillation	66 (25%)
Diabetes	42 (16%)
History of IHD/MI	140 (52%)
COPD	58 (22%)
Stroke	34 (13%)

8.1.1 Smoking history

Smoking is a strong risk factor for cardiovascular disease. Patients who were diagnosed to have LVSD were most commonly ex-smokers 136 (51%), while 83 (31%) patients had never smoked, and 49 (18%) were current smokers.

8.2 Descriptive analysis of clinical features

8.2.1 Referral symptoms

Patients had been symptomatic for an average of 5.46 months (median and mode 3 months, with maximum of 60 months) before they were referred to the HF clinic. Shortness of breath and swelling of ankles were the two most common reasons for referral to the HF clinic. Table 8.2.1

Table 8.2.1 Referral reason

Shortness of breath	262 (98%)
Swelling of ankles	190 (71%)
Orthopnoea	120 (45%)
Paroxysmal nocturnal dyspnoea	70 (26%)
Fatigue	64 (24%)
Palpitations	25 (9%)

8.2.2 NYHA class

The majority of patients were in NYHA class 3. Table 8.2.2

Table 8.2.2 NYHA classification in clinic

	Frequency	Percent
NYHA class 1	4	2
NYHA class 2	117	44
NYHA class 3	134	50
NYHA class 4	13	4
Total	268	100

8.2.3 Clinical examination

At the time of referral by the general practitioner 191 (71%) patients had swollen ankles, but when reviewed in the HF clinic, only 90 (34%) patients had oedema. This may be because the majority of these patients were started on a diuretic by their GP prior to their appointment in the HF clinic.

At the clinic appointment 115 (43%) patients had a raised JVP; other clinical findings are presented in the table below. Table 8.3.3

Table 8.2.3 Clinical examination findings

Swelling of ankles	90 (34%)
Raised JVP	115 (43%)
Systolic murmur	138 (52%)
Diastolic murmur	11 (4%)
Lung crepitation	84 (31%)
Dull bases on chest examination	16 (6%)
Wheeze	24 (9%)

8.2.4 Blood pressure and heart rate

All except one patient had their blood pressure and heart rate recorded at the HF clinic review. Table 8.2.4

Table 8.2.4 Blood pressure and heart rate in the clinic

	Systolic BP	Diastolic BP	Heart rate
Total readings	267	268	268
Missing	1	0	0
Mean value (mmHg)	141.5	78.6	82.5
Median value (mmHg)	140	80	80
Mode (mmHg)	140	80	80
Std. Deviation	23.7	13.2	20.4
Minimum (mmHg)	78	50	34
Maximum (mmHg)	240	140	160

8.2.5 ECG findings

Only 27 (10%) of the patients had a normal ECG. Some patients had more than one abnormality present on ECG. Table 8.2.5

Table 8.2.5 ECG findings

Normal ECG	27 (10%)
LAD	26 (10%)
LBBB	66 (25%)
LVH	38 (14%)
Atrial fibrillation	70 (26%)
Heart block	27 (9%)
T wave changes	55 (21%)
Previous MI	31 (12%)
RBBB	16 (6%)

Most of the patients with heart block had 1st degree heart block (prolonged PR interval). Two patients had trifasicular block and 2 were in complete heart block. (These were referred for permanent pacemaker implantation).

8.2.6 Chest X- ray

All patients had a chest X - ray at the time of clinical appointment. This was reviewed and reported by the physician in the HF clinic. The chest X - rays were also formally reported independently by the radiologist unaware of the results of the echocardiogram, the clinical history, or the clinical findings.

Only a minority (20%) of the patients had a chest X - ray reported as normal. Cardiomegaly (68%) was the most common finding followed by upper lobe venous diversion (29%), both suggestive of fluid overload. A small number of patients had pulmonary oedema (25%). Table 8.2.6

Table 8.2.6 Result of chest X- ray

Normal	54 (20%)
Cardiomegaly	181 (68%)
Upper lobe diversion	77 (29%)
Pulmonary oedema	66 (25%)
Pleural effusion	34 (13%)
COPD changes	20 (7%)

8.2.7 Echocardiography

The echocardiogram remains the cornerstone of diagnosing HF. One hundred and three (38%) patients had severe systolic dysfunction, 90 (34%) had moderate and 75 (28%) had mild LV systolic dysfunction on their echocardiogram. Some patients also had valvular heart disease like mitral regurgitation (MR), tricuspid regurgitation (TR), Aortic regurgitation (AR) and aortic stenosis (AS). Table 8.2.7

Table 8.2.7 Other findings on Echocardiography

E/A reversal	37 (14%)
LVH	63 (24%)
Moderate MR	106 (40%)
Severe MR	29 (11%)
Moderate TR	41 (15%)
Severe TR	15 (6%)
Moderate AR	24 (9%)
Moderate AS	3 (1%)
Severe AS	4 (2%)

8.2.8 Blood tests in the clinic

Blood results for all but one patient were available from the clinic. Table 8.2.8

Table 8.2.8 Blood tests in the clinic

	Sodium (mmol/L)	Potassium (mmol/L)	Urea (mmol/L)	Creatinine (µmol/L)	Cholesterol (mmol/L)	Hb (mg/dl)	Mcv (Fl)
Number	267	267	267	267	196	265	264
Missing value	1	1	1	1	72	3	4
Mean	139	4.3	8	111	4.8	13	89
Median	140	4.2	7	104	4.6	13	90
Mode	141	4	7	110	5	14	90
Std. Deviation	3.6	0.4	3.6	40.2	1.3	1.7	8.1
Minimum	127	3	2	46	2	7	5
Maximum	148	5	26	422	10	19	104

8.2.9 Medications

At the time of the clinic appointment a high proportion of patients (85%) were taking loop diuretics. Some patients were taking an ACEi (55%) and a beta blocker (27%). 60% patients were taking aspirin. Table 8.2.9

Table 8.2.9 Medications at clinic review

ACEi / ARBs	148 (55%)
Beta blockers	72 (27%)
Diuretics	228 (85%)
Aldosterone antagonist	19 (7%)
Digoxin	42 (16%)
Aspirin	162 (60%)
Warfarin	35 (13%)

8.2.10 Other medications in the clinic

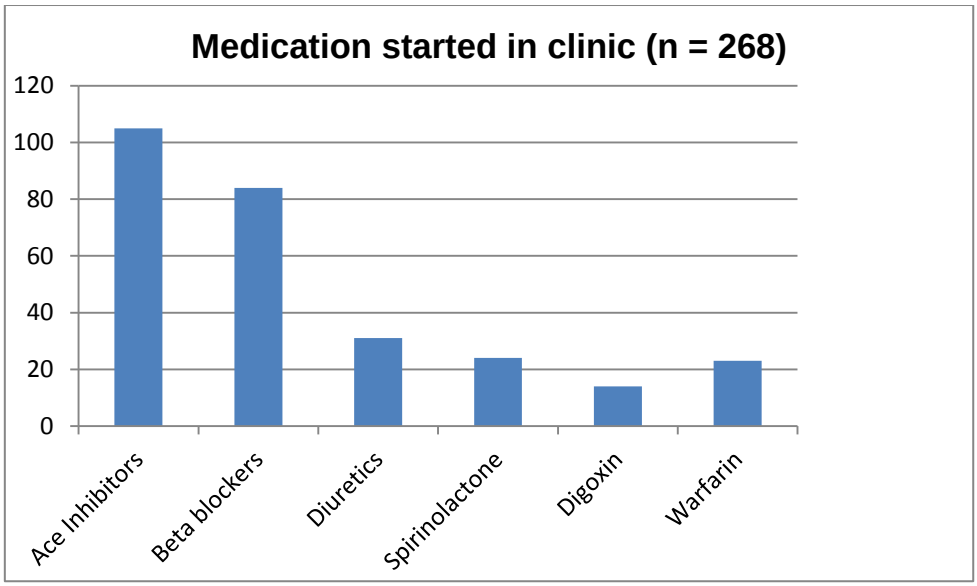
Table 8.2.10 Other medications

Statins	80 (30%)
Calcium channel blockers	46 (17%)
Inhalers	41(15%)
Nitrates	18 (8%)
Clopidogrel	9 (3%)
Alpha blockers	10 (4%)

8.2.11 Changes made to medication

At the clinic appointment the patient's current treatment was reviewed by the physician and changes made to optimise their medical therapy as per the clinical guidelines. Chart 8.2.11

Chart 8.2.11 Medication started in clinic

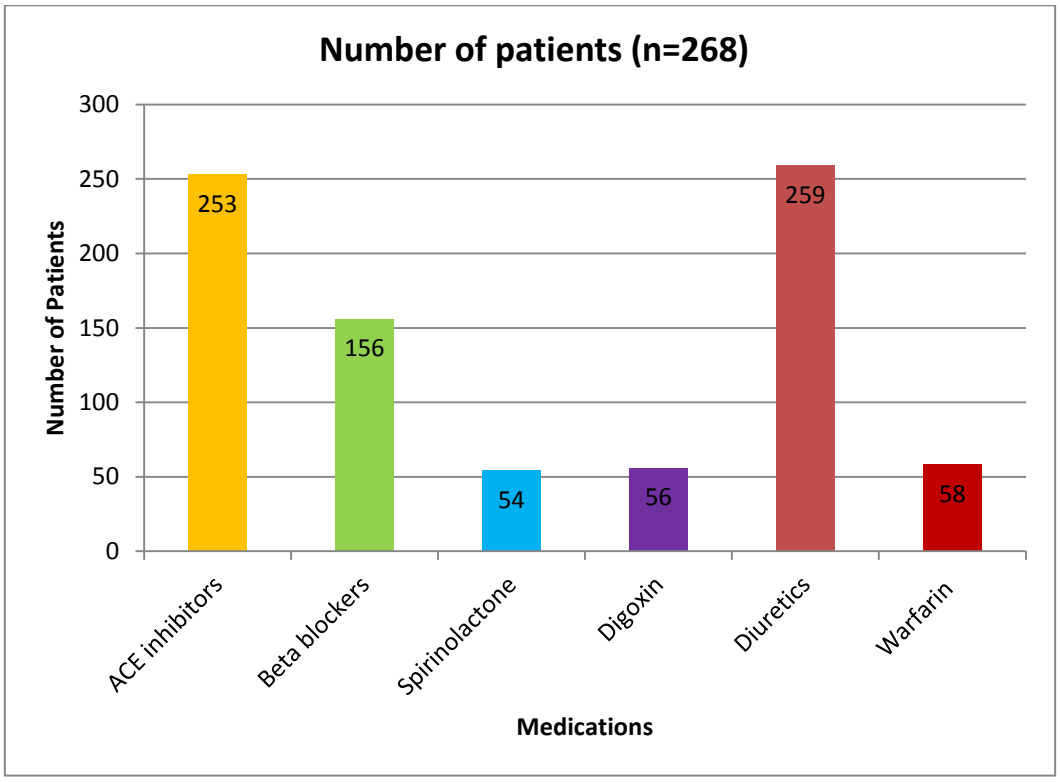


8.2.12 Evidence based medical therapy prescribed in the clinic

Following the first clinic review a high proportion of the patients were prescribed evidence based medical therapy as per clinical guidelines. After the clinic review an ACEi or ARB was prescribed to additional 39% patients and a beta blocker to

additional 31% of the patients. A diuretic was added in 12% of the patients. Thus high proportions of patients were on evidence based treatment at the end of clinic assessment. Chart 8.2.12

Chart 8.2.12 Medications prescribed in the clinic



Some patients were started on evidence based treatment later in the titration clinic.

8.2.13 Cause of LVSD

Patients were not routinely investigated for the cause of HF. From the history, physical examination, and investigations 49 patients were thought to have HF due to ischemia, and 13 were diagnosed with cardiomyopathy.

8.2.14 Follow up in the clinic

Two hundred and seventeen (81%) of the patients had one or more follow up visits to the HF clinic. The average number of visits made was 5.3 (median 4, range 31). The follow up visits were to the titration clinic led by the HF specialist nurse. Patients are assessed for symptom control and side effects. All had a physical examination and

weight was checked. Doses of ACEi /ARBs, and beta blockers were titrated to the maximum tolerated and once patients were on optimal medical therapy (OMT) they were discharged back to their general practitioners.

8.3 Admission to hospital

Seventy percent of the patient had at least one admission to hospital. Table 8.3

Table 8.3 Admission to hospital

	Frequency	Percent
Not admitted	79	30
Admitted	189	70
Total	268	100

8.3.1 Time to first admission

On average patients were admitted 21 months after the clinic appointment. Three patients were quite symptomatic with shortness of breath needing admission form the clinic. Table 8.3.1

Table 8.3.1 Time to first admission from clinic review

Admitted (n)	189
Not admitted	79
Mean (months)	21.1
Median (months)	15.5
Std. Deviation (months)	21
Minimum (months)	0.0
Maximum (months)	84.7

8.3.2 Reason for admission

The most common reason for admission was breathlessness (32%), attributed to decompensated HF. Twenty one patients (11%) presented with symptoms of chest

pain and myocardial infarction. Seven patients presented with bleeding. Unlike the HFpEF group no patient was admitted with a diagnosis of cancer. Table 8.3.2

Table 8.3.2 Reason for admission

Shortness of breath	61 (32%)
Chest pain	21 (11%)
Fall / Fracture	13 (7%)
Collapse	25 (13%)
Stroke	14 (7%)
Cancer	0
Confusion	1
Diarrhoea	5 (3%)
Bleeding	7 (4%)
Acute renal failure	1
Cardiac arrest	2
Other	41 (22%)

Most patients admitted to the hospital were managed on the medical wards and looked after by general medical specialists. One hundred and thirty (69%) patients were under the care of general medical specialists. Forty (21%) patients were looked after by a cardiologist, and 19 (10%) were admitted under the surgical specialists.

8.3.3 Systolic and diastolic blood pressure

All patients had blood pressure checked on admission. Data for systolic BP was not available for 2 patients and the diastolic blood pressure was not available for 1 patient. Heart rate was recorded in all patients. Table 8.3.3

Table 8.3.3 Systolic and diastolic blood pressure

	Systolic BP (mmHg)	Diastolic BP (mmHg)	Heart rate (per minute)
Data available for	187	188	188
Missing data	2	1	0
Mean	128	70	79
Median	128	70	80
Std. Deviation	29	15	19
Minimum	54	32	33
Maximum	210	130	140

8.3.4 Comparison of clinic and admission blood pressures

The mean systolic and diastolic blood pressures were significantly lower at the first admission as compared to the readings at the first clinic appointment. The low BP might simply be as a consequence of the reason for admission or due to the fact that more patients had their treatment for HF optimised with an ACEi and a beta blocker. However the mean heart rate was not significantly different before and after admission. Table 8.3.4 a & b

Table 8.3.4a Blood pressure & Heart rate change [Paired Samples Statistics].

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Systolic BP in clinic	140	186	23.2	1.7
	Systolic BP on admission	128	186	28.5	2.1
Pair 2	Diastolic BP in clinic	77	188	12.5	0.9
	Diastolic BP on admission	70	188	15.1	1
Pair 3	HR in clinic	82	188	20.4	1.5
	HR on admission	80	188	18.6	1.4

Table 8.3.4b Blood pressure and HR (Paired Difference)

		Mean	Std. Deviation	Std. Error Mean	95% CI of the Difference		t	df	p
					Lower	Upper			
Pair 1	Systolic BP clinic – Systolic BP admission	12	30.3	2.2	7.9	16.7	5.5	185	.00
Pair 2	Diastolic BP clinic –Diastolic BP admission	6.6	16.8	1.2	4.2	9.1	5.5	187	.00
Pair 3	HR clinic - HR admission	2.2	24.3	1.8	-1.3	5.6	1.2	187	.22

8.3.5 Clinical characteristics

Shortness of breath was the presenting complaint in 61 (32%) of the patients. Twenty three (9%) had increased weight. JVP was raised in 37 (14%) of the patients and 64 (24%) had swollen ankles. One hundred and ten (41%), patients had NYHA class assessed and the majority were in NYHA class 3. Table 8.3.5

Table 8.3.5 NYHA class on admission

NYHA class I	5 (5%)
NYHA class II	26 (23%)
NYHA class III	44 (40%)
NYHA class IV	35 (32%)

8.3.6 Blood tests on admission

Blood tests at the time of admission showed that mean values for serum sodium and potassium were within the normal range whereas the mean value for serum urea and creatinine were out of range and higher than the values at the time of clinic appointment. Table 8.3.6

Table 8.3.6 Admission blood tests

	Sodium (mmols/L)	Potassium (mmols/L)	Urea (µmols/L)	Creatinine (mmols/L)	Haemoglobin (gm/dl)
Results available	188	187	188	187	188
Missing data	1	2	1	2	1
Mean	137	4.4	13.9	156	12.6
Median	138	4.3	10.2	123	12.6
Mode	137[a]	4[a]	6	98[a]	14
Std. Deviation	4.8	.7	10.7	101	2.1
Minimum	114	3	3	35	6
Maximum	149	8	71	708	18

[a]= Multiple modes exist. The smallest value is shown.

8.3.7 Comparison of the clinic and admission blood tests

Using a paired sample t-test the mean values of the blood results at the time of the clinic appointment and at the time of admission were compared. Only the mean value for serum sodium was lower at the time of first admission than the clinic value, whereas the mean values for other blood tests like serum potassium, urea, and creatinine had gone up. The change in the mean values was also statistically significant for all the four blood tests (Table 9.3.7a & b). The higher mean value was likely to have been from a combination of use of medications but also a marker of a sicker cohort of the population needing hospital admission. The lower mean value for sodium at the time of admission is likely caused by the use of diuretics and as a consequence of fluid overload. Table 8.3.7a & b

Table 8.3.7a Blood tests clinic and on admission (Paired Samples Statistics)

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Na+ on admission	137	187	4.8	0.3
	Na+ in clinic	138	187	3.6	0.2
Pair 2	K+-on admission	4.4	186	0.7	.05
	K+ in clinic	4.3	186	0.4	.03
Pair 3	Urea-on admission	14	187	10	.7
	Urea in clinic	8	187	3.8	.3
Pair 4	Creatinine admission	156	186	101	7.4
	Creatinine in clinic	114	186	44	3.2

Table 8.3.7b Blood tests in clinic and on admission (Paired Samples Test)

		Paired Differences					t	df	p
		Mean	Std. Deviation	Std. Error Mean	95% CI of the Difference				
					Lower	Upper			
Pair 1	Na+ admission – Na+ in clinic	-1.3	5	0.4	-2	-0.6	-3.5	186	.00
Pair 2	K+ admission – K+ clinic	0.1	0.7	.05	.03	0.3	2.6	185	.00
Pair 3	Urea admission – Urea clinic	5.6	9.5	0.7	4.3	7	8.1	186	.00
Pair 4	Creatinine admission - Creatinine clinic	41.7	87.7	6	29	54	6.5	185	.00

On admission hyponatremia (sodium <135 mmol/l) was present in 21%, and hyperkalemia (potassium >6mmol/l) was present in 4% of the patients. An elevated level of urea (>10mmol/l) and an increase in creatinine (>50% from baseline) was

present in 55% and 31% of the patients respectively. Seven percent of the patients had a haemoglobin value of <10 gm/dl on admission.

8.3.8 Other investigations on admission to hospital

An ECG result on admission was available in 178 patients. Table 8.3.8

Table 8.3.8 ECG findings on admission

Normal	80
Atrial fibrillation	63
LBBB	10
T wave changes	5
Heart block	6
Paced rhythm	7
RBBB	4
Cardiac arrest	2
Not available	11

Chest X-ray findings on admission

Normal	59 (22%)
Cardiomegaly	65 (24%)
Pulmonary oedema	40 (15%)
Consolidation	9
Pleural effusion	12
Cancer	1
Not available	3

8.3.9 Medications on admission

On admission to the hospital 156 (83%) patients were taking an ACEi / ARBs, while 91 (48%) were taking a beta blocker. The majority of the patients 166 (88%) were on diuretics, while 33 (17%) and 34 (17%) were on spironolactone and digoxin respectively.

8.3.10 Change in medication doses

Twenty six (12%) patients had their ACEi stopped and 4 had the ACE inhibitor dose reduced during their hospital admission. Twenty two (12%) patients had their beta blockers stopped. The reason for discontinuing the beta blocker was recorded only in a minority of patients. Acute shortness of breath and bradycardia was the reason in 3 patients each, whilst in 2 patients they were stopped due to hypotension. Seven patients had their dose of diuretics increased on admission and 8 had it stopped. Spironolactone was stopped in 7 patients. The reason for stopping the diuretics could be the worsening of the serum urea, creatinine and potassium values on the blood results.

8.3.11 Length of stay in hospital

One hundred patients had more than one admission to the hospital. On average, patients with LVSD had 2.2 admissions to the hospital. Patients also spent a mean of 24 days as an in-patient. Table 8.3.11

Table 8.3.11 Total stay in hospital

[Number admitted = 189, Number not admitted =79]			
	First admission [total days]	Total Admissions [per patient]	Total days in Hospital [per patient]
Mean	9.5	2.2	22.2
Median	5	2	14
Mode	2	1	1
Std. Deviation	11.5	2.3	24
Minimum	0	0	1
Maximum	75	12	138
Sum	1786	423	4202

8.3.12 Co-morbidities developed during follow-up

Table 8.3.12 Co – morbidities developed during follow-up

Atrial fibrillation	8
Fall /collapse	12
Acute renal failure	15
Stroke	17
Cancer	23
COPD	8
Dementia	9

8.4 Optimal medical therapy (OMT) and duration of use

Two hundred fifty six (96%) of the 268 patients in the LVSD group were prescribed an ACE inhibitor with an average duration of use 63 months. Two hundred patients (75%) had been prescribed a beta blocker with an average duration of use of 59 months. Sixty five (24%) patients were prescribed an aldosterone antagonist and they were taking it for an average of 25 months. Seventy (26%) patients were prescribed digoxin with an average duration of use of 43 months. Table 8.4

Table 8.4 Optimal medical therapy and duration of medications prescribed

	ACEi / ARBs	Beta blockers	Digoxin	Spironolactone
Patients prescribed (n)	256 (96%)	200 (75%)	70 (26%)	65 (24%)
Not prescribed	12	68	198	203
Mean duration (months)	63	59	43	25
Median duration (months)	63	53	40	15
Std. deviation (months)	43	45	38	24
Min duration (months)	0.2	0.1	1.7	0.3
Max duration (months)	223	307	152	86

8.5 Univariate analysis of duration of drug use

In univariate analyses the duration of use for all the four medications was associated with a better prognosis. Table 8.5

Table 8.5 Univariate analysis for duration of drug use

	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR)	
							Lower	Upper
ACEi	-.02	.002	57.8	1	.00	.98	.97	.99
Beta blockers	-.02	.003	59.5	1	.00	.97	.97	.99
Spironolactone	-.03	.008	17.1	1	.00	.96	.95	.98
Digoxin	-.02	.005	9.8	1	.00	.98	.97	.99

8.6 Multivariate analysis of duration of drug use

When all the four medications were analysed using a multivariate model the event rate was only 11 and none of the medications were significantly related to survival. When forward conditional regression analysis was done with all the four medications only spironolactone was statistically significant. (Table 8.6a) These data need to be interpreted cautiously as the event rate is small.

Table 8.6a Multivariate analysis of duration of drug use

	B	SE	Wald	df	p.	Odds ratio	95% CI for OR	
							Lower	Upper
Spironolactone	-.04	.01	6.1	1	.01	.96	.94	.99

If only ACEis and beta blockers were in the equation then both were significantly related to survival. Table 8.6b

Table 8.6b Forward conditional regression analysis for duration of drug use

		B	SE	Wald	df	P	Odds ratio	95% CI for OR	
								Lower	Upper
Step 1	Beta blockers	-.02	.003	57.8	1	.00	.97	.97	.98
Step 2	Ace inhibitor	-.00	.003	4.1	1	.04	.99	.98	1
	Beta blockers	-.01	.003	32.8	1	.00	.98	.97	.98

8.7 Survival analysis for all-cause mortality

8.7.1 Place of death

After a median follow up period of 7.07 years the all-cause mortality was 163 (60%). Of these 105 (64%) were males and 58 (36%) were females Of the 163 patients who died 62 (38%) died at home and 81 (50%) died in the hospital. Data for 20 (12%) patients were not available.

8.7.2 Univariate and multivariate survival analysis

In the univariate analysis using the Cox proportional hazards regression model age, Smoker (current), atrial fibrillation, ischemic heart disease, COPD, stroke, admission, and NYHA class were significantly related to all-cause mortality. Table 8.7.2a

Table 8.7.2a Univariate survival analysis of all-cause mortality risk factors

	B	SE	Wald	df	P	Odds ratio	95.0% CI for OR	
							Lower	Upper
Age	.04	.00	28	1	.00	1.0	1	1.1
Gender	-24	.16	2.1	1	.14	0.7	0.5	1.1
Smoker	.24	.09	6.9	1	.00	1.2	1.1	1.5
Hypertension	.01	.15	.005	1	.94	1	0.7	1.3
Atrial fibrillation	.47	.17	7.5	1	.00	1.6	1.1	2.3
Diabetes	-.38	.23	2.1	1	.14	0.7	0.4	1.1
IHD	.32	.15	3.9	1	.05	1.3	1	1.9
MI	.13	.15	.7	1	.38	1.14	.8	1.5
COPD/Asthma	-.18	.09	4.1	1	.04	.83	.6	.9
Stroke	-.26	.10	6.3	1	.01	.76	.6	.9
NYHA class	.50	.12	15.1	1	.00	1.6	1.2	2.1
Admission	.92	.21	19.3	1	.00	2.5	1.7	3.8

In the multivariate analysis only age, ex-smokers, NYHA class, and admission to hospital were the significant risk factors. Atrial fibrillation, ischemic heart disease, COPD, and stroke were no longer significant. Table 8.7.2b

Table 8.7.2b Multivariate survival analysis for all-cause mortality

	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
Age	.04	.00	15.9	1	.00	1.	1	1.05
Sex	-.18	.18	1	1	.32	.8	.6	1.2
Smoker			6.7	2	.03			
Smoker (currant)	.42	.26	2.5	1	.11	1.5	.9	2.5
Smoker (Ex)	.48	.18	6.5	1	.01	1.6	1	2.3
Hypertension	-.12	.16	0.4	1	.48	.9	.6	1.2
Atrial Fibrillation	.15	.19	0.6	1	.42	1.2	.8	1.7
Diabetes mellitus	-.21	.25	0.6	1	.41	.8	.5	1.3
IHD	.29	.28	1.0	1	.31	1.3	.8	2.3
MI	-.33	.27	1.4	1	.23	.7	.4	1.2
COPD / Asthma	.17	.19	0.7	1	.39	1.1	.8	1.7
Stroke	.34	.22	2.2	1	.13	1.4	.9	2.2
NYHA class			9.4	3	.02			
Admission	.7	.2	11.4	1	.00	2	1	3

8.7.3 Forward conditional regression analysis

Using forward conditional regression analysis, age, ex-smokers, and admission to hospital for any cause were significant risk factors related to survival. NYHA class was significant overall. Gender was not significantly associated to survival (Data presented in Appendix 4 -Table 8.7.3)

8.8 All-cause mortality stratification for model checking

The categorical variables (smoking status, and NYHA class) found to be significant in the forward conditional regression analysis were analysed for model checking using stratification.

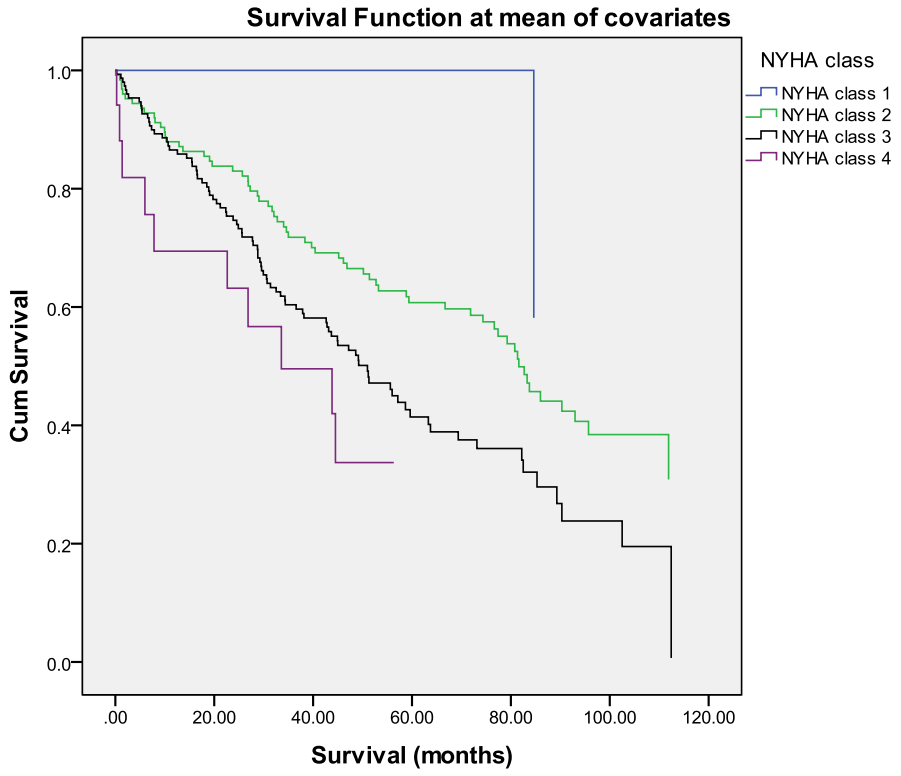
8.8.1 NYHA class

NYHA class 1 had small event rate. NYHA class 2 patients had a better prognosis than NYHA class 3 and 4 patients. Table and graph 8.8.1

Table and graph 8.8.1 NYHA class stratum variable

Stratum	Strata label	Event	Censored	Censored Percent
1	NYHA class 1	1	1	50%
2	NYHA class 2	63	54	46%
3	NYHA class 3	89	45	34%
4	NYHA class 4	10	3	23%
Total		163	103	39%

Graph 8.8.1 NYHA class stratification



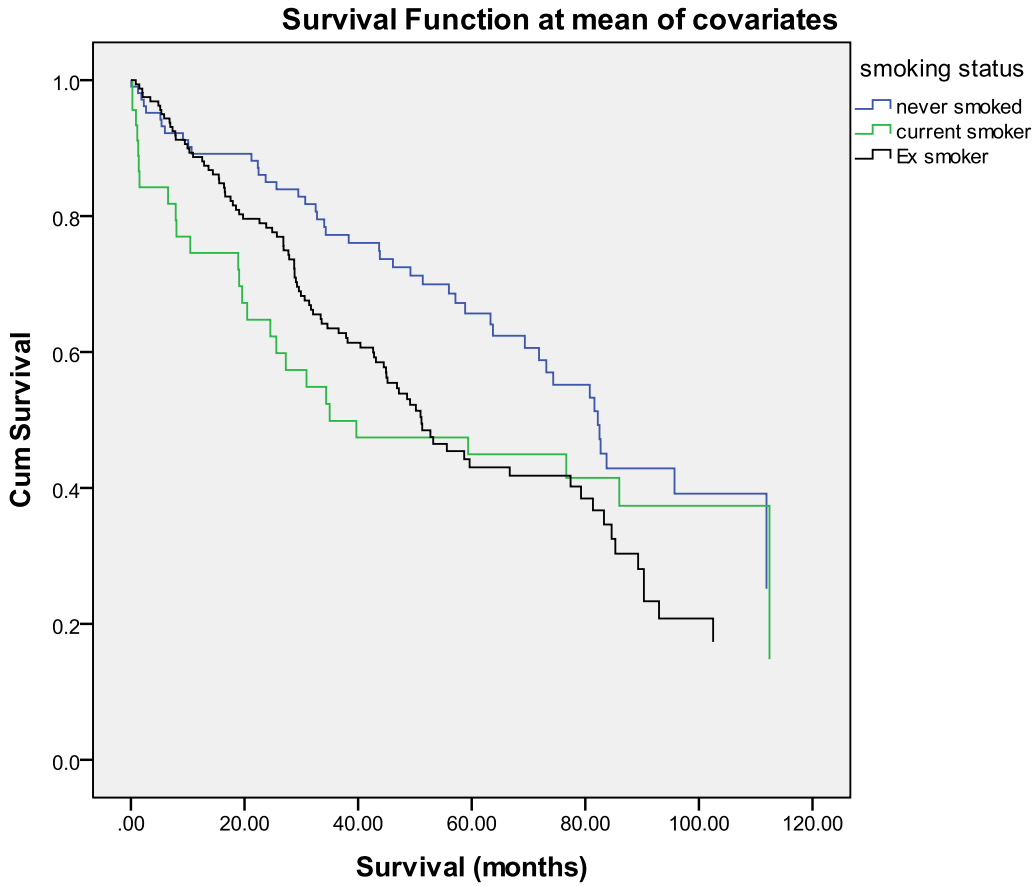
8.8.2 Smoking status

Patients who were current smokers had a poorer outcome than people who were either ex-smokers or who had never smoked. However, the numbers at the end of the survival curves were small. Table and graph 8.8.2

Table and graph 8.8.2 Smoking status as stratum variable

Stratum	Strata label	Event	Censored	Censored Percent
0	Never smoked	45	38	45.8%
1	Current smoker	26	23	46.9%
2	Ex-smoker	92	44	32.4%
Total		163	105	39.2%

Graph 8.8.2 Smoking status and survival

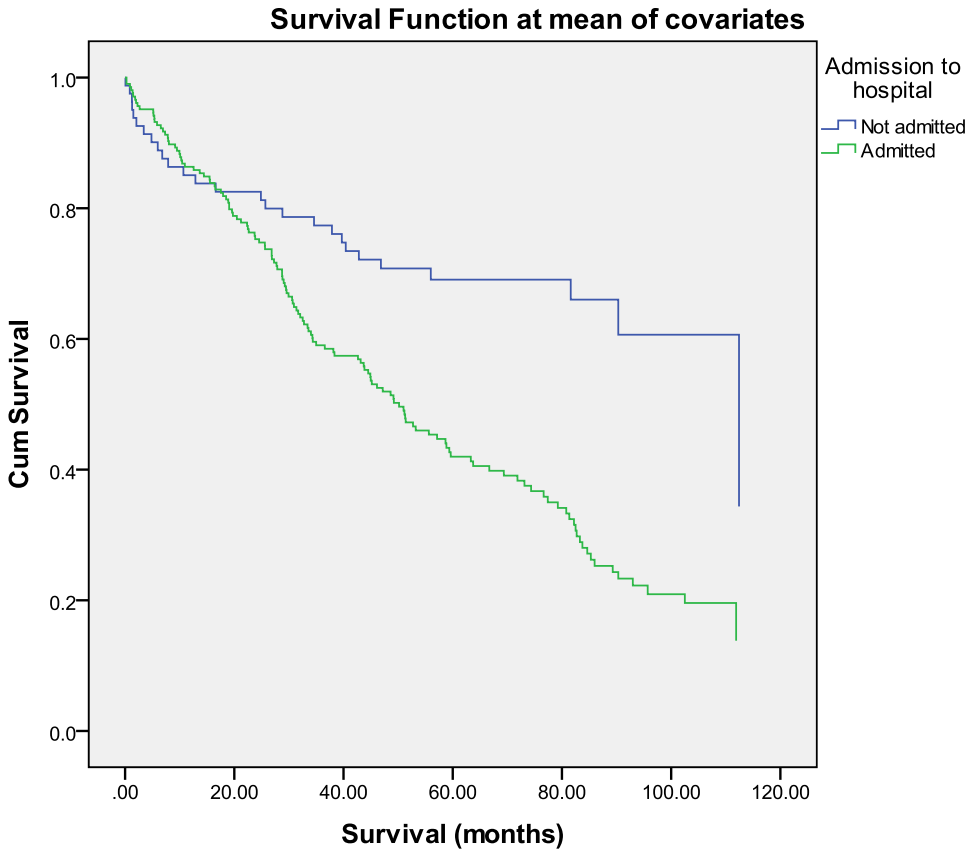


8.8.3 Admission to hospital

Of the 163 patients who died in the LVSD group, 136 had at least one admission to the hospital. When data are analysed by stratification for hospitalisation survival

curves diverge suggesting a better survival in patients with no admissions. Graph 8.8.3

Graph 8.8.3 Admission to hospital stratification



8.9 Age band and gender analysis

We arbitrarily divided patients in to two age bands (≤ 79 vs. ≥ 79) with gender. When analysed together, ageband was significantly related to survival while gender only just reached statistical significance. There was no significant interaction between ageband and gender. Table 8.9a & b

Table 8.9a Age banding

		Frequency (n = 268)
Gender	1=Male	164
	2=Female	104
Ageband	1= LT 80 years	198
	2=MT 79 years	70

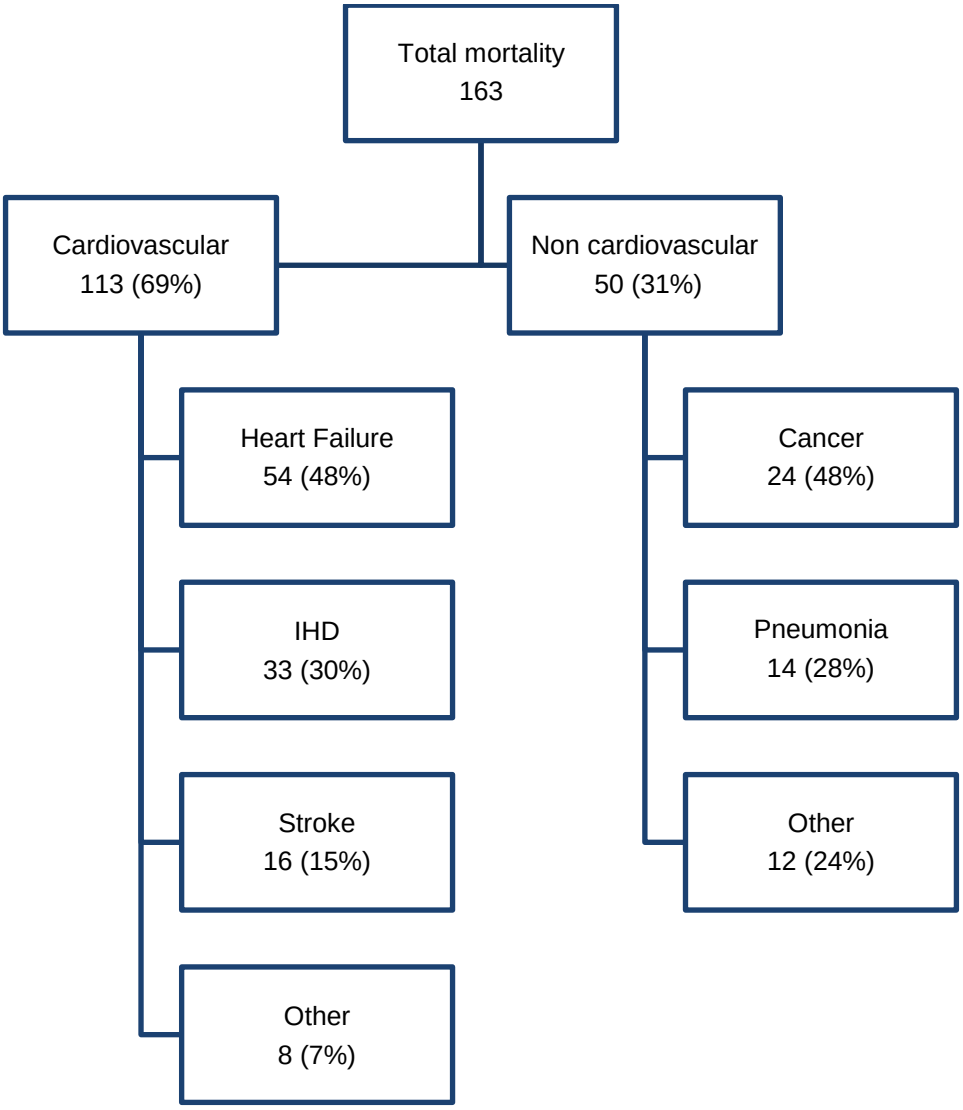
Table 8.9b Ageband and gender interaction

	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
Age band	.66	.2	9.0	1	.00	1.9	1.2	3
Gender	-.40	.2	3.6	1	.06	.6	.4	1
Age band*gender	.17	.3	.2	1	.6	1.2	.6	2.3

8.10 Cause of death

Of the 163 deaths, a high proportion 113 (69%) was attributable to cardiovascular causes. 72 (63%) of these were males and 41 (37%) were females. Flow chart 8.10

Flow chart 8.10 Cause of death



8.11 Survival analysis for death from cardiovascular cause

In the univariate analysis of the risk factors associated with poor prognosis for cardiovascular deaths, age, atrial fibrillation, diabetes, ischemic heart disease, NYHA class and admission to hospital were significantly associated with poor survival. Table 8.11

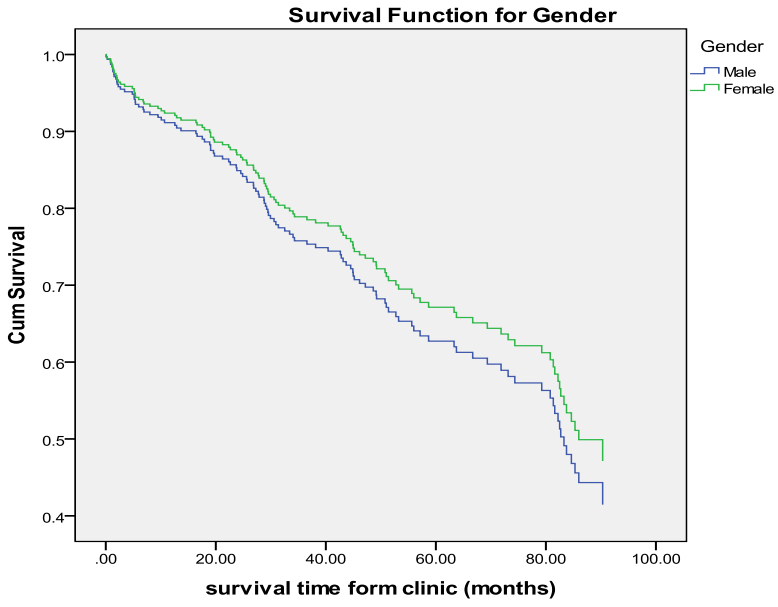
Table 8.11 Univariate survival analysis for death from cardiovascular cause

	B	SE	Wald	df	p	Odds ratio	95% CI for OR	
							Lower	Upper
Age	.05	.01	23	1	.00	1.0	1.0	1.1
Gender	-.20	.19	1	1	.30	.8	.5	1.1
Hypertension	-.04	.19	.05	1	.81	.9	.6	1.3
Atrial fibrillation	.41	.21	3.8	1	.05	1.5	.9	2.2
Diabetes Mellitus	-.62	.31	3.8	1	.05	.5	.2	.9
IHD	.42	.19	4.7	1	.02	1.5	1.0	2.2
MI	.30	.18	2.5	1	.11	1.3	.9	1.9
COPD	-.06	.11	.3	1	.55	.9	.7	1.1
Stroke	-.20	.13	2.3	1	.12	.8	.6	1.0
NYHA	.52	.15	11.6	1	.00	1.6	1.3	2.3
Admission	.83	.24	11.5	1	.00	2.3	1.4	3.7

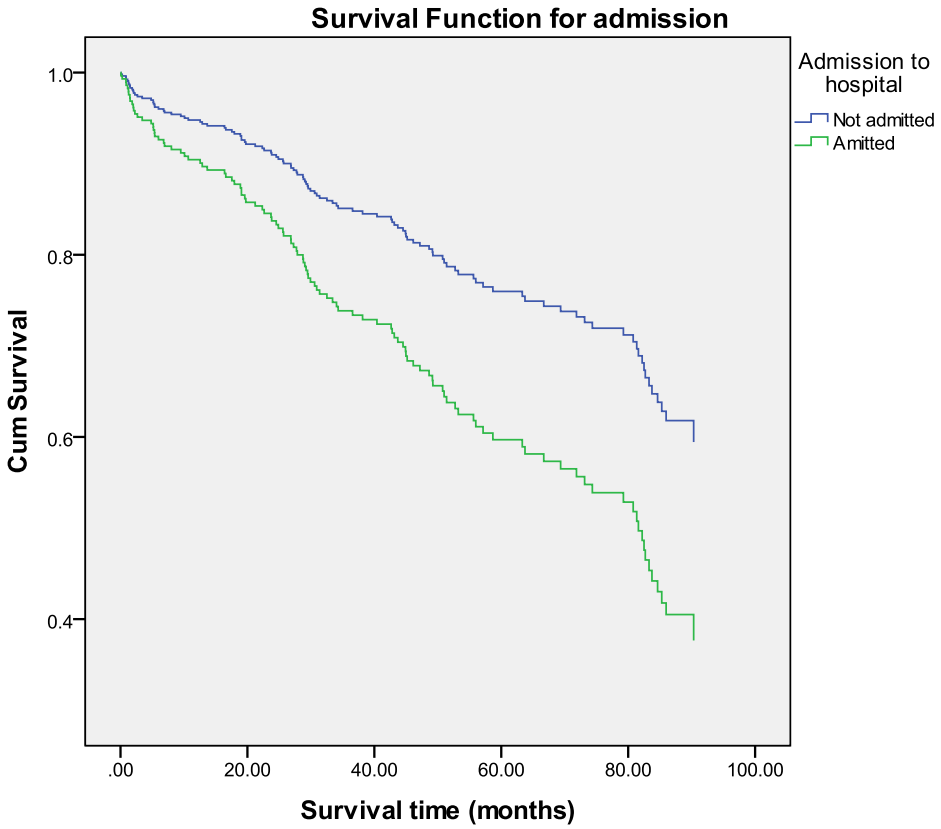
8.11.1 Multivariate survival analysis

Age, NYHA class and admission to hospital, were significant risk factors. Gender was not significant. Graphs 8.10.1a & b [Additional data presented as Table 8.10.1 in appendix 4]

Graph 8.11.1a Survival function for gender



Graph 8.11.1b Survival function for hospital admission



8.11.2 Forward conditional logistic regression

With Cox forward conditional logistic regression analysis, age, NYHA class and admission to the hospital continued to be significant predictors of poor survival. (Table 8.11.2)

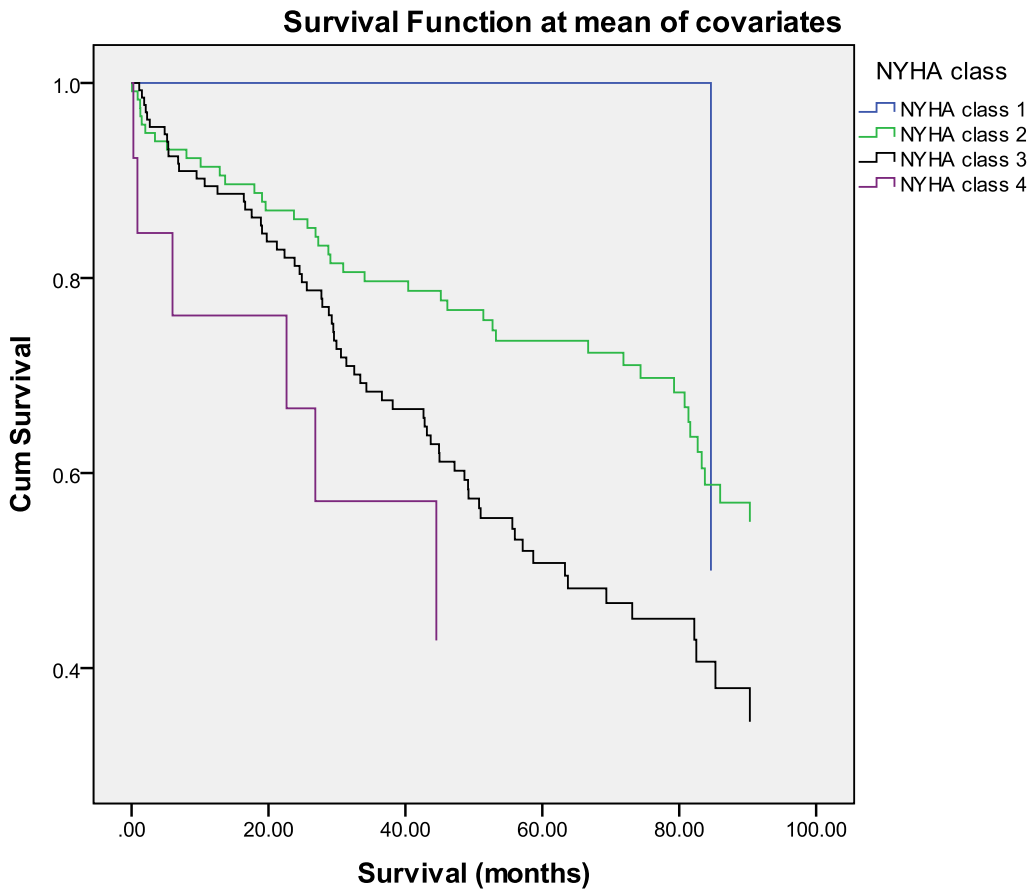
Table 8.11.2 Forward conditional logistic regression

		B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
								Lower	Upper
Step 1	Age	.05	.01	23.7	1	.00	1.0	1.0	1.1
Step 2	Age	.04	.01	19.3	1	.00	1.0	1.0	1.1
	NYHA class	.46	.15	9	1	.00	1.6	1	2
Step 3	Age	.04	.01	18.5	1	.00	1.0	1.0	1.1
	NYHA class	.42	.15	8	1	.00	1.5	1	2
	Admission	.66	.25	6	1	.01	1.9	1.2	3.1

8.11.3 Stratification analysis

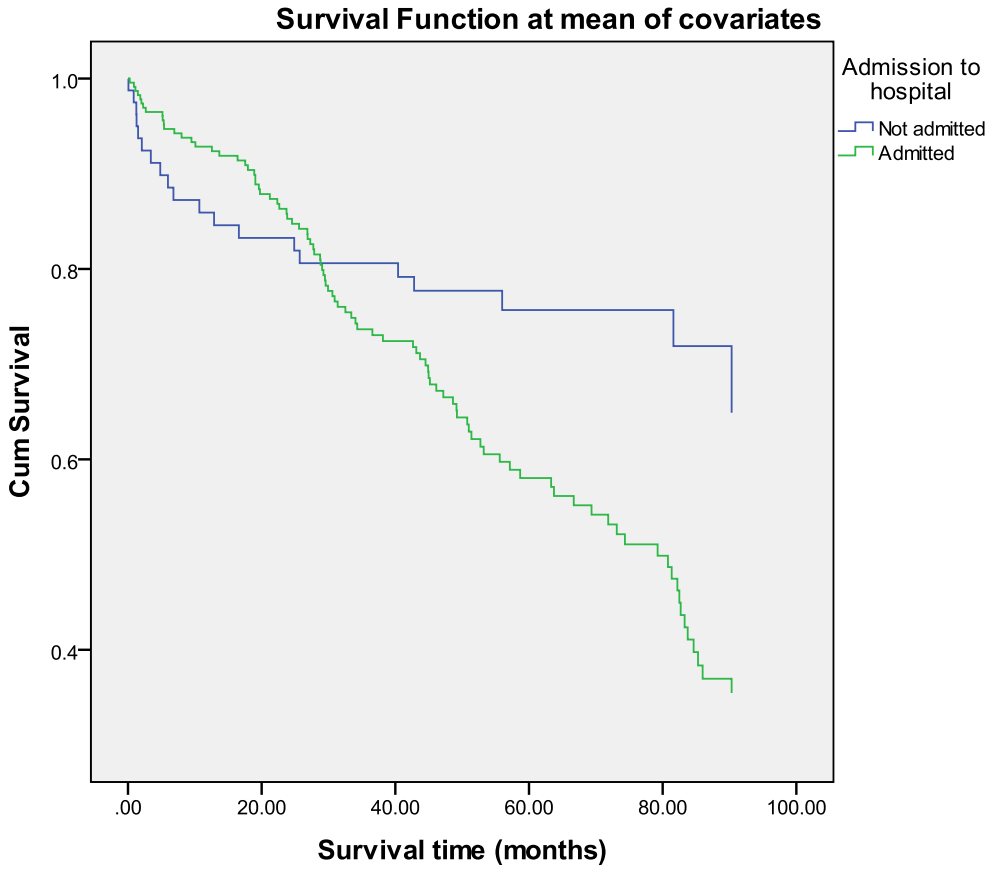
Model checking was done using stratification for categorical variable NYHA class. The event rates in NYHA class 1 were small. For NYHA class 2 and 3 the curves diverge suggesting that NYHA class 2 had better prognosis then NYHA class 3 and 4. Graph 8.11.3a

Graph 8.11.3a Stratification for NYHA class



When data were stratified for admission to hospital, the survival curves initially diverge but then crossover. This suggests that initially patients not hospitalised have a poor outcome but after about 30 months patients who are hospitalised do worse. This data suggests presence of non-proportional hazards in this model and thus the need for cautious interpretation. Graph 8.11.3b

Graph 8.11.3b Stratification for admission to hospital



8.12 Conclusion and discussion

8.12.1 Descriptive analysis

- Of all the patients referred to the heart failure clinic a quarter (26%) were diagnosed with LVSD on the basis of their echocardiogram. This result is consistent with other published studies from hospital based HF services. Shah et al (180) reported that a third (31%) of the patients referred to an open access HF service had LVSD, whilst in a report by Fox et al (155) only 26% of all referrals to the rapid access HF clinic were diagnosed with LVSD.

- Although the number of females referred to our HF clinic was more than the males (600 vs. 431), they were less likely to be diagnosed with LVSD (104 vs. 164). These findings are similar to reports from other studies (123, 157, 180)

and likely to represent the difficulty in diagnosing HF in the community and more so in the female population.

- Shortness of breath was the commonest (98%) reason for referral with 50% having NYHA class 3 symptoms. On clinical examination raised JVP was present in 43% patients while 34% had swollen ankles.

- Atrial fibrillation was the commonest (26%) finding on the ECG followed by LBBB (25%).

- Cardiomegaly (68%) followed by upper lobe diversion (29%) and pulmonary oedema (25%) were the commonest findings on chest x-ray examination.

- Apart from diagnosing systolic dysfunction the one stop diagnostic HF clinic also picked up significant valvular lesions. Moderate mitral regurgitation (MR) was present in 40%, and severe MR in 11%. Severe aortic stenosis was present in 7% of the patients.

- When first seen at the one stop clinic, a high proportion of patients (85%) were taking a diuretic, 55% were also on a ACEi / ARB, and 27% were on a beta blocker. 60% of the patients were taking aspirin. In data published by Shah et al (180) from an open access HF clinic, the majority (57%) of the patients were taking a diuretic. In their study the number of patients taking an ACE inhibitor (21%) and a beta blocker (10%) was small. Higher figures in our study likely represent an increasing awareness of the evidence based clinical guidelines within the medical fraternity over a period of time (241), as the survey by Shah et al was conducted a few years prior to the DROPSY.

- After the first appointment in the HF clinic an additional 40% of the patients were started on an ACEi / ARB, and 31% of the patients were started on a beta blocker de novo.

- The majority (81%) of the patients were referred to the titration clinic. The average number of visits per patient to this clinic was 5.3 (range 31).

- During the study follow up period, 70% of the patients had at least one admission to the hospital. The majority (32%) were admitted with breathlessness. Similar figures have been reported in the 2010 national HF audit (242), where 28% of the patients were admitted with breathlessness and 40% with reduced exercise capacity.

- At the time of the admission a high proportion of the patients were on diuretics (88%), and taking an ACEi (86%).

- The mean value for blood tests (serum urea and creatinine) were higher at the time of admission compared to the clinic results. Hyponatremia was present in 21%, and hyperkalemia in 4% of the patients. An elevated level of urea and creatinine was present in 55% and 31% of the patients respectively. Seven percent of the patients had a haemoglobin value of <10 gm/dl on admission.

- The mean time to admission from the clinic appointment was 21.1 months with a median of 15.5 months. On average patients had 2.2 admissions and spent 24 days as inpatient.

- A new diagnosis of cancer was made in 23 patients, and stroke was diagnosed in 17 patients.

8.12.2 Medication usage

- The HF clinic helped patients to be started on evidence based medical treatment and the majority were on optimal medical therapy. At the end of the follow up period ACEi / ARBs were prescribed in 96%, and beta blockers in 75% of the patients. These figures are better than those reported in other contemporary published surveys. In the Euro Heart Failure Survey programme

(241) only 62% patients were on an ACEi, and 37% on a beta blocker. In the national HF audit 2010 (242) about 85% of the patients were prescribed an ACEi and 60% were prescribed a beta blocker. The higher rate of prescription for evidence based therapy in our study could be due to the specialist HF service that has a dedicated nurse led titration clinic to follow up these patients. The number of patients prescribed an aldosterone antagonist in our study is lower (24%) than that achieved nationally (36%) (242). This probably represents the effect of a smaller evidence base for these agents compared to ACEi / ARBs, and beta blockers (242).

- In univariate analyses for duration of medication use all four drugs (ACEi / ARBs, beta blockers, digoxin, and aldosterone antagonist) were related to a better outcome. This could be due to the fact that the sicker patients were not taking these medications.

- The longer duration of use for ACEi / ARBs, and beta blockers analysed using the multivariate model was associated with a better outcome. This beneficial effect of the persistent use of ACEi / ARBs, and beta blockers in patients with LVSD was also seen by Lapointe et al in a survey of HF patients (129).

8.12.3 Survival analysis for all cause mortality

- In our study more LVSD patients died in the hospital than at home. This is also true nationally where mortality statistics from the office for national statistics (ONS) showed that in 2010 of all the deaths in England, only 21% took place at home (243).

- Independent predictors of all-cause mortality assessed with the Cox proportional hazard model were age, ex smokers, atrial fibrillation, ischemic heart disease, COPD, stroke, NYHA class, and admission to hospital for any cause. Gender was not a predictor of poor survival.

- Analysing these risk factors in the multivariate analysis model only age, ex smokers, and NYHA class and admission to hospital were significant. These factors are similar to those in the published literature. Pocock et al (244) reported age, diabetes, higher NYHA class, male sex, among others as predictors of poor outcome.

- When age band is analysed as a categorical variable with gender, there was no interaction between the two and older age was a risk factor for poor outcome.

8.12.4 Survival analysis for cardiovascular mortality

- LVSD patients were more likely to die of cardiovascular deaths. Almost half the patients died of HF followed by ischemic heart disease and stroke. These results are similar to those reported by other authors. In the Echocardiographic Heart of England screening study (ECHOES) (126) patients with HF and LVSD were more likely to die of heart failure followed by IHD. In a report by Henkel et al (127) the leading cause of death in LVSD patients was coronary heart disease.

- Risk factors for cardiovascular deaths in the univariate model were age, atrial fibrillation, diabetes, ischemic heart disease, and admission to hospital. In the multivariate model, age, and admission to hospital were the only two markers of increased risk.

- In conclusion the LVSD group had more males, more had NYHA class 3 symptoms, and were likely to be prescribed evidence based treatment, though they continued to have a high mortality mainly due to cardiovascular causes.

Chapter 9

The “Other” (OT) group

Of the 1041 patients who were referred to the one stop HF clinic 528 patients did not fulfil the inclusion criteria for HFpEF in this study nor did they have LVSD on their echocardiogram. This group of patients were labelled as the non HF group or the “Other” group. A unique study number was assigned to this group for the purposes of identification. This number started with the initials “OT” signifying “Other” group.

Data using the unique study number were collected in an anonymised format on a separate Microsoft 2007 Excel sheet and then transferred to the SPSS 19 software spreadsheet for the purposes of analysis.

The primary source of data collection for this group was the clinic letter following the appointment at the HF clinic. As such the data collected for this group was for demographics, risk factors, findings of clinical examinations, results of tests, presenting medications, any changes made to medications, and outcomes in terms of cause of shortness of breath.

The mortality data for this group, as for LVSD and HFpEF groups, were obtained from the medical research and information service (MRIS).

The data were analysed with SPSS 19 soft ware. Patient characteristics and risk factors were analysed using descriptive statistics and Cox regression analysis was used for univariate and multivariate risk factor assessment in survival analysis.

Of the 528 patients in this group no data were available for 6 patients and they were not included in the final analysis.

9.1 Demographics and past medical history

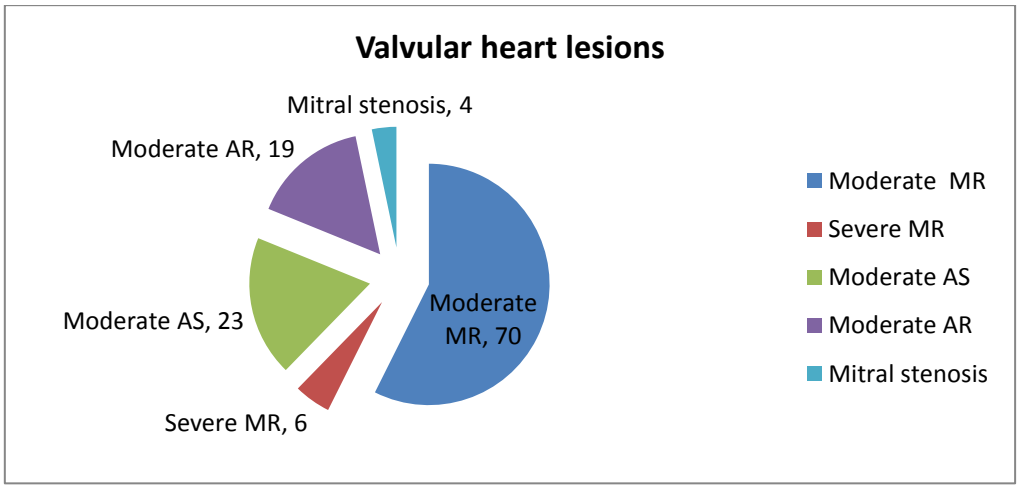
Total number of patients	522
Mean age, years (range)	75 (61)
Male	183 (35%)
Female	339 (65%)
Ischemic heart disease	138 (26%)
Hypertension	253 (49%)
Atrial Fibrillation	73 (14%)
Myocardial infarction	42 (8%)
Diabetes mellitus	63 (12%)
COPD	144 (28%)

9.2 Smoking status

Smoking data were available for 509 patients. The majority 255 (49%) had never smoked, 196 (38%) were ex smokers, and only 58 (11%) were current smokers.

9.3 Echocardiographic findings

Echocardiograms were performed for all patients as part of clinical assessment. LV systolic function was normal in all patients. Valve lesions on the echocardiogram are presented below. (**Chart 9.3**)



9.4 ECG and Chest x-ray findings

Three hundred and twenty one (62%) patients had a normal ECG, while in the remaining 201 (38%) of the patients the ECG was reported as abnormal. The data for the type of abnormality on the ECG was not recorded.

Similarly in 359 (69%) patients the chest X - ray was reported as normal and in 159 (31%) the chest X - ray was reported as abnormal. Individual findings of the chest x-ray were not recorded.

9.5 Medications on presentation

At the time of review in the clinic 293 (56%) patients were taking a loop diuretic. A small proportion of patients were also taking a thiazide diuretic. One hundred and seventy nine (34%) patients were on an ACE inhibitor and a quarter of them were taking a beta blocker. Table 9.5

Table 9.5 Medication on presentation

Type of medication	Frequency (N = 522)
ACE inhibitors	179 (34%)
Angiotensin Receptor Blockers	42 (8%)
Bendroflumethiazide	77 (15%)
Furosemide	293 (56%)
Beta blockers	130 (25%)
Spironolactone	29 (6%)
Digoxin	43 (8%)

9.6 Cause of shortness of breath

These patients when reviewed in the HF clinic had an echocardiogram that showed good left ventricular systolic function. This group of patients did not fulfil the inclusion

criteria for the HFpEF group so their symptoms of shortness of breath were apparently not due to heart failure.

After their clinic appointment patients were ascribed a possible cause for their symptoms of shortness of breath. Table 9.6

Table 9.6 Cause of shortness of breath

Conditions	Frequency (n = 522)
COPD	102 (20%)
Drug induced	23 (4%)
Atrial Fibrillation	34 (6%)
IHD	52 (10%)
Obesity	27 (5%)
Anxiety	4 (1%)
Hypertension	48 (9%)
Cancer	2 (0.5%)
Lack of fitness	5 (1%)
Anaemia	5 (1%)
Peripheral vascular disease	22(4%)
Valvular heart disease	40 (8%)
Diastolic dysfunction	10 (2%)
Left ventricular hypertrophy	30 (6%)
Patient denied shortness of breath	36 (7%)
No cause found	82 (16%)

Chronic obstructive airways disease (COPD) was ascribed as the commonest cause of shortness of breath in 20% of the patients. This was followed by 82 patients where no cause could be ascribed for their symptoms. Thirty six (7%) patients denied any symptoms when seen in the clinic. Ischemic heart disease and hypertension were thought to be the cause for the symptoms in 10% of the patients.

9.7 Mortality

From 01 Feb 2002 to 31 Aug 2011 (mean follow up period of 6.81 years) 213 (41%) patients of 522 in this cohort died. Of these 88 (41%) were males and 125 (59%) were females. The survival time from the clinic appointment was calculated in months. Table 9.7

Table 9.7 Survival time (months) from clinic review

Mean		40
Median		38
Std. Deviation		26
Minimum		0.07
Maximum		95
Percentiles	25	20
	50	38
	75	60

9.7.1 Cause of death

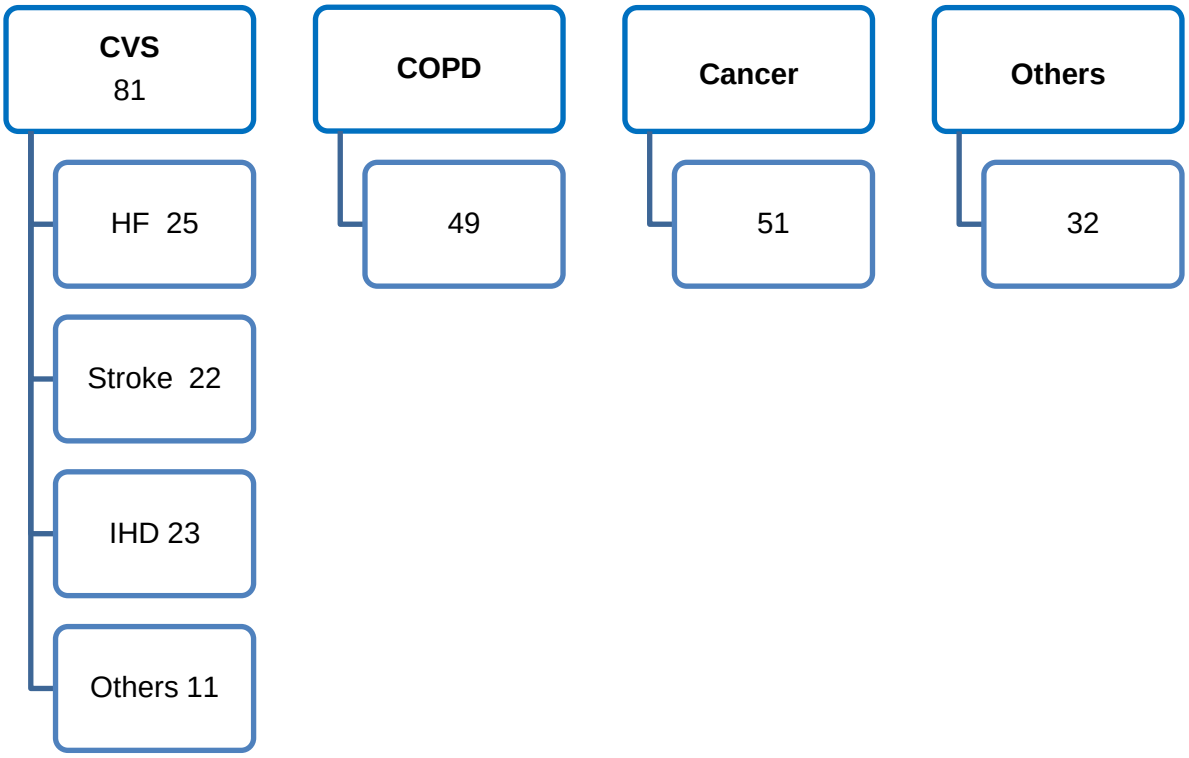
The cause of death as put on the death certificate for these patients was analysed. Cause of death was classified according to the World Health Organisation's international classification of disease (ICD-10).(245)

The three leading cause of deaths were

- Cardiovascular disease (CVS)
- Chest infection/ Chronic obstructive airways disease (COPD)
- Cancer

Of the 213 deaths, 81(38%) patients died of cardiovascular (CVS) disease. Further classification for the CVS disease showed that 25 (12%) of these patients had HF as the underlying cause of death on their death certificates.

Flow chart 9.7.1 Cause of death



Twenty five patients who died of HF had normal LV systolic function on echocardiography and also did not fulfil the inclusion criteria for HFpEF. So why did they die of HF? It's possible that these patients had underlying risk factors and developed cardiovascular disease at some time in future, resulting in death due to HF.

9.7.2 All-cause mortality survival analysis

The Cox proportional hazard model was used to assess co variants related to poor survival. Age was the only variable associated with a poor prognosis in the univariate model. While in the multivariate analysis none of the co variants were significantly related to poor survival. Table 9.7.2a & b

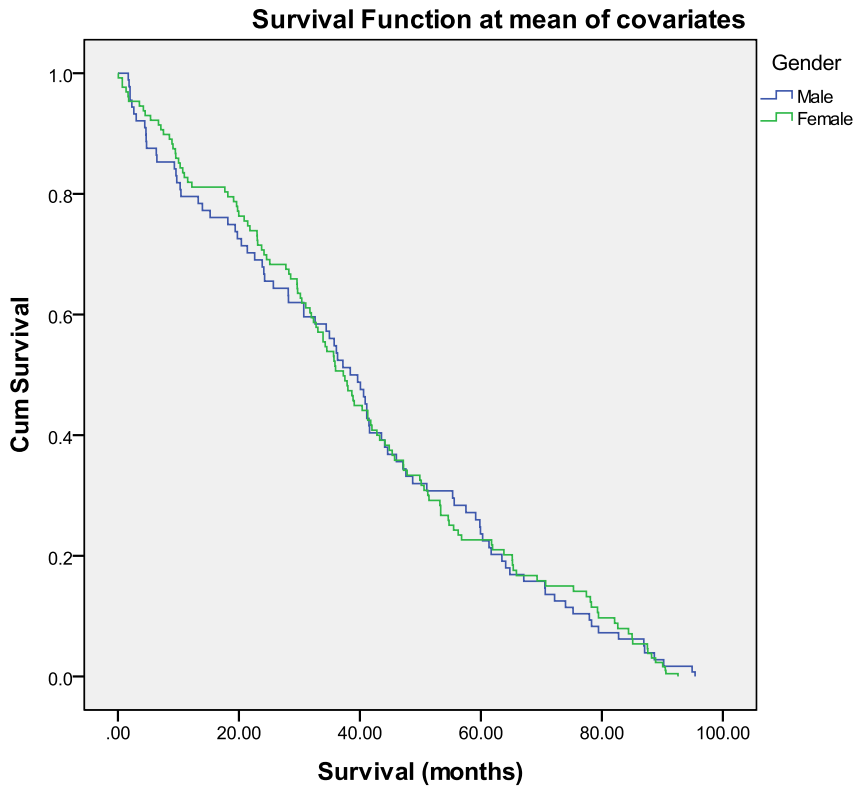
Table 9.7.2a Univariate analysis for all-cause mortality

	B	SE	Wald	df	P	Odds ratio	95% CI for OR	
							Lower	Upper
Age	.02	.01	4.2	1	.03	1	1.0	1.03
Gender	.02	.14	.0	1	.85	1	.7	1.3
IHD	-.17	.16	1.1	1	.28	.8	.6	1.1
AF	.19	.17	1.2	1	.27	1.2	.9	1.7
MI	-.09	.27	.1	1	.73	.9	.5	1.5
HT	.17	.13	1.5	1	.22	1.1	.9	1.5
DM	.12	.24	.2	1	.61	1.1	.7	1.8
COPD	-.06	.15	.2	1	.65	.9	.7	1.2
Non smoker	-.22	.14	2.4	1	.12	.8	.6	1
Ex-smoker	.22	.14	2.3	1	.12	1.2	.9	1.6
Current smoker	-.16	.23	.5	1	.47	.8	.5	1.3

Table 9.7.2b Multivariate analysis for all-cause mortality

	B	SE	Wald	Df	p	Odds ratio	95% CI for OR	
							Lower	Upper
Age	.01	.01	2.5	1	.11	1.0	.9	1
Gender	.01	.15	.01	1	.93	1.0	.7	1.3
IHD	-.24	.17	1.7	1	.19	.7	.5	1.1
AF	.10	.18	.31	1	.57	1.1	.7	1.6
MI	-.22	.29	.5	1	.45	.8	.4	1.4
HT	.21	.15	1.9	1	.16	1.2	.9	1.7
DM	.07	.26	.07	1	.79	1	.6	1.8
COPD	.00	.17	.00	1	.98	1	.7	1.4
Non Smoker	-.70	.37	3.5	1	.06	.5	.2	1
Ex-smoker	-.45	.38	1.4	1	.23	.6	.3	1.3
Current smoker	-.72	.45	2.6	1	.1	.5	.2	1.2

Graph 9.7.3 Survival function for gender



No further survival analysis was carried out as none of the risk factors were predictors of poor outcome.

9.8 Discussion and conclusion

Limited data were collected for the non-heart failure “Other” group. Any conclusions drawn are only confined to the descriptive analysis.

- The average age of patients was 74 years and females were 65% of the cohort.
- The majority (49%) of the population had never smoked.
- A diuretic had been prescribed to 56% of the patients.
- The commonest cause of shortness of breath ascribed in clinical practice to this cohort was COPD.

- During the mean follow up of 6.81 years, there were 213 (41%) deaths.

- The mean survival time from the time of the clinic appointment to death was 40 months.

- Death was attributed to cardiovascular disease in 81 (38%) patients. Of these HF was the leading cause followed by stroke and ischemic heart disease. These figures are similar to the data from the ONS (243) where cardiovascular disease remain the leading cause of deaths in the UK population nationally.

- The high number (12%) of patients who had HF as cause of death would suggest that diagnosing HF in the clinical practice remains a challenge.

- Though these patients had been reassured from the HF point they still had high mortality. This raises questions as to the accuracy of the diagnosis. It is possible that more detailed assessment of the cardiac function, including newer echo techniques and cardiac magnetic resonance imaging may have demonstrated abnormalities not apparent on the original scan. Also it is possible that the HF clinic was too narrowly focused on heart failure management and not on the overall cardiovascular risks or the management of other conditions.

- Age was the only risk factor predictor for poor survival in univariate analysis. In the multivariate model none of the variables were significant predictors of a poor outcome.

- In conclusion, these patients had been reassured from the heart failure point of view, but continued to have a high mortality with cardiovascular disease being the leading cause of mortality. Diagnosing HF in the real world remains a challenge as a significant number of patients died of HF.

Chapter 10

Comparative analysis of LVSD and HFpEF patients

Baseline characteristics of the two groups show that in the HFpEF group patients were older and more likely to be females. More had hypertension, and atrial fibrillation. Whereas in the LVSD group more had ischemic heart disease and stroke. Diabetes was not different in the two groups. Table 10

Table 10: Baseline characteristics of LVSD and HFpEF groups

	LVSD	HFpEF	p value
Total number of patients	268	241	
Average age years (range)	74 (60)	78 (52)	.01
Males	164 (61%)	84 (35%)	00
Females	104 (39%)	157 (65%)	00
Hypertension	114 (43%)	202 (84%)	.01
Atrial fibrillation	66 (25%)	86 (36%)	.01
Ischemic heart disease	140 (52%)	101 (42%)	.01
Diabetes	42 (16%)	55 (23%)	.40
Stroke	34 (13%)	10 (4%)	.01
ACE inhibitors	148 (55%)	109(45%)	.02
Beta blockers	72 (27%)	83 (34%)	.06

10.1 Referral symptoms

For both LVSD and HFpEF groups shortness of breath was the leading reason for referral to the HF clinic. The LVSD group was likely to have more patients with orthopnoea, paroxysmal nocturnal dyspnoea (PND), fatigue and palpitations, whereas HFpEF patients were more likely to complain of swollen ankles at the time of referral. Table 10.1

Table 10.1 Referral symptoms

	LVSD	HFpEF
Shortness of breath (SOB)	262 (98%)	231(96%)
Swelling of the ankles (SOA)	190 (71%)	188 (78%)
Orthopnoea	120 (45%)	47(20%)
Paroxysmal nocturnal dyspnoea (PND)	70 (26%)	13 (5%)
Fatigue	64 (24%)	7(3%)
Palpitations	25 (9%)	7(3%)

10.1.1 New York Heart Association (NYHA) class

More patients in the LVSD group had NYHA class 3 symptoms compared to the HFpEF group, more of whom had NYHA class 2 symptoms. Table 10.1.1

Table 10.1.1 NYHA classification in the clinic

	NYHA class 1	NYHA class 2	NYHA class 3	NYHA class 4
LVSD, n (%)	4(1)	117 (44)	134 (50)	13 (5)
HFpEF, n (%)	6 (3)	157 (65)	75 (31)	3 (1)

10.1.2 Blood pressure and heart rate

The mean systolic and diastolic blood pressure measurements in the HF clinic in the HFpEF group were significantly higher than the LVSD group while heart rate was significantly higher in the LVSD group. Table 10.1.2a [Data for independent t-test presented in appendix 4 as Table 10.1.2b]

Table 10.1.2a Blood pressure and heart rate in clinic

	1=LVSD. 2=HFpEF	Number	Mean	Std. Deviation	Std. Error Mean
Systolic BP (mmHg)	1	267	142	23.6	1.4
	2	239	154	21.7	1.4
Diastolic BP (mmHg)	1	268	77	13.2	.8
	2	239	84	13.4	.8
Heart Rate (per minute)	1	268	83	20.4	1.2
	2	240	76	17.5	1.1

10.1.3 Jugular Venous Pressure

Raised jugular venous pressure (JVP) is a marker of increased right heart pressure, usually due to volume overload. Patients with LVSD were more likely to have raised JVP (43%) than the HFpEF patients (27%). Table 10.1.3

Table 10.1.3 JVP comparison

	LVSD		HFpEF	
	Frequency	%	Frequency	%
Normal	156	57	214	89
Raised	115	43	27	11
Total	241	100.0	241	100.0

10.1.4 Clinical Findings

Seventy eight percent patients in the HFpEF group and 71% in the LVSD group were referred because of swollen ankles (this could be a consequence of calcium channel blockers, which were more often prescribed to HFpEF patients), though only a minority had ankle oedema at the clinic appointment. Table 10.1.4

Table 10.1.4 Clinical Findings

	LVSD	HFpEF
Swelling of ankles	90 (34%)	102 (42%)
Systolic murmur	138 (52%)	78 (32%)
Diastolic murmur	11 (4%)	7 (3%)
Lung crepitation	84 (31%)	30 (12%)
Dull bases on chest examination	16 (6%)	3 (1%)
Wheeze	24 (9%)	7 (3%)

10.1.5 Chest X-ray findings

Ninety percent of the patients in the HFpEF group had cardiomegaly (cardio-thoracic ratio >0.5), while pulmonary oedema, and upper lobe diversion, were more common in the LVSD group. Table 10.1.5

Table 10.1.5 Chest X-ray findings

Chest X-ray	LVSD	HFpEF
Normal	54 (20%)	18 (8%)
Cardiomegaly	181 (68%)	217 (90%)
Upper lobe diversion	77 (29%)	61(25%)
Pulmonary oedema	66 (25%)	12 (5%)
Pleural effusion	34 (13%)	9 (4%)
Other findings	20 (7%)	1

10.1.6 Echocardiogram findings

Whilst patients in the LVSD group had systolic dysfunction patients in the HFpEF group were more likely to have left ventricular hypertrophy and E/A reversal on their echocardiogram as markers of impaired filling and impaired relaxation. Table 10.1.6

Table 10.1.6 Echocardiographic findings

	LVSD	HFpEF
E/A reversal	37 (14%)	86 (36%)
LVH	63 (24%)	136 (56%)
Moderate MR	106 (40%)	52 (21%)
Severe MR	29 (11%)	0
Moderate TR	41 (15%)	27 (11%)
Severe TR	15 (6%)	0
Moderate AR	24 (9%)	0
Moderate AS	3 (1%)	0
Severe AS	4 (2%)	0

10.1.7 ECG findings

In the HFpEF group patients were more likely to have either a normal ECG or atrial fibrillation. In the LVSD group patients had more left bundle branch block (LBBB) pattern and ischemic changes on their ECG. This would be consistent with the findings that the commonest cause of LVSD is ischemic heart disease. Table 10.1.7

Table 10.1.7 ECG findings

	LVSD (n = 268)	HFpEF (n = 241)
Normal	27 (10%)	71 (30%)
Left axis deviation	26 (10%)	11 (5%)
Left bundle branch block	66 (25%)	15 (6%)
Left ventricular hypertrophy	38 (14%)	34 (14%)
Bradycardia	25 (9%)	11 (5%)
Atrial fibrillation	70 (26%)	87 (36%)
Right bundle branch block	16 (6%)	14 (6%)
Ischemic changes	55 (21%)	12 (5%)

10.2 Blood test results

In both LVSD and the HFpEF groups, the mean values of the blood tests checked in the clinic were similar. Analysing the results using student t test did not show any statistical difference between the observed means (Table 10.2). [Additional data analysis are presented in appendix 4 as Table 10.2a & b]

Table 10.2 Blood test results in the clinic

	LVSD (mean)	HFpEF (mean)
Sodium (mmol/l)	140	140
Potassium (mmol/l)	4.3	4.2
Urea (mmol/l)	8	7
Creatinine (µmol/l)	111	109
Cholesterol (mg/l)	4.8	5
Haemoglobin (mg/dl)	13	13
MCV (fl)	87	90

10.3 Medications on presentation

The LVSD group was more likely to be on an ACEi / ARB and aspirin, whilst more HFpEF patients were on a beta blocker, calcium channel blocker, and a statin. Table 10.3

Table 10.3 Medications on presentation

	LVSD	**HFpEF**
ACEi / ARBs	148 (55%)	109 (45%)
Beta blockers	72 (27%)	83 (34%)
Diuretics	228 (85%)	192 (80%)
Digoxin	42 (16%)	39 (16%)
Aspirin	162 (60%)	118 (49%)
Warfarin	35 (13%)	38 (16%)
Calcium channel blockers	46 (16%)	83 (34%)
Statins	80 (30%)	90 (37%)

10.3.1 Medications started in the clinic

Patients in the LVSD group were more likely to be started on an ACEi / ARB, beta blocker, loop diuretic and an aldosterone antagonist. The HFpEF group were mostly discharged back to their primary care physicians for further management and usually did not have any intervention initiated in the HF clinic. Table 10.3.1

Table 10.3.1 Medications started in the clinic

	LVSD	**HFpEF**
ACE i / ARBs	105 (39%)	20 (8%)
Beta blockers	84 (31%)	26 (11%)
Loop diuretics	31 (12%)	7 (3%)
Aldosterone antagonist	24 (9%)	7 (3%)
Digoxin	14 (5%)	5 (2%)
Warfarin	23 (9%)	23 (10%)

10.3.2 Follow up in HF titration clinic

Two hundred seventeen (81%) patients with LVSD, made 5.29 visits on average to the HF clinic, while in the HFpEF group 57 (24%) patients made 1.19 visits to the HF clinic [p = 0.001]. Table 10.3.2

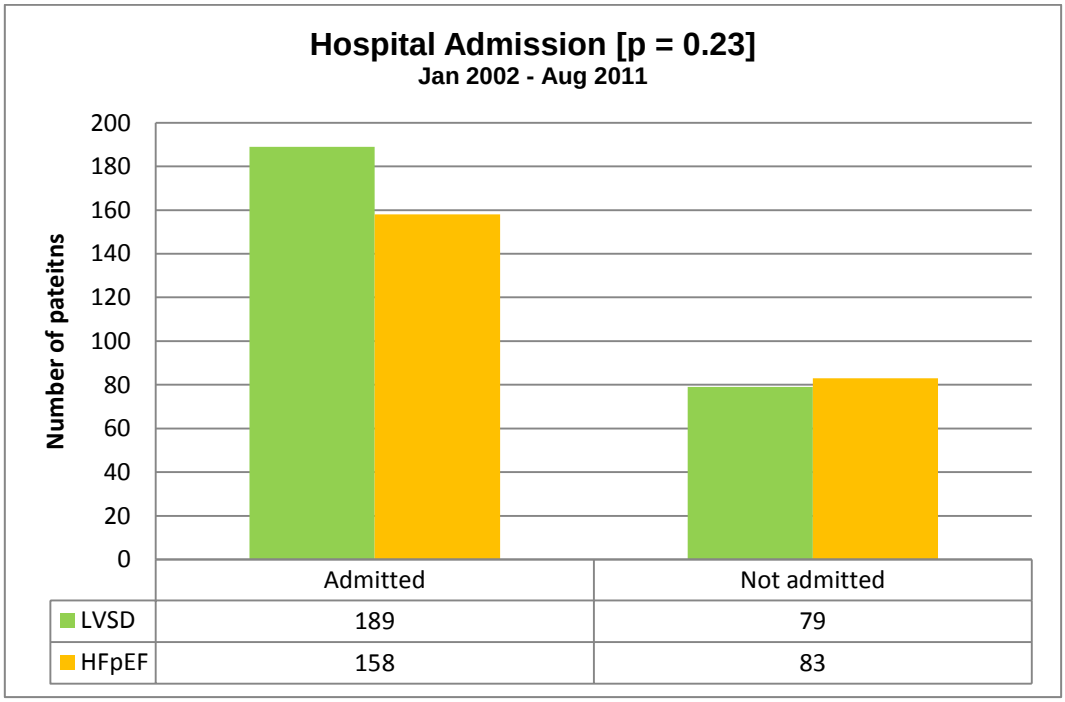
Table 10.3.2 Follow up in the HF titration clinic

	Followed up	Not followed up
LVSD (n=268)	217 (81%)	51 (19%)
HFpEF (n=241)	57 (24%)	184 (76%)

10.4 Admission

The number of patients admitted to the hospital was not statistically different in the two groups [p = 0.23]. Chart 10.4

Chart 10.4 Hospital admission



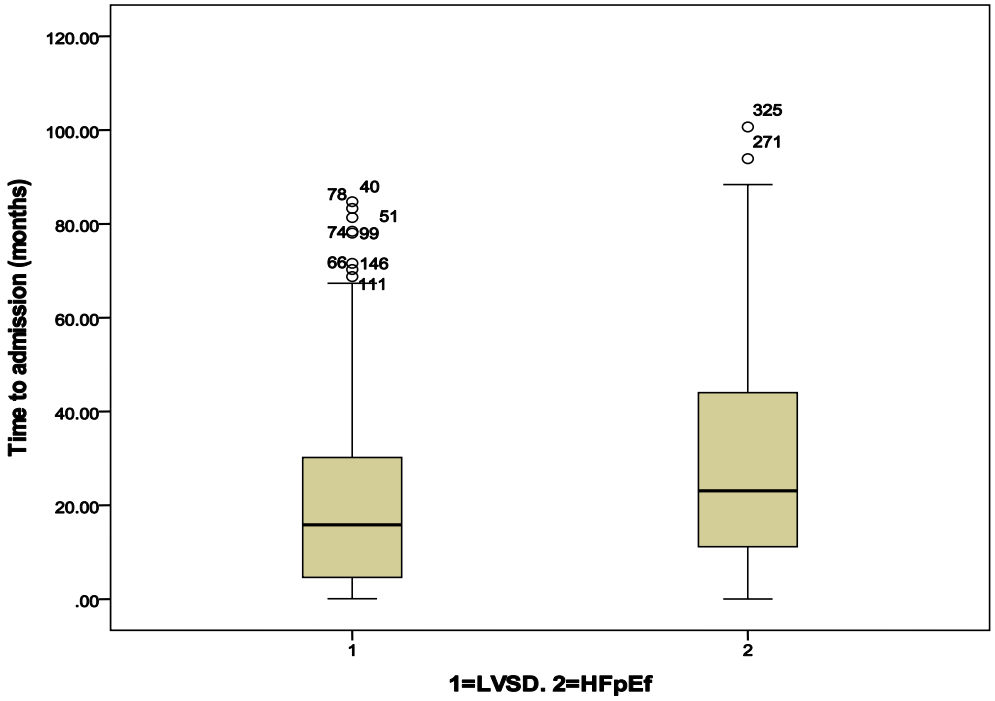
10.4.1 Time to admission

From the time of clinic appointment to first admission the mean duration (months) was longer for HFpEF group [29.41 months], compared to [21.13 months] for the LVSD group. Three patients from the LVSD group were particularly unwell and were admitted to the hospital from the HF clinic on the same day. Box plot chart & table 10.4.1

Table 10.4.1 Time to admission

	LVSD (months)	**HFpEF** (months)
Mean	21 [95%CI 17.98 - 24.29]	29 [95%CI 25.97 - 32.87]
Median	15.5	23
Std. Deviation	21	23
Minimum duration	0.0	0.03
Maximum duration	85	100

Chart 10.4.1 Box and plot chart for time to first admission



Using Student's independent samples t test to compare the means in the two groups the difference in the mean duration of admission from the time of clinic appointment to the first admission to the hospital was statistically significant, [p = 0.001, 95% CI -12.63 – 3.24], suggesting that patients in the LVSD group were more likely to be admitted to the hospital sooner compared to the HFpEF group. Table 10.4.1a

Table 10.4.1a Time to admission (months) - Independent Samples Test

Levene's Test for Equality of Variances			t-test for Equality of Means						
	F	Sig.	T	df	p	Mean Difference	Std. Error Difference	95% CI of the Difference	
								Lower	Upper
Equal variances assumed	2.8	.09	-3.3	342	.01	-7.9	2.3	-12.6	-3.2
Equal variances not assumed			-3.3	319	.01	-7.9	2.4	-12.6	-3.2

10.4.2 Reasons for first admission

	LVSD (n=189)	**HFpEF** (n=158)
Shortness of breath	61 (32%)	36 (23%)
Chest pain	21 (11%)	24 (15%)
Fall	13 (7%)	15 (9%)
Collapse	25 (13%)	21 (13%)
Stroke	14 (7%)	8 (5%)
Cancer	0	2
Confusion	1	10 (6%)
Diarrhoea	5 (3%)	8 (5%)
Generally unwell	7 (4%)	11 (6%)
Acute renal failure	1	2
Cardiac arrest	2	1
Other	41 (22%)	20 (13%)

While shortness of breath was the commonest cause for admission in both the groups, chest pain was the second most common cause in the HFpEF group and “collapse” was more common than chest pain in the LVSD group. Seven percent of the patients were admitted with stroke in the LVSD group compared to 5% in the HFpEF. More patients in the HFpEF group were admitted with confusion than the LVSD group. This could be because the HFpEF group had an older population.

10.4.3 Blood pressure and heart rate on admission

The mean systolic but not diastolic blood pressure, for the HFpEF group was significantly higher [p = 0.01, 95% CI -19 to - 6.7] than the LVSD group. This would most likely be due to higher baseline blood pressure in the HFpEF group. Table 10.4.3a [Additional data analysis for t-test is presented in appendix 4 as table 10.4.3b]

Table 10.4.3a Blood pressure and heart rate comparison on admission

1 = LVSD. 2 = HFpEF		N	Mean	Std. Deviation	Std. Error Mean
Systolic BP on admission	1	187	128	28.5	2.1
	2	156	140	28.8	2.3
Diastolic BP on admission	1	188	70	15.1	1.1
	2	158	73	14.3	1.1
HR on admission	1	188	79	18.6	1.3
	2	158	82	19.4	1.5

10.4.4 Clinical findings on admission

Table 10.4.4 JVP and swelling of ankles

	LVSD	HFpEF
JVP raised	37 (14%)	27 (11%)
SOA	64 (24%)	70 (29%)

10.4.5 Blood tests on admission

The mean values of sodium, potassium, urea, creatinine, and haemoglobin on admission were similar in both the groups and using independent samples t - test, there was no statistical difference in the two groups. (Table 10.4.5)

Table 10.4.5 Blood tests on admission

	LVSD	**HFpEF**	**p [95% CI]**
Sodium (mean)	137	138	0.51 [-1.32 - 0.66]
Potassium (mean)	4.4	4.4	0.69 [-0.12 - 0.19]
Urea (mean)	14	12	0.16 [-0.38 – 3.9]
Creatinine (mean)	102	138	0.55 [-153.6 - 81.9]
Haemoglobin (mean	12.6	12.3	0.12 [-0.09 - 0.07]

10.4.6 NYHA class on admission

Not all patients on admission had their NYHA class assessed or recorded in the admission notes. In the LVSD group 110 patients had NYHA assessed, while in the HFpEF group only 94 of the patients admitted had the NYHA class recorded in their notes. The majority of patients who had their NYHA class recorded in both groups were in class 3. Significantly more patients in the LVSD group presented with NYHA class 4 symptoms than the HFpEF group [p = 0.001] Table 10.4.6

Table 10.4.6 NYHA class on admission

	LVSD (n = 110)	HFpEF (n = 94)
NYHA class 1	5 (5%)	1 (1%)
NYHA class 2	26 (23%)	30 (32%)
NYHA class 3	44 (40%)	49 (52%)
NYHA class 4	35 (32%)	14 (15%)

10.4.7 ECG on admission

	LVSD (n = 189)	HFpEF (n = 158)
Normal	80 (42%)	50 (32%)
Atrial fibrillation	63 (33%)	73 (46%)
LBBB	10 (5%)	5 (3%)
Ischemic	5 (3%)	3 (2%)
Heart block	7 (4%)	1
RBBB	4 (2%)	1
Paced	7 (4%)	3 (2%)
Cardiac arrest	2 (1%)	0
Not available	11 (6%)	22 (14%)

10.4.8 Medications on admission

Patients in the LVSD group were more likely to be on an ACEi / ARB and a beta blocker when admitted to hospital. Table 10.4.8

Table 10.4.8 Medication on admission

	LVSD (n = 189)	HFpEF (n = 158)
ACE inhibitors	158 (83%)	98 (58%)
Beta blockers	91 (48%)	58 (37%)
Diuretics	166 (88%)	113 (76%)
Digoxin	34 (17%)	34 (26%)
Aldosterone antagonist	33 (17%)	16 (10%)

10.5 First admission

Though the mean number of days spent in the hospital on first admission was greater in the HFpEF group this was not statistically significant. [p = 0.13: 95% CI = -5.061 to 0.647]. Table 10.5

Table 10.5 First admission [Total days in hospital]

	LVSD (n = 189)	HFpEF (n = 158)
Mean	9.4	12
Median	5	6
Mode	2	2
Std. Deviation	11.5	14.9
Minimum	0	1
Maximum	75	90
Sum	1786	1856

10.5.1 Total number of admissions

The number of admissions per patient in both the groups was not statistically different [p = 0.11: 95% CI = -0.29 to 0.52]. Table 10.5.1

Table 10.5.1 Number of admissions per patient

	LVSD (n = 189)	HFpEF (n = 158)
Mean	2.2	2.3
Median	2	2
Mode	1	1
Std deviation	2.4	1.6
Minimum	0	0
Maximum	12	9
Sum	423	367

10.5.2 Total days as inpatient

The mean number of all days spent in the hospital by the HFpEF group was more than but not statistically different from the LVSD group. [p = 0.119: 95% CI= -9.308 to 1.065]. Table 10.5.2

Table 10.5.2 Total days as inpatient (per patient)

	LVSD (n = 189)	HFpEF (n = 158)
Mean	22.2	26.4
Median	14	17
Mode	1	2
Std deviation	23.8	25.1
Minimum	1	1
Maximum	138	123
Sum	4202	4164

10.6 Exposure to medications

Duration of use of ACEi / ARBs, beta blockers, aldosterone antagonist, and digoxin was analysed for the LVSD and HFpEF patients, using univariate analysis with a Cox proportional hazard model.

10.6.1 ACE inhibitors / ARBs

The mean duration of use of ACEi / ARBs in LVSD group was 51.23 months compared to 56.16 months in the HFpEF group. When these data were analysed using the univariate analysis, all-cause mortality was significantly lower in the HFpEF group compared to the LVSD group. Table 10.6.1a and b, chart 10.6.1

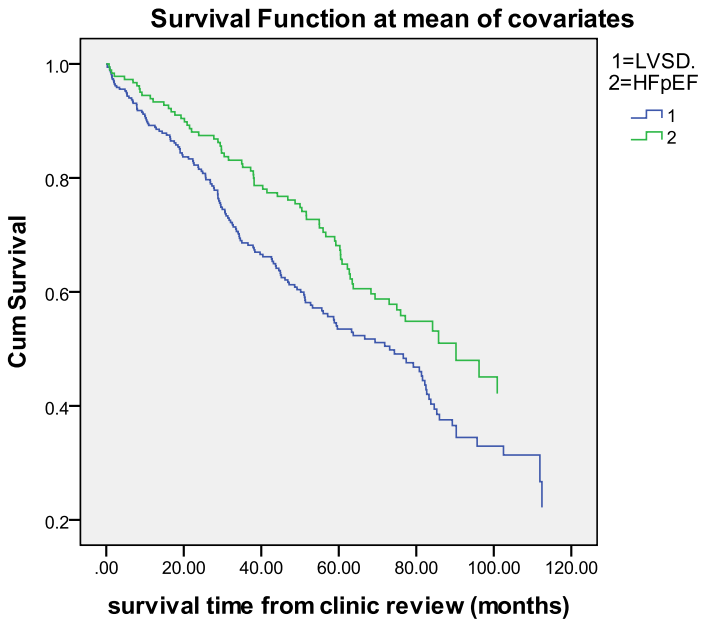
Table 10.6.1a Stratum status for ACEi / ARB use

Stratum	Event	Censored	Censored (percent)
1 (LVSD)	153	103	40.2%
2 (HFpEF)	71	90	55.9%
Total	224	193	46.3%

Table 10.6.1b Univariate analysis for duration of ACEi / ARB use

	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
ACE inhibitor / ARB exposure duration (months)	-.01	.00	85.3	1	.00	.98	.97	.98

Chart 10.6.1 Survival function for duration of ACEi / ARB use



10.6.2 Beta blockers

The mean duration of use of beta blockers in the LVSD group was 42.78 months compared to 63.96 months in the HFpEF group. Univariate analysis for all-cause mortality with beta blockers favoured a better outcome for the HFpEF group. Table 10.6.2a and b, Chart 10.6.2

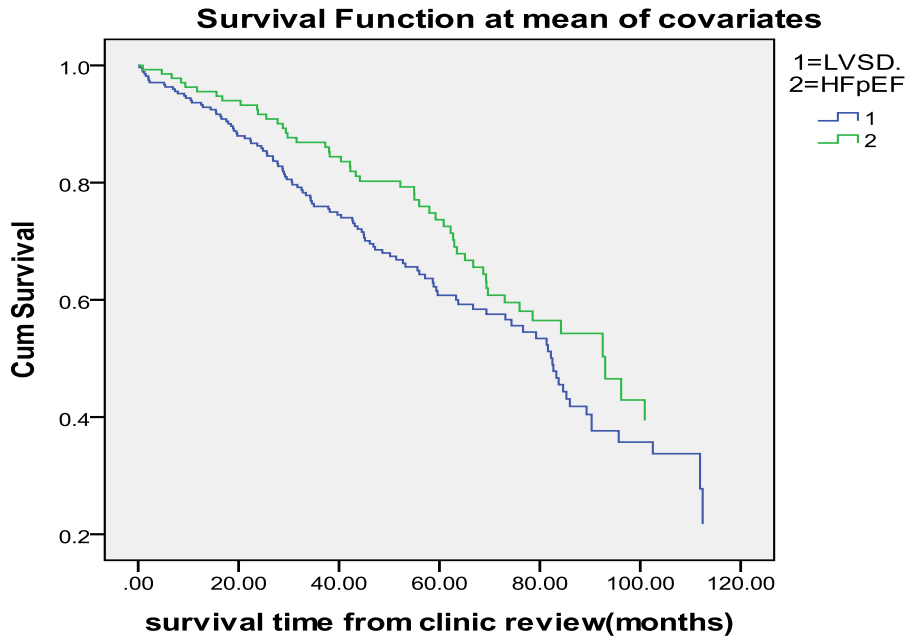
Table 10.6.2a Stratum status for duration of beta blocker use

Stratum	Event	Censored	Censored (Percent)
1 (LVSD)	110	90	45.0%
2 (HFpEF)	50	71	58.7%
Total	160	161	50.2%

Table 10.6.2b Stratum status for duration of beta blocker use

Beta blocker (duration)	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
	-.01	.00	60.2	1	.01	.9	.9	1

Chart 10.6.2 Survival function for duration of beta blocker use



10.6.3 Aldosterone antagonist

On average LVSD patients were taking an aldosterone antagonist for 17.33 months and the HFpEF patients for 27.92 months. When the aldosterone antagonists use data were analysed the survival curves converge towards the end suggesting presence of non-proportional hazards. Table 10.6.3a and b, chart 10.6.3

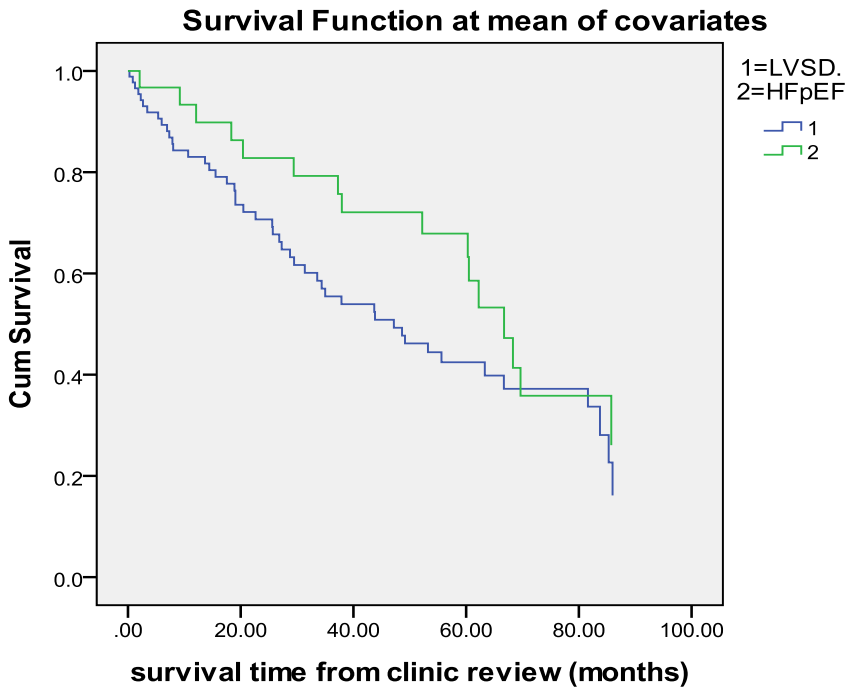
Table 10.6.3a Stratum status for aldosterone antagonist use

Stratum	Event	Censored	Censored (%)
1(LVSD)	47	23	33
2 (HFpEF)	16	13	45
Total	63	36	36

Table 10.6.3b Stratum status for aldosterone antagonist

Aldosterone antagonist duration	B	SE	Wald	df	p	Odds ratio	95% CI for OR	
							Lower	Upper
	-.03	.00	18.6	1	.01	.97	.95	.98

Chart 10.6.3 Survival function for duration of aldosterone antagonist



10.6.4 Digoxin

As with aldosterone antagonist usage the survival curves converge at the end suggesting non proportional hazards. Table 10.6.4a and b, chart 10.6.4

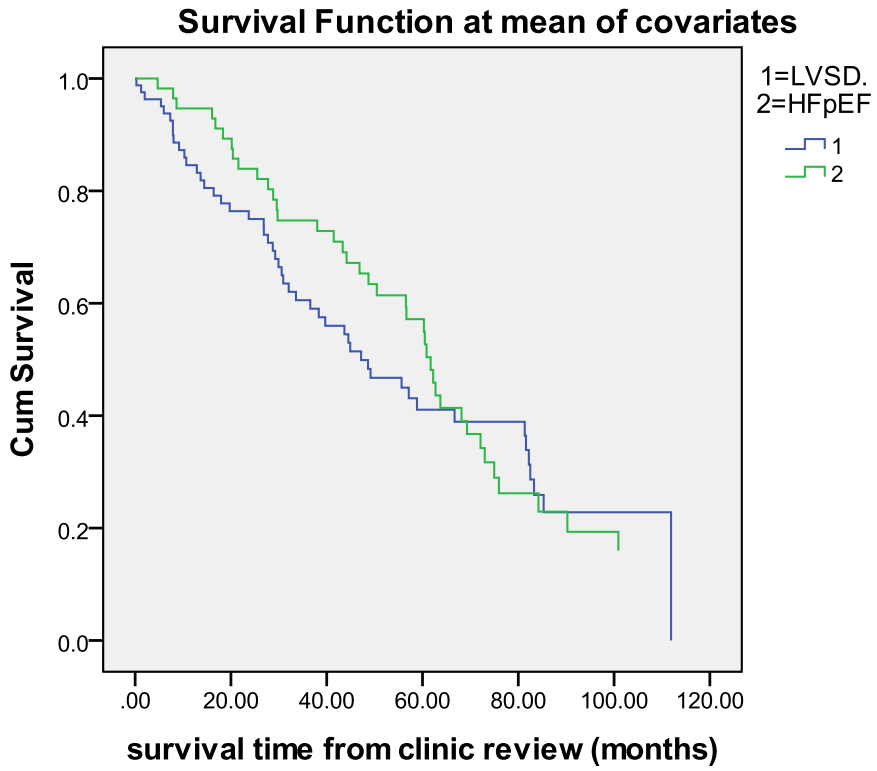
Table 10.6.4 Stratum Status for digoxin

Stratum	Event	Censored	Censored (%)
1(LVSD)	49	16	25
2 (HFpEF)	39	18	32
Total	88	34	28

Table 10.6.4 Stratum status for digoxin

Digoxin (duration use)	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
	-.01	.00	13.4	1	.01	.98	.98	.99

Chart 10.6.4 Survival function for digoxin use duration



10.7 All cause mortality

When all-cause mortality was analysed using a Cox proportional hazard model for adjusted data, HFpEF group had a better survival compared to LVSD group. Table 10.7 & chart 10.7a & b

Table 10.7 Stratum Status for all-cause mortality

Stratum	Event	Censored	Censored (percent)
1(LVSD)	163	105	39.2%
2 (HFpEF)	118	123	51.0%
Total	281	228	44.8%

Chart 10.7a Survival function for all cause mortality

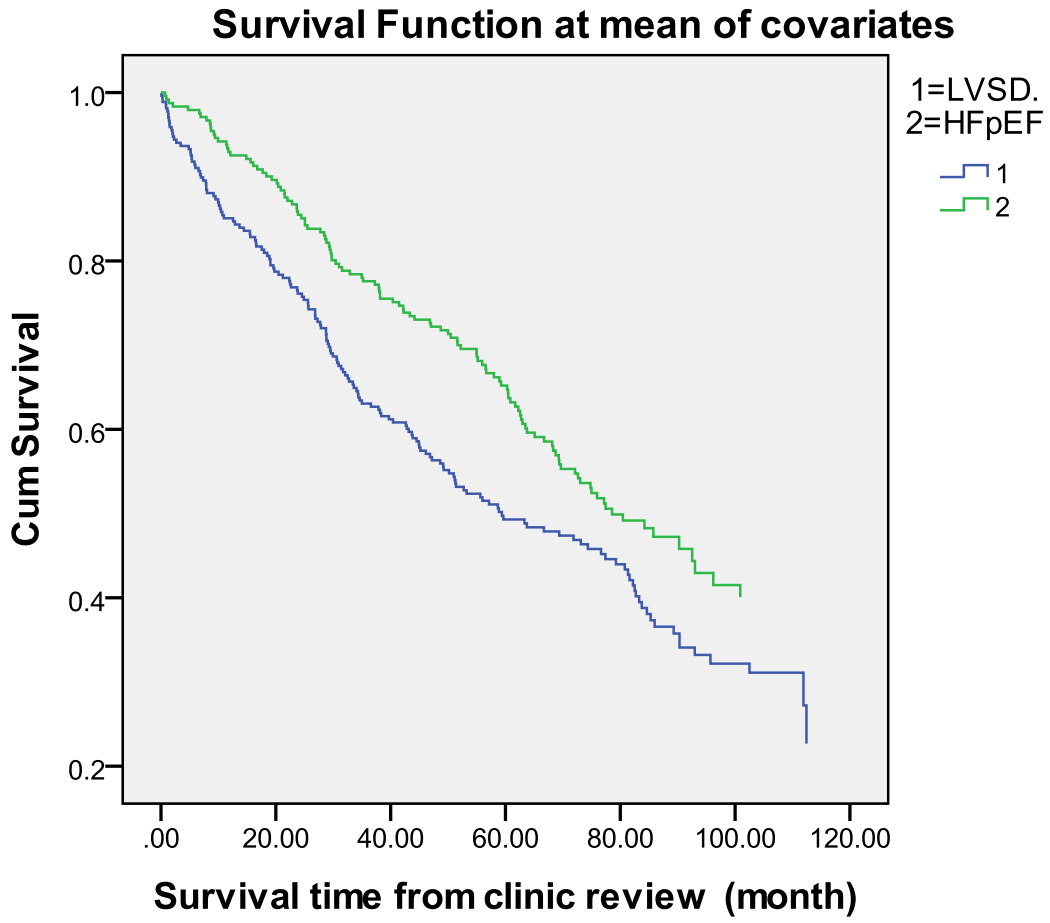
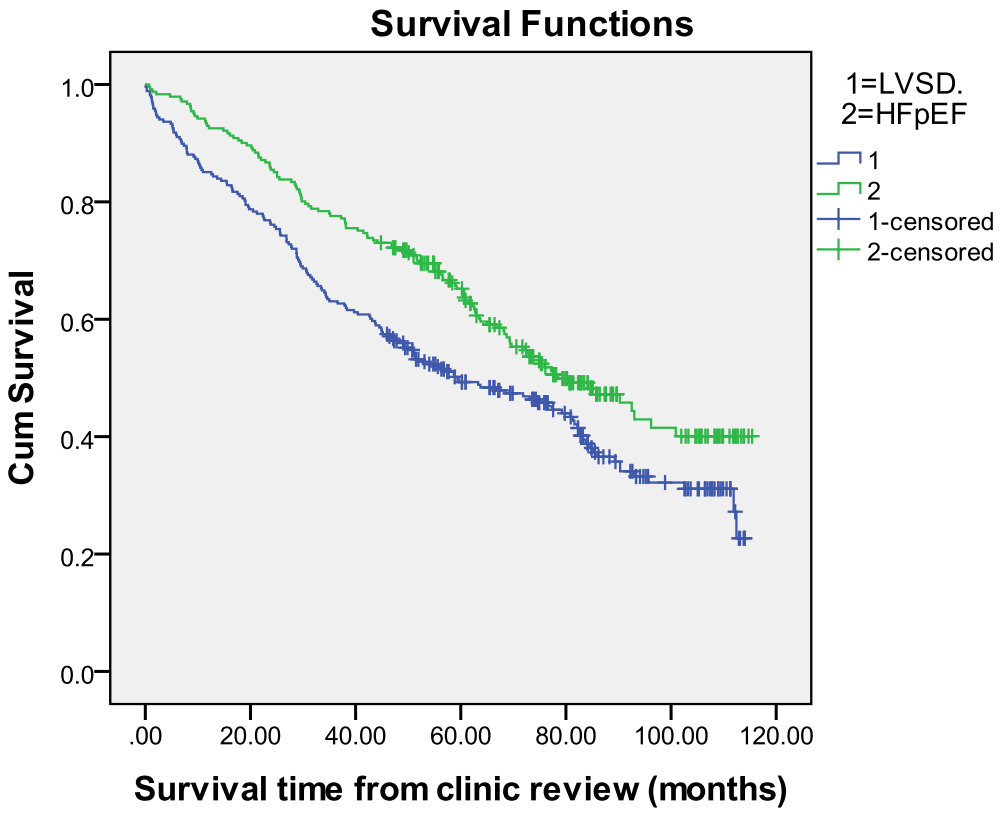


Chart 10.7b Kaplan Meier all cause mortality survival curve



10.8 Cardiovascular mortality

Cardiovascular deaths were significantly more common in the LVSD group as compared to the HFpEF group. Table 10.8a, b & c, chart 10.8

Table 10.8a Cause of death

	Cardiovascular deaths	Non cardiovascular deaths
LVSD (n=163)	113 (69%)	50 (31%)
HFpEF (n=118)	51 (43%)	67 (57%)

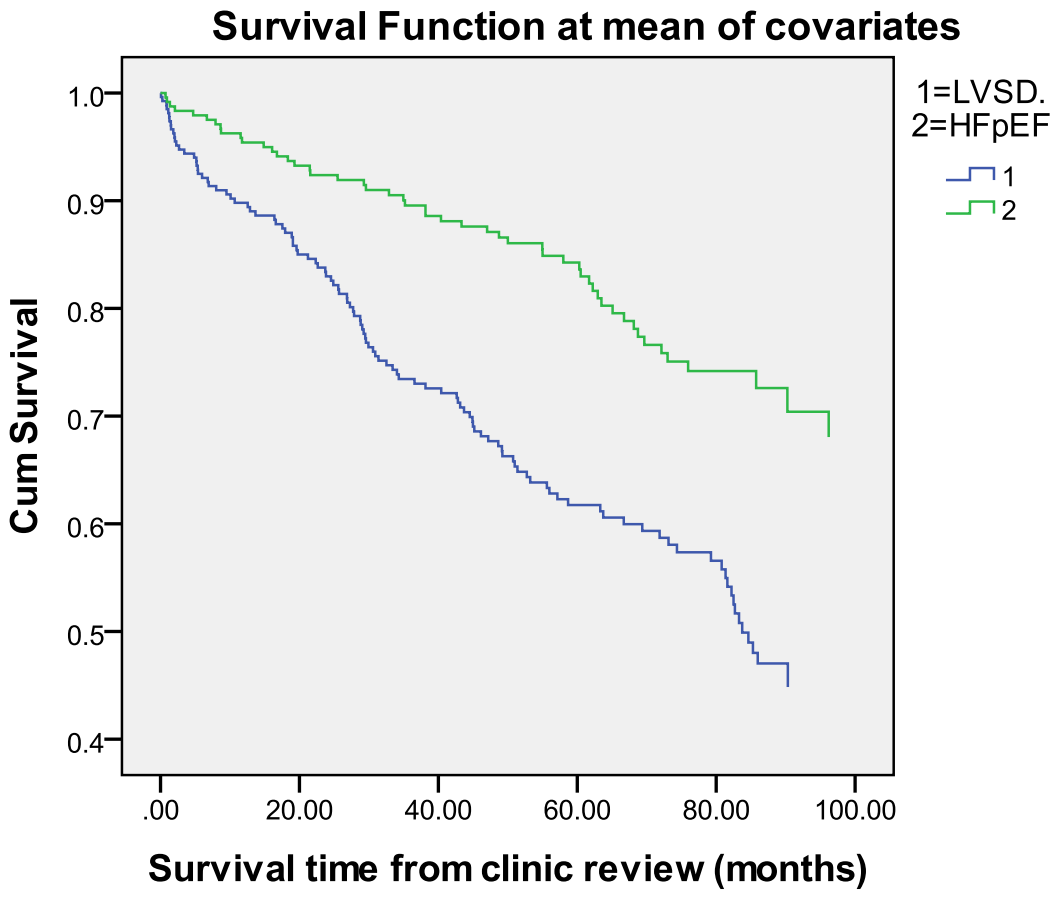
Table 10.8b Univariate analysis for cardiovascular mortality in LVSD and HFpEF groups

LVSD & HFpEF groups	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
	-.82	.16	23.8	1	.01	.44	.31	.61

Table 10.8c Stratum for cardiovascular mortality

Stratum	Event	Censored	Censored (percent)
1 (LVSD)	113	155	57.8%
2 (HFpEF)	51	190	78.8%
Total	164	345	67.8%

Chart 10.8 Cardiovascular mortality in LVSD and HFpEF



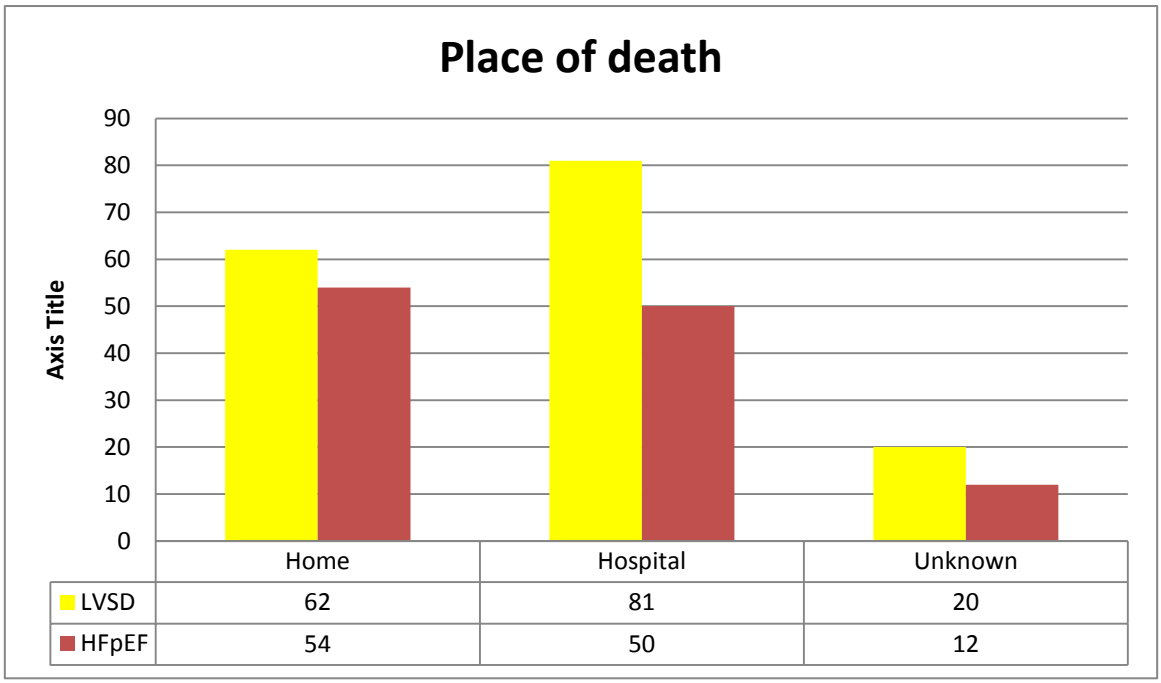
10.9 Other co morbidities developed

Stroke and cancer were the commonest co morbidities developed. Table 10.9

Table 10.9 Co morbidities developed in LVSD and HFpEF groups

	LVSD, n (%)	HFpEF, n (%)
AF	8 (3)	9 (4)
Cancer	23 (9)	26 (11)
CKD	16 (6)	17 (7)
COPD	10 (4)	7 (3)
Dementia	9 (3)	15 (6)
Diabetes	1 (1)	4 (2)
Fall	12 (4)	7 (3)
Stroke	17 (6)	22 (9)

10.10 Place of death



More patients died at hospital in the LVSD group while more patients died at home in the HFpEF group.

10.11 Conclusions and discussion

10.11.1 HF Clinic review analysis

- Of all the three groups HFpEF patients were the oldest.
- Overall more females were referred to the one stop HF clinic than males.
- Females were more likely to be diagnosed with HFpEF
- LVSD patients were more likely to have NYHA class 3 symptoms and have raised JVP, while HFpEF patients were slightly more likely to have complained of swollen ankles.
- Blood pressure was significantly higher in the HFpEF patients, while heart rate was significantly higher in the LVSD group.
- Cardiomegaly on the chest X-ray was more common in the HFpEF patients while the LVSD group were more likely to have pulmonary oedema.
- The ECG in the HFpEF group was more likely to be normal or have atrial fibrillation, while the LVSD group had more LBBB on the ECG.
- LVH and E/A ratio reversal were more likely in the HFpEF patients.
- Blood test results were not significantly different in the two groups.
- At the clinic appointment the average values of blood tests (serum sodium, potassium, urea, creatinine, and haemoglobin) were similar in both the groups.
- At the clinic appointment more LVSD patients were on an ACEi /ARB, and aspirin, while more HFpEF patients were on a beta blocker. A large number of patients in both groups had been prescribed a diuretic.

- After the clinic appointment the LVSD patients were more likely to be started on an ACEi / ARB, a beta blocker, an aldosterone antagonist, and a diuretic while warfarin was more commonly prescribed in the HFpEF group.

- HFpEF patients more likely to be discharged from the specialist HF clinic.

10.11.2 Admission to hospital data analysis

- The number of patients admitted to the hospital was not significantly different in the two groups.

- The duration to first admission following the clinic appointment was significantly longer for the HFpEF patients. Shortness of breath was the leading cause for admission in both groups. The shorter duration to admission in the LVSD group is likely due to the higher NYHA class in these patients with a higher probability to develop decompensated symptoms precipitating an admission.

- Results for blood tests were not significantly different in the two groups on admission.

- The admission ECG was more likely to be normal in the LVSD group, while HFpEF patients were more likely to have atrial fibrillation.

- A raised JVP was more likely in the LVSD group on admission while swelling of the ankles was more likely to be present in the HFpEF group.

- At the time of admission more HFpEF patients had NYHA class 3 symptoms while more LVSD patients had NYHA class 4 symptoms.

- At admission more LVSD patients were taking an ACEi /ARB, and a beta blocker.

- Although the total number of admissions per patient was similar in both the groups, HFpEF patients spent a significantly longer time as inpatients. The reasons for this are not clear and this study has not looked into the details of individual episodes of admission. The longer duration of hospital stay by HFpEF patients would suggest that these patients are equally, if not more unwell than the LVSD patients (with more complex co-morbidities) and needing more resources to look after them.

10.11.3 Mortality

- Patients with HFpEF, who were prescribed an ACEi /ARB, had a better survival rate than patients with LVSD on an ACEi / ARB, and similarly for those prescribed a beta blocker. The reason why patients in the HFpEF group had a better prognosis with an ACEi / ARB and a beta blocker is difficult to explain. There is no published literature available where the use of these medications has been compared in the two groups.

- LVSD patients were more likely to die of cardiovascular causes while HFpEF patients had more non cardiovascular deaths. LVSD patients were more likely to die at the hospital while HFpEF patients were more likely to die at home.

- The HFpEF group had more patients diagnosed with cancer and stroke.

- In conclusion both LVSD and HFpEF patients had poor prognosis but different causes of death. While LVSD patients were more likely to die of cardiovascular deaths, HFpEF patients died of non-cardiovascular causes.

Chapter 11

Heart rate and survival

There is a growing body of evidence from the epidemiological and experimental studies of a strong association between elevated heart rate (HR) and increased cardiovascular risk (246). Also there have been experimental and observational studies suggesting that increased HR is associated with a worse prognosis in HFpEF patients and better HR control could be a therapeutic target (118, 247, 248).

We analysed the role of base line HR on survival in the LVSD and HFpEF groups. When HR was analysed as a continuous variable the impact on survival was non-significant.

11.1 LVSD group

For the LVSD group the median heart was 80 beats per minute (b.p.m). patients were stratified in to two groups. (Group 1 = HR 0-80 b.p.m and Group 2 = HR 81-160 b.p.m) When data were analysed for all-cause mortality median HR of more than 80 b.p.m was not a significant predictor of poor survival. Table 11.1a

Table 11.1a Median HR analysis for all-cause mortality in LVSD group

LVSD	B	SE	Wald	df	P	Odds ratio	95.0% CI for OR	
							Lower	Upper
Median HR	.20	.15	1.7	1	.18	1.2	.9	1.6

For cardiovascular deaths and hospitalisation in the LVSD group, the median HR was not significant risk factor. Thus the data for the LVSD group were not analysed any further. Table 11.1b

Table 11.1b Median HR analysis for cardiovascular deaths and hospitalisation

LVSD	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
CVS deaths	.07	.18	.15	1	.69	1.1	.7	1.5
Hospitalisation	.21	.16	2.07	1	.14	1.2	.2	1.6

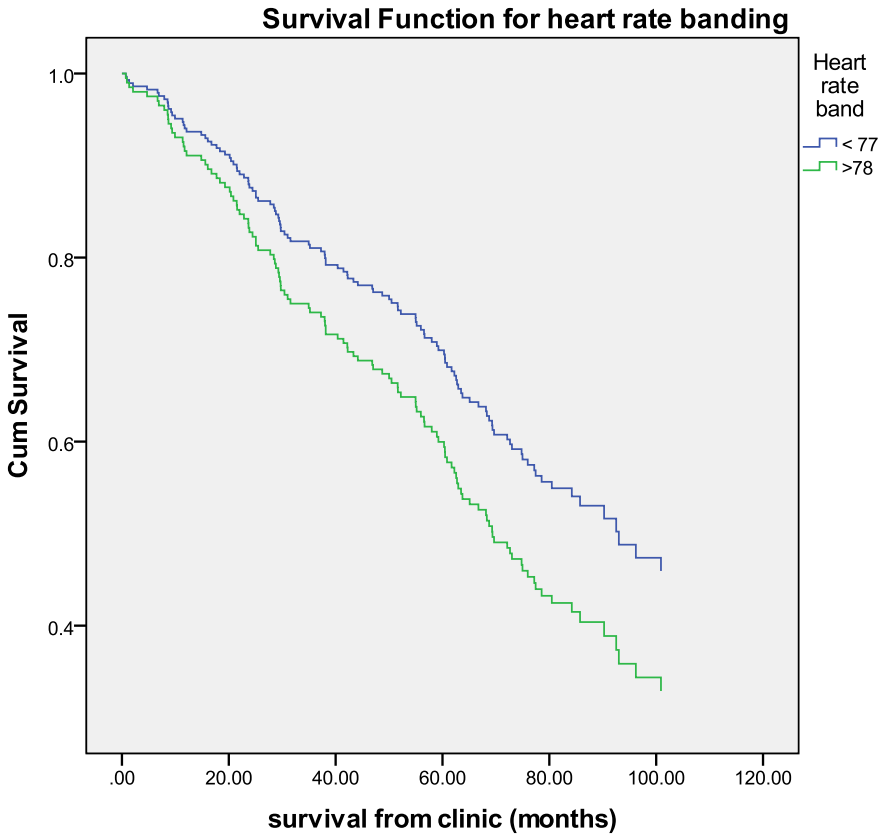
11.2 HFpEF group

The median HR for the HFpEF patients at the time of the clinic review was 77 b.p.m. Using the median HR as a cut off value, the HFpEF patients were stratified in to two groups: group 1 (HR 1 – 77), and group 2 (HR 78 – 150) b.p.m. There were 132 patients with HR ≤ 76 b.p.m and 108 with HR ≥ 77 b.p.m. Higher baseline HR (>78 b.p.m) was a marker of higher all-cause mortality in the HFpEF group.

Table 11.2 Median HR analysis for all-cause mortality in HFpEF group

HFpEF	B	SE	Wald	df	P	Odds ratio	95.0% CI for OR	
							Lower	Upper
Median HR	.35	.18	3.7	1	.05	1.4	.9	2

Graph 11.2 Heart rate banding and survival



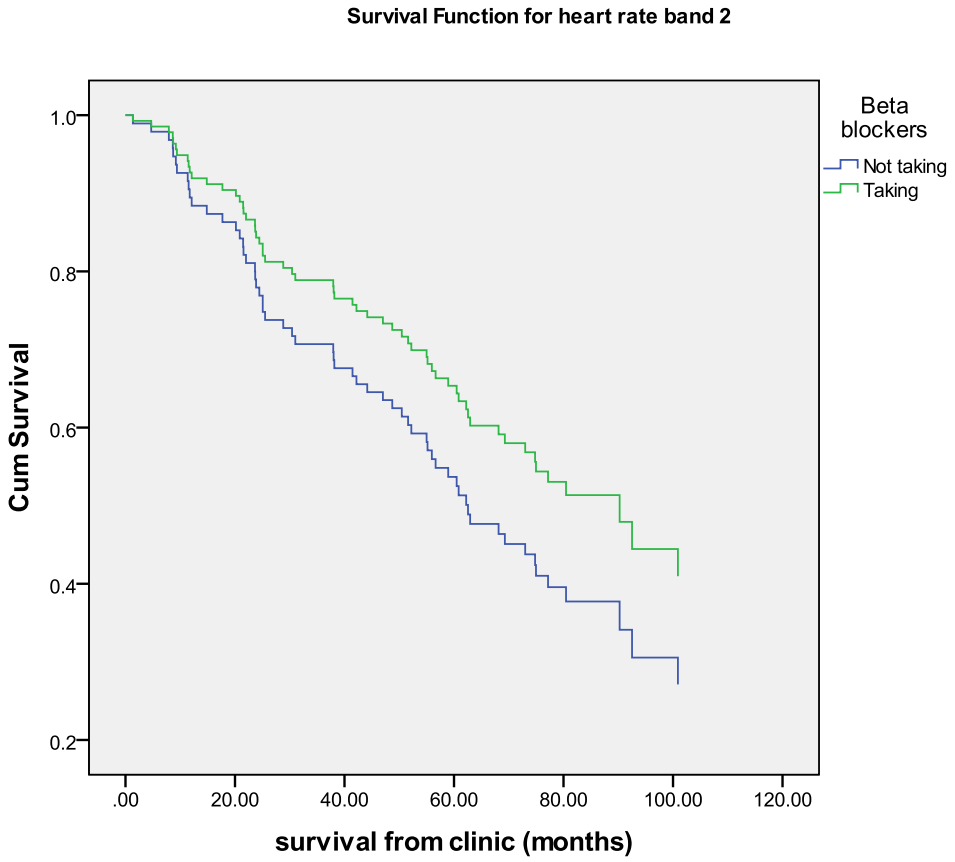
11.3 Heart rate and beta blockers

HFpEF patients who had a higher base line HR (≥ 78 b.p.m), and were taking a beta blocker had significantly better outcome. Table and Graph 11.3

Table 11.3 Patients taking beta blockers

	B	SE	Wald	df	p	Odds ratio	95% CI for OR	
							Lower	Upper
Taking Beta blockers	-.38	.19	4	1	.04	.68	.5	.9

Graph 11.3 Survival function for beta blockers and median HR ≥ 78 b.p.m



Median HR banding at baseline, before the initiation of a beta blocker, was not significantly related to all-cause mortality in the HFpEF group. Table 11.3a

Table 11.3a Survival analysis before beta blocker initiation

Before initiating beta blockers	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
	-.09	.20	.1	1	.66	.91	.6	1.3

Use of ACE inhibitors was not significantly related to survival with median HR banding [odds ratio 0.70; p = 0.06: 95% .48 – 1.01].

11.4 Conclusion and Discussion

In our study an elevated baseline HR in the HFpEF patients is an independent predictor of all-cause mortality, with a trend to increased hospitalisation. HFpEF patients who were taking a beta blocker had a significantly better outcome.

Under physiological conditions increase in heart rate (HR) results in increased relaxation and reduced diastolic filling pressure in the ventricle. In HFpEF patients increased HR impairs ventricle filling pressure and delays relaxation. Also the late atrial contribution to ventricular filling reduces with increased HR (249, 250).

Selby et al (251) have carried out experimental work using LV biopsy samples during coronary bypass surgery. They have shown that in patients with normal EF and increased LV mass there is a tachycardia induced incomplete relaxation of the myocardium.

In patients with LVSD a resting heart rate of > 60 b.p.m has been recognised as a predictor of poor outcome (105, 252). Similarly the role of beta blockers to reduce death and rehospitalisation in patients with LVSD is well established (248, 253) and recommended in the clinical guidelines (24).

No treatment has yet been shown to reduce morbidity and mortality in patients with HFpEF and there are no large scale trials that have investigated the role of resting HR in HFpEF patients.

In the SENIORS trial (254) in a subgroup analysis of patients with a baseline HR ≤ 80 and > 80 b.p.m, the primary outcome of all-cause mortality or cardiovascular hospitalisation was not different in the two groups. This result is unlike our study where a resting HR of ≥ 78 b.p.m was associated with poor survival. The reasons for this most likely include the different selection criteria used in the two studies. The inclusion criteria in the SENIORS trial were age > 70 years and an EF of ≥ 35% while

for our study the inclusion criteria were age >18 years and an EF ≥ 40%. Though, similar to our study, in the SENIORS trial use of beta blockers significantly reduced the cardiovascular death and hospitalisation in HF patients regardless of the EF, age, or gender.

There are few studies that have examined the role of beta blockers in providing protection to HFpEF patients. Smith et al (255) examined the association between use of beta blockers and frequent hospitalisation in HFpEF patients. They showed that use of beta blockers was associated with a decreased risk of hospitalisation for patients with HFpEF and coronary heart disease.

Two studies (256, 257), with less than 30 patients each have shown that the HR lowering calcium channel blocker verapamil may improve exercise capacity and symptoms in HFpEF patients.

In conclusion, for HFpEF patients in our study, an elevated HR at baseline was an independent predictor of all-cause mortality. The use of beta-blockers in those with a higher baseline HR was associated with a significantly better outcome. These data suggest a potential therapeutic target in HFpEF patients.

Chapter 12

Discussion and conclusions

Heart failure is a common condition that is responsible for significant morbidity and mortality (1). The incidence and prevelance of HF is increasing (258).

The importance of the systolic function for pumping blood around the body and its impairment causing symptoms of HF has been well recognised. In the past four decades research has mainly focused on impaired systolic function leading to an improved appreciation of the pathophysiology of heart failure (HF) and its management. Thus there is now a strong evidence base for managing patients with left ventricular systolic dysfunction (LVSD).

Equally, in the last two decades there has been an increasing appreciation that patietns who present with signs and symptoms of HF did not always have impaired systolic function as an explanation for their symptoms.

This prompted researchers to look at the filling and relaxation properties of the left ventricle to explain the symptoms. Thus the concept of “diastolic” heart failure or heart failure with normal or preserved ejection fraction (HFpEF) came about (259).

Over a period of time it has become clear that by focusing all our attention on the systolic dysfunction of the heart, an almost equal number of patients with signs and symptoms of heart failure, but with mildly reduced or preserved systolic function, may have been falsely reassured.

Once it had been recognised that a cohort of patients with signs and symptoms of heart failure had HFpEF, there was an attempt to extrapolate evidence from studies done in patients with LVSD and apply it to the HFpEF population, on the assumption that both these groups were part of the same pathophysiological process. Major trials

using ACEi / ARBs or beta blockers did not show any mortality benefit in HFpEF patients (115-117, 229, 230).

A complete gamut of questions still remains unanswered about the HFpEF patients. What are their clinical characteristics? What risk factors do they have? How are they managed in real life? Why and how often are they admitted to the hospital? What other co morbidities do they develop? Where do they die and what do these patients die from?

The Darlington Retrospective Out Patient Study (DROPSY) has tried to answer some these questions.

12.1 Main findings of the study

Our research is highlighted by two factors. First it was a pragmatic real life study based on patients referred in an unrestricted manner to the HF clinic. Secondly, notwithstanding issues of compliance, some 96% of the patients with LVSD were on evidence based therapy, specifically an ACEi. Thus our results, when compared to other studies, which are mainly based on clinical trials, have real life validity in a clinical setting.

The DROPSY study has shown that patients who were referred to the HF clinic had overall poor survival, as has been shown in other studies.

In the LVSD group 163 (60%) of the 268 patients who were seen in the HF clinic died during the median follow up of 7 years. These figures suggest a continuing high mortality in the LVSD patients, despite the majority of these patients being on optimal medical therapy (an ACEi, a beta blocker and an aldosterone antagonist). The reasons for this high mortality are not clear. The published literature for mortality in the LVSD group has similar figures. Henkel et all (127) in 2008 from the Olmsted County community HF based cohort reported a 5 year survival of only 40%. Mehta et

al (260) in 2009 reported all-cause mortality of 14% at 6 months after a new diagnosis of HF in the UK population. Patients who are admitted to hospital have an even worse prognosis. The national heart failure audit in 2010 reported that 32% of patients died within a year of admission.

In the LVSD group, of the 113 patients who died of cardiovascular causes, 54 (48%) died due to HF. These results are similar to those reported by other authors. In the Echocardiographic Heart of England screening study (ECHOES) (126) patients with HF and LVSD were more likely to die of HF followed by IHD. In a report by Henkel et al (127) the leading cause of death in LVSD patients was coronary heart disease. A more recent meta analysis [Meta-analysis Global Group in Chronic Heart Failure (MAGGIC)] by Doughty et al (135) compared survival in patients with HFpEF and those with LVSD using individual patient data. They included 31 studies comprising 41972 patients. LVSD was present in 31625 patients and they had a higher risk of cardiovascular death [hazard ratio 0.55: 95% CI: 0.49 - 0.61].

There have been some reports that have looked at the long term trend in HF mortality. Sutcliffe et al (261) analysed trends in community mortality for HF patients in England and Wales from 1950 to 2003. They reported that HF deaths rose by a factor of four between 1950 and 1974, and then fell by a quarter by 2003. A similar trend has been reported from Scotland by Murdoch et al (262). In another community based cohort from the Olmsted County, Roger et al (263) found that the 5 year age-adjusted survival was 43% in 1979-1984 vs. 52% in 1996-2000.

These reports suggest that HF patients saw a steady improvement in survival over the last four decades which coincides with more and more patients being managed in accordance with the evidence based guidelines. The improved survival especially in the community based cohorts could also be due to early detection and treatment of HF, improved survival and decline in cardiovascular disease and improved control of

hypertension (264). In the UK this has probably been aided by the health policy initiative of rewarding GP practices through the Quality and Outcomes Framework (QOF) (265).

Recent data on mortality of patients with LVSD suggest that the benefit provided by the current treatment options have reached a plateau. In a recent paper Loh et al (266) analysed three 6 year eras 1993-98, 1999-2004, and 2005-10. According to the authors, although the overall mortality for all patients at the three year follow up point fell from 36.4% in the first era to 31.5% in the third era, the mortality still remains high. Despite an improvement of care and outcomes for HF patients, the overall mortality and morbidity remains high. Thus, there is an urgent need for further research to develop and investigate new modalities of treatment for these patients.

The mortality in the HFpEF group was comparable (50% vs. 60%) to the LVSD group. There were 118 (50%) deaths during the follow up period. Various published studies have produced conflicting results for mortality in HFpEF studies. Cleland et al in the PEP-CHF (116) trial, reported 12.8% deaths after a mean follow up of 26 months, whereas a literature based meta analysis by Somaratne et al (134) reported a 32% mortality after a mean follow up of 47 months. The national HF audit 2010 (242) reported that the prognosis in patients with HFpEF was as poor as patients with LVSD.

In our study HFpEF patients had more non cardiovascular deaths than cardiovascular deaths. This result is in contrast to the data from the prospective trials but consistent with other population based cohort studies. In the I-PRESERVE (117) trial 70% of patients had cardiovascular deaths. Similar results were reported by Chan et al (267). While in a community based cohort Henkel et al (127) reported that HFpEF patients had a higher (49%) rate of non-cardiovascular deaths. The conflicting results from various studies are likely due to study design, sample size, and how the cause of

death has been ascertained. The DROPSY cohort, unlike the prospective trials, included patients with other serious illnesses and co morbidities which also affect survival.

Compared to the LVSD cohort, the five year survival of patients with HFpEF in our study was only marginally better, 50% vs. 40%. Studies that have compared the mortality in patients with HFpEF and LVSD have generally reported either similar or slightly better survival in the HFpEF patients. Few studies have reported a higher mortality for HFpEF patients. One of the earlier studies by Vasan et al (268) reported an annual mortality of 18.9% in the HFpEF group vs. 8.7% in the LVSD group. The sample size of this study was small, which may have affected the result. Most of the other studies have reported a better survival for the HFpEF group. Owan et al (132) studied all consecutive patients hospitalised with decompensated HF and found the survival rate was higher in the HFpEF patients than among the LVSD patients, with mortality rates at one year of 29% vs. 32% and 65% and 68% at five years respectively. Lenzen et al (133) in the Euro Heart Failure survey, during a 12 week follow up, reported a higher incidence of all-cause mortality in the LVSD group (12%) vs. the HFpEF group (10%). Bhatia et al (131) reported no significant difference in the 30 day and 1 year mortality in patients with HFpEF and LVSD 5% vs.7% and 22% vs. 26% respectively.

Thus HFpEF patients have a slightly better five year survival but overall the mortality remains high. In the absence of any evidence based treatment for this group this is unlikely to improve. For the present, better management of the major risk factors like hypertension, diabetes, atrial fibrillation, ischemic heart disease is the only approach available.

In our study HFpEF patients who were taking ACEi /ARBs and beta blockers had a better survival. DROPSY was not randomised so the group taking and not taking any

particular drug will differ in other ways and our data need to be interpreted with caution. The Heart Failure Society (269) recommends, that an ACEi should be considered in all patients with HFpEF who have symptoms of atherosclerotic cardiovascular disease or diabetes.

Using univariate and multivariate analysis, the confounding variables can be explored. This has been explored in chapters 7 and 11. Age ≥ 80 years, hypertension, atrial fibrillation, NYHA class, and admission to hospital were significant predictors of a poor outcome in HFpEF patients.

In our study a median resting heart rate of 78 / min or more in the HFpEF patients was an independent predictor of a poor outcome. An elevated HR has been recognised as a major predictor of cardiovascular morbidity and mortality (246).

In the HFpEF patients there is a dearth of published data about the role of increased resting heart rate on morbidity and mortality. There is some evidence that increased resting heart rate induces relaxation abnormalities in the normal myocardium. Donald et al (251), in an experimental study, observed that there was incomplete relaxation even at lower heart rates in those with left ventricular hypertrophy compared with those with normal muscle mass. There is also some evidence that selective HR reduction with Ivabradine in patients with HFpEF leads to changes in hemodynamic parameters demonstrating unloading of the Left ventricle (270) and improved function and exercise capacity (271). Targeting the resting heart rate may be a potential new treatment option in HFpEF patients that could improve symptoms and survival.

In the third “Other” group there were 213 (41%) deaths. The majority of patients, 81 (38%), died of cardiovascular causes. The leading cardiovascular cause of death was HF, followed by stroke and ischemic heart disease. These figures are similar to the data from the ONS (243) where cardiovascular disease remains the leading cause of deaths in the UK population nationally.

The reasons for the high proportion (12%) of HF deaths in our third “Other” group of patients are not clear. There could be two plausible explanations for the high proportion of HF deaths. The first reason may be due to the fact that data for this cohort of patients were only collected from the HF clinic appointment letter with no further input from the case records. It is possible that some of the patients who had underlying cardiovascular risk factors (diabetes, hypertension, coronary artery disease, obesity, peripheral vascular disease, family history of cardiomyopathy, history of exposure to cardiac toxins, arrhythmia, sleep disordered breathing) subsequently developed HF. It can be argued that patients who have risk factors for HF require aggressive management of modifiable risk factors. These patients may have undetected abnormalities of cardiac structure and function and depending on their risk factors may warrant invasive or non-invasive evaluation to ascertain their cardiac structure and function.

The second plausible reason could be that these patients in spite of a normal echocardiogram and no clinical evidence of HF really had HF but were missed by the present diagnostic algorithm used in clinical practice.

This raises the question as to whether different diagnostic approaches might be beneficial in these patients. Could this be by using different echocardiographic parameters, using markers like B-type natriuretic peptide (BNP) / N-terminal pro-BNP or a detailed analysis of cardiac structure and function using MRI scan as well?

B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-pro BNP) have been widely available for some time (272) but there is wide variation in the recommended cut off values in clinical guidelines (22, 269). Despite recommendations that natriuretic peptides should be a part of the diagnostic pathway for HF they remain underutilised in clinical practise (273). For our study BNP/ NT-pro BNP test was done from Feb 2002- June 2004 in the HF clinic as part of a different

research project. Subsequently patients seen in the HF clinic after June 2004 did not have BNP/NT-pro BNP levels measured and as such BNP and NT-pro BNP has not been used in the analysis of this study.

The role of echocardiography is central in the assessment of the management of the HF patients. For the present, two dimensional echocardiography remains the preferred modality to diagnose HF (269). It provides a good general assessment of LV systolic function but can be limited due to both inter and intra operator variability, poor acoustic windows and the need for geometric assumptions in quantifying LV systolic function (274). Recently newer techniques have been developed. These include micro bubble contrast which result in improved left ventricular definition and thus improved assessment of the LV volumes, wall motion and ejection fraction (275).

3D echocardiography allows real time imaging with accurate and reproducible regional and global LV assessment.

Strain and strain rate imaging measure actual deformation of the LV and can differentiate between active (fibre shortening or lengthening) and passive (translation or tethering) movement of myocardial segments and to quantify dyssynchrony (276, 277). Speckle tracking involves the detection of multiple unique patterns of echocardiographic pixel intensity that can be tracked throughout the cardiac cycle (276).

Imaging, by providing more precise, sensitive, and reproducible information of the LV function will help eliminate some of the limitations at present.

Cardiac MRI on the other hand is potentially the ideal technique to assess myocardial anatomy, regional and global function, and viability. It reveals the underlying cause of HF, can monitor disease progression and treatment effect, and also provide

prognostic information (227, 274). At the present moment cardiac MRI scan is not widely available and more of less used as a research tool.

Thus, for the present, diagnosing HF in clinical practice remains a challenge and there is an urgent need to improve the diagnostic and investigative algorithms.

12.2 Limitations of the study

This was a retrospective cohort study design. There are both advantages and disadvantages to this design. The main advantages are that less time is required to conduct the study as the disease or outcome has already occurred, it lets you simultaneously look at multiple outcomes, it is a useful means of an initial study to establish associations, is less likely to lose patients to follow up, and can answer questions that may not be answered through other study designs.

The main disadvantages of the retrospective study design are issues around data quality (as it relies on the data that has been recorded), there is no control group, and selection bias.

The data were collected from the case notes of the patients. Accuracy of the data depended upon the details recorded in the case notes. It is possible that some of the information recorded in the notes was not up to date or accurate. Every effort was made to make sure that the data collected were as representative as possible. The majority of the data collected (e.g. blood tests, chest X - ray reports) were also double checked from the hospital information system thus minimising the chance of error.

Data were collected by the researcher solely, but to minimise the chance of any systemic reproduction of error in data collection, double data entry was done for 10% of the data by a research nurse. Only small discrepancies in data values were found with no systematic errors.

This study did not recruit any patients and had no patient contact. Though the two groups (LVSD and HFpEF) have been compared in the analysis the results should be interpreted with caution, as data have been collected retrospectively and no intervention was performed.

Medications prescribed to the patient may or may not be taken and compliance has been an issue both in the trials and real life (278). For this study the data on medications was collected from the patient prescriptions. This form of data collection assumes that the patients have been taking their medications as per the prescription, but there is no way to verify this.

12.3 Implications of the research

A pragmatic and practical case definition was used for identification of patients in the HFpEF group. The results of this study have raised some important points. The HFpEF patients have equally high five year mortality and admission rates as the LVSD cohort to the hospital but likely to spend significantly more days as inpatient.

The use of ACEis and beta blockers was associated with a lower mortality in the HFpEF group. This result is contrary to the major trials (115-117, 279) that showed marginal or no benefit of ACE inhibitor or beta blocker usage. This should inform further research including randomised controlled studies to answer some of the questions.

12.4 Reflections

When I undertook the work to look at the heart failure patients referred to the one stop HF clinic at Darlington Memorial Hospital, I had very basic experience of research work.

It was a sharp learning curve. The initial steps were to get the project registered with various organisations and obtain ethical approval. The issue of obtaining patient

consent was the main focus of the ethical discussions and guidance was needed from different organisations. The issue of obtaining patient data from GP practices was also the main focus of the ethical discussion. The main issue with data collection was getting patient notes. Some of the notes had to be requested repeatedly and there were some that we did not manage to find.

Data were collected on a Microsoft Excel sheet. When data were transferred from one sheet to another or from one computer to another the dates sometimes changed. I discovered that this was because the way date is calculated by Excel is set up in two different ways. This had implications for the data collection as we had to go back and recheck the dates for patients. This took considerable time. Transferring data from the Excel sheet to the SPPS 19 for analysis also changed the date function and created similar issues.

12.5 Future work

This was a retrospective cohort work that used a practical definition for identifying patients with HFpEF. There is still uncertainty regarding the proper diagnosis and management of the HFpEF patient.

We used a pragmatic and practical definition for defining the HFpEF patients. Following from this work further research should be possible to look in greater detail at these patients and compare interventions such as ACEi /ARBs, beta blockers, or to explore newer treatment modalities.

12.6 Conclusions

Despite the numerous randomised controlled trials that have shown survival benefit with ACEi /ARBs and beta blockers in patients with LVSD, the mortality in this group in real life remains high with most deaths due to cardiovascular disease.

HFpEF patients have an equally high mortality, spend a long time in hospital and are more likely to die of non-cardiovascular causes. Despite the lack of evidence from large randomised controlled trials, use of ACEi / ARBs, and beta blockers in our study was associated with a lower death rate in HFpEF patients. This needs further investigation. Resting heart rate appears to be a marker of poor outcome in the HFpEF patients and could be a new therapeutic target that should be investigated further.

References

1. Cowie MR MA, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, Grobbee DE. The epidemiology of heart failure. European Heart Journal 1997;18:208-25.

2. McKee PA CW, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. N Engl J Med 1971(285):1441-6.

3. Senni M TC, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM. Congestive heart failure in the community: trends in incidence and survival in a 10-year period. Arch Intern Med. 1999(159):29-34.

4. Stewart AL, Greenfield, S., Hays R.D,. Functional status and well-being of patients with chronic conditions: results from the Medical Outcomes Study. JAMA. 1989(262):907-13.

5. Fryback D.G. DEJ, Klein R. The Beaver Dam Health Outcomes Study: initial catalogue of health-state quality factors. Med Decis Making. 1993(13):89-102.

6. Anoop CP, Tang WHW, Gary SF, Ritesh G, James BY. Why do patients fail to receive β-blockers for chronic heart failure over time? A “real-world” single-center, 2-year follow-up experience of β-blocker therapy in patients with chronic heart failure. American heart journal. 2005;149(5):921-6.

7. Fuat A, Hungin APS, Murphy JJ. Barriers to accurate diagnosis and effective management of heart failure in primary care: qualitative study. British Medical Journal. 2003;326:196-200.

8. Fuat A. Bridging the treatment gap: the primary care perspective. Heart. 2005 May 2005;91(suppl 2):ii35-ii8.

9. Francis CM, Caruana L, Kearney P, Love M, Sutherland GR, Starkey IR, et al. Open access echocardiography in management of heart failure in the community. BMJ. 1995 March 11, 1995;310(6980):634-6.

10. Khunti K. Systematic review of open access echocardiography for primary care. Eur J Heart Fail. 2004;6:79 - 83.

11. Hampton JR, Barlow AR. Open access (Ordering tests is easy, but a specialist opinion may be more valuable). British Medical Journal. 1995;310:611-2.

12. Denolin H, Kuhn H, Krayenbuehl H, Loogen F, Reale A. The defintion of heart failure. European Heart Journal. 1983 July 1, 1983;4(7):445-8.

13. Lewis. T. Diseases of the heart. New York: The MacMillan Co; 1937.

14. Purcell IF, Poole-Wilson PA. Heart failure: why and how to define it? Eur J Heart Fail. 1999 Mar;1(1):7-10.

15. Wood P. Diseases of the heart and circulation. London: Eyre and Spottiswoode; 1950.

16. Wagner S, Cohn K. Heart Failure: A Proposed Definition and Classification. Arch Intern Med. 1977 May 1, 1977;137(5):675-8.

17. Braunwald E. Clinical manifestations of heart failure. In Braunwald E, editor. Heart disease: a textbook of cardiovascular medicine. Philadelphia: Saunders,; 1988.

18. Members ATF, Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. European Heart Journal. 2008 October 1, 2008;29(19):2388-442.

19. European Society of Cardiology. Guidelines for the diagnosis of heart failure. European Heart Journal. 1995 June 1, 1995;16(6):741-51.

20. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. European Heart Journal. 2001 September 1, 2001;22(17):1527-60.

21. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). European Heart Journal. 2005 June 2005;26(11):1115-40.

22. Members ATF, McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2012 July 1, 2012;33(14):1787-847.

23. Mueller X, Stauffer JC, Jaussi A, Goy JJ, Kappenberger L. Subjective visual echocardiographic estimate of left ventricular ejection fraction as an alternative to conventional echocardiographic methods: Comparison with contrast angiography. Clinical Cardiology. 1991;14(11):898-902.

24. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults. Circulation. 2009 April 14, 2009;119(14):1977-2016.

25. Dolgin M, Committee. NYHAC. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels / the Criteria Committee of the New York Heart Association. 9 ed. Boston Little, Brown; 1994.

26. Davis RC, Hobbs FDR, Lip GYH. ABC of heart failure: History and epidemiology. BMJ. 2000 January 1, 2000;320(7226):39-42.

27. Nobel Lectures, Physics 1901-1921. [home page on the internet] Elsevier Publishing Company, Amsterdam, 1967 [cited 2010 30/05/2010]; Available from: http://nobelprize.org/nobel_prizes/physics/laureates/1901/rontgen-bio.html.

28. Nobel Lectures, Physiology or Medicine 1922-1941. [home page on the internet]: Elsevier Publishing Company, Amstredam 1965; [cited 2010 30/05/2010]; Available from: http://nobelprize.org/nobel_prizes/medicine/laureates/1924/einthoven-bio.html.

29. Nirav J. Mehta, Ijaz A. Khan. Cardiology's 10 Greatest Discoveries of the 20th Century. Tex Heart Inst J. 2002;29(3):164-71.

30. Roelandt JRTC. Seeing the Invisible: A Short History of Cardiac Ultrasound. European Journal of Echocardiography. 2000 March 2000;1(1):8-11.

31. Holmer N-G, Lindström K, Lundström N-R, Marsal K, Olsson B, Pettersson H, et al. In Memoriam: Inge Edler -- the father of echocardiography. European Journal of Ultrasound. [doi: DOI: 10.1016/S0929-8266(01)00137-9]. 2001;13(3):179-82.

32. Gowda RM, Khan IA, Vasavada BC, Sacchi TJ, Patel R. History of the evolution of echocardiography. International Journal of Cardiology. [doi: DOI: 10.1016/j.ijcard.2003.07.018]. 2004;97(1):1-6.

33. Richard LM, Timothy AS. The history of interventional cardiology: Cardiac catheterization, angioplasty, and related interventions. American heart journal. 1995;129(1):146-72.

34. Meyer J. Werner Forssmann and catheterization of the heart, 1929. Ann Thorac Surg. 1990 July 1, 1990;49(3):497-9.

35. Peter Curtis. Family Pactice History: Bloodletting. Canadian Family Physician. 1981;27:1030-2.

36. The Ayurvedic Pharmacopoeia of India. Government of India, Ministry of health and family welfare, department of AYUSH; [cited 2010 05/06/2010]; Available from: http://ccras.nic.in/PharmacopoeialWork/Links/API/API-Vol-2.pdf.

37. Lee MR. William Withering (1741-1799): a biographical sketch of a Birmingham Lunatic.: The James Lind Library 2005 [cited 2010 02/06/2010]; Available from: www.jameslindlibrary.org.

38. Aronson JK An account of the Foxglove and its medical uses 1785-1985. Oxford: Oxford University Press.; 1985.

39. Withering W. An account of the foxglove and some of its medical uses: with practical remarks on dropsy and other diseases. . London: J and J Robinson; 1785.

40. Charles Murchison. Lectures on the practice of medicine. The British Medical Journal, May 25. 1872:545-8.

41. Harold A. Shoemaker. The pharmacology of mercury and its compounds. Annals of the New York Academy of Sciences. 1957;65(Mercury and its Compunds):504-10.

42. Lant AF. Evolution of diuretics and ACE inhibitors, their renal and antihypertensive actions--parallels and contrasts. Br J Clin Pharmacol. 1987;23 Suppl 1:27S-41S.

43. William E. Lawrence, Margaret S. Klapper. The outpatient management of the cardiac patietn with mercurial diuretics. Annals of the New York Academy of Sciences. 1957;65(Mercury and its Compunds):619-22.

44. Weston RE. The mode and mechanism of mercurial diuresis in normal subjects and edematous cardiac patients. Annals of the New York Academy of Sciences. 1957;65(Mercury and its Compunds):576-600.

45. The pharmacopoeia of St. George's hospital 1943. St. George's Hospital; 1943 [cited 2010 02/05/2010]; Available from: http://www.space-age.com/std/pharmacopoeia.pdf.

46. Nobelprize.org. Physiology or Medicine 1939 - Presentation Speech. 1939 [cited 2010 05/06]; Available from: http://nobelprize.org/nobel_prizes/medicine/laureates/1939/press.html.

47. N. U. Meldrum, Roughton. FJW. Carbonic anhydrase. Its preparation and properties. the Journal of Physiology. 1933 December 5;80(2):113-42.

48. MAREN TH. Carbonic Anhydrase: The Middle Years, 1945–1960, and Introduction to Pharmacology of Sulfonamides. Annals of the New York Academy of Sciences. 1984;429(Biology and Chemistry of the Carbonic Anhydrases):10-7.

49. Henry M. Shanoff. Diuretics in Cardiac Edema—1969. Can Med Assoc J. 1969;101(7):66-70.

50. Novello FC, Sprague JM. Benzothiadiazine dioxides as novel diuretics. Journal of the American Chemical Society. [doi: 10.1021/ja01565a079]. 1957;79(8):2028-9.

51. Slater JDH, Nabarro JDN. Clinical experience with chlorthiazide. The Lancet. [doi: DOI: 10.1016/S0140-6736(58)90611-1]. 1958;271(7012):124-7.

52. Bayliss RIS, Pirkis J, Marrack D, Rees JR, Zilva J. Chlorthiazide: an oral diuretic. The Lancet. [doi: DOI: 10.1016/S0140-6736(58)90610-X]. 1958;271(7012):120-4.

53. Dollery CT, Corr L. Drug treatment of heart failure. British Heart Journal. 1985 September 1985;54(3):234-42.

54. Goldberger E. The role of aldosterone in the pathogenesis of cardiac edema. Acta Med Scand. 1957 Jun 5;157(5):417-21.

55. Driscol TE, Maultsby MM, Farrell GL, Berne RM. Aldosterone Secretion in Experimental Congestive Heart Failure. Am J Physiol. 1957 September 30, 1957;191(1):140-4.

56. Nicholls MG, Espiner EA, Donald RA, Hughes H. Aldosterone and its regulation during diuresis in patients with gross congestive cardiac failure. Cli Sci Mol Med 1974;47:301-15.

57. R K Knight, P A Miall, L A Hawkins, J Dacombe, C R Edwards, J Hamer. Relation of plasma aldosterone concentration to diuretic treatment in patients with severe heart disease. British Heart Journal. 1979;42(3):316-25.

58. STASON WB, CANNON PJ, HEINEMANN HO, LARAGH JH. Furosemide: A Clinical Evaluation of Its Diuretic Action. Circulation. 1966 November 1, 1966;34(5):910-20.

59. Stokes W, Nunn LCA. A New Effective Diuretic--Lasix. Br Med J. 1964 October 10, 1964;2(5414):910-4.

60. Waagstein F, Hjalmarson A, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. British Heart Journal. 1975 October 1, 1975;37(10):1022-36.

61. Erdos EG. The ACE and I: how ACE inhibitors came to be. FASEB J. 2006 June 1, 2006;20(8):1034-8.

62. Coleman JE. Carbonic anhydrase: zinc and the mechanism of catalysis. Ann N Y Acad Sci,. 1984;429:26-48.

63. Ferreira S H, Vane J R. The disappearance of bradykinin and eledoisin in the circulation and vascular beds of the cat. British Journal of Pharmocology. 1965;30:417-24.

64. Bahkle YS. Conversion of angiotensin I to angiotensin II by cell-free extracts of dog lung. Nature, . 1968;220:919-21.

65. Cushman DW, Ondetti MA. 2 Inhibitiors of Angiotensin-Converting Enzyme. In: G.P. Ellis DSPDFRIC, G.B. West BPDSPDFIB, editors. Progress in Medicinal Chemistry: Elsevier; 1980. p. 41-104.

66. Patchett AA. The chemistry of enalapril. . J clin Pharmac. 1984;18(suppl. 2):201S-7S.

67. Stapleton MP. Sir James Black and Propranolol. The Role of the Basic Sciences in the History of Cardiovascular Pharmacology. (Tex Heart Inst J 1997;24:336-42). 1997;24(4):336-42.

68. Ahlquist RP. A study of the adrenotropic receptors. Am J Physiol. 1948 June 1, 1948;153(3):586-600.

69. Black J. Drugs from emasculated hormones: the principle of syntopic antagonism. Science. 1989 August 4, 1989;245(4917):486-93.

70. Viviane Q. Putting Theory into Practice: James Black, Receptor Theory and the Development of the Beta- Blockers at ICI, 1958–1978. Medical History. 2006; 50(1): 69–92.

71. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. Captopril Multicenter Research Group. J Am Coll Cardiol. 1983 October 1, 1983;2(4):755-63.

72. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med. 1987 June 4, 1987;316(23):1429-35.

73. The SOLVD, Investigators. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. New England Journal of Medicine. 1991;325(5):293-302.

74. The SOLVD, Investigators. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. NewEngland journal of Medicine. 1992;327(10):685-91.

75. Pfeffer MA BE, Moyé LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. The new England Journal Of Medicine. 1992;327(10):669-77.

76. The Acute Infarction Ramipril Efficacy Study I. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Lancet. 1993;342(8875):821-8.

77. Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, et al. A Clinical Trial of the Angiotensin-Converting–Enzyme Inhibitor Trandolapril in Patients with Left Ventricular Dysfunction after Myocardial Infarction. New England Journal of Medicine. 1995;333(25):1670-6.

78. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, et al. Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure. Circulation. 1999 December 7, 1999;100(23):2312-8.

79. NICE. Chronic heart failure, National clinical guideline for diagnosis and management in primary and secondary care August 2010. NICE. 2010;108.

80. Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. The Lancet. 2003;362(9386):772-6.

81. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). The Lancet. 1997;349(9054):747-52.

82. Bertram P, Philip AP-W, Robert S, Felipe AM, Kenneth D, Camm AJ, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial?the Losartan Heart Failure Survival Study ELITE II. The Lancet. 2000;355(9215):1582-7.

83. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. The Lancet. 2002;360(9335):752-60.

84. Pfeffer MA, McMurray JJV, Velazquez EJ, Rouleau J-L, Køber L, Maggioni AP, et al. Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both. New England Journal of Medicine. 2003;349(20):1893-906.

85. McMurray JJV, Östergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. The Lancet. 2003;362(9386):767-71.

86. Henry Krum PC, Csaba Farsang, Aldo P. Maggioni, Robert D. Glazer, Nora Aknay, Yann-Tong Chiang, and Jay N. Cohn. Effect of valsartan added to background ACE inhibitor therapy in patients with heart failure: results from Val-HeFT Eur J Heart Fail 2004;6(7): 937-45.

87. K Swedberg, A Hjalmarson, F Waagstein, Wallentin I. Beneficial effects of long-term beta-blockade in congestive cardiomyopathy. British Heart Journal. 1980;44(2):117-33.

88. Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. . Lancet December. 1993;342(8885):1441-6.

89. CIBIS. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. Circulation. 1994 October 1, 1994;90(4):1765-73.

90. Packer M, Coats AJS, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. The effect of carvedilol on survival in severe chronic heart failure. The new England Journal Of Medicine. 2001;344(22):1651-8.

91. MERIT-HF, Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF). The Lancet. 1999;353(9169):2001-7.

92. Packer M, Fowler MB, Roecker EB, Coats AJS, Katus HA, Krum H, et al. Effect of Carvedilol on the Morbidity of Patients With Severe Chronic Heart Failure: Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study. Circulation. 2002 October 22, 2002;106(17):2194-9.

93. Poole-Wilson PA, Swedberg K, Cleland JGF, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. The Lancet. 2003;362(9377):7-13.

94. A Trial of the Beta-Blocker Bucindolol in Patients with Advanced Chronic Heart Failure. New England Journal of Medicine. 2001;344(22):1659-67.

95. Smart NA, Kwok N, Holland DJ, Jayasighe R, Giallauria F. Bucindolol: A Pharmacogenomic Perspective on Its Use in Chronic Heart Failure. Clinical Medicine Insights: Cardiology. 2011;5(2744-CMC-Bucindolol:-A-Pharmacogenomic-Perspective-on-Its-Use-in-Chronic-Heart-.pdf):55-66.

96. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. The Lancet. 2001;357(9266):1385-90.

97. Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, et al. Effect on Survival and Hospitalisation of Initiating Treatment for Chronic Heart Failure With Bisoprolol Followed by Enalapril, as Compared With the Opposite Sequence: Results of the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005 October 18, 2005;112(16):2426-35.

98. Liu PP, Maggioni A, Velazquez EJ. Use of Valsartan in Post-Myocardial Infarction and Heart Failure Patients. Journal of Renin-Angiotensin-Aldosterone System. 2006 March 1, 2006;7(1 suppl):S19-S22.

99. Pitt B. ACE inhibitor co-therapy in patients with heart failure: Rationale for the Randomized Aldactone Evaluation Study (RALES). European Heart Journal. 1995 December 1, 1995;16(suppl N):107-10.

100. Husain A. The chymase-angiotensin system in humans. Journal of Hypertension. 1993;11(11):1155-60.

101. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. New England Journal of Medicine. 1999;341(10):709-17.

102. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction. New England Journal of Medicine. 2003;348(14):1309-21.

103. Zannad F, McMurray JJV, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. New England Journal of Medicine. 2011;364(1):11-21.

104. The Effect of Digoxin on Mortality and Morbidity in Patients with Heart Failure. New England Journal of Medicine. 1997;336(8):525-33.

105. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. The Lancet. 2010;376(9744):875-85.

106. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. The Lancet. 2008;372(9641):807-16.

107. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction. New England Journal of Medicine. 2002;346(12):877-83.

108. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure. New England Journal of Medicine. 2005;352(3):225-37.

109. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac Resynchronization in Chronic Heart Failure. New England Journal of Medicine. 2002;346(24):1845-53.

110. Michael R. Bristow MD, Leslie A. Saxon, M.D., John Boehmer, M.D., Steven Krueger, M.D., David A. Kass, M.D., Teresa De Marco, M.D., Peter Carson, M.D., Lorenzo DiCarlo, M.D., David DeMets, Ph.D., Bill G. White, Ph.D., Dale W. DeVries, B.A., and Arthur M. Feldman, M.D., Ph.D. for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure. New England Journal of Medicine. 2004;350(21):2140-50.

111. Cleland JGF, Daubert J-C, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure. New England Journal of Medicine. 2005;352(15):1539-49.

112. NICE. Cardiac resynchronisation therapy for the treatment of heart failure. NICE. 2007.

113. Gold M, Linde C, Lozano I, Daubert C, Abraham W. Impact of QRS duration on clinical response with cardiac resynchronization therapy: results from the REVERSE trial. Circulation. 2009;120:S814.

114. Breithardt G. MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy): cardiac resynchronization therapy towards early management of heart failure. Eur Heart J. 2009 Nov;30(21):2551-3.

115. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. The Lancet. 2003;362(9386):777-81.

116. Cleland JGF, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006 October 1, 2006;27(19):2338-45.

117. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction. N Engl J Med. 2008 December 4, 2008;359(23):2456-67.

118. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). European Heart Journal. 2005 February 2005;26(3):215-25.

119. Stern MP. The recent decline in ischemic heart disease mortality. Annals of Internal Medicine 1979;91(4):630-40.

120. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KKL, et al. Long-Term Trends in the Incidence of and Survival with Heart Failure. N Engl J Med. 2002 October 31, 2002;347(18):1397-402.

121. Kelly DT. 1996 Paul Dudley White International Lecture: Our Future Society: A Global Challenge. Circulation. 1997 June 3, 1997;95(11):2459-64.

122. Redfield Mm JSJBJJCMDWBKRRRJ. Burden of systolic and diastolic ventricular dysfunction in the community: Appreciating the scope of the heart failure epidemic. JAMA. 2003;289(2):194-202.

123. Cowie MR, Wood DA, Coats AJS, Thompson SG, Poole-Wilson PA, Suresh V, et al. Incidence and aetiology of heart failure; a population-based study. European Heart Journal. 1999 March 1, 1999;20(6):421-8.

124. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJV. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. European Journal of Heart Failure. 2001 June 1, 2001;3(3):315-22.

125. Ho K, Anderson K, Kannel W, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation. 1993 July 1, 1993;88(1):107-15.

126. Hobbs FDR, Roalfe AK, Davis RC, Davies MK, Hare R. Prognosis of all-cause heart failure and borderline left ventricular systolic dysfunction: 5 year mortality follow-up of the

Echocardiographic Heart of England Screening Study (ECHOES). European Heart Journal. 2007 May 1, 2007;28(9):1128-34.

127. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in Heart Failure. Circulation: Heart Failure. 2008 July 1, 2008;1(2):91-7.

128. Cowie MR, Wood DA, Coats AJS, Thompson SG, Suresh V, Poole-Wilson PA, et al. Survival of patients with a new diagnosis of heart failure: a population based study. Heart. 2000 May 1, 2000;83(5):505-10.

129. Allen LaPointe NM, Zhou Y, Stafford JA, Hernandez AF, Kramer JM, Anstrom KJ. Association Between Mortality and Persistent Use of Beta Blockers and Angiotensin-Converting Enzyme Inhibitors in Patients With Left Ventricular Systolic Dysfunction and Coronary Artery Disease. The American journal of cardiology. 2009;103(11):1518-24.

130. Taffet GE, Teasdale TA, Bleyer AJ, Kutka NJ, Luchi RJ. Survival of Elderly Men with Congestive Heart Failure. Age and Ageing. 1992 January 1, 1992;21(1):49-55.

131. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of Heart Failure with Preserved Ejection Fraction in a Population-Based Study. N Engl J Med. 2006 July 20, 2006;355(3):260-9.

132. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2006 July 20, 2006;355(3):251-9.

133. Lenzen MJ, Scholte op Reimer WJM, Boersma E, Vantrimpont PJMJ, Follath F, Swedberg K, et al. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. European Heart Journal. 2004 July 1, 2004;25(14):1214-20.

134. Somaratne JB, Berry C, McMurray JJV, Poppe KK, Doughty RN, Whalley GA. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. European Journal of Heart Failure. 2009 September 1, 2009;11(9):855-62.

135. MAGIC. (Meta-analysis Global Group in Chronic Heart Failure) The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. European Heart Journal. 2012 July 1, 2012;33(14):1750-7.

136. Annual Mid-year Population Estimates, 2010 [database on the Internet]2011 [cited 02/07/2011]. Available from: http://www.statistics.gov.uk/pdfdir/pop0611.pdf.

137. Health Profile 2011 Darlington [database on the Internet]. Department of Health. 2011 [cited 02/07/2011]. Available from: http://www.apho.org.uk/resource/view.aspx?RID=50215&SEARCH=darlington&SPEAR=.

138. Facts and figures. [webpage] 2006 [cited 2010 30/05/2010]; Available from: http://www.onenortheast.co.uk/facts_and_figures.cfm.

139. Kathryn Bailey SG, John Wilkinson, Tricia Cresswell. Towards a Healthier North East: A Profile of Health and its Determinants in the North East of England. wwwnyphoorguk [serial on the Internet]. 2001: Available from: www.onenortheast.co.uk/ne_prof/_ffs/sumdebateage.pdf.

140. Peter Scarbrough P, Bhatnagar, Kremlin Wickramasinghe, Kate Smolina, Mike Rayner. Coronary heart disease stastics2010: Available from: http://www.bhf.org.uk/heart-health/statistics/heart-statistics-publications.aspx.

141. Annual Report of the Director of Public Health in county durham and darlington. Narrowing the gap in coronary heart disease and cancers. [annual report]. 2007-2008.

142. The Association of PublicHealth Observatories. Health Profile 2009, Darlington. [homepage] 2009 [cited 2010 30/05]; Available from: www.healthprofiles.info.

143. Heart Failure morbidity. [home page on the internet]: British Heart Foundation statistics website; 2007 [cited 2010 30/05/2010]; Available from: http://www.heartstats.org/temp/2008.Chaptersp2.pdf.

144. Stewart S, MacIntyre K, Capewell S, McMurray JJV. Heart failure and the aging population: an increasing burden in the 21st century? Heart. 2003 January 2003;89(1):49-53.

145. The NHS Information Centre. The National Heart Failure Audit 2008-2009. [home page on the internet] 2008 [cited 2010 25/05/2010]; Available from: http://www.ic.nhs.uk/webfiles/Services/NCASP/audits%20and%20reports/NHS_National_Heart_Failure_Audit_09_INTERACTIVE.pdf.

146. The Information Centre. Hospital episode statistics. [home page on the internet] 2007-2008 [cited 2010 25/05/2010]; Available from: http://www.hesonline.nhs.uk

147. Benatar D, Bondmass M, Ghitelman J, Avitall B. Outcomes of Chronic Heart Failure. Arch Intern Med. 2003 February 10, 2003;163(3):347-52.

148. Reitsma JB, Mosterd A, de Craen AJ, Koster RW, van Capelle FJ, Grobbee DE, et al. Increase in hospital admission rates for heart failure in The Netherlands, 1980-1993. Heart. 1996 November 1996;76(5):388-92.

149. Brown AM, Cleland JGF. Influence of concomitant disease on patterns of hospitalisation in patients with heart failure discharged from Scottish hospitals in 1995. European Heart Journal. 1998 July 1, 1998;19(7):1063-9.

150. Department of Health (2000). National Service Framework for Coronary Heart Disease: Chapter 6 – Heart Failure. London: Department of Health.

151. Healthcare Commission (2005). Getting to the heart of it. Coronary Heart Disease in England: A review of progress towards the national standards.

152. Healthcare Commission (2007). Pushing the boundaries. Improving services for people with heart failure.

153. Nicol ED, Fittall B, Roughton M, Cleland JGF, Dargie H, Cowie MR. NHS heart failure survey: a survey of acute heart failure admissions in England, Wales and Northern Ireland. Heart. 2008 February 2008;94(2):172-7.

154. The information centre. Quality and Outcomes Framework. [home page on the internet] 2008-2009 [cited 2010 20/05/2010]; Available from: www.qof.ic.nhs.uk.

155. Fox KF, Cowie MR, Wood DA, Coats AJS, Poole-Wilson PA, Sutton GC. A Rapid Access Heart Failure Clinic provides a prompt diagnosis and appropriate management of new heart failure presenting in the community. European Journal of Heart Failure. 2000 Dec;2(4):423-9.

156. Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. European Heart Journal. 1991 March 1, 1991;12(3):315-21.

157. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. QJM. 1993 January 1, 1993;86(1):17-23.

158. Hancock HC, Close H, Mason JM, Murphy JJ, Fuat A, Singh R, et al. High prevalence of undetected heart failure in long-term care residents: findings from the Heart Failure in Care Homes (HFinCH) study. European Journal of Heart Failure. 2012 October 30, 2012.

159. Chambers J, Sprigings D, de BD. Open access echocardiography. Br J Cardiol 2001;8(369):365 –6.

160. Rimington H, Adam G, Chambers J. Open-access echocardiography. The Lancet. 1996;348(9026):555-6.

161. Saltissi S, Chambers J. Quality issues for echocardiography in the community. Heart. 1998 July 1, 1998;80(suppl 1):S9-S11.

162. Lacey L, Tabberer M. Economic burden of post-acute myocardial infarction heart failure in the United Kingdom. European Journal of Heart Failure. 2005 June 1, 2005;7(4):677-83.

163. Murphy JJ, John P, Frain J, Ramesh P, Siddiqui RN, Bossingham CM. Open-access echocardiography to general practitioners for suspected heart failure. British Journal of General Practice. 1996;46:475-6.

164. Galasko G, Henein M. Direct Access Echocardiography. The International Journal of Cardiovascular Imaging (formerly Cardiac Imaging). 2006;22(1):29-31.

165. A report of a working group of the BCS: Cardiology in the district hospital. Br Heart J. 1994;72(3):303-8.

166. Mahadevan VS, Earley M, McClements B. Open access echocardiography has diagnostic yield similar to outpatient echocardiography and is highly rated by general practitioners and patients. International Journal of Cardiology. 2005;99(3):389-93.

167. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A Multidisciplinary Intervention to Prevent the Readmission of Elderly Patients with Congestive Heart Failure. New England Journal of Medicine. 1995;333(18):1190-5.

168. Fonarow G, Stevenson L, Walden J, Livingston N, Steimle A, Hamilton M, et al. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. J Am Coll Cardiol. 1997 September 1, 1997;30(3):725-32.

169. West MDJA, Miller RNNH, Parker RNKM, Senneca RND, Ghandour PG, Clark RDMPHM, et al. A Comprehensive Management System for Heart Failure Improves Clinical Outcomes and Reduces Medical Resource Utilization. The American journal of cardiology. 1997;79(1):58-63.

170. Ekman I, Andersson B, Ehnfors M, Matejka G, Persson B, Fagerberg B. Feasibility of a nurse-monitored, outpatient-care programme for elderly patients with moderate-to-severe, chronic heart failure. European Heart Journal. 1998 August 1, 1998;19(8):1254-60.

171. Strömberg A, Mårtensson J, Fridlund B, Levin L-Å, Karlsson J-E, Dahlström U. Nurse-led heart failure clinics improve survival and self-care behaviour in patients with heart failure. European Heart Journal. 2003 June 1, 2003;24(11):1014-23.

172. McAlister FA, Stewart S, Ferrua S, McMurray JJJV. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: A systematic review of randomized trials. J Am Coll Cardiol. 2004 August 18, 2004;44(4):810-9.

173. Whellan DJ, Gaulden L, Gattis WA, Granger B, Russell SD, Blazing MA, et al. The Benefit of Implementing a Heart Failure Disease Management Program. Arch Intern Med. 2001 October 8, 2001;161(18):2223-8.

174. McDonald K, Ledwidge M, Cahill J, Kelly J, Quigley P, Maurer B, et al. Elimination of early rehospitalisation in a randomized, controlled trial of multidisciplinary care in a high-risk, elderly heart failure population: the potential contributions of specialist care, clinical stability and optimal angiotensin-converting enzyme inhibitor dose at discharge. European Journal of Heart Failure. 2001 March 1, 2001;3(2):209-15.

175. Strömberg A, Mårtensson J, Fridlund B, Dahlström U. Nurse-led heart failure clinics in Sweden. European Journal of Heart Failure. 2001 January 1, 2001;3(1):139-44.

176. Doughty RN, Wright SP, Pearl A, Walsh HJ, Muncaster S, Whalley GA, et al. Randomized, controlled trial of integrated heart failure management. The Auckland Heart Failure Management Study. European Heart Journal. 2002 January 1, 2002;23(2):139-46.

177. Gonseth J, Guallar-Castillón P, Banegas JR, Rodríguez-Artalejo F. The effectiveness of disease management programmes in reducing hospital re-admission in older patients with heart failure: a systematic review and meta-analysis of published reports. European Heart Journal. 2004 September 1, 2004;25(18):1570-95.

178. NSF, Coronary H, Disease,. National Service Framework for Coronary Heart Disease Modern Standards and Service Models. DOH; 2000 [cited 2011 20/10/2011]; Available from: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4057526.pdf.

179. Galatius S, Gustafsson F, Nielsen PH, Atar D, Hildebrandt PR. An integrated approach to diagnosis and therapeutic management of patients with systolic heart failure in the Copenhagen metropolitan area. American heart journal. 2002;144(2):E2.

180. Shah S, Davies MK, Cartwright D, Nightingale P. Management of chronic heart failure in the community: role of a hospital based open access heart failure service. Heart. 2004 July 1, 2004;90(7):755-9.

181. Azevedo A, Pimenta J, Dias P, Bettencourt P, Ferreira A, Cerqueira-Gomes M. Effect of a heart failure clinic on survival and hospital readmission in patients discharged from acute hospital care. European Journal of Heart Failure. 2002 June 1, 2002;4(3):353-9.

182. Gates LJ, MacLeod MJ, Criuckshank MA, Webster J, McLay JS. Are there benefits for patients attending a heart failure clinic? A 5 year review. Proceedings of the Royal College of Physicians of Edinburgh. 2000;30:298-301.

183. Houghton AR, Cowley AJ. Managing heart failure in a specialist clinic. Journal of the Royal College of Physicians of London. 1997;31(3):276-9.

184. Fuat A. The Diagnosis and Management of heart failure across primary and secondary care. stockton on tees: Durham University; 2006.

185. Mair FS, Crowley TS, Bundred PE. Prevalence, aetiology and management of heart failure in general practice. British Journal of General Practice. 1996;46:77-9.

186. McMurray JJ. Failure to practice evidence-based medicine: why do physicians not treat patients with heart failure with angiotensin-converting enzyme inhibitors? European Heart Journal. 1998;19 Suppl L:L15-L21.

187. Horne R, Coombes I, Davies G, Hankins M, Vincent R. Barriers to optimum management of heart failure by general practitioners. British Journal of General Practice. 1999 May;49(442):353-7.

188. Clarke K, Gray D, Hampton JR. Evidence of inadequate investigation and treatment of patients with heart failure. British Heart Journal. 1994;71:584-7.

189. Toal M, Walker R. Angiotensin converting enzyme (ACE) inhibitors in the treatment of heart failure in general practice in North Cumbria. European Journal of Heart Failure. 2000;2(2):201-7.

190. Bungard TJ, McAlister FA, Johnson JA, Tsuyuki RT. Underutilisation of ACE inhibitors in patients with congestive heart failure. Drugs. 2001;61:2021-33.

191. McCallum J, Doherty J, Marshall H. Can the SIGN guidelines on heart failure due to LVSD be implemented in general practice? British Journal of Cardiology. 2001;8(2):112-8.

192. Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. European Heart Journal. 1991;12:315-21.

193. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. Quarterly Journal of Medicine. 1993;86:17-23.

194. Scottish Intercollegiate Guidelines Network. A National Clinical Guideline. Diagnosis and treatment of heart failure due to left ventricular systolic dysfunction. Edinburgh: SIGN1999.

195. Swedberg K, Writing Committee:, Cleland J, Dargie H, Drexler H, Follath F, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. European Heart Journal. 2005 June 1, 2005;26(11):1115-40.

196. Eccles M, Freemantle N, Mason J. North of England evidence based development project: guideline for angiotensin converting enzyme inhibitors in primary care management of adults with symptomatic heart failure. British Medical Journal. 1998;316:1369-75.

197. National Institute for Clinical Excellence. Chronic Heart Failure. Clinical Guideline No.52003 July 2003.

198. O'Toole L, Oates A, Channer KS. Open access to specialist opinion is preferable. British Medical Journal. 1995;311:326.

199. European Society of Cardiology. The Task Force for the Diagnosis and Treatment of Chronic Heart Failure. Guidelines for the diagnosis and treatment of chronic heart failure. European Heart Journal. 2001;22:1527-60.

200. Remme WJ, Cleland JGF, Dargie H, Erdmann E, Ferrari R, Kjekshus J, et al. The treatment of heart failure. Task Force of the Working Group on Heart Failure of the European Society of Cardiology. European Heart Journal. 1997 May 1, 1997;18(5):736-53.

201. Department of Health. National Service Framework for Coronary Heart Disease. London.2000.

202. Department of Health. Investing in General Practice: The New General Medical Services Contract.2003.

203. National., Research, Ethics, Service. NRES Leaflet: Defining research. 2012; Available from: http://www.nres.npsa.nhs.uk/applications/guidance/research-guidance/?entryid62=66985.

204. Ho KKL, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: The Framingham Study. Journal of the American College of Cardiology. [doi: DOI: 10.1016/0735-1097(93)90455-A]. 1993;22(4, Supplement 1):A6-A13.

205. Gottlieb SS. Dead is dead--artificial definitions are no substitute. The Lancet. 1997;349(9053):662-3.

206. Hauptman PJ. Does It Matter Why and How Patients With Heart Failure Die? Circulation: Heart Failure. 2008 July 1, 2008;1(2):89-90.

207. Zile MR, Gaasch WH, Anand IS, Haass M, Little WC, Miller AB, et al. Mode of Death in Patients With Heart Failure and a Preserved Ejection Fraction. Circulation. 2010 March 30, 2010;121(12):1393-405.

208. Cox DR. Regression models and life tables Journal of the Royal Statistical Society Series B (Methodological). 1972;34(2):187-220.

209. Breslow N. Statistical methods for censored survival data. Environ Health Perspect 1979;October(32):181-92.

210. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Controlled clinical trials. 1996;17(4):343-6.

211. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association. 1958 1958/06/01;53(282):457-81.

212. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. Lancet. 1993;353:9-13.

213. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. N Engl J Med. 1999 September 2, 1999;341(10):709-17.

214. CIBIS II I, and Committee. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. Lancet. 1993;353:9-13.

215. Vasan R, Benjamin E, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol. 1995 December 1, 1995;26(7):1565-74.

216. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol. 2004 February 4, 2004;43(3):317-27.

217. Theophilius EO, Margaret MR. Epidemiology of Diastolic Heart Failure. Progress in cardiovascular diseases. 2005;47(5):320-32.

218. How to diagnose diastolic heart failure. European Heart Journal. 1998 July 1, 1998;19(7):990-1003.

219. Fischer M, Baessler A, Hense HW, Hengstenberg C, Muscholl M, Holmer S, et al. Prevalence of left ventricular diastolic dysfunction in the community. European Heart Journal. 2003 February 1, 2003;24(4):320-8.

220. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, et al. Congestive Heart Failure in the Community : A Study of All Incident Cases in Olmsted County, Minnesota, in 1991. Circulation. 1998 November 24, 1998;98(21):2282-9.

221. Cowie MR, Fox KF, Wood DA, Metcalfe C, Thompson SG, Coats AJS, et al. Hospitalization of patients with heart failure. A population-based study. European Heart Journal. 2002 June 1, 2002;23(11):877-85.

222. Klapholz M, Maurer M, Lowe AM, Messineo F, Meisner JS, Mitchell J, et al. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: Results of the New York heart failure registry. J Am Coll Cardiol. 2004 April 21, 2004;43(8):1432-8.

223. Ratnakar Pernenkil MD, Janice M Vinson MD, Atul S Shah MD, Valerie Beckham RN, Carol Wittenberg RN, Michael W Rich MD. Course and Prognosis in Patients ≥70 Years of Age With Congestive Heart Failure and Normal Versus Abnormal Left Ventricular Ejection Fraction. The American journal of cardiology. 1997;79(2):216-9.

224. Redfield MM, Jacobsen SJ, Burnett JC, Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of Systolic and Diastolic Ventricular Dysfunction in the Community: Appreciating the Scope of the Heart Failure Epidemic. JAMA. 2003 January 8, 2003;289(2):194-202.

225. Edward FP, Thomas AR, Norman WL, Kathleen U, Paul LJ. Systolic versus diastolic heart failure in community practice: clinical features, outcomes, and the use of angiotensin-converting enzyme inhibitors. The American journal of medicine. 2000;109(8):605-13.

226. Mirsky I. Assessment of diastolic function: suggested methods and future considerations. Circulation. 1984 April 1, 1984;69(4):836-41.

227. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J. 2007 October 2, 2007;28(20):2539-50.

228. Salim Yusuf, Marc A Pfeffer, Karl Swedberg, Christopher B Granger, Peter Held, John J V McMurray, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARMPreserved Trial. Lancet. 2003;362:777-81.

229. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005 February 1, 2005;26(3):215-25.

230. Yip GWK, Wang M, Wang T, Chan S, Fung JWH, Yeung L, et al. The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. Heart. 2008 May 2008;94(5):573-80.

231. Zhou J, Shi H, Zhang J, Lu Y, Fu M, Ge J, et al. Rationale and design of the {beta}-blocker in heart failure with normal left ventricular ejection fraction ({beta}-PRESERVE) study. Eur J Heart Fail. 2010 February 1, 2010;12(2):181-5.

232. Amico AF, Lichtenberg GS, Reisner SA, Stone CK, Schwartz RG, Meltzer RS. Superiority of visual versus computerized echocardiographic estimation of radionuclide left ventricular ejection fraction. American Heart Journal. [doi: DOI: 10.1016/0002-8703(89)90018-5]. 1989;118(6):1259-65.

233. Stuart Rich M.D. ASMD, Jose Gallastegui M.D. , George T. Kondos M.D. , Theresa Mason M.D. and Wilfred Lam M.D. Determination of left ventricular ejection fraction by visual estimation during real-time two-dimensional echocardiography. American Heart Journal. 1982;104(3):603-6.

234. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. Eur Heart J. 1998 July 1, 1998;19(7):990-1003.

235. Brutsaert DL. Diagnosing primary diastolic heart failure. European Heart Journal. 2000 January 1, 2000;21(2):94-6.

236. Zile MR, Gaasch WH, Carroll JD, Feldman MD, Aurigemma GP, Schaer GL, et al. Heart Failure With a Normal Ejection Fraction: Is Measurement of Diastolic Function Necessary to Make the Diagnosis of Diastolic Heart Failure? Circulation. 2001 August 14, 2001;104(7):779-82.

237. Little WC. Diastolic Dysfunction Beyond Distensibility: Adverse Effects of Ventricular Dilatation. Circulation. 2005 November 8, 2005;112(19):2888-90.

238. Cahill JM, Horan M, Quigley P, Maurer BJ, McDonald K. Doppler-echocardiographic indices of diastolic function in heart failure admissions with preserved left ventricular systolic function. Eur J Heart Fail. 2002 August 1, 2002;4(4):473-8.

239. Dae-Won S, Jong-Min S, Joo-Hee Z, In-Ho C, Hyo-Soo K, Hong-Gu C, et al. Mitral Annulus Velocity in the Evaluation of Left Ventricular Diastolic Function in Atrial Fibrillation. Journal of the American Society of Echocardiography 1999;12(11):927-31.

240. Harjola V-P, Follath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H, et al. Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. Eur J Heart Fail. 2010 March 1, 2010;12(3):239-48.

241. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, et al. The EuroHeart Failure Survey programme—a survey on the quality of care among patients with heart failure in Europe. European Heart Journal. 2003 March 1, 2003;24(5):464-74.

242. The NHS Information Centre. The National Heart Failure Audit 2009-2010. [home page on the internet] 2010 [cited 2013 02/05/2013]; Available from: https://catalogue.ic.nhs.uk/publications/clinical/heart/nati-hear-fail-audi-2010/nati-hear-fail-audi-2010-rep.pdf.

243. Mortality Statistics: Deaths Registered in 2010 [database on the Internet]. ONS. 2011 [cited 12/05/2013]. Available from: http://www.ons.gov.uk/ons/datasets-and-tables/index.html?pageSize=50&sortBy=none&sortDirection=none&newquery=hospital+death.

244. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJV, Swedberg KB, et al. Predictors of mortality and morbidity in patients with chronic heart failure. European Heart Journal. 2006 January 2006;27(1):65-75.

245. International Classification of Diseases (ICD-10) [database on the Internet]. WHO. 1994 [cited 30 Aug 2012]. Available from: http://www.who.int/classifications/icd/en/.

246. Palatini P, Julius S. Elevated Heart Rate: A Major Risk Factor for Cardiovascular Disease. Clinical and Experimental Hypertension. 2004;26(7-8):637-44.

247. El-Refai M, Peterson EL, Wells K, Swadia T, Sabbah HN, Spertus JA, et al. Comparison of Beta-Blocker Effectiveness in Heart Failure Patients With Preserved Ejection Fraction Versus Those With Reduced Ejection Fraction. Journal of Cardiac Failure. 2013;19(2):73-9.

248. Massie BM, Nelson JJ, Lukas MA, Greenberg B, Fowler MB, Gilbert EM, et al. Comparison of Outcomes and Usefulness of Carvedilol Across a Spectrum of Left Ventricular Ejection Fractions in Patients With Heart Failure in Clinical Practice. The American journal of cardiology. 2007;99(9):1263-8.

249. Little WC, Brucks S. Therapy for Diastolic Heart Failure. Progress in Cardiovascular Diseases. 2005;47(6):380-8.

250. Braunwald E. The Management of Heart Failure: The Past, the Present, and the Future. Circulation: Heart Failure. 2008 May 1, 2008;1(1):58-62.

251. Selby DE, Palmer BM, LeWinter MM, Meyer M. Tachycardia-Induced Diastolic Dysfunction and Resting Tone in Myocardium From Patients With a Normal Ejection Fraction. Journal of the American College of Cardiology. 2011;58(2):147-54.

252. Cullington D, Goode KM, Clark AL, Cleland JGF. Heart rate achieved or beta-blocker dose in patients with chronic heart failure: which is the better target? European Journal of Heart Failure. 2012 July 1, 2012;14(7):737-47.

253. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel J-P. Clinical Effects of β-Adrenergic Blockade in Chronic Heart Failure: A Meta-Analysis of Double-Blind, Placebo-Controlled, Randomized Trials. Circulation. 1998 September 22, 1998;98(12):1184-91.

254. van Veldhuisen DJ, Cohen-Solal A, Böhm M, Anker SD, Babalis D, Roughton M, et al. Beta-Blockade With Nebivolol in Elderly Heart Failure Patients With Impaired and Preserved Left Ventricular Ejection Fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). Journal of the American College of Cardiology. 2009;53(23):2150-8.

255. Smith DT, Farzaneh-Far R, Ali S, Na B, Whooley MA, Schiller NB. Relation of β-Blocker Use With Frequency of Hospitalization for Heart Failure in Patients With Left Ventricular Diastolic Dysfunction (from the Heart and Soul Study). The American journal of cardiology. 2010;105(2):223-8.

256. Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. The American journal of cardiology. 1990;66(12):981-6.

257. Hung MJ, Cherng WJ, Kuo LT, Wang CH. Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure. International Journal of Clinical Practice 2002;56:57-62.

258. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007 September 1, 2007;93(9):1137-46.

259. Maurer MS, Kronzon I, Burkhoff D. Ventricular Pump Function in Heart Failure with Normal Ejection Fraction: Insights from Pressure-Volume Measurements. Progress in Cardiovascular Diseases.49(3):182-95.

260. Mehta PA, Dubrey SW, McIntyre HF, Walker DM, Hardman SMC, Sutton GC, et al. Improving survival in the 6 months after diagnosis of heart failure in the past decade: population-based data from the UK. Heart. 2009 November 15, 2009;95(22):1851-6.

261. Sutcliffe S, Phillips C, Watson D, Davidson C. Trends in heart failure mortality in England and Wales since 1950. European Journal of Internal Medicine. 2007;18(8):576-80.

262. Murdoch DR, Love MP, Robb SD, McDonagh TA, Davie AP, Ford I, et al. Importance of heart failure as a cause of death. Changing contribution to overall mortality and coronary heart disease mortality in Scotland 1979–1992. European Heart Journal. 1998 December 1, 1998;19(12):1829-35.

263. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, et al. Trends in Heart Failure Incidence and Survival in a Community-Based Population. JAMA. 2004 July 21, 2004;292(3):344-50.

264. Changes in Mortality From Heart Failure--United States, 1980-1995. JAMA. 1998 September 9, 1998;280(10):874-5.

265. The, Information, Centre. Quality and Outcomes Framework. The information centre for health and social care; 2004 [cited 2013 23/06/2013]; Available from: http://www.qof.ic.nhs.uk/.

266. Loh JC, Creaser J, Rourke DA, Livingston N, Harrison TK, Vandenbogaart E, et al. Temporal Trends in Treatment and Outcomes for Advanced Heart Failure With Reduced Ejection Fraction From 1993–2010: Findings From a University Referral Center. Circulation: Heart Failure. 2013 May 1, 2013;6(3):411-9.

267. Chan MMY, Lam CSP. How do patients with heart failure with preserved ejection fraction die? European Journal of Heart Failure. 2013 April 21, 2013.

268. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: Prevalence and mortality in a population-based cohort. J Am Coll Cardiol. 1999 June 1, 1999;33(7):1948-55.

269. Heart Failure Society of A. HFSA 2010 Comprehensive Heart Failure Practice Guideline. Journal of Cardiac Failure. 2010;16(6):e1-e2.

270. Reil J-C, Reil G-H, Böhm M. Heart Rate Reduction by If-Channel Inhibition and its Potential Role in Heart Failure with Reduced and Preserved Ejection Fraction. Trends in Cardiovascular Medicine. 2009;19(5):152-7.

271. De Masi De Luca G. Ivabradine and diastolic heart failure. Journal of the American College of Cardiology. 2012;59(13s1):E1009-E.

272. Maisel A, Mueller C, Adams K, Anker SD, Aspromonte N, Cleland JGF, et al. State of the art: Using natriuretic peptide levels in clinical practice. European Journal of Heart Failure. 2008 September 1, 2008;10(9):824-39.

273. Healthcare C. Pushing the boundaries: improving services for

the people with heart failure. London: Healthcare Commission 2007 [cited 2013 01/06/2013]; Available from: http://archive.cqc.org.uk/_db/_documents/Pushing_the_boundaries_Improving_services_for_patients_with_heart_failure_200707020413.pdf.

274. Karamitsos TD, Francis JM, Myerson S, Selvanayagam JB, Neubauer S. The Role of Cardiovascular Magnetic Resonance Imaging in Heart Failure. Journal of the American College of Cardiology. 2009;54(15):1407-24.

275. Senior R, Becher H, Monaghan M, Agati L, Zamorano J, Vanoverschelde JL, et al. Contrast echocardiography: evidence-based recommendations by European Association of Echocardiography. European Journal of Echocardiography. 2009 March 1, 2009;10(2):194-212.

276. Dandel M, Lehmkuhl H, Knosalla C, Suramelashvili N, Hetzer R. Strain and Strain Rate Imaging by Echocardiography – Basic Concepts and Clinical Applicability. Current Cardiology Review. 2009;5(2):133-48.

277. D'hooge J, Heimdal A, Jamal F, Kukulski T, Bijnens B, Rademakers F, et al. Regional Strain and Strain Rate Measurements by Cardiac Ultrasound: Principles, Implementation and Limitations. European Journal of Echocardiography. 2000 September 1, 2000;1(3):154-70.

278. Dunlay SM, Eveleth JM, Shah ND, McNallan SM, Roger VL. Medication Adherence Among Community-Dwelling Patients With Heart Failure. Mayo Clinic Proceedings. 2011;86(4):273-81.

279. Carson P, Massie BM, McKelvie R, McMurray J, Komajda M, Zile M, et al. The Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) Trial: Rationale and Design. Journal of cardiac failure. 2005;11(8):576-85.

Appendix 1

County Durham and Darlington NHS
NHS Foundation Trust

Research and Development Department
Darlington Memorial Hospital
Pierremont Unit
Hollyhurst Road
Darlington
DL3 6HX

Tel: 01325 743458 / 743768

All studies are subject to the requirements of the DoH's Research Governance Framework 2005 Second Edition and subsequent amendments. If you have not read this document, or are unfamiliar with its contents you are strongly advised to refer to it before commencing with any research or data collection. You may not commence data collection until you have written formal authorisation from the Chair of the Research Review Board and an appropriate ethics committee.

1st December 2009

Ethics Committee

Dear Ethics Chair

Re: **Outcome in patients with heart failure & treated as per guidelines.**

R & D Ref: MED-097-2009

Please find enclosed the above titled study for Ethics Review as evidence of IRAS Question A54. This project has been through the Trust's peer review process and has been given provisional approval by the Trust's Research Review Board. We have enclosed copies of correspondence for your information.

If you have any further queries please contact the R&D Office.

Yours sincerely

Dr Y Yiannakou
Chair – Research Review Board

Enc.

Quality | Care | Respect
County Durham and Darlington NHS
NHS Foundation Trust
Research and Development Department
Darlington Memorial Hospital
Pierremont Unit
Hollyhurst Road
Darlington
DL3 6HX

Tel: 01325 743458 / 743768

All studies are subject to the requirements of the DoH's Research Governance Framework 2005 Second Edition and subsequent amendments. If you have not read this document, or are unfamiliar with its contents you are strongly advised to refer to it before commencing with any research or data collection. You may not commence data collection until you have written formal authorisation from the Chair of the Research Review Board and an appropriate ethics committee.

Private & Confidential

1st December 2009

Dr Rajender Singh
Senior Trust Fellow
Darlington Memorial Hospital

Dear Dr Singh

Re: Outcome in patients with heart failure & treated as per guidelines.

R & D Ref: Med-097-2009

Thank you for your submission for research governance approval to undertake the above study. The application has been reviewed and I write to inform you of the decision.

The documents reviewed where:

Document Type	Version	Dated	Date Received
R&D Form	2.0	-	01/12/09
Draft proposal	2	15/11/09	16/11/09
GP Info leaflet	2	15/11/09	16/11/09

Your study can now be submitted to an ethics committee for ethical review.

- I have enclosed a letter of Trust R&D Support to be submitted along with this letter and correspondence from the Research Review Board to the REC reviewing your study as evidence for IRAS question A54.

- The North East Central Allocation telephone number is 0191 4283305, you can either submit to the next available meeting in the North East or choose CDTV REC 1.
- As the Trust is the sponsor for your study (QA64). Lynne Williams, Research & Development Manager will have to sign your IRAS form QD2. This can be done electronically through IRAS. (Please see attached guidance.)
- Once the Ethics Committee have given your study a favourable ethical opinion, please forward a copy of the letter and copies of amended documents in response to the REC request to the R&D Office at the above address, so that, Trust R&D approval is given to the correct version your study.
- The study **must not** be started until you have obtained both Ethics and Trust R&D approval letters.

If you require any further advice please do not hesitate to contact either myself or Joanne Stephenson.

Yours sincerely

Dr Y Yiannakou
Research Review Board Chair

cc. Dr Jerry Murphy
Consultant Cardiologist
Darlington Memorial Hospital

Appendix 2

Durham University

Wolfson Research Institute
Improving health and well-being

Rebecca Perrett
Research and Development Manager, Wolfson Research Institute
Chair, School of Medicine and Health Ethics Committee

Tel: 0191 334 0425
Email: Rebecca.Perrett@durham.ac.uk

Dr Rajender Singh
School of Medicine and Health
The Wolfson Research Institute
Durham University Queen's Campus
Stockton-on-Tees
TS17 6BH
United Kingdom

13th January 2010

Dear Rajender,

RE: What is the long term outcome in patients having heart failure and treated according to evidence based guidelines?

Ref: ESC2/2009/20

Thank you for sending the above application to the School of Medicine and Health Ethics Committee and for attending the committee meeting on the 16th December.

As you know the committee were initially confused by the nature of the study, and believed it may not be considered research by the NHS. You were able to clarify that due to the collection of information at GP practices this was an NHS research study.

The committee were also concerned by the use of data in the absence of consent. You were able to confirm that the National Information Governance Board had been consulted about the study, and the absence of consent, but that no formal application to the NIGB was being made.

You also confirmed that R&D approval for the study had been obtained from County Durham and Darlington NHS Foundation Trust.

The committee requested that the following changes and information be provided prior to approval:

1. Copies of the emails to and from the NIGB, followed to their conclusion
2. The inclusion of the information about your discussions with the NIGB in the REC application form
3. The information being sent to GPs about the study
4. Ensure that patients will be identified by a unique study number

5. A13 Revisions to the timelines for the research
6. The risk assessment form needed to be completed and sent to Paul Yeo
7. A72 – the number of GP practices needed to be completed

I can now confirm that all of the items above have been addressed in the revised documentation that you have sent me.

The committee does have concerns regarding the use of data without consent and without a formal application to the NIGB, but is happy to grant approval for the study on the condition that the recommendations from the discussions with the NIGB are followed throughout the study, specifically those as outlined in the email to Jerry Murphy on 22nd December 2009 from Claire Edgeworth, and appended to this letter.

Please do not hesitate to contact me should you have any further questions. I hope that the study goes well.

With best wishes

Rebecca Perrett

Appendix 3

NHS
National Research Ethics Service
Newcastle & North Tyneside 2 Research Ethics Committee
Room 002
TEDCO Business Centre
Rolling Mill Road
Jarrow
NE32 4BW

Telephone: 0191 428 3565
Facsimile: 0191 428 3432
Email: gillian.mayer@sotw.nhs.uk

30 March 2010

Dr J J Murphy
Consultant Cardiologist
County Durham & Darlington NHS Foundation Trust
Darlington Memorial Hospital
Hollyhurst Road
Darlington DL3 6HX

Dear Dr Murphy

Study Title:	**What is the long term outcome in patients having heart failure and treated according to evidence based guidelines?**
REC reference number:	**10/H0907/8**
Protocol number:	**v 2**

Thank you for your letter of 19 March 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a **Favourable** ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter	R Singh	29 January 2010
REC application	7903/90373/ 1/907 (v 2.0)	25 January 2010
Protocol	v 2	15 November 2009
Investigator CV	J Murphy	18 January 2010
Letter from Sponsor	Y Yiannakou	01 December 2009
CV for key investigator/student	R Singh	25 January 2010
CV for academic supervisor	A Hungin	19 January 2010
Referees or other scientific critique report	R Perrett - Durham University	13 January 2010
Emails from National Information Governance Board Ethics Committee		22 December 2009
Response to Request for Further Information	Dr J J Murphy	19 March 2010
GP/Consultant Information Sheets	v 3	19 March 2010
Caldicott Guardian Approval - Email Correspondence	Alan McCulloch	15 December 2009
Letter confirming Approval of peer review - Durham University	Prof A P S Hungin	10 March 2010
Letter of Approval from Trust R & D	Dr Y Yiannakou	01 December 2009
Email correspondence from R & D Lead, Co Durham PCT	Richard Errington	16 October 2009

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H0907/8	**Please quote this number on all correspondence**

Yours sincerely

Professor Philip M Preshaw
Chair

Enclosures: 'After ethical review – guidance for researchers' SL- AR2

Copy to: *Dr Rajender Singh – Honorary Research Associate/Snr Trust Fellow, 4 Cedar House, Darlington Memorial Hospital, Darlington DL3 6HX*

Ms Lynne Williams – R & D Dept, Co Durham & Darlington NHS Trust, Pierremont Unit, Darlington memorial Hospital, Darlington DL3 6HX

Appendix 4

Table 7.19.2 HFpEF forward conditional regression analysis for cardiovascular mortality

		B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
								Lower	Upper
Step 1	Atrial Fibrillation	1.02	.28	12.5	1	.00	2.7	1.5	4.8
Step 2	Age	.06	.02	8.2	1	.00	1.0	1.0	1.1
	Atrial Fibrillation	.88	.29	9.3	1	.00	2.4	1.3	4.3
Step 3	Age	.07	.02	12.3	1	.00	1.0	1.0	1.1
	Gender	-.97	.29	10.7	1	.00	.3	.2	.6
	Atrial fibrillation	.86	.28	8.9	1	.00	2.3	1.3	4.1
Step 4	Age	.09	.02	15.2	1	.00	1.0	1.0	1.1
	Gender	-.89	.30	8.8	1	.00	.4	.2	.7
	Atrial Fibrillation	.80	.28	7.8	1	.00	2.2	1.2	3.9
	Diabetes M	.85	.31	7.3	1	.00	2.3	1.2	4.3

Table 8.7.3 LVSD forward conditional regression analysis for all cause mortality

		B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
								Lower	Upper
Step 1	Age	.04	.01	28.0	1	.00	1.0	1.0	1.0
Step 2	Age	.04	.01	21.7	1	.00	1.0	1.0	1.0
	Admission	.79	.21	13.9	1	.00	2.2	1.4	3.3
Step 3	Age	.03	.01	20.9	1	.00	1.0	1.0	1.0
	NYHA class			10.8	3	.01			
	NYHA class(1)	-1.42	1.0	1.8	1	.17	.2	.0	1.8
	NYHA class(2)	-.57	.34	2.8	1	.09	.5	.2	1.1
	NYHA class(3)	-.08	.33	.05	1	.81	.9	.4	1.7
	Admission	.76	.21	12.8	1	.00	2.1	1.4	3.2
Step 4	Age	.04	.01	21.0	1	.00	1.0	1.0	1.0
	smoker			7.8	2	.01			
	Smoker (currant)	.44	.25	2.9	1	.08	1.5	.9	2.5
	Smoker (ex)	.51	.18	7.6	1	.00	1.6	1.1	2.3
	NYHA class			10.9	3	.01			
	NYHA class(1)	-1.54	1.05	2.1	1	.14	.2	.02	1.6
	NYHA class(2)	-.53	.34	2.4	1	.11	.5	.2	1.1
	NYHA class(3)	-.03	.33	.01	1	.90	.9	.4	1.8
	Admission	.77	.21	13.2	1	.00	2.1	1.4	3.3

Table 8.10.1 Multivariate survival analysis of cardiovascular risk factors

	B	SE	Wald	df	p	Odds ratio	95.0% CI for OR	
							Lower	Upper
Age	.04	.01	14.1	1	.00	1.0	1.0	1.0
Gender	-.19	.21	.77	1	.37	.8	.5	1.2
Smoker			3.34	2	.18			
Smoker (currant)	.12	.33	.14	1	.70	1.1	.5	2.1
Smoker (ex)	.38	.21	3.17	1	.07	1.4	.9	2.2
Hypertension	-.17	.20	.72	1	.39	.8	.5	1.2
Atrial fibrillation	.01	.23	.00	1	.96	1.0	.6	1.5
Diabetes	-.45	.32	1.89	1	.16	.6	.3	1.2
Ischemic heart	.16	.35	.20	1	.64	1.1	.5	2.3
Myocardial infarction	-.02	.34	.0	1	.95	.9	.4	1.9
COPD/ Asthma	-.05	.25	.09	1	.76	.9	.5	1.5
Stroke	.22	.28	.66	1	.41	1.2	.7	2.1
NYHA class			9.14	3	.02			
NYHA class(1)	.64	1.02	.39	1	.52	1.9	.2	14.2
NYHA class(2)	1.25	1.02	1.50	1	.22	3.5	.4	25.9
NYHA class(3)	1.22	1.11	1.21	1	.27	3.4	.3	30.1
Admission	.63	.25	6.10	1	.01	1.8	1.1	3.1

Table 10.1.2b Blood pressure and heart rate in clinic [Independent Samples t Test]

		Levene's Test for Equality of Variances		T-test for Equality of Means						
		F	Sig.	t	df	p	Mean Difference	Std. Error Difference	95% CI of the Difference	
									Lower	Upper
Systolic BP	Equal variances assumed	.05	.81	-6.05	504	00	-12.2	2.0	-16.2	-8.2
	Equal variances not assumed			-6.08	503.7	00	-12.2	2.0	-16.2	-8.3
Diastolic BP	Equal variances assumed	.00	.95	-4.38	505	00	-5.1	1.1	-7.5	-2.8
	Equal variances not assumed			-4.37	497.2	00	-5.1	1.1	-7.5	-2.8
Heart Rate	Equal variances assumed	2.87	.09	3.84	506	00	6.5	1.6	3.1	9.8
	Equal variances not assumed			3.87	505.2	00	6.5	1.6	3.2	9.8

Table 10.2a Blood tests in clinic comparative analysis data

Group Statistics					
	1=LVSD. 2=HFpEF	N	Mean	Std. Deviation	Std. Error Mean
Sodium	1	268	140	3.3	.20
	2	241	140	3.3	.21
Potassium	1	267	4.2	.5	.03
	2	241	4.3	.5	.03
Urea	1	267	8	3.5	.22
	2	241	7.6	3.0	.19
Creatinine	1	267	111	40.1	2.49
	2	241	109	55.0	3.56
Hb	1	265	13	1.7	.10
	2	236	13	1.5	.10
MCV	1	264	90	6.1	.38
	2	237	90	6.0	.39
Cholesterol	1	196	4.8	1.3	.09
	2	157	5.1	1.7	.13

Table 10.2b Blood tests in the clinic -Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% CI of the difference	
									Lower	Upper
Sodium	Equal variances assumed	.00	.92	.11	507	.91	.03	.30	-.55	.62
	Equal variances not assumed			.11	500	.91	.03	.30	-.55	.62
Potassium	Equal variances assumed	.23	.62	-.13	506	.89	-.06	.04	-.10	.08
	Equal variances not assumed			-.13	495	.89	-.00	.04	-.10	.08
Urea	Equal variances assumed	5.22	.02	1.34	506	.17	.40	.30	-.18	.99
	Equal variances not assumed			1.35	504	.17	.40	.29	-.18	.99
Creatinine e	Equal variances assumed	.07	.78	.57	506	.56	2.42	4.28	-5.94	10.78
	Equal variances not assumed			.56	435	.57	2.42	4.31	-6.05	10.9
Hb	Equal variances assumed	3.28	.07	1.03	499	.29	.15	.14	-.13	.44
	Equal variances not assumed			1.04	498	.29	.15	.14	-.13	.44
MCV	Equal variances assumed	1.15	.28	-.58	499	.55	-.31	.54	-1.37	.75
	Equal variances not assumed			-.58	495	.55	-.32	.54	-1.39	.75
Cholesterol	Equal variances assumed	2.08	.15	-1.86	351	.07	-.28	.16	-.60	.02
	Equal variances not assumed			-1.75	286	.08	-.28	.16	-.61	.03

Table 10.4.3b Independent samples t - test for equality of means of blood pressure and heart rate on admission to hospital

Levene's Test for Equality of Variances				t-test for Equality of Means						
		F	Sig.	t	Df	p	Mean Difference	Std. Error Difference	95% CI of the Difference	
									Lower	Upper
Systolic BP on admission	Equal variances assumed	.31	.57	-4.1	341	.00	-12.8	3.1	-19	-6.7
	Equal variances not assumed			-4.1	328	.00	-12.8	3.1	-19	-6.7
Diastolic BP on admission	Equal variances assumed	.11	.73	-1.8	344	.06	-2.9	1.5	-6	.2
	Equal variances not assumed			-1.8	338	.068	-2.9	1.5	-6	.2
HR on admission	Equal variances assumed	.00	.95	-1.3	344	.17	-2.8	2.0	-6	1.2
	Equal variances not assumed			-1.3	328	.17	-2.8	2.0	-6	1.2