Contemporary Heart Failure Management

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Abstract

The research presented within this thesis aims to add to the current knowledge regarding contemporary heart failure (HF) management.

Chapter 2 describes a study collating twenty years of HF admissions and mortality data from New Zealand (1988-2008). This study describes changes in HF epidemiology to provide context for further research focusing on indivudual patient aspects of HF management in the current era.

Chapter 3 comprises a literature review examining the roles of B-type natriuretic peptide (BNP, BNP-32 and NT-proBNP) and echocardiography in contemporary HF management. BNP and echocardiography have important diagnostic and prognostic utility in HF management and provide non-invasive assessment of left ventricular filling pressure. This review provides background for the following two chapters.

Chapter 4 describes a study that evaluates the relationship between BNP-32 and echocardiographic measures of diastolic function (E/Ea) in patients admitted to hospital with acute decompensated HF.

Chapter 5 describes a study that evaluates the relationship between NT-proBNP and E/Ea in HF patients during NT-proBNP guided treatment titration.

These chapters add to current knowledge regarding the utility of E/Ea in patients with HF.

Chapters 6 and 7 focus on co-morbidity associated with HF. It has been uncertain from previously published data whether the presence of atrial fibrillation (AF) in patients with HF is associated with an adverse prognosis.

Chapter 6 comprises a literature-based meta-analysis of the prognostic effect of AF in HF compared to those with sinus rhythm. This study combines the results of 20 studies (32,946 patients, 10,819 deaths) and confirms that AF is associated with an adverse prognosis in HF.

Chapter 7 describes a study that evaluates trans-myocardial metabolism of aldosterone, angiotensin II, BNP-32, and a marker of collagen synthesis in patients with ischaemic heart disease or severe aortic stenosis who have normal left ventricular ejection fraction. This study confirms myocardial release of aldosterone despite normal circulating aldosterone

levels, strengthening the rationale for evaluation of aldosterone receptor antagonists in clinical situations not characterised by increased circulating aldosterone.

This research has added to current understanding of HF and HF therapy, particularly focused on measures that may help to improve individual patient outcomes.

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Publications

Chapter 2: Heart failure admissions and mortality in New Zealand 1988-2008; *submitted to the British Medical Journal July 2009.*

Chapter 3: The roles of brain natriuretic peptide and echocardiography in the contemporary management of heart failure; CA Wasywich, GA Whalley, RN Doughty. Expert Review of Cardiovascular Therapy 2005; 3 (1): 71-84 and Expert Review of Cardiovascular Therapy 2005; 3 (1): 51-70.

Chapter 4: The relationship between BNP and E/Ea in patients hospitalised with acute heart failure; CA Wasywich, GA Whalley, HA Walsh, GD Gamble, RN Doughty. International Journal of Cardiology 2008; 125 (2): 280-2.

Chapter 5: Changes in tissue-Doppler echocardiographic assessment of left ventricular filling during NT-proBNP guided heart failure treatment: a pilot study; CA Wasywich, GA Whalley, HA Walsh, GD Gamble, RN Doughty. Heart, Lung and Circulation 2009; 18: 38-44

Chapter 6: Atrial fibrillation and the risk of death in patients with heart failure: a literature based meta-analysis; CA Wasywich, AJ Pope, J Somaratne, KK Poppe, GA Whalley, RN Doughty. In press, 2009 Internal Medicine Journal.

Chapter 7: Coronary sinus and ascending aortic levels of aldosterone, angiotensin II and B-type natriuretic peptide in patients with aortic stenosis and in patients with coronary heart disease: CA Wasywich, MWI Webster, AM Richards, HD White, RA Stewart. Am J Cardiol 2006; 97: 1068-1072.

Abbreviations

2-D	two dimensional
ACE	angiotensin converting enzyme
AF	atrial fibrillation
ALVD	asymptomatic left ventricular dysfunction
ANP	atrial natriuretic peptide
ARA	aldosterone receptor antagonist
ARB	angiotensin receptor blocker
AS	aortic stenosis
AVPD	atrioventricular plane displacement
βB	beta blocker
BL	baseline/initial study visit
BNP	B-type natriuretic peptide
BNP-32	B-type natriuretic peptide, active peptide hormone
CRT	cardiac resynchronisation therapy
ECG	electrocardiogram
EDTA	ethylene diamine tetra-acetic acid
EF	ejection fraction
ESV	end systolic volume
IVRT	isovolumic relaxation time
HF	heart failure
HFNEF	heart failure with normal ejection fraction
ICD	implantable cardioverter defibrillator
IHD	ischaemic heart disease
LA	left atrial
LV	left ventricular
LVEDD	left ventricular end diastolic dimension
LVEDP	left ventricular end diastolic pressure
LVEF	left ventricular ejection fraction
LVFP	left ventricular filling pressure
LVH	left ventricular hypertrophy
LVESD	left ventricular end systolic dimension
NT-proBNP	B-type natriuretic peptide, inactive N-terminal fragment
NYHA	New York Heart Association
OR	odds ratio
PIIINP	pro-collagen type III amino terminal peptide
PAC	pulmonary artery catheter
RCT	randomised controlled trial
SR	sinus rhythm
SV	stroke volume
VO_{2max}	peak oxygen uptake
Vp	propogation velocity of mitral inflow colour Doppler
USA	United States of America

Chapter 1. Introduction

Heart failure (HF) is a major health problem. It is a common cause of hospitalisation [1-3] and consumes a significant proportion of health care resources [4]. A diagnosis of HF is associated with a high risk of death or hospitalisation and with a reduction in quality of life compared to the general population [5] and other chronic disorders [6]. HF is a syndrome which includes typical symptoms (dyspnoea, fatigue), signs of fluid retention (such as pulmonary congestion, oedema) and evidence of a structural or functional abnormality of the heart at rest. A response to treatment may also be helpful for diagnosis [7, 8].

1.1. Epidemiology

1.1.1. Incidence and prevalence

Many studies have reported the incidence (number of newly diagnosed cases during a specific time period), usually reported as an annualised number of cases per/1000, and prevalence (the number of cases present in a population on a certain date) of HF in multiple populations. Estimation of the true incidence and prevalence of HF requires that the general population be studied using validated questionnaires, properly conducted physical examinations, and objective measures of cardiac function. The Rochester Epidemiology Project [9] evaluated residents from Olmstead County Minnesota, USA. The age-adjusted incidence of HF was 3.78/1000 person-years in men and 2.89/1000 in women. No significant changes in HF incidence were observed over time. Of HF cases diagnosed, 42% were outpatients and of these 26% were never hospitalised during the study (mean follow up 4.2 years). Similar findings were noted in the Hillingdon Heart Failure study; the incidence of HF was strongly age dependant (1.4/1000 for the whole study population aged 25-85+, with an incidence of 0 in those aged 25-34 and an incidence of 16.8/1000 in those aged 85+) [10]. The incidence of HF was slightly higher in the Framingham population (3.27/1000 in women and 5.64/1000 in men between 1990-1999) with a reduction in the incidence of HF observed between 1950 and 1999 [11]. The Rotterdam Study [12] is a prospective population based study of residents of Rotterdam, the Netherlands aged >55 years. This study reports an incidence of HF of 17.6/1000 person years in men

and 12.5/1000 in woman. The incidence of HF increased with age (to 47.4/1000 in persons aged 90 or older). Several studies from multiple countries have reported the age standardised incidence rates of first hospitalisation for HF of between 1.2-5.5/1000 persons [13-18]. Universally, the incidence of HF hospitalisation is higher in men than women, and increases with age. Different populations have observed different temporal changes in first HF hospitalisation. In Scotland, a progressive rise from 1986, peaking in 1993/4 and subsequently falling was observed [14]. Conversely, data from the USA Medicare/Medicaid population describe a progressive increase in hospitalisation rates from 1979 to 2004 [15]. The prevalence of HF has also changed over time. In The Rotterdam Study, point prevalence of HF was ~7% and increased sharply with increases in patient age (0.9% for those aged 55-64 years to 17.4% for those aged ≥85 years) [12]. Prevalence of HF in a US integrated health care system progressively increased from ~4% in 1989 to ~14% in 1999 [18].

1.1.2. Mortality and morbidity

Diagnosis of HF portends an adverse short and long term prognosis. Population based studies describe a median survival of 2.1 years after the initial diagnosis of HF [12] and one year mortality rates of 24-37% [9, 11, 12, 19]. Mortality rates after a first admission to hospital with HF are remarkably similar (17-37% depending on the population studied) [13, 17, 18, 20]. Mortality rates are lower in women than men, and increase as patient age increases. Reductions in HF mortality rates over time have been observed in Scotland [14], Australia [16], and USA [9, 11] but these findings are not universal [21, 22].

Hospitalisation for HF is associated with significant morbidity. Within the first year after admission for HF 35-60% of patients are readmitted to hospital [23, 24]. A diagnosis of HF is associated with a reduction in quality of life [25] and increased rates of depression [26].

Chapter Two of this thesis comprises a study of HF admissions and mortality in New Zealand from 1988-2008 which describes the burden of HF in New Zealand during this period and the changing epidemiology which has occurred during this time frame. The number of days alive and out of hospital after first HF hospitalisation are

described, this tool is used to understand the shifting HF burden between the hospital and community.

1.2. Treatment

Major advances have been made in HF pharmacotherapy over the last 15 years. Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta blockers (βB), and aldosterone receptor antagonists (ARA) are now firmly established as part of the pharmacological armoury and in randomised controlled studies are associated with an important reduction in mortality [7, 8]. Implantable devices (including cardiac resynchronisation (CRT) and implantable cardioverter-defibrillators, ICD) may be added to pharmacotherapy in selected patients and this strategy is associated with a reduction in morbidity and mortality [7, 8]. Unfortunately these evidenced based therapies apply only to HF patients with a reduced left ventricular ejection fraction (LVEF). Approximately 50% of patients with the HF syndrome have an EF of 40-45% or greater, these patients have a similar prognosis to HF patients with a reduced EF [27, 28]. Pharmacological therapies are less well studied in this large group of HF patients. Some studies suggest an improvement in symptoms [29, 30] and small improvements in survival [30] with therapeutic strategies including ARB's. Overall, pharmacologic strategies specifically directed at this patient group have been disappointing and HF guidelines recommend treatment of risk factors and co-morbidities such as hypertension, coronary artery disease, and atrial fibrillation (AF), and symptom control with diuretics [7, 8].

Despite major advances in HF therapy, prognosis for patients remains poor and there is a need for therapeutic strategies directed at improving outcomes in individual patients and for targeting proven therapies at those who will benefit the most. A tool analogous to haemoglobin A1C or peak expiratory flow rate (asthma) to guide therapy would potentially be of significant benefit in this large patient group. Emerging potential tools to guide HF therapy in individual patients include cardiac neurohormones, in particular B-type natriuretic peptide (BNP), encompassing the active peptide hormone, BNP-32 and the inactive N-terminal fragment, NT-proBNP. BNP has a role in the diagnosis of HF both in primary and secondary care and is a powerful prognostic marker in HF patients. Echocardiography is also used for HF

diagnosis and prognostic assessment. Echocardiographic measures of diastolic function may be a potential tool to assist in the management of HF patients.

Chapter Three of this thesis is a literature review of the role of BNP and echocardiography in the management of HF patients. This literature review provides background to two studies examining the relationship between BNP and echocardiographic measures of diastolic function in patients with HF.

Chapter Four of this thesis is a study exploring the relationship between BNP and echocardiographic measures of diastolic function in patients admitted to hospital with decompensated HF.

Chapter Five of this thesis is a study exploring the relationship between BNP and echocardiographic measures of diastolic function in outpatients with decompensated HF during BNP guided HF treatment titration.

1.3. Co-morbid disease

HF does not occur in isolation. Most patients have important cardiovascular co-morbidities which add additional complexity to the management of patients. HF is frequently caused by ischaemic heart disease, arrhythmias and valvular heart disease. AF is the most common arrhythmia in HF patients. The incidence of AF increases with severity of HF [31]. Many studies have described the prognostic impact of a diagnosis of AF in HF patients with conflicting conclusions. In addition studies evaluating a "rate control" versus "rhythm control" therapeutic approach in patients with and without HF suggest that a strategy of rhythm control does not improve outcomes [32-34].

Chapter Six of this thesis is a literature based meta-analysis examining the prognostic impact of AF in patients with HF. This study combines the results of 20 studies (32946 patients, 10819 deaths).

1.4. Biomarkers in other cardiovascular disease

Treatment with an ARA improves outcomes in patients with severe HF and in patients with impaired left ventricular systolic function after myocardial infarction [35, 36]. However it is not known whether the adverse effects of aldosterone, which include

vascular [37] and myocardial inflammation and fibrosis [38, 39] are due to increased circulating aldosterone alone. Some animal [40, 41] and human studies [41-43] suggest aldosterone can be synthesised within the myocardium as well as from the adrenal gland. It is therefore possible aldosterone could have pathophysiological roles in cardiovascular disease which are independent of the systemic renin-angiotensin-aldosterone system [44].

A small number of studies have evaluated trans-myocardial aldosterone metabolism by comparing plasma levels in samples taken from the aorta and coronary sinus with varying results [42, 43, 45, 46]. Results of these studies are therefore inconsistent; there is a need for further research to determine both whether aldosterone is released by myocardium, and whether any release is greater in specific cardiac diseases.

Aortic stenosis (AS) is characterised by progressive left ventricular hypertrophy and fibrosis. Both angiotensin II and aldosterone promote myocardial fibrosis in experimental models, and activation of myocardial angiotensin synthesis has been demonstrated in patients with aortic valve disease [47]. However it is not known whether aldosterone has a role in the adverse left ventricular remodelling of AS. In experimental studies aldosterone can cause vascular dysfunction [48] and promote atherosclerosis [49], this suggests a pathophysiological role in coronary artery disease [50].

Chapter Seven of this thesis is a study which determines whether myocardial release of aldosterone, detected as a step-up in coronary sinus levels, occurs in patients with severe AS and/or in patients with stable coronary artery disease who have a normal LVEF and no clinical evidence of HF. This study also evaluated the presence or absence of myocardial release angiotensin II, BNP-32 and pro-collagen type III amino terminal peptide were measured in blood samples taken from the coronary sinus and aortic root before diagnostic coronary angiography.

This thesis collates several studies together, all relating to the theme of "contemporary HF management", recognising the importance of HF as a public health problem for New Zealand, and exploring potential tools to assist in individual patient management. The final chapter of this thesis adds to current knowledge regarding myocardial production of multiple neurohormones, some of which are used as treatment targets in HF patients.

Chapter 2. Heart failure admissions and mortality in New Zealand 1988-2008

2.1. Introduction

HF is a major public health problem [51]. It consumes a significant proportion of health care resources [4, 52] and causes significant morbidity and mortality for patients. Over the last two decades significant changes have occurred in population demographics (the aging population) [53] in the management of HF [7, 54] (such as improvements in pharmacotherapy, the development of structured programs for HF disease management, and more aggressive treatment of co-morbid disease) and in the management of medical conditions which predispose to HF (such as ischaemic heart disease [55, 56]). Several studies have reported changes in HF incidence and mortality over this time period. Most recently reported populations observe an increase in the incidence of HF and a decrease in mortality in patients with HF. Data from the Scottish population (1986-2003) show an initial rise and subsequent fall in the incidence of first HF hospitalisation and improvements in survival from 1986 to 2000 [14], data from Sweden (1987-2003) are very similar [57, 58]. In Australia, progressive decreases in both the incidence of first HF hospitalisation (1989-2003) and in survival (1980-2001) have been observed [16]. With changes in HF epidemiology, it is possible that the burden of disease may have shifted from the hospital (where most of the resources for HF management are consumed) to the community. If this were the case there would be significant public policy implications. Conversely, while initial HF hospitalisation rates may have decreased, it is possible that hospitalisation readmissions may have increased due to factors such as reduction in length of stay of the initial admission (i.e. patients being discharged too early), an aging population, and an increase in co-morbidity. For example, in the United States of America the incidence of hospitalisation (including initial admission and readmissions) for HF has progressively increased (1979-2004) [15]. If this were the case in other countries, then the burden of disease would remain within secondary care.

The aims of this study were to describe changes in HF epidemiology from 1988-2008 in New Zealand, specifically to determine the in-hospital and community burden of HF in the context of changing patterns of hospitalisation and survival. The number of days alive and out of hospital after an initial admission for HF were calculated to understand the impact of changes in both hospitalisation and survival over the 20 year study period.

2.2. Methods

2.2.1. Data Sources

The New Zealand Health Information Service is a group within the New Zealand Ministry of Health responsible for the collection of health-related information. Data on hospital admissions are obtained from all public and private hospitals. The cause of hospital admission is obtained from the diagnosis made at separation from hospital (i.e. discharged alive or died in hospital). The error rate in coding of primary and secondary diagnoses is low (5-6%) based on audit data [59-61], and a coded diagnosis of HF highly specific [62]. Cause of death is obtained from the legal death certificates or coroners report together with autopsy reports, if available, with the cause of death based on the underlying cause. Each patient has a unique identifying healthcare user number that allows tracking of individual patients within databases. For the purposes of this study, data on hospital admissions due to HF in those aged 18 years or older were obtained from this source for the years 1988 to 2008 inclusive. Individual patients were identified by an encrypted identifying number. The following codes, using the 9th version of the International Classification of Disease (ICD-9CM), for HF as a primary diagnosis were used: HF-cause unspecified (428, 429.1, 429.3); hypertensive heart disease (402); primary cardiomyopathy (425.4); alcoholic cardiomyopathy (425.5); myocarditis (422, 429.0); and other causes of HF (429.4, 425[except 425.4]). In addition, data were obtained for hospital admissions where HF (428, 429.1 or 429.3) was a secondary diagnosis associated with a primary diagnosis of chronic rheumatic heart disease (393-398), ischaemic heart disease (410-414) or valvular heart disease (non-rheumatic) (424).

All cause mortality data were obtained for all patients in the hospital admission dataset. The first admission for each patient was identified from the admissions

database and subsequent survival calculated. Mortality data was available to 31st December 2008. To integrate changes in mortality and hospitalisation, the number of days alive and out of hospital at various time points (30 days, 6, 12, and 24 months) were calculated from mortality and hospitalisation data from the date of the initial admission (to account for in-hospital mortality). Admissions less than 24 hours were excluded from this calculation. To ensure complete data ascertainment, days alive and out of hospital at 12 and 24 months is reported to 2007 and 2006 respectively. For example; if a patient died during their initial HF hospitalisation they were assigned 0 days alive and out of hospital, if a patient was admitted for 5 days, then re-hospitalised for 6 days 90 days later then subsequently died at 103 days after their initial hospitalisation they were assigned 92 days alive and out of hospital, if a patient was admitted for 7 days but then was not re-hospitalised and survived to the end of the ascertainment period (for instance 180 days) they were assigned 173 days alive and out of hospital. As all patients were identified during their initial HF hospitalisation, no patients had 180 (100%) days alive and out of hospital. The number of days lost due to death or hospitalisation is presented at a percentage (at each time point).

The HF-specific casemix index is a score that accounts for the presence of socio-demographic variables, co-morbidities, and disease specific variables based on ICD-9CM coding [63]. This index allows assessment of disease severity in large datasets and has been shown to be predictive of mortality in patients with HF [63]. The HF casemix index was calculated for each patient according to the previously published methodology [63].

2.2.2. Statistical analysis

Data were analysed using the statistical software package SAS (SAS v8.2, SAS Institute Inc. Cary, North Carolina, USA). Standardised mortality ratios were calculated from direct standardisation against the Segi population. Kruskal-Wallis test was used to compare median length of stay across the years. Stratified survival analysis was performed using the lifetable method and data are presented as Kaplan-Meier figures. Normally distributed data (or data rendered normal by transformation) were compared using ANOVA. Significant main and interaction effects were

explored using the method of Tukey. All tests were two-tailed and a 5% significance level was maintained.

2.3. Results

2.3.1. Population Demographics and changes 1988-2008

2.3.1.1. Heart failure admissions

Table 1 describes year-by-year HF admissions from January 1, 1988 to December 31, 2008. During these two decades, 120,302 patients were hospitalised for the first time with HF. There were a total of 221,471 hospitalisations for HF in New Zealand (54% first admissions, 46% readmissions). The number of first admissions per year increased from 5050 in 1989 to a peak of 6517 in 1999, subsequently decreasing to 5413 in 2008. Total admissions followed a similar pattern, increasing from 7538 per year in 1988 to 12563 in 1999 and subsequently decreasing to 10,892 in 2008 (Table 1). The population of New Zealand increased from 3.33 million (1988) to 4.27 million (2008) over this time [64].

Age standardised incidence of HF hospitalisation (per 100,000 population) increased from 122.9 (F) and 207.7 (M) in 1988 to 155.3 (F) and 244 (M) in 1998. After peaking in 1998-1999 a gradual decline in the incidence of HF hospitalisation occurred thereafter (2008: 106.9 (F), 174.3 (M), Figure 1.

Median age at the time of first HF admission increased from 74.5 to 78.1 years between 1988 and 2008. Median hospital LOS decreased from 8 (IQR 5, 14) to 5 (IQR 3, 9) days between 1988 and 1997. No further reduction in LOS was observed thereafter. Casemix index, as a measure of HF specific co-morbidity, gradually increased between 1988 and 2008. Mean casemix index was 2.41 (SD 1.00) in 1988 and increased to 3.01 (SD 1.49) in 2008.

Table 1: Hospital admissions for heart failure 1988-2008 in New Zealand

Year	Total Admissions	Index Admissions	Age, years Median (IQR)	LOS, days Median (IQR)	Casemix Mean (SD)
1988	7538	5962	74.5 (65.7, 80.9)	8 (5, 14)	2.41 (1.00)
1989	7546	5050	75.1 (66.5, 81.5)	8 (4, 14)	2.41 (1.00)
1990	8013	5113	74.8 (66.1, 81.3)	8 (4, 13)	2.43 (1.01)
1991	8305	5157	75.2 (66.5, 81.5)	7 (4, 12)	2.44 (1.01)
1992	8868	5175	75.2 (66.6, 81.9)	7 (4, 11)	2.47 (1.03)
1993	9001	5182	75.7 (67.1, 82.2)	7 (4, 11)	2.47 (1.02)
1994	9408	5253	75.4 (66.8, 82.2)	6 (3, 11)	2.50 (1.07)
1995	9961	5634	75.2 (66.1, 82.3)	6 (3, 10)	2.59 (1.15)
1996	10712	5965	75.5 (66.3, 82.4)	6 (3, 9)	2.70 (1.25)
1997	11905	6448	75.5 (66.6, 82.6)	5 (3, 9)	2.81 (1.30)
1998	12323	6416	75.6 (66.6, 82.7)	5 (3, 9)	2.90 (1.37)
1999	12563	6517	75.8 (66.4, 82.9)	5 (3, 8)	2.93 (1.37)
2000	12455	6487	76.4 (67.1, 83.4)	5 (3, 8)	2.95 (1.38)
2001	12209	6128	76.8 (67.2, 83.6)	5 (3, 8)	2.94 (1.41)
2002	12253	6065	77.3 (67.5, 84.2)	5 (3, 8)	2.99 (1.43)
2003	11674	5774	77.6 (67.6, 84.3)	5 (3, 8)	3.06 (1.46)
2004	11557	5783	78.0 (67.5, 84.4)	5 (3, 9)	3.01 (1.42)
2005	11504	5647	77.4 (66.7, 84.5)	5 (3, 9)	3.01 (1.47)
2006	11500	5608	77.8 (67.1, 84.8)	5 (2, 8)	3.05 (1.50)
2007	11284	5595	77.1 (66.3, 84.7)	5 (3, 8)	3.00 (1.50)
2008	10892	5413	78.1 (66.6, 85.1)	5 (3, 8)	3.01 (1.49)
Total	221471	120372			

LOS, length of stay; IQR, interquartile range; SD, standard deviation; Casemix, mean casemix index

Figure 1: Age and sex standardised admission rates for HF in New Zealand 1988-2008
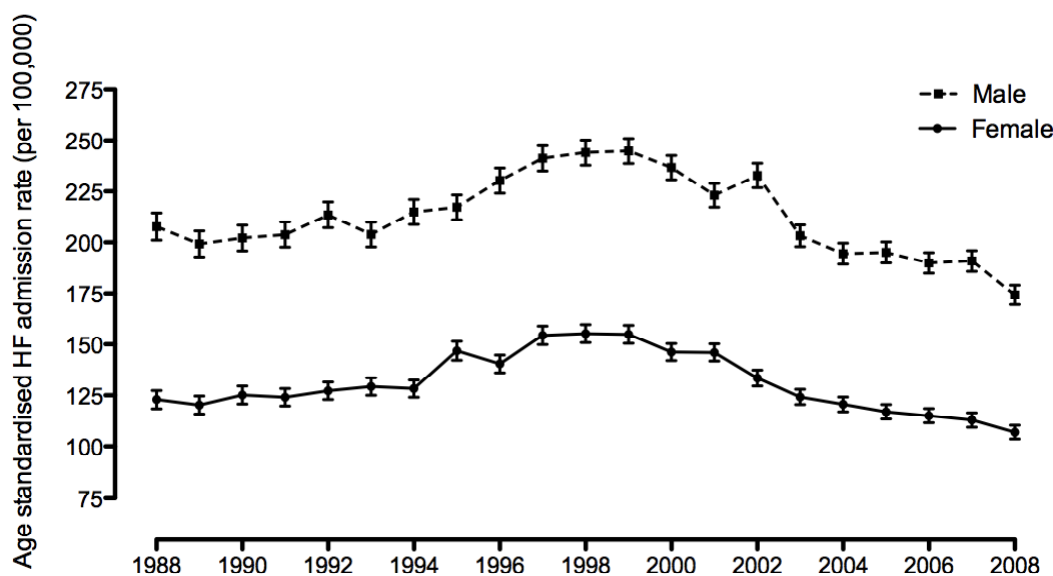
2.3.1.2. Influences of patient age and gender

Between 1988 and 2008 the proportion of patients aged ≥75 years increased from 48.1% to 58.2%. Patients aged ≥75 stayed in hospital approximately one day longer for the duration of the study (Table 2). Approximately 48% of all HF admissions occurred in females, this proportion did not change over the two decades of the study. Median LOS was about a day longer for females compared to males between 1988 and 1998; thereafter LOS was the same (5 days). HF casemix index was slightly higher in females compared to males at all time periods. At the time of their first admission women were approximately five years older than males, this difference persisted: 1998; F 76.7 (IQR 68.9, 83) vs. M 71.8 (IQR 62.8, 79.2); 2008; F 80.8 (IQR 71.2, 86.7) vs.M 75.6 (IQR 64.2, 83) years (Table 3).

2.3.2. Hospital days

Total hospital days at 30 days, 6 months, 12 months, and 24 months (from day one of the index admission) progressively decreased from 1988 to 1992-4. An increase in total hospital days occurred between 1994 and 1998-2002, progressively declining thereafter (Figure 2). Most of the hospital days were due to HF rather than non-HF reasons (Figure 3).

Table 2: Influence of age on HF epidemiology 1988-2008

	Index Admissions			LOS, days Median (interquartile range)		30 Day Mortality, %		12 Month Mortality, %	
Year	Total	<75 (%)	≥75 (%)	<75	≥75	<75	≥75	<75	≥75
1988	5962	3094 (51.9)	2868 (48.1)	8 (4, 13)	9 (5, 16)	11.9	18.9	31.5	47.2
1989	5050	2498 (49.5)	2552 (50.5)	7 (4, 12)	9 (5, 16)	9.9	19.3	27.9	46.1
1990	5113	2573 (50.3)	2540 (49.7)	7 (4, 11)	8 (5, 15)	10.7	16.6	27.4	41.6
1991	5157	2549 (49.4)	2608 (50.6)	7 (4, 11)	8 (4, 14)	10.4	17.9	28.4	44.3
1992	5175	2555 (49.4)	2620 (50.6)	6 (3, 10)	7 (4, 13)	11.2	17.8	27.3	44.2
1993	5182	2490 (48.1)	2692 (51.0)	6 (3, 10)	7 (4, 13)	11.6	18.3	29.3	42.5
1994	5253	2571 (48.9)	2682 (51.1)	6 (3, 9)	7 (4, 12)	9.2	16.3	24.8	42.1
1995	5634	2764 (49.1)	2870 (50.9)	6 (3, 9)	6 (4, 11)	8.5	16.4	23.6	39.9
1996	5965	2873 (48.2)	3092 (51.8)	5 (3, 8)	6 (4, 11)	8.6	16.6	21.9	39.8
1997	6448	3119 (48.4)	3329 (51.6)	5 (3, 8)	6 (3, 10)	8.1	14.9	20.8	38.6
1998	6416	3061 (47.7)	3355 (52.3)	5 (2, 8)	6 (3, 10)	6.8	14.8	19.4	38.7
1999	6517	3108 (47.7)	3409 (52.3)	5 (2, 8)	5 (3, 9)	6.8	13.6	17.5	35.4
2000	6487	2931 (45.2)	3556 (54.8)	5 (2, 8)	5 (3, 9)	6.4	14.8	17.6	37.3
2001	6128	2694 (44.0)	3434 (56.0)	5 (2, 8)	5 (3, 9)	6.4	15.1	16.8	38.5
2002	6065	2584 (42.6)	3481 (57.4)	4 (2, 8)	5 (3, 9)	6.4	15.0	18.0	36.8
2003	5774	2389 (41.4)	3385 (58.6)	5 (2, 8)	5 (3, 9)	7.1	14.9	17.8	39.0
2004	5783	2343 (40.5)	3440 (59.5)	5 (2, 8)	5 (3, 9)	6.6	15.3	16.4	38.8
2005	5647	2368 (41.9)	3279 (58.1)	5 (2, 8)	5 (3, 9)	6.1	14.6	16.2	38.2
2006	5608	2346 (41.8)	3262 (58.2)	4 (2, 8)	5 (3, 8)	4.8	14.1	15.3	37.3
2007	5595	2458 (43.9)	3137 (56.1)	5 (2, 8)	5 (3, 9)	5.9	13.7	15.8	37.8
2008	5413	2264 (41.8)	3149 (58.2)	4 (2, 8)	5 (3, 9)	5.0	12.4		
Total	120372	55632	64740						

Table 3: Influence of patient gender on HF epidemiology 1988-2008

	Index Admissions N, (%)			LOS, days Median (IQR)		Casemix Mean (SD)		Age Median (IQR)		30 Day Mortality,%		12 Month Mortality,%	
Year	Total	F	M	F	M	F	M	F	M	F	M	F	M
1988	5962	2827 (47.4)	3135 (53.6)	9 (5, 15)	8 (5, 13)	2.51 (0.92)	2.32 (1.06)	76.7 (68.9. 83)	71.8 (62.8, 78.2)	14.9	15.6	38.3	39.7
1989	5050	2468 (48.9)	2582 (51.1)	8 (5, 13)	7 (4, 13)	2.49 (0.94)	2.33 (1.04)	77.1 (69, 83.1)	71.9 (62.8, 79.2)	14.8	14.5	36.2	37.9
1990	5113	2483 (48.6)	2630 (51.4)	8 (4, 14)	7 (4, 12)	2.54 (0.97)	2.33 (1.04)	77.5 (69.2, 83)	71.5 (63, 78.4)	13.7	13.7	34.1	34.9
1991	5157	2471 (47.9)	2686 (52.1)	7 (4, 13)	7 (4, 12)	2.54 (0.97)	2.36 (1.05)	77.3 (69.4, 82.9)	71.6 (63.2, 78.9)	14.0	14.4	35.3	37.5
1992	5175	2481 (47.9)	2694 (52.1)	7 (4, 12)	6 (4, 11)	2.59 (1)	2.35 (1.05)	77.6 (69.9, 83.5)	72.0 (63.3, 79.3)	14.6	14.5	35.6	36.2
1993	5182	2555 (49.3)	2627 (50.1)	7 (4, 12)	6 (4, 11)	2.56 (0.98)	2.38 (1.06)	78.1 (69.8, 83.5)	72.9 (64.2, 79.8)	15.3	14.9	35.9	36.4
1994	5253	2513 (47.8)	2740 (52.2)	7 (4, 12)	6 (3, 10)	2.61 (1.01)	2.4 (1.11)	78 (69.5, 83.8)	72.5 (64.2, 79.5)	13.0	12.7	33.0	32.2
1995	5634	2684 (47.6)	2950 (52.4)	6 (3, 11)	6 (3, 10)	2.66 (1.06)	2.54 (1.23)	77.8 (69.4, 83.8)	72.5 (63.7, 79.8)	12.1	13.0	30.5	33.2
1996	5965	2845 (47.7)	3119 (52.3)	6 (3, 10)	5 (2, 9)	2.81 (1.17)	2.59 (1.3)	78.5 (69.8, 84.1)	72.6 (63.6, 79.9)	13.4	12.2	31.1	31.3
1997	6448	3113 (48.2)	3335 (51.8)	6 (3, 10)	5 (3, 9)	2.86 (1.2)	2.76 (1.38)	78.5 (70.2, 84.4)	73.0 (64, 80.2)	12.0	11.3	30.5	29.5
1998	6416	3098 (48.3)	3318 (51.7)	6 (3, 9)	5 (3, 8)	2.95 (1.25)	2.86 (1.48)	78.6 (70.7, 84.5)	73.2 (64, 80.3)	11.2	10.8	30.2	28.9
1999	6517	3148 (48.3)	3369 (51.7)	5 (3, 9)	5 (3, 8)	3 (1.3)	2.87 (1.5)	78.6 (70.8, 85.0)	73.3 (63.7, 80.4)	10.7	10.1	27.4	26.4
2000	6487	3108 (47.9)	3379 (52.1)	5 (3, 9)	5 (3. 8)	3.01 (1.27)	2.91 (1.48)	79.2 (71, 85.3)	74.1 (64.5, 81)	11.7	10.3	28.3	28.5
2001	6128	3050 (49.8)	3078 (51.2)	5 (3, 9)	5 (3, 8)	2.99 (1.33)	2.9 (1.49)	79.5 (71.5, 85.6)	74.3 (64.1, 81.3)	12.3	10.2	30.4	27.6
2002	6065	2916 (48.1)	3149 (51.9)	5 (3, 8)	5 (2, 8)	3.07 (1.31)	2.92 (1.53)	80 (71.8, 86)	73.9 (62.6, 81.4)	11.9	10.8	30.1	27.6
2003	5774	2789 (48.3)	2985 (51.7)	5 (3, 9)	5 (3, 8)	3.11 (1.37)	3.01 (1.54)	80.5 (72.4, 86.3)	75.7 (65.8, 82.1)	12.0	11.4	31.2	29.3
2004	5783	2773 (48.0)	3010 (52.0)	5 (3, 9)	5 (3, 8)	3.09 (1.32)	2.93 (1.51)	80.7 (72.7, 86.4)	75.5 (64.8, 82.3)	12.4	11.3	31.1	28.4
2005	5647	2688 (47.6)	2959 (52.4)	5 (3, 9)	5 (3, 8)	3.12 (1.37)	2.91 (1.56)	80.8 (72.2, 86.6)	75.3 (64, 82.4)	12.5	9.7	31.1	27.1
2006	5608	2684 (47.9)	2924 (52.1)	5 (3, 8)	5 (2, 8)	3.16 (1.35)	2.96 (1.54)	80.8 (72.1, 86.6)	75.1 (64, 82.3)	10.8	9.7	29.0	27.3
2007	5595	2567 (45.9)	3028 (54.1)	5 (3, 9)	5 (2, 8)	3.09 (1.39)	2.93 (1.58)	80.3 (70, 86.5)	74.9 (63.5, 82.5)	10.3	10.3	29.1	27.2
2008	5413	2580 (47.7)	2833 (53.3)	5 (3, 9)	5 (2, 8)	3.13 (1.38)	2.9 (1.58)	80.8 (71.2, 86.7)	75.6 (64.2, 83)	10.0	8.9		
Total	120372	57841 (48.1)	62530 (51.9)										

Figure 2: Total days in hospital after a HF admission 1988-2008
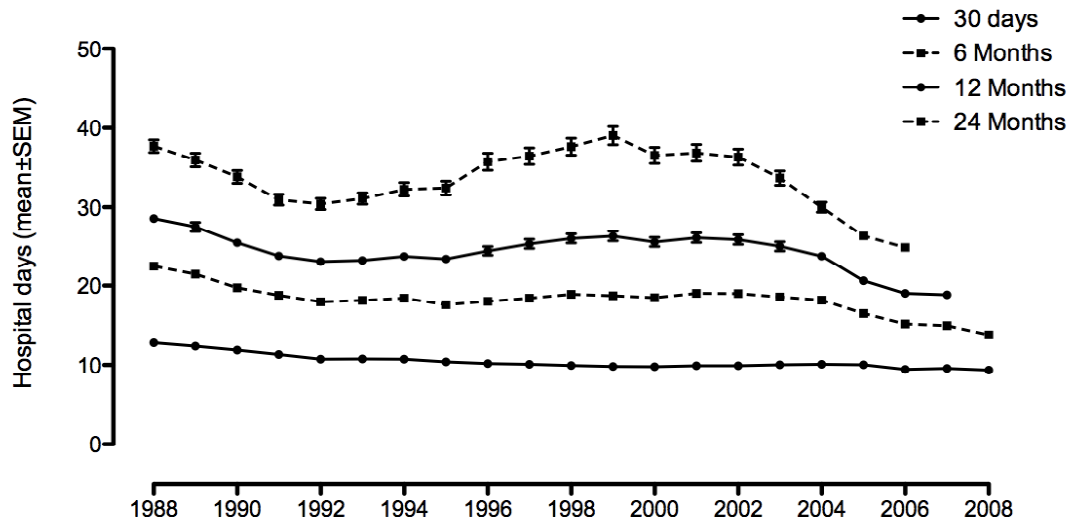
Figure 3: Hospital days due to HF and non-HF reasons
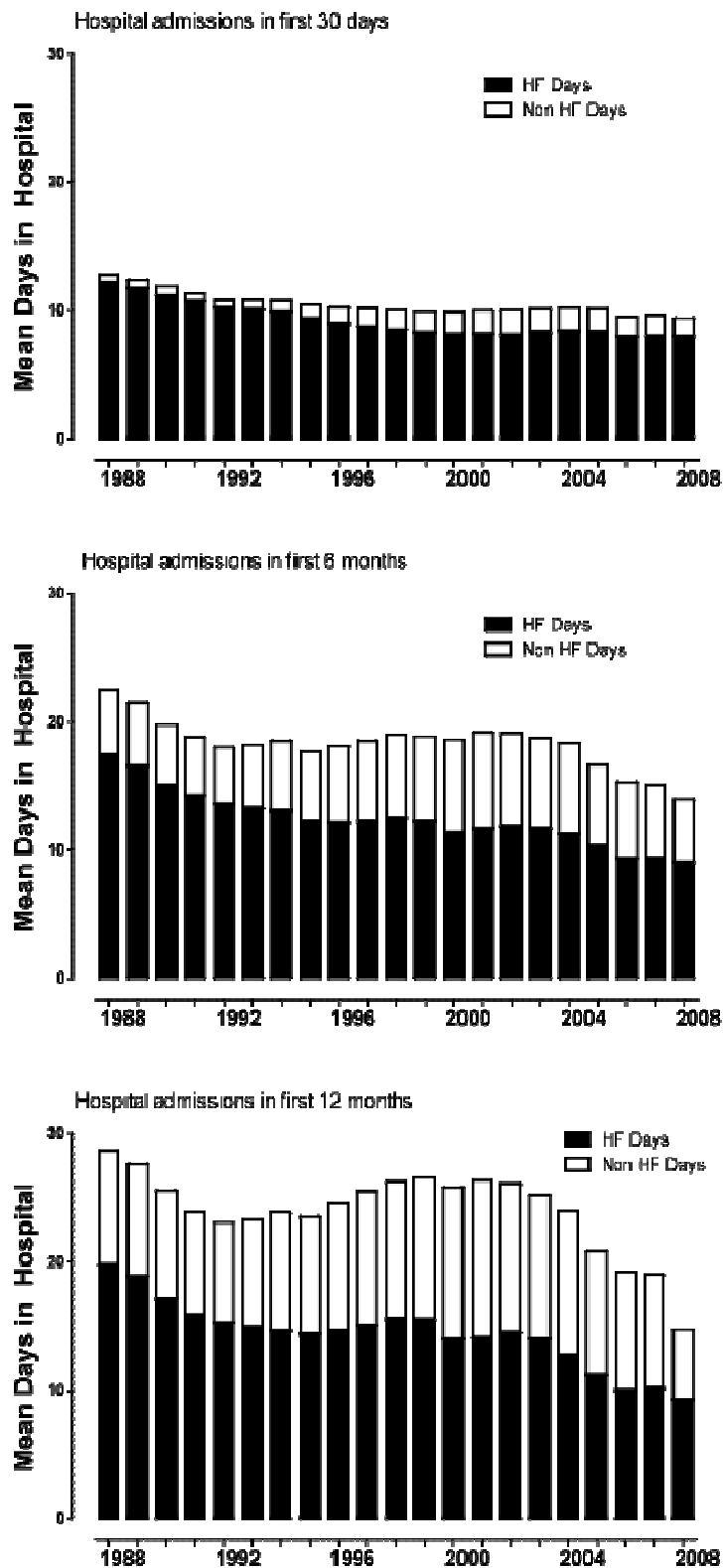
2.3.3. Mortality

Changes in overall mortality between 1988 and 2008 are shown in Figure 4. Significant decreases in mortality after an admission for HF were observed: in-hospital mortality decreased from 14.2% to 6.5%; 30 day mortality decreased by from 15.2% to 9.3%; 6 month mortality decreased from 30.9% to 21.1%; and 12 month mortality decreased from 39.0% to 28.1% respectively. Mortality rates were 2-3 fold higher in patients aged ≥75 (Table 2). Gender did not significantly influence mortality after a hospitalisation for HF (Table 3), although as noted above this is heavily influenced by patient age (females were approximately five years older than males at index admission).

Changes in 4 year survival during the study period are illustrated in Figure 5, survival progressively improved until 2000. No further improvements in survival were observed after 2000. Median survival has increased by 1.5 years, from 2.02 years in 1988 to 3.46 years in 2004. Median survival was substantially longer in those aged <75 at all time periods during the study. Larger improvements in 4 year survival were seen in those aged <75 compared to older patients, little improvement was noted after 2000 (Figure 6). Conversely, although median survival after index HF hospitalisation was better in females compared to males in 1988 (F 2.25 years, M 1.82 years), less substantial improvements in 4 year survival were noted over time so that median survival in 2004 was less than that in males (F 3.06 years, M 3.82 years), Figure 7. Median survival after a hospitalisation for HF in New Zealand improved most in younger men between 1988 and 2008.

Figure 4: Changes in mortality after an admission for HF in New Zealand 1988-2008
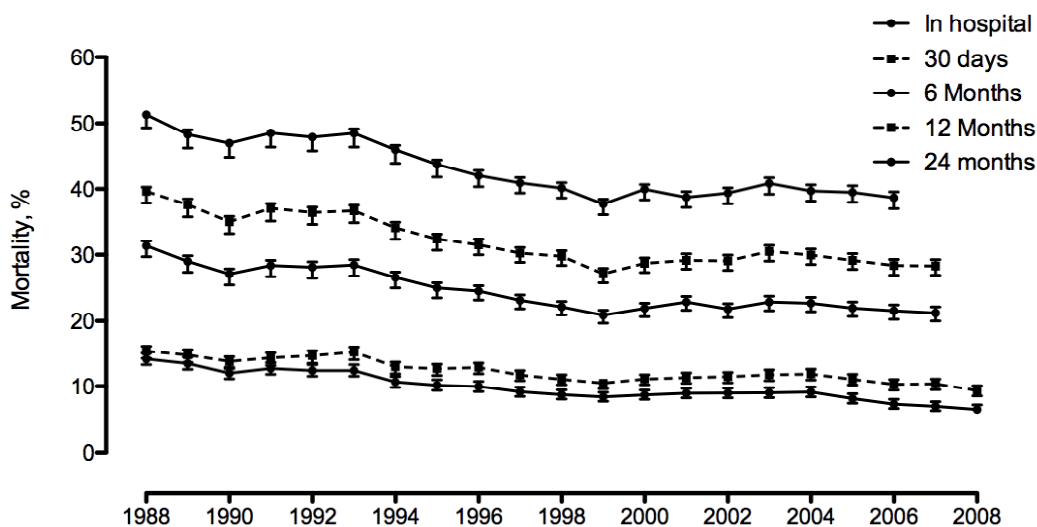
Figure 5: Four year survival after an admission for HF in New Zealand 1988-2008
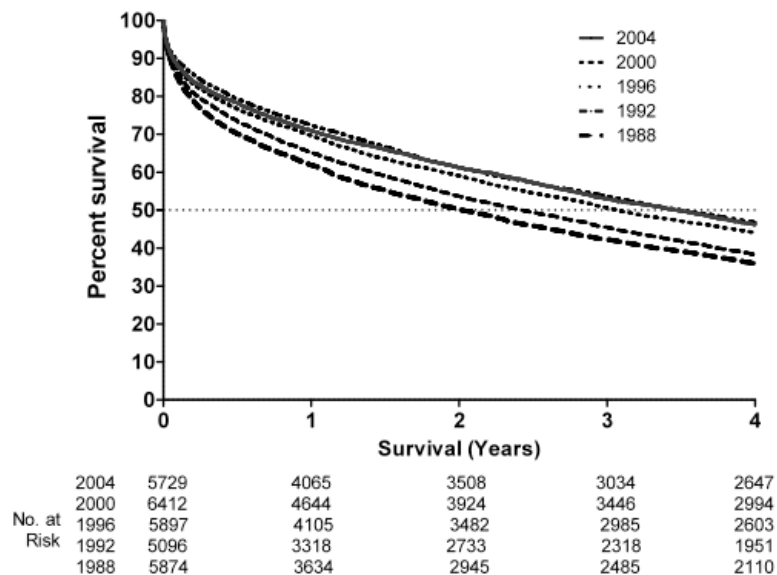
Figure 6: Influences on age on survival after an admission for HF 1988-2008
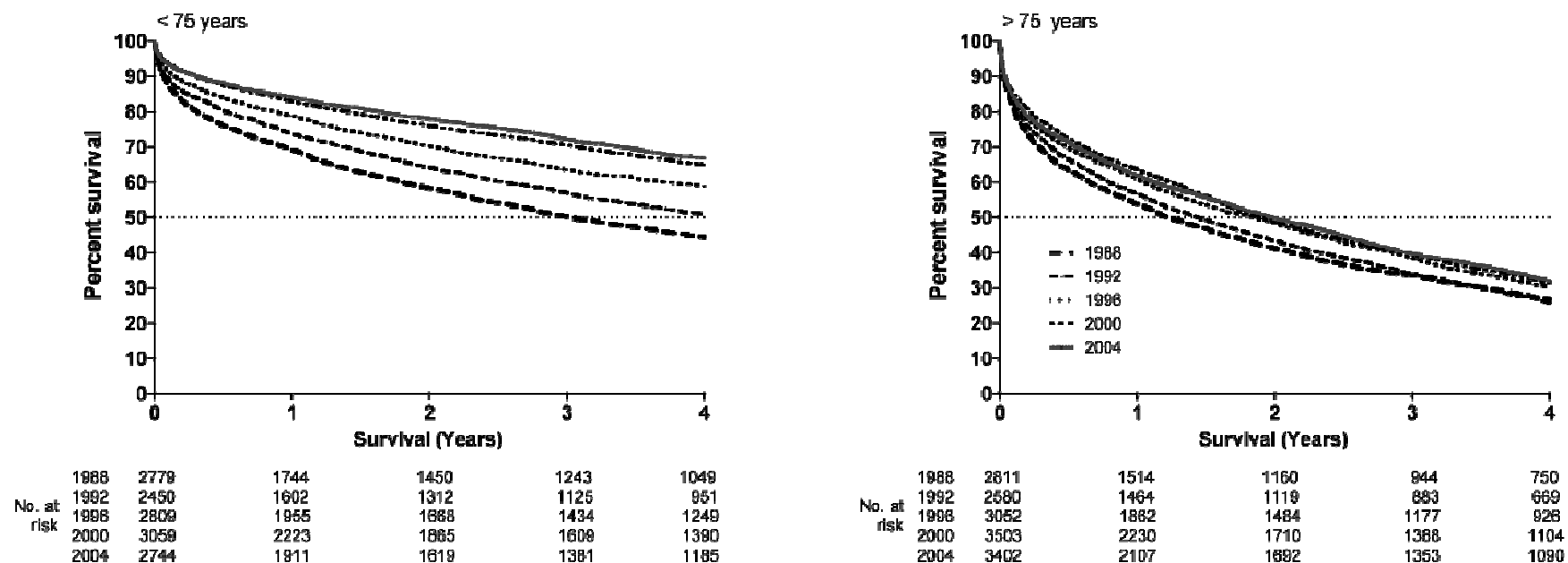
Figure 7: Influences of patient gender on survival after an admission for HF 1988-2008
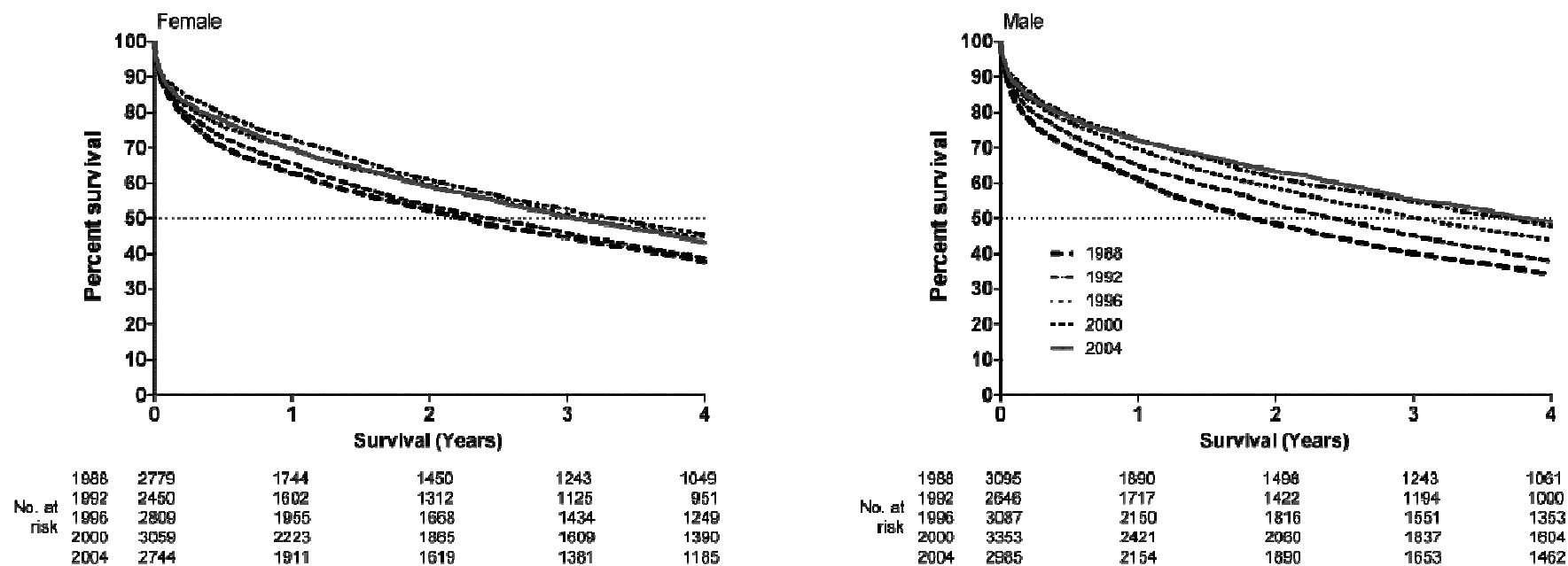
2.3.4. Days alive and out of hospital after a first admission with HF

To explore the impact of relative contributions from changes in hospitalisation and changes in mortality during the 20 year study period, the number of days alive and out of hospital after an admission for HF are illustrated in Figure 8. A progressive increase in the number of days alive and out of hospital was observed at 30 days (15.4 to 18.5 days), 6 months (126.4 to 141.8 days), 12 months (244.9 to 274.2 days) and 24 months (448.8 to 511.3 days). The number of days alive and out of hospital continue to increase after 2000 despite unchanging mortality rates as hospital days continue to decrease. Between 1988 and 2008 patients were alive and out of hospital for 3.1 more days at 30 days, 15.4 more days at 6 months, 29.3 days at 12 months, and 62.5 days at 24 months.

The proportion of days lost because of death or hospitalisation has decreased from 48.7% to 38.3% (30 days), 29.8 to 21.2% (6 months), 32.9 to 24.9% (12 months) and 38.5 to 30.0% (24 months).

Figure 8: Days alive and out of hospital (DAOH) after an admission for HF in New Zealand 1988-2008
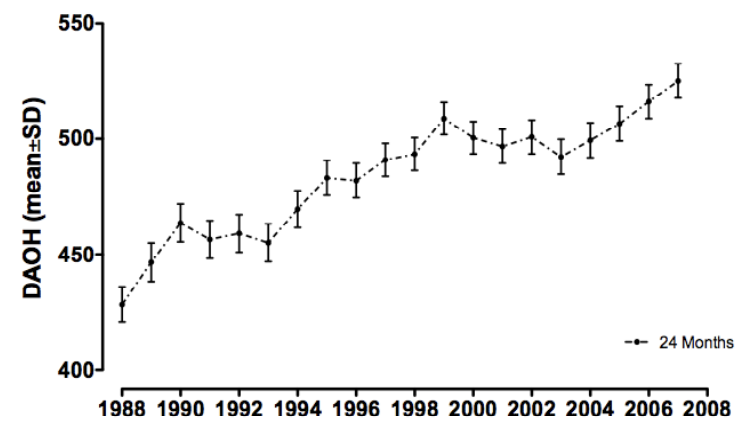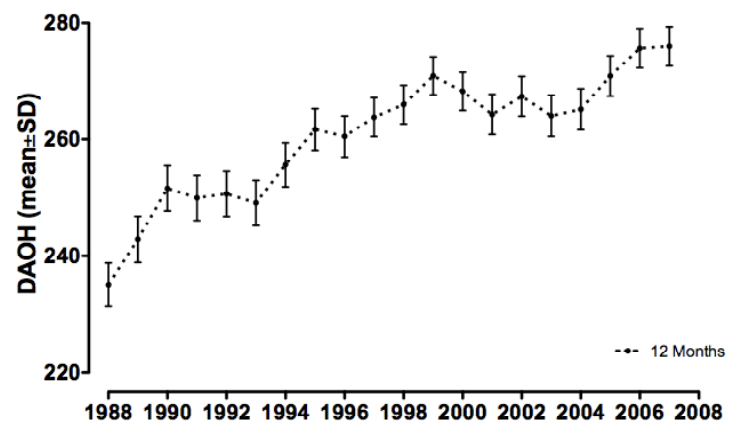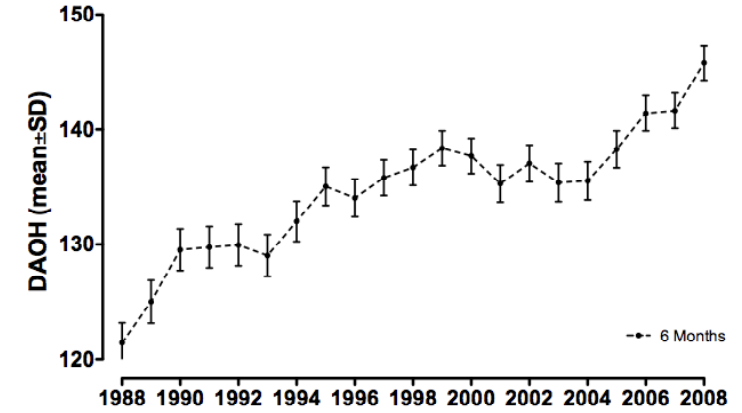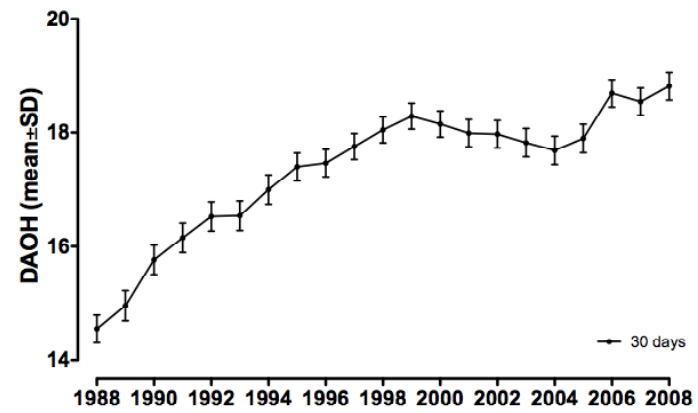
2.4. Discussion

This study describes changes in HF epidemiology for the entire population of New Zealand over two decades, from 1988 to 2008. Over two decades there has been a rise and subsequent fall in the incidence of first hospitalisation for HF (Figure 1). At the time of initial hospitalisation, HF patients are older and have more co-morbidity in the current era compared to previously. Despite this, hospital length of stay has decreased from 8 to 5 days and the number of hospital days after a HF admission continue to decrease (Figure 2). Mortality rates progressively decline from 1988 to 2000. No further mortality improvements occurred between 2000 and 2008 (Figure 4). The New Zealand data is similar to that from other countries. Data from the Scottish population (1986-2003) show a rise and subsequent fall in the incidence of first HF hospitalisation and improvements in survival from 1986 to 2000, with little subsequent improvement [14], and data from Sweden (1987-2003) are very similar [57, 58]. In Australia, progressive decreases in both the incidence of first HF hospitalisation (1989-2003) and in survival (1980-2001) have been observed [16]. Conversely, in the United States of America, the incidence of hospitalisation for HF has progressively increased (1979-2004) [15]. These changes have been observed internationally on the background of significant societal changes (including the aging population and lengthening life expectancy) and changes in the way patients with HF are managed (including advances in pharmacotherapy, treatment of co-morbid disease and risk factors for the development of HF, and the recognition of the value of HF disease management programs) [7, 54].

HF is a chronic disease that imposes a substantial burden on patients, health care systems, and the community. Mortality associated with a diagnosis of HF and the time to the first HF readmission remain the focus of many publications, the endpoint in many HF studies, and are incorporated into HF performance measures [65, 66]. The need for alternative endpoints in clinical trials in acute HF syndromes has been recognised [67, 68]. Although mortality and time to first readmission provide important information, they do not provide a measure of the total disease burden for this chronic condition and therefore do not fully inform the planning of healthcare delivery for these patients during their HF journey. In addition, changes in HF

management which improve mortality may increase the number of patients with HF and persistent symptoms.

In an attempt to incorporate changes in mortality associated with a diagnosis of HF and changes in hospitalisation which have occurred over the two decades of this study, we have adapted a tool developed by others which has been used to assess the patient's clinical journey [69]. The patient journey incorporates mortality/survival and the number of days spent in hospital, but also incorporates a score that discounts days alive dependent on patient symptoms and changes in treatment (assuming that these have an impact on patient quality of life). This measure has been used to compare the effects of treatment on patient well-being, morbidity, and mortality in clinical trials [70, 71] and may allow better understanding of how symptoms, quality of life and the values placed on survival vary for different therapies and individually for patients [72].

This data are derived from discharge coding of a HF hospital admission and therefore do not incorporate an adjustment for symptoms or changes in treatment as in other studies. All days spent in hospital from day one of the index admission are incorporated (hospitalisation is likely to be associated with worse symptoms and impaired quality of life compared to not being hospitalised). This is the first time that such data have been available for a population cohort. This data encompass a considerable time period; two decades, during which major changes in HF epidemiology and treatment have occurred.

During the two decades described in this study the number of days alive and out of hospital has increased by one month (12 months after the initial hospitalisation) and two months (2 years after the initial hospitalisation), Figure 8. Many factors have influenced the increase in days alive and out of hospital; there is an improvement in survival up until 2000, the number of days spent in hospital follow a bi-modal pattern with an initial reduction in days, then an increase during the 1990's, and subsequent decline between 2000-2008. The duration of the index hospital admission has decreased from 8 to 5 days. These changes have occurred alongside an aging population [53]. We have seen an increase in the median age of patient admitted with HF (from 73.3 to 78.5 years), and an increase in co-morbidity (casemix index

increasing from 2.41 to 3.01), factors which are likely to increase the hospital needs of HF patients.

Examining the number of days alive and out of hospital at various time points allows understanding of different tensions which influence the changes that have been observed. Days alive and out of hospital at 30 days follows a bi-modal pattern, with progressive improvements until 2000 with no further improvements thereafter. It is likely that this is driven primarily by changes in early mortality after an admission for heart failure. Days alive and out of hospital at 6, 12 and 24 months continuously improve at each time point. The addition of an extra month out of hospital at 12 months and two months at 2 years suggests that hospital days are not simply being shifted to a later time period (i.e. increasing the time to readmission). Rather there is a sustained effect of both improved survival (until 2000) and a reduction in total hospital days (the predominant influence of days alive and out of hospital from 2000 to 2008). The progressive increase in the number of days alive and out of hospital between 1988 and 2008 are likely contributed to by multiple other factors captured within our data but also not able to be captured by our data (such as changes in HF management, changes in primary care, thresholds for admission). This study describes meaningful improvements in the number of days alive and out of hospital for patients over the last two decades (two months at 2 years). Thus patients are situated within the community (i.e. out of the hospital) for longer in the current era.

The recently published NICE guidance document "Focus on HF" [73] aims to help health communities and organisations to improve the quality and value of the care they deliver. Planning healthcare service delivery for patients with chronic conditions should be built on a clear understanding of the major population burden of such conditions. Understanding how and where patients need to be managed is important. Our current data confirms that patients with HF are living longer and are out of hospital more. These changing patterns support the concept of improving community based delivery of appropriate HF management [74] with the aim of improving patient outcomes in the broadest sense. Despite major improvements in the outcomes of patients with HF, prognosis remains poor (median survival after first admission 3.46 years in our population). Delivery of evidence based care is complex and multifaceted (including, but not limited to, accurate diagnosis, appropriate initial investigations, establishment of multiple medications at appropriate doses, re-

evaluation after an appropriate time interval, consideration of devices, and provision of community care/education to improve patient adherence and to reduce hospitalisation) [7, 54]. To improve outcomes in this large population of patients systems should be developed which provide specialist care within the community.

2.5. Limitations

This study is inherently limited by the fact that our data was obtained from DRG coding of a hospitalised cohort. We are unable to describe prevalent cases of HF who are not hospitalised. In addition we have no information on specific aspects of HF management during the study (such as ventricular function, medications, or community aspects of care).

2.6. Conclusions

Important changes have occurred over the last two decades in HF epidemiology in New Zealand. Population based age adjusted hospitalisation rates have decreased and survival has improved. The number of days alive and out of hospital after an HF hospitalisation has increased by two months at 2 years. Patients are living in the community for longer. Our data provide an opportunity for health communities and organisations to better understand the HF patient journey and to focus resource toward the patient in the community to further improve outcomes.

Chapter 3. The roles of B-type natriuretic peptide and echocardiography in the contemporary management of heart failure

3.1. Introduction

HF is a common clinical syndrome associated with impaired quality of life for patients, frequent hospital admissions, and poor survival. The syndrome is characterised by a constellation of symptoms and signs associated with some abnormality of cardiac dysfunction [75]. Hospitalisation rates for HF are high [2, 3], HF median survival is poor, and one-year mortality high (15-21%) [9, 18].

Multiple neurohormonal and renal responses occur in response to cardiac dysfunction in the HF syndrome and contribute to the progressive nature of the disease. Over the last 20 years there have been considerable advances in medical therapy for patients with HF, such that HF pharmacotherapy now is strongly evidence-based, including the use of ACE inhibitors, βBs, and ARAs. More recently this evidence has extended to include device-based therapies such as implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy/bi-ventricular pacing (CRT).

While the above mentioned therapies have made a substantial improvement in clinical outcomes for patients with HF the condition remains difficult to manage. Optimum selection of evidence-based treatment for patients with HF is increasingly important due to wide range of potential therapies available. Before evidence-based therapies can be applied for patients with HF the diagnosis of the clinical syndrome needs to be made accurately and in a timely manner. Often patients present with HF in the community and yet clinical symptoms and signs have poor sensitivity and specificity in this setting. Consequently, recent research has been directed towards evidence-based assessment of diagnostics.

Much interest has been focussed toward the role of cardiac neurohormones; atrial natriuretic peptide (ANP) and BNP and their potential role in refining the clinical management of patients with HF. BNP has emerged as a neurohormone with potential clinical applications across the spectrum of HF management. This review will focus on the role of BNP in

multiple facets of HF management; diagnosis, prognostic assessment, screening for asymptomatic left ventricular dysfunction (ALVD) and HF treatment.

3.2. Brain Natriuretic Peptide

The natriuretic peptide family consists of several related peptides that share structural homology. Each peptide is produced by a separate precursor prohormone and has tissue specific production and regulation. BNP has emerged as an important cardiac neurohormone with multiple potential roles in the management of patients with cardiac dysfunction. The BNP gene encodes a 108 peptide protein pro-BNP [76], this protein is cleaved within the heart to two fragments; BNP-32 the active hormone and the inactive amino terminal portion (NT-proBNP) in a 1:1 manner [77, 78]. BNP is secreted from the cardiac ventricles in response to an increase in wall stress and has multiple actions including inhibition of central sympathetic outflow [79], peripheral vasodilatation [80], inhibition of the production of aldosterone [81], renin and endothelin [82], and promotion of natriuresis [83]. The increase in BNP in response to cardiac dysfunction is thought to reflect their beneficial counter-regulatory role in opposing many of the neurohormonal pathways involved in the pathophysiology of HF.

Both BNP-32 and NT-proBNP are stable in samples of whole blood for up to 3 days [77, 84]. Several commercially available assays are currently available including the Roche Diagnostics assay for NT-proBNP which utilises the Elecsys[®] laboratory platform found in many centralised laboratories and the Biosite Triage[®] point of care assay for BNP-32. This is designed for bedside use and is currently the most common assay used in the United States.

In normal individuals both peptides are present in low levels. The plasma half life of NT-proBNP is longer than that of BNP-32 (approximately 2 hours compared with 20 minutes) which accounts for the significantly greater level of NT-proBNP compared to BNP-32 in the presence of cardiac dysfunction [85].

BNP levels increase with progressively worsening LV systolic dysfunction [85, 86] and are also elevated in other conditions associated with abnormal ventricular wall stress such as valvular stenosis and regurgitation [87-89] and pulmonary embolism [90-92].

In HF, BNP-32 and NT-proBNP are correlated closely with symptomatic status [93], LV systolic function, and non-invasive and invasive measures of diastolic function [94-96].

Compared to other cardiac peptides, BNP-32 and NT-proBNP appear to be most closely related to LV systolic function [86].

Several patient variables may affect BNP levels independently of cardiovascular disease. Levels increase with age [97-99], female gender [100-102], and renal impairment [103]. Levels may decrease in obese individuals as adipose tissue contains the clearance receptor for natriuretic peptides [104]. Levels are also decreased by loop diuretics [105, 106] and, to a smaller degree, by spironolactone [107] and ACE inhibitors [108].

The close relationship of BNP-32 and NT-proBNP to cardiac function has lead to a large body of research evaluating their role in multiple aspects of HF management, including diagnosis, assessment of prognosis, risk stratification, screening for LV dysfunction, and to guide treatment of patients with HF. Subsequent sections of this review will discuss the potential use of BNP-32 and NT-proBNP in these aspects of HF management.

3.2.1. BNP for diagnosis of heart failure

HF can be defined as a syndrome consisting of symptoms of HF and objective evidence of cardiac dysfunction (and, in cases where the diagnosis is in doubt, evidence of a response to treatment) [75]. Unfortunately the clinical signs and symptoms of HF are non-specific and often present in other medical conditions such as respiratory disease. Simple investigations such as chest x-ray and electrocardiogram (ECG) are similarly non-specific for HF diagnosis [109]. Documentation of abnormal cardiac function (usually by echocardiography) may not only be relatively inaccessible in many settings such as primary care, but importantly simply detecting abnormalities of cardiac structure and function does not make the diagnosis of the clinical syndrome of HF. While cardiac imaging is essential in those with a diagnosis of HF, a simple test which is readily available test and aids in the diagnosis of HF would be of great benefit. BNP-32 and NT-proBNP have been extensively evaluated in this regard and appear to be useful in ruling out the diagnosis of HF in breathless individuals (a normal or low BNP level makes the diagnosis of HF very unlikely). The role of BNP in the diagnosis of HF has been evaluated in both primary and secondary care settings in multiple studies, which are summarised in Table 4 and Table 5.

3.2.1.1. Studies based in primary care

For BNP testing to be a useful adjunct to clinical evaluation in patients with suspected HF it must add diagnostic accuracy in addition to usual measures. Ideally a test would be inexpensive and readily available in a community setting. The reliance on symptoms and signs (which are themselves non-specific) means HF diagnosis in primary care is frequently inaccurate, only 25-30% of cases with an initial diagnosis of HF will have this diagnosis confirmed by further evaluation [110, 111]. Open access echocardiography for primary care physicians has been advocated by some but there is no evidence that access to this test improves the diagnostic accuracy of the diagnosis of HF by primary care physicians [112]. A test that improves the accuracy of clinical diagnosis would be of benefit.

The Hillingdon Heart Failure Study evaluated the role of BNP testing in the evaluation of 122 patients with suspected HF referred from general practice to a rapid access clinic [113] (Table 4). Thirty-five patients (29%) satisfied the case definition for HF (based on European Society of Cardiology guidelines). Mean BNP concentration was significantly higher in HF patients (63.9 vs. 13.9pmol/L, p<0.001). BNP concentration was independently predictive of the presence of HF in a logistic regression model. BNP was superior to other measures (ANP and cardiothoracic ratio on chest x-ray) according to receiver operating curve analysis. Although this study suggested that that BNP testing may; assist in diagnosis for patients with HF symptoms, reduce inappropriate HF diagnoses, and perhaps assist in triaging patients for further evaluation, the study did not compare the accuracy of diagnostic strategies with and without BNP-32 measurement so the additive value of BNP-32 testing in this clinical setting is not possible to determine from this study. The Natriuretic Peptides in the Community study was a randomised, controlled trial evaluating the effect of NT-proBNP testing on the accuracy of HF diagnosis in primary care [114]. Three hundred and five patients presenting to general practitioners with symptoms of dyspnoea or peripheral oedema were involved and the accuracy of GP's diagnosis with and without the addition of NT-proBNP results was evaluated. The addition of NT-proBNP to customary clinical evaluation improved GP's diagnostic accuracy by 21%, compared to 8% in the control group, p=0.002. NT-proBNP testing was most useful in allowing GP's to accurately rule out HF. This study confirmed that the availability of NT-proBNP results improved the ability of GP's to confidently rule out HF.

The studies in primary care now provide the evidence base to recommend that the integration of BNP (either BNP-32 or NT-proBNP) testing into usual clinical assessment allows primary care practitioners to accurately rule out HF. This will have substantial impact in view of the frequent over diagnosis of HF in this setting.

Table 4: Diagnostic studies based in primary care

Studies in Primary care	Study design	Setting	N	Diagnostic Standard	% HF	Peptide, level	AUC	Sens	Spec	NPV	PPV
Cowie, 1997[113]	Prospective observational study	Rapid access HF clinic	122	Expert panel	29	BNP-32, 22.2pmol/L	0.96	97%	84%	98%	70%
	Clinical diagnosis of HF by expert panel (rather than EF cut off). High diagnostic value of elevated BNP-32.										
Wright, 2003[114]	Randomised controlled trial	Suspected HF primary care	305	Expert panel	25	NT-proBNP, 100pmol/L	0.85	NA	NA	NA	NA
	NT-proBNP result improved diagnostic accuracy compared to customary clinical evaluation. NT-proBNP<50 accurate to rule out HF										
Nielsen, 2004[115]	Prospective observational study	Rapid access HF clinic	345	Expert panel	23	BNP-32, M 11pmol/L	0.93	96%	67%	97%	57%
						W 17pmol/L	0.90	94%	69%	97%	48%
McDonagh, 2004[116]	Retrospective pooled analysis of 3 studies	European Community based epidemiology studies	3051	LVEF <2.5th centile and symptoms	3	NT-proBNP 49-88pg/mL	0.85	75%	79%	99%	10%
	Analysis of the diagnostic value of NT-proBNP from three large epidemiology studies										

HF, heart failure; AUC, area under receiver operating characteristic curve; Sens, sensitivity; Spec, specificity; NPV, negative predictive value;

PPV, positive predictive value; NA, not available; mL, millilitre; pmol, picomol

3.2.1.2. Studies based in secondary care

Many studies have evaluated the potential role of BNP testing to aid diagnosis in the emergency department or hospital setting (Table 5). In 1994, Davis et al described a series of patients admitted to hospital with breathlessness [106]. In this cohort, patients with HF alone or HF with underlying primary lung disorder had significantly greater BNP-32 levels than those with a primary lung disorder as the cause for their dyspnoea. BNP-32 was better at identifying patients with HF than LVEF. This study was the first to suggest that measuring BNP-32 levels may aid diagnosis in those patients admitted to the emergency department with dyspnoea (particularly in those where the diagnosis was in doubt). Since then several other studies of similar design have evaluated the role BNP testing in the emergency department to aid in the diagnosis of HF [117-121]. The Breathing Not Properly study [117] prospectively enrolled 1586 patients presenting to an emergency department with dyspnoea. In this study, BNP-32 was the most accurate predictor of the presence or absence of HF. Multiple logistic regression analyses determined that the addition of BNP-32 increased the combined explanatory power of the history, symptoms, signs and investigations. A BNP-32 level of 100pg/mL was associated with a thirty-fold increased likelihood of HF. The authors concluded that use of BNP-32 testing in the emergency department may lead to more accurate initial diagnosis of HF. Emergency department based studies have consistently shown that BNP levels are greater in those patients with HF than those with breathlessness of other causes, and that BNP appears to be a superior diagnostic test when compared to other investigations, and particularly that a low or normal BNP level makes HF very unlikely. None of these studies however takes the step of incorporating BNP testing into the diagnostic algorithm in the emergency department (and comparing to usual practice) and evaluating if there is additional benefit. Compared to primary care, patients attending the emergency department are a selected population who are likely to have more severe HF, this may make clinical diagnosis more accurate and therefore the additive value of BNP testing may be different to the primary care setting.

The BASEL study [122] was a prospective, randomised, single blind study in an emergency department which evaluated the management of patients presenting with dyspnoea, in whom the diagnostic strategy included BNP-32 testing, compared with

usual clinical care. Use of rapid BNP-32 testing reduced the time to correct diagnosis (63 minutes vs. 90 minutes, p=0.03), reduced the need for hospitalisation and intensive care (75% vs. 85% of patients, p=0.008), reduced hospital stay (median stay 8.0 days vs. 11.0 days, p=0.001), and lead to a lower cost of treatment (mean treatment cost $5,410 vs. $7,264, p=0.006). This study confirmed that the addition of BNP-32 testing to usual care improved diagnosis and treatment outcomes in patients presenting to emergency departments with breathlessness.

Integrating the studies evaluating the role of BNP testing in the diagnosis of HF, there is robust evidence that in addition to BNP levels being closely associated with HF, the addition of BNP testing to usual clinical evaluation improves diagnostic accuracy in primary care. The addition of BNP also improves diagnostic accuracy and leads to improved outcomes in secondary care. BNP testing appears to be particularly useful in excluding the diagnosis of HF in patients presenting with breathlessness. If BNP levels are elevated and HF is considered likely then further investigation is still required, for example cardiac function may be assessed with echocardiography and other tests performed to identify the cause of HF. In the secondary care setting BNP testing may be of most benefit in patients with undifferentiated breathlessness in whom the diagnosis is in doubt. To date all studies of the use of BNP in the emergency department include all patients with dyspnoea (some of whom may have had easily diagnosed HF). Further studies evaluating the role of BNP in selected groups will continue to define the most appropriate diagnostic use in the emergency department setting.

Table 5: Diagnostic studies based in secondary care

Studies in secondary care	Study design	Setting	N	Diagnostic Standard	% HF	Peptide, level	AUC	Sens	Spec	NPV	PPV
Davis, 1994[106]	Prospective observational study	Emergency Department	52	Expert panel	23	BNP-32, 22pmol/L	NA	93%	90%	NA	NA
	First study to evaluate prognostic value of BNP-32										
Maisel, 2002[117]	Prospective observational study	Emergency Department	1586	Expert panel	47	BNP-32, 100pg/mL	0.91	90%	76%	NA	NA
Logeart, 2002[121]	Prospective observational study	Emergency Department	163	Expert panel	71	BNP-32, 300pg/mL	0.93	88%	87%	94%	75%
	BNP-32 compared to echocardiography, BNP-32 and restrictive mitral filling pattern added significant incremental diagnostic value.										
Lainchbury, 2003[118]	Prospective observational study	Emergency Department	205	Expert panel	34	BNP-32, 60pmol/L	0.89	94%	70%	61%	96%
						NT-proBNP 340pmol/L	0.89	80%	87%	76%	89%
Bayes-Genis, 2004[119]	Prospective observational study	Emergency Department	89	Expert panel	58	NT-proBNP, 115pmol/L	0.96	90%	93%	NA	NA
Dokainish, 2004[120]	Prospective observational study	Inpatients, suspected HF	122	Expert cardiologist	57	BNP-32, 250pg/mL	0.87	86%	77%	NA	NA
	BNP-32 and echocardiographic E/Ea ratio similarly accurate for HF diagnosis										
Mueller, 2004[122]	Randomised controlled study	Emergency Department	452	"Final discharge diagnosis"	NA	BNP-32, 100pg/mL	NA	NA	NA	NA	NA
	BNP-32 group had shorter time from presentation to appropriate therapy, reduced hospital stay, reduced admission rate intensive care and less expensive hospital admission										

HF, heart failure; AUC, area under ROC curve; Sens, sensitivity; Spec, specificity; NPV, negative predictive value; PPV, positive predictive value; NA, not available; mL, millilitre; pmol, picomol

3.2.2. BNP to assess prognosis in patients with heart failure

HF is a disease that is associated with a poor prognosis. Mortality rates are very high (15-21% per year) [9, 18] and morbidity is significant. Hospital admissions are frequent [2, 3, 13] and quality of life is substantially impaired [5]. Prognostic indicators in HF are of value in the management of individual patients and may become useful in targeting therapy toward high risk groups (in a similar way to the use of troponin measurements in acute coronary syndromes; positive troponin measurements signifies very high risk and mandates an invasive rather than conservative management strategy). BNP levels are correlated with LVEF and maximal oxygen uptake (both prognostic variables) and as they are a surrogate measure of ventricular dysfunction it is not surprising that they have been evaluated as a prognostic marker in a large number of studies in various HF populations.

3.2.2.1. Patients without known heart failure

The Framingham Offspring Study is a prospective community based study. The relationship of BNP-32 and NT-proBNP levels and long term mortality and morbidity over 5.2 years of follow up were evaluated among 3,346 patients without clinical evidence of HF [123]. Increasing tertiles of BNP-32 were associated with increased risk of death. BNP-32 levels above the 80th centile (20pg/mL in men, 23pg/mL in women) were strongly predictive of the development of HF, AF, and stroke. Notably, in this study increasing risk occurred well below the BNP levels used for the diagnosis of HF suggesting that even minor elevations in BNP level may reflect myocardial dysfunction and subsequently increased risk.

3.2.2.2. Patients with known heart failure

Multiple studies have evaluated the prognostic importance of BNP levels in populations with known HF [124-130] (Table 6). These studies have consistently shown that an elevated BNP level is associated with a poor prognosis irrespective of patient group. BNP level appears to be the most powerful neurohormonal marker of prognosis [128] and provides important independent prognostic information compared to peak oxygen consumption [125, 129]. The combination of a very high BNP and very low peak oxygen consumption appears to afford a particularly poor prognosis.

A high pre-discharge BNP-32 (350ng/L) is a powerful predictor of death or readmission at six months in patients admitted with decompensated HF [130].

Similar to the studies in patients with IHD, the literature to date does not provide a BNP cut point at which a particular prognosis may be determined, and does not integrate prognostic assessment using BNP levels into clinical management guidelines [75, 131]. It is unclear if prognostic assessment using BNP influences clinical management or provides improved outcomes. These questions require further study.

Table 6: Prognostic studies in patients with known HF

Known HF	Study design	Patient population	N	Endpoint of interest	Peptide, level	Result
Anand, 2003[124]	Observational sub study of Val-HeFT	Stable symptomatic HF	4305	All cause mortality	BNP-32, 181pg/mL	All cause mortality significantly higher if baseline BNP-32 above median. Greatest change in BNP-32 at 4 months had highest mortality.
Fisher, 2003[126]	Observational sub study	HF inpatients	87	Event free survival	NT-proBNP, 2994pg/mL	NT-proBNP level a strong independent predictor of death or hospitalisation.
Isnard, 2003[125]	Prospective observational study	Stable symptomatic HF	250	Event free survival	BNP-32 , 137pg/mL	Elevated BNP-32 provided incremental prognostic information compared to peak VO2 testing. VO2<14 and BNP-32>137pg/mL highest risk group.
Gwechenberger, 2004[127]	Prospective observational study	Patients with stable severe HF	100	Worsening HF	BNP-32, 277fmol/ml	Above median BNP-32 levels independent predictors of worsening HF
Latini, 2004[128]	Observational sub study of Val-HeFT	Stable symptomatic HF	4300	All cause mortality	BNP-32 , 97pg/mL	Above median BNP-32 powerful predictor of increased mortality. Hazard ratio 1.94
de Groote, 2004[129]	Prospective observational study	Stable symptomatic HF	407	Cardiac survival	BNP-32, 109pg/mL	Above median BNP-32 level provides independent prognostic information to peak VO2 testing, lowest survival rate if BNP-32>109pg/mL and VO2<50% predicted
Logeart, 2004[130]	Prospective observational study	HF inpatients	224	Six month mortality	BNP-32, 350mg/L	Above median BNP-32 level strongly predictive of an increased risk of death or re-admission

HF, heart failure; VO2, oxygen uptake; mL, millilitre

3.2.2.3. Studies in patients with ischaemic heart disease

Several observational studies evaluate the relationship between BNP level and outcome in patients with IHD (Table 4). These studies consistently show that in various patient cohorts as BNP levels increase the risk of adverse outcomes are increased. This relationship holds across the spectrum of acute coronary syndromes including unstable angina [132-135] and myocardial infarction [86, 136], and in patients with both acute ischaemic events [86, 133-136] and chronic ischaemic LV systolic dysfunction [137]. BNP testing adds prognostic information independent of troponin levels and LVEF. Compared to LVEF, BNP is a superior prognostic tool (this is not surprising as clinical HF and associated morbidity is common in patients with normal LVEF).

The mechanism of increased BNP in individuals with IHD is unclear. BNP level correlates with degree of angiographic coronary disease [138] and impaired epicardial and myocardial perfusion[139] suggesting that BNP may be a marker of ischemia in this setting.

Although BNP levels appear to add important prognostic information in patients with IHD, the literature to date has not been able to establish a cut point at which this patient group has an adverse prognosis (one can't apply "above median" levels to individual patients). Integration of BNP testing into algorithms for managing acute coronary syndromes (similar to the way that an elevated troponin level dictates a certain management path) and formally evaluating their additive prognostic value on disease outcomes has yet to be achieved.

Table 7: Prognostic studies in patients with ischaemic heart disease

Studies in IHD	Study design	Setting	N	Endpoint of interest	Peptide, level	AUC	Sens	Spec	NPV	PPV
Richards, 1998[86]	Prospective observational study	Acute MI	121	2 year mortality	NT-proBNP, 160pmol/L BNP-32, 34pmol/L	NA	91% 86%	72% 72%	97% 96%	39% 39%
De Lemos, 2001[133]	Substudy of TIMI 16 trial	Acute coronary syndrome	2525	30 day mortality	BNP-32, 80pg/mL	NA	NA	NA	NA	NA
	Baseline BNP-32 predicts 30 day mortality (153 vs. 80pg/mL). BNP-32 >80pg/mL independently predicts 10 month mortality									
Richards, 2001[137]	Substudy of ANZ carvedilol trial	Chronic stable HF due to IHD	297	All cause mortality, event free survival	NT-proBNP	NA	NA	NA	NA	NA
	Above median NT-proBNP level powerfully predicts all cause mortality, carvedilol substantially improved event free survival in those with above median NT-proBNP									
Omland, 2002[134]	Prospective observational study	Acute coronary syndrome	609	All-cause mortality	NT-proBNP, 545 pmol/L	NA	NA	NA	NA	NA
	Above median NT-proBNP levels associated with an adjusted OR for mortality of 2.6									
Jernberg, 2002[135]	Prospective observational study	Acute coronary syndrome	775	Mortality at 35 months	NT-proBNP	0.82	NA	NA	NA	NA
	Increasing admission NT-proBNP associated with increased risk of mortality during follow up. Patients who died during follow up had largest increases in NT-proBNP at 6 hours									
Richards, 2003[136]	Prospective observational study	Acute MI	666	Death/HF	NT-proBNP, 162pmol/L BNP-32, 33pmol/L	0.81 0.81	80% 71%	72% 76%	97% 96%	25% 25%

IHD, ischaemic heart disease; AUC, area under ROC curve; Sens, sensitivity; Spec, specificity; NPV, negative predictive value; PPV, positive predictive value; MI, myocardial infarction; NA, not available; mL, millilitre; OR, odds ratio; pmol, picomol

3.2.3. BNP for screening of LV dysfunction

It is well recognised that HF is a progressive disorder that frequently begins with a (usually undetected) period of asymptomatic LV dysfunction (ALVD). This has been recently defined as Stage A HF [131]. Treatment of ALVD with ACE inhibitor therapy prevents disease progression to symptomatic HF in a proportion of patients [140, 141]. For this reason the recent AHA/ACC guidelines for the management of HF suggest treatment with this class of drug in Stage A HF [131]. Currently identification of such patients requires echocardiography or other measures to determine LV dysfunction. The prevalence of ALVD in the general population is unknown, several studies have attempted to quantify this and report rates of 1.1%-12.5% depending on the definition of ALVD and the population studied [142]. Screening for ALVD and HF in a population appears to meet many of the criteria for a successful screening program; it is an important health problem with serious consequences, the natural history of the disease is well understood, and there appears to be a pre-symptomatic stage which is amenable to therapy which may alter the natural history of the disease. The cornerstone of any screening program is the availability of a suitable diagnostic test. Due to the relative inaccessibility and expense of echocardiography several studies have evaluated the role of BNP measurement in screening for ALVD. A test with has high accuracy in identifying disease in symptomatic patients (such as BNP) may not be equally effective in asymptomatic populations with low disease prevalence. A suitable screening test should have a high "rule in value" (high specificity and positive predictive value) [142] to allow accurate identification of individuals with disease.

3.2.3.1. BNP for screening the general population

Several studies have evaluated the role of BNP testing to screen for ALVD, HF or undifferentiated heart disease in the community setting (Table 8). These studies are not all consistent; the utility of BNP testing for screening appears to be directly related to the prevalence of disease in the population studied. Data from the Framingham Offspring Study (where the prevalence of ALVD was 5.6%) suggests that although BNP-32 levels are associated with LVSD they perform poorly as a screening tool, with low positive predictive value leading to very high false positive rates [98]. Incorporating BNP-32 testing into multivariate models incorporating

clinical risk factors resulted in a minimal increase in accuracy suggesting that BNP-32 testing adds little to clinical screening for LVSD. The SCREEN study [143], based in primary care, reported similar findings. Conversely studies from community [144, 145] and general practice [146] populations suggest that population screening using BNP-32 or NT-proBNP testing may be a useful strategy. BNP testing to select patients who require further evaluation with echocardiography appears to be a particularly attractive strategy.

Three studies have attempted to assess the cost effectiveness of screening strategies using BNP testing. Nakamara and colleagues [144] estimated that the cost of screening with a BNP-32 measurement to assess who should undergo further detailed evaluation (including ECG and echocardiography) was approximately half that of their standard screening approach. Nielsen and colleagues [147] conclude, in their cost effectiveness analysis of McDonagh's community based study [145], that screening patients with a simple health questionnaire and BNP-32 test reduces the need for echocardiography and is associated with cost reductions of 9-54% (depending on risk group of individual patients) when compared to a strategy of echocardiography in all subjects. Heidenreich and colleagues [148] performed a formal cost effectiveness analysis using computer modelling based on a population prevalence of LVSD of 1%. A screening strategy of BNP-32 testing and if abnormal, echocardiography was associated with a cost of $22,300 per quality adjusted life year (QALY) (or $23,500 per life year gained) in men or $77,000 per QALY ($91,800 per life year) in women. Forty-four men (or 278 women) required screening to identify one with depressed EF, 133 men (or 909 women) required screeing to gain one year of life, and 127 men (or 769 women) required screening to gain one QALY. These authors concluded that this screening strategy was economically attractive in men and possibly in women. The cost-effectiveness is highly sensitive to the prevalence of depressed EF which is why screening men (prevalence 3.5%) is more economically attractive than screening women (prevalence 0.45%).

Table 8: Screening for asymptomatic left ventricular dysfunction

Study	Study Design	Setting	N	Definition of ALVD	% ALVD	Peptide, level	AUC	Sens	Spec	NPV	PPV
McDonagh, 1998[145]	Prospective observational study	Primary Care	1252	LVEF<30%	1.5	BNP-32, 17.9pg/ml	0.88	76	87	97.5	16
	IHD most significant predictor of low EF. Screening higher risk population (older age, previous IHD) may improve performance of BNP-32										
Maisel, 2001[149]	Prospective observational study	Echocardiogram Laboratory	200	Abnormal LV function	47.5	BNP-32, 75pg/mL	0.96	86	98	89	98
	Selected population with high prevalence of disease										
Vasan, 2002[98]	Prospective observational study	Community based (Framingham offspring study)	3177	LVEF<55% or FS<29%	5.6 all LVSD	BNP-32, M 21pg/mL	0.72	53	84	95	26
						F 34pg/mL	0.56	26	89	98	6
					2.2 >moderate LVSD	BNP-32, M 24pg/mL	0.79	65	86	97	16
						F 34pg/mL	0.85	80	90	100	4
	Low disease prevalence; false positives far outnumber true positives. Mass population screening using BNP-32 may not be warranted										
Nakamura, 2002[144]	Retrospective observational study	Health maintenance organization	1110	Heart disease of various causes (no LVSD)	3.6	BNP-32, 50pg/mL	0.97	90	96	100	44
	BNP-32 levels useful for detection of various forms of heart disease that may be precursors to the development of HF.										
Ng, 2003[143]	Prospective observational study	Primary Care	1331	LVEF<35%	1.3	BNP-32, 19 fmol/mL	0.94	NA	44	NA	2.2
						NT-proBNP, 38 fmol/mL	0.87	NA	46	NA	2.4
	Number needed to scan to detect one case 44 (BNP-32) or 52.4 (NT-proBNP)										
Groenning, 2004[146]	Prospective observational study	Primary Care	672	LVEF<50%	11.4	NT-proBNP, 41.5pmol/L	0.7	70	63	94	20
				HF + LVEF<50%	7.3	NT-proBNP, 72.8pmol/L	0.97	77	65	20	80
	LVSD: 8 diagnoses made, 3 diagnoses missed, 33 false positives/100 screened Systolic HF: 5 diagnoses made, 3 diagnoses missed, 19 false positives/100 screened										
Bibbins-Dimingo,	Prospective observational study	Outpatients with stable coronary disease	293	LVSD LVEF<55%	16	BNP-32, 100pg/mL	0.59	NA	NA	NA	NA

2004[150]	LVDD EF>55%, pulmonary vein VTI D>S	10.6	BNP-32, 100pg/mL	0.79	NA	NA	NA	NA	
	Elevated BNP-32 levels associated with LVSD and LVDD but their utility in detecting asymptomatic ventricular dysfunction in patients with stable coronary disease limited								

ALVD, asymptomatic left ventricular dysfunction; AUC, area under receiver operating characteristic curve; Sens, sensitivity; Spec, specificity;

NPV, negative predictive value; PPV, positive predictive value; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic

dysfunction; LVDD, left ventricular diastolic dysfunction; NA, not applicable ; mL, millilitre; pmol, picomol

3.2.3.2. BNP for screening selected populations

Patients with stable coronary disease

The utility of BNP-32 testing to screen for systolic or diastolic dysfunction was evaluated in a sub-study of the Heart and Soul study [150]. In this group of stable outpatients with known coronary disease an elevated BNP-32 level (>100pg/mL) was associated with both systolic and diastolic dysfunction however the test performed poorly as a screen for ALVD with an area under the receiver operator curve of 0.59 and 0.75 for systolic and diastolic dysfunction respectively. If 1000 patients were tested in this population with a 16.4% prevalence of LVSD 98 new cases of systolic dysfunction would be identified. Sixty-six cases would be missed and 443 patients would undergo unnecessary echocardiograms.

Patients referred for echocardiography to assess LV function

In a consecutive series of 200 patients referred for echocardiographic assessment of LV function [149] those with normal function had substantially lower BNP-32 levels than those with LV (systolic, diastolic, or combined) dysfunction. In this population with a very high prevalence of LV dysfunction (47.5%) a BNP-32 of ≥75pg/mL was highly accurate at identifying such patients. In this highly selected group BNP-32 testing appears to be a very good screening tool however the clinical applicability of such testing in the population studied may be limited (perhaps selecting out inappropriate echo referrals in a resource limited environment).

In summary HF is a disease where the availability of a screening program to identify patients with ALVD (and subsequently treat with disease modifying therapy) would be attractive. Studies evaluating the role of BNP testing to screen for ALVD in the community setting report conflicting results. The preponderance of evidence suggests that a strategy of limited clinical evaluation (perhaps by health questionnaire) and BNP testing, followed by echocardiography in those identified to be at high risk is likely to be an effective screening modality. This approach may lead to improved outcomes at an acceptable cost. Formal evaluation of such screening programs needs to be undertaken prior to widespread adoption

3.2.4. BNP in management of HF

3.2.4.1. BNP guided HF therapy

Decompensated HF is a clinical syndrome characterised by elevation of left ventricular filling pressure (LVFP). Therapy for decompensated HF aims to normalise LVFP and improve symptoms and outcomes. Unrecognised hypervolaemia is associated with adverse outcomes in patients with chronic HF [151]. The limited reliability of physical signs to estimate haemodynamics in HF is recognised [152], because of this studies have investigated the role of tailoring HF therapy to invasive measures of LVFP in patients with advanced HF [153, 154]. Therapy guided by LVFP is associated with sustained haemodynamic improvement compared to usual clinically guided HF therapy. Therapy guided by direct measurement of LVFP is obviously not practical for the vast majority of HF patients and hence attention has focused on the potential use of non-invasive surrogate measures of LVFP for tailoring of HF therapy such as BNP.

In-hospital treatment titration

Kazanegra and colleagues report the association between BNP level and LVFP in 20 patients admitted to hospital with decompensated HF [95]. In this study pulmonary capillary wedge pressure (PCWP) and BNP-32 level were closely correlated (r=0.73, p<0.5). Changes in PCWP during treatment were mirrored by changes in BNP level. In addition a rise in BNP level (or PCWP) during hospitalisation was associated with a poor 30 day prognosis, suggesting that BNP level may be a useful non-invasive means of tailoring HF treatment in decompensated in-patients. The same group of investigators have also evaluated the relationship between BNP-32 level during hospitalisation with decompensated HF and short term outcome [155]. In this study, changes in BNP level during hospitalisation were associated with 30 day outcome (death or re-hospitalisation). A fall in BNP level during treatment was associated with a good outcome, minimal change in BNP level was associated with an increased risk of hospitalisation and a rise in BNP level was associated with death during hospitalisation. Patients with a falling BNP during treatment had a 16% risk of an endpoint compared to those with a rise in BNP who had a 52% risk of death or re-hospitalisation at 30 days, p<0.001). These two studies suggest that BNP is a useful

clinical surrogate marker for wedge pressure and treatment outcomes in HF inpatients and may be helpful for treatment titration.

Out-patient treatment titration

Several studies have investigated the potential role of BNP as a means to guide titration of outpatient HF [93, 156, 157]. Murdoch et al evaluated the utility of BNP-32 guided ACE inhibitor titration (target BNP<50pg/mL) compared to clinically guided titration in a small randomised trial [156]. Comprehensive haemodynamic assessment was performed at the study onset and after eight weeks of treatment. At study end the ACE inhibitor dose was significantly greater (p=0.006) and heart rate was significantly reduced (p=0.02) in the BNP-32 group compared to the clinically guided group. These authors concluded that a BNP-tailored vasodilator approach was well tolerated and safe in stable HF outpatients. Troughton and colleagues conducted a randomised controlled trial (RCT) comparing NT-proBNP guided treatment titration with clinically guided treatment in 69 HF outpatients [157]. In this study NT-proBNP guided treatment (with an aim of reducing NT-proBNP level to below 200pmol/L) over a 12 month period was associated with a significant reduction in the primary endpoint (combined cardiovascular death, hospital admission, and outpatient HF); 19 vs. 54 events, p=0.02. Patients in the NT-proBNP guided group were on higher doses of ACE inhibitor, diuretic, and spironolactone at study end. This study suggested that NT-proBNP guided HF therapy was superior to expert clinical judgment in HF outpatients. This study was conducted prior to widespread uptake of ßB therapy in HF management and the applicability of a BNP guided approach to treatment titration in the ßB era is uncertain. Although BNP levels continue to have prognostic value in patients on ßB [158] and treatment with carvedilol is associated with a reduction in BNP-32 level over one year [159] the response of BNP-32 level to ßB therapy over the short term appears to be heterogeneous [160]. Currently several large randomised studies are underway evaluating BNP guided HF treatment titration in the beta-blocker era.

Since this literature review was undertaken, two randomised controlled studies have been published [161, 162] and two presented in abstract form [163, 164] evaluating BNP guided HF therapy. The STARS-BNP study [162] randomised patients with New York Heart Association (NHYA) class II or III HF, thought to be optimally treated with standard therapy (ACE inhibitors, βBs, and diuretics), to medical

treatment according to current guidelines or to treatment with a goal of reducing BNP-32 to <100pmol/L. This study showed a reduction in HF related death or hospitalisation in the BNP guided therapy group however all cause mortality was not significantly different between treatment groups. The TIME-CHF study [161] randomised patients with NHYA class II or greater HF to guideline based HF therapy (aimed at reducing symptoms to NHYA class II or less) or treatment aimed at reducing NT-proBNP level to less than two times the upper limits of normal and symptoms to NYHA class II or less. In this study, survival free of HF hospitalisation was greater in the NT-proBNP guided group. The benefit of this strategy was restricted to patients aged <75 years. Preliminary data from two other studies, the STARBRITE study [163] and BATTLESCARRED study [164] are consistent; suggesting that BNP guided HF therapy is associated with a reduction in hospitalisation. The BATTLESCARRED study also observed benefits only in those patients aged <75 years. These data combined suggest that BNP guided HF therapy may be particularly beneficial in patients aged <75 years and could be expected to be associated with a reduction in HF hospitalisations and a modest reduction in mortality for some patients.

Recombinant BNP as a therapy for HF

The actions of natriuretic peptides in HF include attenuation of sympathetic outflow [79], inhibit production of molecules such as renin, aldosterone [81] and endothelin [82], promotion of myocardial and vascular smooth muscle relaxation and vasodilatation [80], and promotion of natriuresis [83]. These actions appear to play a beneficial role in the HF syndrome and oppose many of the deranged pathways which play a part in the pathophysiology of HF. Because of these beneficial effects, recombinant human BNP (nesiritide) has been developed and evaluated as a treatment for decompensated HF.

Initial studies evaluating the effects of nesiritide in patients with decompensated HF showed that bolus [165] or continuous infusions [166, 167] of the drug were associated with dose dependent improvements in haemodynamics (reductions in PCWP and systemic vascular resistance, and increases in stroke volume [SV]). The major effects of nesiritide appeared to be due to its vasodilator properties rather than natriuresis [167]. The beneficial haemodynamic effect of nesiritide observed in these studies lead to several further randomised studies comparing treatment with nesiritide

to placebo [168] or other intravenous therapies[168-171] for decompensated HF. The Nesiritide Clinical Efficacy Trial [168] randomised 127 patients hospitalised with decompensated HF to treatment with a six hour infusion of nesiritide (at one of two doses) or placebo. Haemodynamic effects were consistent with previous studies, showing dose dependant improvements in PCWP, systemic vascular resistance, blood pressure (BP), and cardiac index. Global clinical status, dyspnoea and fatigue were significantly improved in the nesiritide treated groups compared to placebo. The Nesiritide Comparative Trial [168] was performed by the same group of investigators. Patients in this trial were randomised to nesiritide (one of two doses) or standard therapy (an infusion of a single vasoactive agent; dobutamine, milrinone, nitroglycerin or nitroprusside). Treatment continued for up to seven days at the discretion of the investigators. In this study all groups had similar improvements in clinical status and similar weight loss. Smaller doses of diuretic were administered to the patients treated with nesiritide compared to standard therapy. Since then, three randomised controlled studies have compared treatment with nesiritide to dobutamine [169, 170] or nitroglycerin [171] therapy in patients with decompensated HF. Compared to dobutamine, treatment with nesiritide was associated with shorter duration of intravenous therapy, reduced all cause readmissions, reduced six month mortality [169] and substantially reduced ventricular arrhythmia [170]. Compared to intravenous nitroglycerin, patients treated with nesiritide had substantially greater improvements in haemodynamic parameters [171]. Unlike nitroglycerin, no tolerance to nesiritide was observed during the 24 hour study period [172]. An economic analysis of two of the large randomised nesiritide trials [168, 170] suggests that treatment with nesiritide is associated with improved mean survival and reduced cost compared with dobutamine; the higher cost of the drug is offset by a less resource intensive hospital admission, lower readmission rates, and improved survival at six months [173].

Recombinant human BNP (nesiritide) is an effective treatment for patients admitted to hospital with decompensated HF. It has beneficial haemodynamic effects and appears to be a superior treatment compared to other intravenous agents such as dobutamine and nitroglycerin. Information regarding the comparative efficacy of nesiritide and other intravenous treatments for decompensated HF such as milrinone or levosimendan would be of interest; however this data is not currently available.

3.3. Echocardiography in the management of congestive heart failure

Echocardiography is a well established tool in HF management. It is the commonest modality used to demonstrate cardiac dysfunction for the diagnosis of HF. It is also able to provide information on potential causes of HF and provide prognostic information by the assessment of systolic and diastolic function. Echocardiography may also be useful in monitoring HF treatment. This review will briefly discuss the diagnostic and prognostic role of echocardiography in HF management before exploring the potential of newer measures of diastolic function in patients with HF.

3.3.1. Echocardiography for heart failure diagnosis

According to the AHA/ACC guideline for the diagnosis and management of HF [8] HF is defined as a "…complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or ejection blood". The diagnostic requirement for symptoms *and* the demonstration of cardiac abnormalities is mirrored in the ESC guideline for the diagnosis and treatment of HF [7], which requires "…symptoms of HF… and objective evidence of an abnormality of the structure or function of the heart at rest". The wide availability of echocardiography means that this imaging modality is commonly used to determine aetiology, to document the degree of ventricular dysfunction, and to determine reversible or treatable causes of HF [131, 174].

Echocardiography is used to establish whether the structure of the LV is normal or abnormal, to assess whether the LVEF is preserved or reduced, and to identify other structural abnormalities (such as valvular, pericardial, or right ventricular abnormalities) which could account for the clinical presentation. A comprehensive echocardiogram (combining two dimensional imaging (2-D), M-mode, and Doppler examination) provides a wealth of information regarding cardiac structure and function. Left ventricular dilatation can be reliably detected by either M-mode or 2-D echocardiographic methods. The easiest and most commonly used method for detecting LV dilatation is chamber diameter measured from the parasternal M-mode or 2-D view [175]. LV size is more accurately determined using a biplane volumetric approach (typically the modified Simpson's or summation of discs method) from the apical four and two chamber views [175]. It is important to index M-mode linear

dimensions and left ventricular end-systolic (LVESV) and end-diastolic volumes (LVEDV) to body size. LV hypertrophy (LVH) is commonly seen in patients with HF resulting from hypertension [10] and can be assessed by M-mode measurements of the LV walls. These measurements can be used to calculate LV mass [176]. 2-D echocardiography allows identification of regional wall motion abnormalities in patients with HF due to ischaemic heart disease (IHD).

3.3.1.1. Assessment of LV ejection fraction

A primary goal of echocardiography in HF is the assessment of LVEF as this has important diagnostic, prognostic, and therapeutic implications [8]. Multiple approaches exist ranging from expert qualitative data (normal, mild, moderate, or severe impairment) to complex quantitation. The simplest quantification technique measures chamber diameter change during the cardiac cycle (usually with M-mode) to measure LV fractional shortening. This also allows LVEF to be estimated but is biased to the basal segments and is unreliable in the presence of regional wall motion abnormalities [177]. Global LVEF may be assessed qualitatively by subjective assessment of systolic function. Typically, LV function is viewed in several views and a thoughtful judgment is made about overall systolic function (the "eye-ball" EF). Eye-ball EF requires individual assessment of segmental function and is unquestionably subjective. Eye-ball EF has been shown to quite accurate in experienced hands [178, 179] but the results may be inconsistent in smaller laboratories [180]. The gold standard of echocardiographic assessment of systolic LV function is currently 2-D biplane volume assessment. The Simpson's summation of discs is the recommended method [175] and it provides an accurate assessment of LV volumes and EF, although it requires adequate image quality and technical expertise.

3.3.1.2. Assessment of LV diastolic function

The recognition of the clinical importance of the syndrome of HF with a normal EF (HFNEF) (also referred to as "diastolic HF") [7, 8], and the recognition that abnormalities of LV systolic function (or LVEF) rarely exist in isolation [181, 182] means that the assessment of LV diastolic function with echocardiography has become more important. Echocardiography allows diastolic function to be indirectly

assessed by using Doppler to measure pressure gradients, blood flow and annular motion during the diastolic phase of the cardiac cycle and by integrating this data to estimate LVFP [183]. Based upon the ratio of early to late mitral valve diastolic filling (mitral E and A waves) and deceleration time, five progressive filling categories have been described: normal, abnormal relaxation, pseudonormal, reversible restrictive filling and non-reversible restrictive filling [184-187]. This technique is routinely used in clinical practice to non-invasively assess LV diastolic filling, although assessment is complicated in the presence of AF or a paced rhythm. The addition of pulmonary venous Doppler flow measurements [186, 188-192] or preload reduction (with the Valsalva manoeuvre or sublingual glyceryl trinitrate) [186, 193, 194] allow differentiation between pseudonormal (moderate LV diastolic dysfunction associated with elevated LV end diastolic pressure [LVEDP]) and normal LV filling, as well as reversible from non-reversible restrictive filling [195] in multiple populations. Importantly, the Doppler changes observed with the Valsalva are correlated with changes in LVEDP [196]. Propagation velocity of the mitral inflow colour Doppler has also been used to assess advanced phases of diastolic filling [197-200] although this technique is rarely used in clinical practice [201, 202]. Tissue Doppler assessment of diastolic mitral annular motion (using pulsed wave Doppler to assess the velocity of myocardial motion rather than blood flow) [203, 204] is another technique used to assess LV diastolic function and the pattern of the mitral annular early and late velocities (the Ea and Aa velocities) allow confident differentiation between pseudonormal and normal filling. Additionally, the ratio of mitral inflow velocity (E) to annular early velocity (Ea, also known as Em or E') provides the most accurate non-invasive correlate of LA pressure regardless of EF [204], mitral filling pattern [203], in patients with sinus tachycardia and normal or reduced EF [205], and in patients with AF [206]. The E/Ea ratio correlates well with and predicts both PCWP [203] and LVEDP [204].

Figure 9: Classification of diastolic filling and representative mitral inflow pulsed wave Doppler and mitral annulus pulsed wave tissue Doppler signals.

Diastolic Filling Grades
Using Pulsed Wave Mitral Doppler and Tissue Doppler Mitral Annular Measurements

Grade 0 - Normal Filling	Grade 1 - Abnormal relaxation	Grade 2 - Pseudonormal Filling	Grade 3 - Restrictive Filling
E:A: > 1 < 2	E:A: < 1	E:A: > 1 < 2	E:A: > 1.5
Deceleration time: > 150 ms	Deceleration time: > 230 ms	Deceleration time: > 150 ms	Deceleration time: < 150 ms
Ea/Aa: > 1	Ea/Aa: < 1	Ea/Aa: < 1	Ea/Aa: < 1
$A_{mitral} \geq AR_{pulmonary}$	$A_{mitral} =$ or $< AR_{pulmonary}$	$A_{mitral} < AR_{pulmonary}$	$A_{mitral} < AR_{pulmonary}$
Valsalva: no change E:A	Valsalva: no change E:A	Valsalva: E:A ↓	Valsalva: E:A ↓ =reversible
			E:A no change = non-reversible

3.3.2. Echocardiography for prognostic assessment in heart failure

Like neurohormones, several echocardiographic tools have been identified as having prognostic utility in HF patients, allowing stratification of patients into high and lower risk groups.

3.3.2.1. Systolic function/Ejection Fraction

Since the 1980's the prognostic importance of LV dilatation and a reduction in LVEF has been recognised. Several studies have confirmed that mortality increases as LVEDD increases and as LVEF decreases [207-210]. Simple M-mode measurements may be useful for determining prognosis [209, 211]. In the Val-HeFT trial, patients with the largest LVEDD (≥7.5cm) were twice as likely to die as those with the smallest (although still dilated) ventricles (<6.3cm) [209]. The same was true for EF although patients with the worst EF and largest LVEDD responded better to treatment. However, the difference between the first (EF≥32 %) and fourth quartile (EF<22%) was only 10 absolute points. In such a large cohort of patients (N=5010) small differences in EF yielded important prognostic information, but current echocardiographic techniques are not sensitive enough to detect such small differences in individual patients.

Patients with severely depressed systolic function have poor prognosis and in the Digitalis Investigation Group trial those patients with an EF of <45% had a linear increase in mortality was observed as EF decreased, with every 10% reduction in EF associated with about a 10% increase in mortality at 4 years. Mortality rates were similar for patients with EF above 45% [208]. Similarly, in a small cohort of Framingham subjects that had HF at the time of study enrolment, patients with a normal EF (>50%) had better survival rates than those with EF < 50% but were still significantly worse than population controls [212]. Although survival may be better in patients with preserved EF, readmission rates are similar to those observed in patients with reduced EF [213] and once a patient is admitted to hospital for exacerbation of HF symptoms there may be little difference in either death or readmission rates [214]. Subjective assessment of LV systolic function (i.e. normal/mild versus moderate/severe impairment) by a single experienced cardiologist has also been shown to predict death in an unselected group of patients [179].

Another echocardiographic measure of systolic function, atrioventricular plane displacement (AVPD), is predictive of mortality in HF patients [215] and in patients with coronary artery disease with no or mild LV impairment where EF was not predictive [216]. Tissue Doppler systolic annular velocity (Sa) is an analogous measure to AVPD and has also been shown to predict death in a cohort of patients with a variety of cardiac diseases [217] and more recently in patients with HF and a reduced EF [218].

3.3.2.2. Diastolic function

The importance of the contribution of diastolic abnormalities to the syndrome of HF has been recognised [181]. Multiple studies confirm that traditional echocardiographic diastolic parameters and newer tissue Doppler diastolic parameters also provide prognostic information in patients with HF. Patients with more advanced diastolic impairment have a worse prognosis.

Many authors have described the adverse prognostic impact of the presence of the restrictive filling pattern (see Figure 9) in patients with HF. The differentiation of restrictive filling patterns (E:A ratio >2, short deceleration time) from non-restrictive patterns provides important independent prognostic information [195, 211, 219-227]. Short deceleration time is also a useful prognostic indicator in isolation [219, 221, 222, 228-231], in patients with AF [232] and in patients after myocardial infarction [233]. When restrictive filling is further categorized into reversible (responsive to pharmacological preload reduction) and non-reversible (unresponsive) the latter is associated with worse outcome [195, 227, 234, 235]. Further, patients who respond to preload manipulation also respond better to βB therapy [235]. Peak oxygen uptake (VO$_{2max}$) is also reduced in CHF patients with restrictive filling [236] and the combination of both restrictive filling and reduced peak VO$_{2max}$ provides additional prognostic information to either on their own [211, 219]. Similarly, the addition of the restrictive filling to QRS duration provides incremental and independent prognostic information in HF patients [237]. Shortened isovolumic relaxation time (IVRT) is also associated with increased mortality [238].

Additional prognostic information is provided by the further classification of patients with non-restrictive filling patterns. Separation of patients with pseudonormal filling

from those with an abnormal relaxation pattern reveals a group of patients at intermediate risk of hospitalisation and/or death [220, 224, 239]. This maybe achieved by the using preload reduction [224], colour M-mode propagation velocity [239], or pulmonary venous Doppler [220].

Diastolic tissue Doppler measures, in particular E/Ea, also provide incremental prognostic information. In patients with a variety of cardiac diseases survival at 40 months was predicted by Ea [217], E/Ea >15 is a powerful predictor of mortality after myocardial infarction [240]. E/Ea >12.5–15 [241-244] independently predicts future cardiac events and mortality in patients with chronic systolic HF. When combined with NT-proBNP measurement E/Ea provides independent prognostic stratification [242]. In patients with advanced HF, E/Ea correlates with NYHA functional class and prognosis (cardiac mortality and hospitalisation) [245]. E/Ea >15 predicts lower event free survival in patients with HF and preserved EF [246].

3.3.3. Relationship of Diastolic Echocardiographic Measures with Left Atrial and Ventricular Pressure

Many Doppler indices of diastolic filling have been correlated with LA or LVEDP and as such are used as surrogates for these variables.

3.3.3.1. Traditional Doppler measures

The E:A ratio is related to filling pressure [190, 247, 248], and mitral E wave deceleration time is negatively correlated with LVFP in many studies [248-254] and is associated with higher neurohormonal activity [255]. These relationships are valid in AF where PCWP is negatively correlated with mitral deceleration time [250, 251, 253], IVRT [253] and pulmonary deceleration time[251].

Pulmonary venous signals have also been correlated with LA pressure in a number of studies of patients in SR [247, 249, 256] and AF [253]. The difference between the mitral and pulmonary venous A duration is observed in higher grades of diastolic filling abnormalities and correlates with LVFP [190-192, 196]. These relationships have also been tested under manipulated loading conditions [193].

3.3.3.2. Colour M-mode

Propagation velocity of the mitral inflow colour Doppler (Vp) is a preload-independent measure of ventricular relaxation that is correlated with the time constant of relaxation (tau) [257]. The ratio of E velocity to Vp (E/Vp) correlates with invasively measured LVEDP [258] and may also be useful for predicting both pulmonary congestion and LVEDP [198]. E/Vp appears to be the best correlate of PCWP in normal subjects [199]. The clinical applicability of E/Vp has been limited due to the lack of agreed standards for acquiring the data [201] and the relatively high inter-observer variability [202].

3.3.3.3. Tissue Doppler

Tissue Doppler measures, in particular E/Ea have emerged as one of the most promising echocardiographic means for assessment of filling pressures. In unselected patients, regardless of EF, E/Ea correlates closely with LVEDP, and an E/Ea partition value of >10 [203] or >15 [204] identifies patients with elevated LVFP, conversely E/Ea <8 accurately predicts normal LVEDP [204]. In patients with HF E/Ea correlates with LVEDP, and E/Ea partition values of >11 (EF >45%) and >15 (EF ≤45%) accurately predicted an LVEDP ≥15mmHg [259]. Close correlations have been observed between PCWP and E/Ea in sinus tachycardia [205] and AF [260]. In the setting of intensive care E/Ea predicts PCWP more accurately than BNP levels [120]. Several studies have generated formulae that include various echocardiographic measurements to estimate filling pressure [249, 251] but these are difficult to apply in everyday clinical situations.

3.3.4. The relationship between filling pressure, BNP and E/Ea

There are many parallels between the utility of BNP and tissue Doppler E/Ea in HF patients; both biomarkers are commonly acquired, they provide diagnostic [106, 113, 114, 117-121, 181] and prognostic [123-130, 217, 240-244] information, and appear to have incremental utility. Many studies have described correlations between BNP and E/Ea HF patients [261, 262]. These biomarkers are also related to LVFP (PCWP or LVEDP) [95, 203, 204, 206, 263]. It is tempting, therefore, to substitute these measures for each other in patients with HF. This approach is not currently supported by published data and further study is required.

Figure 10: The relationship between filling pressure, BNP and E/Ea
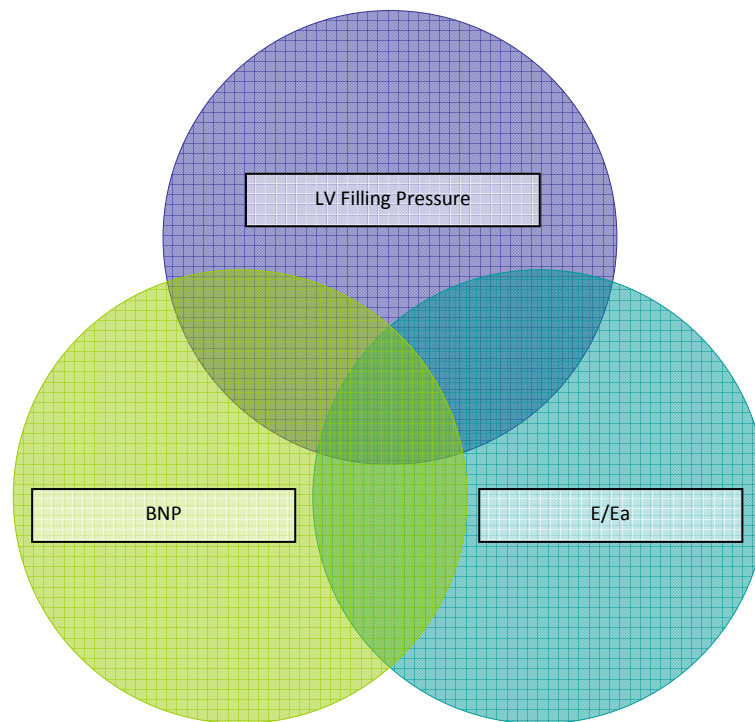
Chapter 4. The relationship between BNP-32 and E/Ea in patients hospitalised with acute heart failure

4.1. Introduction

HF remains a clinical syndrome characterised by frequent hospitalisations and significant morbidity, mortality, and cost to the healthcare system. Considerable attention has been focused towards strategies for managing patients with HF [264]. Tools that allow optimisation of individual patient therapy may assist with HF management. BNP (BNP-32 and NT-proBNP) and echocardiographic measures of diastolic function and LVFP (in particular E/Ea; the ratio of mitral E velocity to mitral annular Ea velocity) have been shown to provide complementary information in the management of patients with decompensated HF. Several recent studies have described the strong relationships between BNP-32 and NT-proBNP [265-268], E/Ea [203, 204, 259, 265] and directly measured cardiac filling pressure (PCWP or LVEDP) in patients with HF. Both BNP and E/Ea provide complementary diagnostic [106, 114, 117, 118, 120] and prognostic [130, 244, 269-271] information in patients with HF. A recent study suggested that E/Ea more closely reflects measured PCWP than BNP-32 [265]. Most of the literature exploring the relationship between natriuretic peptides and E/Ea in HF patients is related to single measurements. Little data exists on the relationship of these variables during a hospital admission for decompensated HF. Abnormal levels of both measures, in part, reflect abnormal hemodynamics (in particular elevated PCWP) and we therefore hypothesised that both parameters may change during treatment for decompensated HF and that these changes may be related.

This pilot study aimed to explore the relationship between BNP-32 and E/Ea during a hospital admission for HF.

4.2. Materials and Methods

Patients with LV ejection fraction (EF) ≤45% were enrolled in the study at the time of admission to hospital with decompensated HF. Patients were excluded from the study if; they were not in sinus rhythm (SR), if their HF was primarily due to a current acute

coronary syndrome or valvular heart disease, if echocardiographic views were inadequate for assessment of diastolic parameters, or if they were unable to provide informed consent. The study was approved by the Auckland Ethics Committee and patients provided written informed consent.

4.2.1. Study protocol

Patients were evaluated as soon as practical after their admission to hospital (<24 hours for all patients). A comprehensive clinical evaluation was performed (including clinical examination focused on the cardiovascular system, ECG, chest radiograph, BNP-32 measurement, and echocardiogram). Patients were re-evaluated at hospital discharge at which time the clinical examination, BNP-32 measurement and echocardiogram was repeated. The study investigators were not involved in patient care for study participants during their hospitalisation and were not involved in discharge timing decisions. At the time this study was conducted neither BNP-32 nor NT-proBNP testing were routinely available at the study hospital.

Prospective follow up with regard to re-hospitalisations and deaths were obtained from patient records. Follow up was censored at 1000 days.

4.2.2. BNP-32 measurements

Two millilitres of venous blood was drawn immediately prior to the echocardiogram and analysed within 30 minutes using the Biosite MeterPlus® machine (Biosite Diagnostics, San Diego, California).

4.2.3. Echocardiographic methods

Standard 2-D, M-mode and Doppler echocardiography were performed, according to a standard research protocol, using a Phillips HDi5000 ultrasound machine (Phillips, Bothell, USA). Measurements of LV volume and EF (Simpson's biplane summation of discs) and LA area were assessed from the apical four-chamber view. Detailed assessment of diastolic parameters were undertaken as follows: Doppler trans-mitral inflow velocities (E, A) were recorded by placing a pulsed wave sample volume at the tips of the mitral valve in the apical four chamber view, with the Doppler beam aligned parallel to the direction of blood flow. Images were recorded at the end of

normal expiration and following a valsalva maneuver. IVRT was estimated with a 5mm pulsed wave sample volume in the LV outflow tract. Tissue Doppler Ea velocities were obtained by placing a 5mm pulsed wave sample volume at the medial and lateral aspects of the mitral annulus, the average of these two measurements was used for analysis.

All echocardiographic images were analysed off-line in random order using the Digiview® (Digisonics, Houston, Texas) cardiac measurement system by a trained observer who was blind to the BNP-32 result. The average of three measurements for each variable was used for the analysis.

4.2.4. Endpoints

The primary endpoint of the study was the change in the E/Ea ratio between admission and discharge. Secondary endpoints included the change in BNP-32 between admission and discharge and changes in other echocardiographic systolic and diastolic indices between admission and discharge.

4.2.5. Statistics

A sample size of 22 was chosen to provide adequate power (80%) to detect (at the 5% significance level) a large change (effect size [Cohen] = 0.6) between admission and discharge. The sample size was increased by 10% to compensate for loss to follow up either through death or unplanned early discharge. Differences between admission and discharge were sought using the Wilcoxon matched pair sign rank test for non-parametrically distributed data, Student's paired t-test for normally distributed data, and McNemar's test for categorical variables. Pearson's correlations are presented.

Procedures of SAS (SAS Institute Inc v 9.2) were used for all analyses. All analyses were two tailed and $p < 0.05$ was considered significant.

4.3. Results

Twenty-four patients (17 male, 7 female) were studied, in whom HF aetiology was ischaemic in 12 and non-ischaemic in 12. Mean age was 69.6 ± 3.2 years. Table 9 details clinical and echocardiographic variables at admission and at discharge. On admission, all patients were in NYHA functional class III or higher, heart rate was 88

± 15 beats per minute (BPM) and BP 130/78 ± 21/16 mmHg. Admission BNP-32 was 721 pmol/L (IQR 315, 1150). Admission echocardiographic parameters are presented in Table 9, mean LV dimensions and volumes were increased; median LVEF was 26% (IQR 22%, 45%), E/A ratio 1.46 ± 0.9, and E/Ea 22 ± 13. There were no significant correlations between baseline BNP-32 and any index of LV size, EF, or diastolic function (E/Ea: r -0.10, P=0.65).

Table 9: Clinical parameters, BNP-32 and echocardiographic parameters at admission and discharge

	Admission	Discharge	P
Clinical Parameters			
Weight, kg	79.6±18.9	79.5±16.1	0.25
Heart Rate, bpm	88±15	85±15	0.53
Systolic BP, mmHg	130±21	124±23	0.27
Diastolic BP, mmHg	78±18	69±11	0.067
NYHA class, I/II/III/IV	0/0/10/14	0/10/13/1	<0.001
BNP-32, pmol/L	721 (315, 1150)	508 (222, 1015)	0.013
Echocardiographic Parameters			
LA area, cm^2	25.2±5.8	25.9±6.7	0.40
LVEDD, cm	6.6±1.1	6.6±0.7	0.16
LVESD, cm	5.6±1.3	5.5±1.2	0.09
LVEDV, mL	162.6±55.4	111.2±50.2	0.23
LVESV, mL	177.5±45.4	124.2±42.6	0.47
Ejection fraction, %	26 (22, 45)	30 (18, 36)	0.71
E, cm/sec	70.7±17.5	68.2±24.6	0.87
Ea, cm/sec	4.2±2.0	4.3±2.4	0.86
E/A	1.46±0.90	1.53±1.19	0.83
E/Ea	22±13	22±16	0.61
Deceleration time, msec	175±78	174±72	0.30

Data are presented as mean ± standard deviation or median (inter-quartile range).

BP, blood pressure; NYHA, New York Heart Association; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume.

4.3.1. Changes during hospitalisation

Average duration of hospital stay was 5.5 ± 4.2 days. Patients were treated in hospital with standard HF therapies (directed by the patients physician) and all patients had sufficient improvement in their symptoms to be discharged from hospital. Consistent with this, there was a reduction in NYHA functional class (P<0.001) between admission and discharge. However, there were no significant changes in patient weight, heart rate, BP, or echocardiographic measures. In particular there was no change in mitral E velocity (admission 70.7 ± 17.5, discharge 68.2 ± 24.6 cm/sec, P=0.87), IVRT (admission 65.2 ± 18.7 discharge 60.9 ± 25.3 msec, P=0.35), or LA area (admission 25.2 ± 5.8 discharge 25.9 ± 6.7 cm^2, P=0.39), Table 9. Median BNP-32 was significantly lower by hospital discharge but remained elevated (admission 721 [315, 1150], discharge 508 [222, 1015], P=0.013). All but five patients experienced a decrease in BNP-32 during hospitalisation. In this small group of five patients, BNP-32 actually rose in response to treatment. Mean E/Ea was increased at hospital admission (22.0 ± 12.5) and unlike NHYA functional class or BNP-32, did not decrease by hospital discharge (22.3 ± 16.1, P=0.61, Figure 11).

Figure 11: Change in BNP-32 and E/Ea during hospitalisation
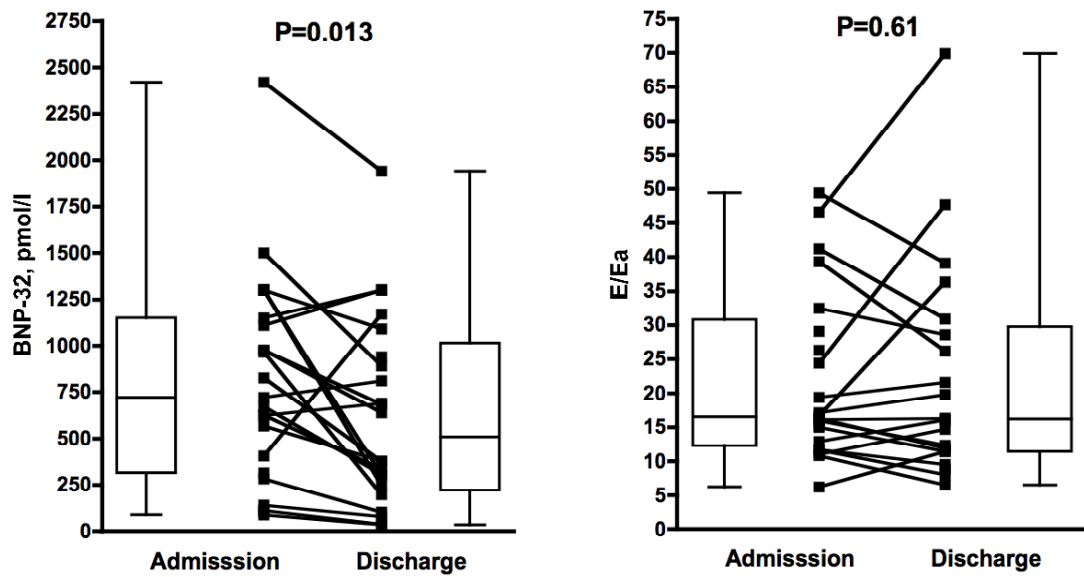
Figure 12: Relationship between BNP-32 and E/Ea
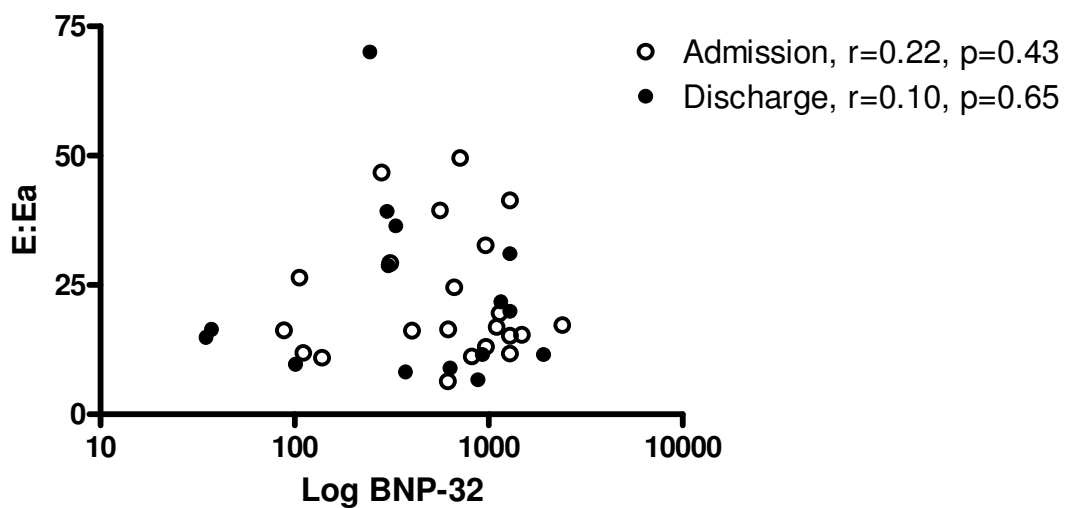
4.3.2. Relationship between BNP-32 and E/Ea during hospitalisation

There were no significant associations between baseline BNP-32 and any index of LV size, systolic function, or diastolic function, at admission or discharge. Figure 12 illustrates the relationship between log BNP-32 and E/Ea at admission and discharge, no significant association was observed (r=0.01, P=0.94). Similarly, no significant associations were observed between changes in BNP-32 and E/Ea in individual patients during HF hospitalisation (r=-0.04, P=0.83).

4.3.3. Post discharge follow up

Figure 13 illustrates the time to first HF re-hospitalisation. Median time to first re-hospitalisation was 288 days. No differences in time to first re-hospitalisation were observed in those who had increases in BNP-32 during hospitalisation compared to those with decreases (329 days vs. 247 days, P=0.44). Similarly, there were no differences in time to re-hospitalisation in those with increases in E/Ea compared to those with decreases (329 vs. 247 days, P=0.87).

Figure 13: Time to first heart failure re-hospitalisation
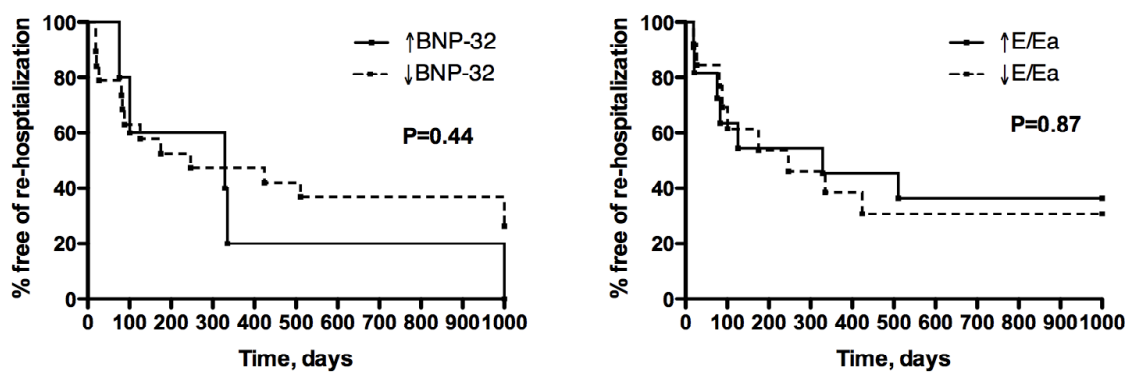
4.4. Discussion

This exploratory pilot study of patients admitted to hospital with acute decompensated HF has demonstrated that a simple echocardiographic measure of LV filling pressure, E/Ea, does not decrease in parallel with improving symptoms and a reduction in BNP-32 in response to therapy. To our knowledge, this is the first study to describe the relationship between admission and discharge BNP-32 and E/Ea in patients admitted with acute decompensated HF. Despite an improvement in symptoms and a reduction in BNP-32, there was no significant change in E/Ea with treatment of decompensated HF. Although the patients in this study had improved symptomatically to a point that they could be discharged, discharge BNP-32 levels and E/Ea remained markedly abnormal suggesting that LV filling pressure remained elevated.

There are many parallels between BNP and E/Ea. Both variables have been shown to be closely associated with LV filling pressure. Various cut-off levels of E/Ea have been proposed to indicate elevated filling pressure in patients with HF due to preserved or reduced ejection fraction [203, 204, 259, 265]. Recent data suggests that in certain sub-populations of patients, E/Ea may be more closely related to PCWP than BNP-32 [265]. Both BNP-32 [106, 114, 117, 118] and E/Ea [120] aid in the diagnosis of HF in patients presenting with breathlessness and have similar diagnostic utility [120]. BNP has been shown to be a powerful marker of prognosis in HF patients [130, 269, 270], E/Ea however appears to provide independent and incremental prognostic information in addition to BNP-32, NT-proBNP, and other echocardiographic indices of diastolic function in patients admitted with acute decompensated HF [237, 244, 271]. In addition, BNP level [136, 138, 139] and E/Ea greater than 15 [240] are important predictors of prognosis after myocardial infarction.

Early studies suggested that in patients admitted for haemodynamically guided HF treatment, BNP-32 levels were closely associated with measured PCWP and changes in PCWP were associated with similar changes in BNP-32 [95, 272]. More contemporary data highlight the fact that although BNP and PCWP are correlated, BNP does not necessarily track with changes in PCWP in more diverse groups of patients such as those in intensive care [265, 273] and those with severe HF [267, 274]. However, a decrease in BNP-32 or NT-proBNP during a hospitalisation for acute decompensated HF has been shown to be associated with improved outcomes [155, 275]. In addition there is much interest in the concept of BNP-guided HF therapy after early data suggested that this approach might be associated with

improved outcomes [156, 157]. RCTs are currently underway evaluating this treatment approach [276]. This study suggests that the response of E/Ea to treatment of decompensated HF may differ temporally to the response of BNP-32.

Although much data supports a close relationship between BNP-32, NT-proBNP and E/Ea in patients with acute decompensated HF, the association between changes in BNP-32 or NT-proBNP levels and changes in E/Ea is uncertain. A recent study describes changes in E/Ea and BNP-32, compared to changes in PCWP in 9 patients admitted to an intensive care unit. These data suggested that temporal changes in PCWP were 'tracked' by changes in both E/Ea and BNP-32 [265] however whether this can be generalised outside of the intensive care setting is uncertain.

It is also unclear whether E/Ea can be utilised as a continuous variable. Data correlating E/Ea with PCWP have almost universally used an E/Ea cut point to indicate an abnormal PCWP (usually ≥15 in patients with impaired LV ejection fraction and ≥12 in those with preserved LV ejection fraction) [203, 204, 259]. It is not known if further elevations in E/Ea signify progressive increases in PCWP, or conversely if reductions in E/Ea within the abnormal range equate to reductions in PCWP. The difficulty in comparing reductions in E/Ea to reductions in BNP-32 in patients with decompensated HF (who by inference have elevated LV filling pressure) is emphasised by another pilot study describing the changes in E/Ea during NT-proBNP guided HF treatment. In this study reductions in NT-proBNP were associated with a reduction in E/Ea over several weeks however E/Ea did not appear to fall until the NT-proBNP level fell below 300pmol/L, at which time it fell to a level in the 'intermediate' range [277].

It is uncertain why this study did not demonstrate a relationship between baseline E/Ea and BNP-32. It may be a reflection of the small sample size of this pilot study, however although many studies have evaluated relationships between BNP or E/Ea and LV filling pressure or between BNP or E/Ea and HF the few that have described relationships between BNP and E/Ea report conflicting results [120, 261]. In a study of 122 patients with suspected HF a significant correlation was observed between logBNP-32 and E/Ea (r=0.57, P<0.001) [120]. Conversely, in 108 patients referred for echocardiographic evaluation of LV function, no correlation was observed between E/Ea and BNP (r=0.48, P=0.96).

Furthermore there are practical difficulties in measuring Ea velocities in patients with advanced HF because velocities are markedly reduced (see Table 9) when compared to those

from normal hearts. A previous study describes tissue Doppler parameters in 60 normal subjects, and showed that mean Ea velocities range from 7 to 17 cm/sec at various sites in the mitral annulus [278]. By comparison Ea velocities in our study population range from 1.1 to 5.6 cm/sec. Very little is known about changes in Ea velocity in individuals over the space of a few days. With markedly reduced Ea velocity and relatively elevated E velocity (in this study E at baseline ranged from 40 to 100 cm/sec) any change in E/Ea will predominantly reflect changes in E. No change in E was observed between admission and discharge in this study.

To clarify the relationship between BNP-32 and E/Ea during hospitalisation for acute decompensated HF a randomised controlled study should be performed comparing usual treatment to intensive treatment targeted to reducing E/Ea to <15

4.4.1. Limitations

This study is limited by the fact that BNP-32 remained elevated at discharge suggesting that LV filling pressures remained high. Despite symptomatic improvement, it is highly likely that patients' clinical HF status was not optimally treated at discharge. This reflects the clinical reality of in-hospital HF management and emphasises the need for tools to improve the care of patients with acute decompensated HF. BNP-32 was used as a surrogate measure of LV filling pressure in this study. Ideally direct measurement of LV filling pressure, BNP-32 and E/Ea would have been performed at admission and discharge. The use of pulmonary artery catheters (PAC) is not routinely recommended in this patient population [279] and was not practical in the general hospital in which this pilot study was conducted. The relationship between LV filling pressure and both BNP-32 and E/Ea during episodes of acute decompensated HF could be further explored in patients with implantable haemodynamic monitoring devices.

4.5. Conclusions

This pilot study demonstrates that in patients with acute decompensated HF, E/Ea does not appear to decrease in parallel with decreasing symptoms and BNP-32. Our data suggests that although BNP-32 and E/Ea are related to PCWP and to each other; they may not be interchangeable indices and may respond differently during treatment of acute decompensated HF.

Chapter 5. Changes in tissue-Doppler echocardiographic assessment of left ventricular filling during NT-proBNP guided heart failure treatment titration: a pilot study

5.1. Introduction

Medical treatment for HF is well established and the routine use of ACE inhibitors [280-282], βB [283-285], and ARA [35, 36] have led to substantial improvements in morbidity and mortality. Despite these improvements HF remains an important health problem, accounting for a large proportion of hospital admissions [2]. In recent years there has been a focus on tools that allow optimisation of HF treatment in individual patients including clinical parameters, neurohormones [157], and PCWP [154]. BNP (BNP-32 and NT-proBNP) is increased in HF in response to diastolic wall stress [286] and has emerged as a potential target for HF treatment titration, with data suggesting that treatment optimisation aimed at reducing BNP levels is associated with improved outcomes [156, 157]. Tissue Doppler echocardiography is a relatively new technique with many features that suggest it may be another potential tool for the optimisation of HF treatment. The E/Ea ratio is a surrogate for LVFP [203, 204, 287] that has been shown to correlate well with BNP [120] and also to be an important marker of prognosis in HF patients [217, 240]. Most of the data on the relationship between E/Ea and BNP relates to measurements at a single time point. No data exists on the relationship of these variables during a period of HF treatment optimisation where changes in response to therapy might be anticipated.

This pilot study explored the relationship between tissue Doppler parameters, in particular E/Ea, and NT-proBNP in a group of ambulatory outpatients during BNP guided HF treatment titration.

5.2. Methods

5.2.1. Study Population

The study population consisted of patients with decompensated HF; decompensated HF was defined as either hospitalisation for HF exacerbation or worsening HF identified at a specialist clinic visit (increasing dyspnoea, reduction in exercise tolerance, and clinical signs

of HF). Patients were required to have reduced LV EF (LVEF ≤ 45%), and an elevated BNP level (NT-proBNP>200pmol/L). This NT-proBNP level was chosen as a reasonable marker of decompensated HF and target for treatment titration based on previously published data [157]. Patients were excluded from the study if their HF was primarily due to a current acute coronary syndrome or severe valvular heart disease, if echocardiographic views were inadequate for assessment of diastolic parameters, or if they were unable to provide informed consent. Recruitment took place between January and July 2003. No patient was excluded from the study due to poor echocardiographic image quality. The Auckland Ethics Committee approved the study.

5.2.2. Treatment titration protocol

The initial study visit (BL) occurred at hospital discharge (for in-patients) or within two weeks of their outpatient visit and included a comprehensive clinical evaluation (including clinical examination focused on the cardiovascular system, ECG, chest radiograph, NT-proBNP assay, six minute walk test, and echocardiogram). Patients subsequently attended five additional visits (V1-5) at two-week intervals (total follow up 10 weeks). At each treatment visit patients were clinically assessed by an experienced HF physician, blood was drawn for NT-proBNP assay, and an echocardiogram was performed. HF treatment was titrated at V1-5 based on the clinical examination findings and the NT-proBNP result. The aim of the study was to investigate the relationship between changes in NT-proBNP and E/Ea, hence we titrated therapy aiming to reduce NT-proBNP in accordance with other investigators [157]. The aim of treatment titration was to reduce the NT-proBNP level to <200pmol/L according to the following standardised protocol: Increase in diuretic dose (no maximum dose specified), up-titration of ACE inhibitor (or ARB if ACE inhibitor intolerant) to target dose (40mg/day enalapril or equivalent), and addition of spironolactone if patients remain in NYHA class III or IV and presence of fluid overload persists. βB were initiated and up-titrated to target dose (50mg/day carvedilol or equivalent) once clinical congestion was reduced and BP stable (according to standard practice at that time). Digoxin was added if patients had AF or were symptomatic after other therapy has been maximised. Figure 14 outlines the decision tree for drug titration.

This protocol was derived from the ACC/AHA guidelines for chronic HF management[131] and the titration protocol used in a pilot study of NT-proBNP guided HF management[157].

Figure 14: Titration Protocol


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                    ┌─────────────────────────┐
                    │   Clinical Evaluation   │
                    │   NYHA Class, Weight    │
                    │   Physical Examination  │
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Clinical Evaluation
NYHA Class, Weight
Physical Examination

Compensated
NYHA class II, JVP<3
Negative HJR
No oedema

Decompensated
NT-proBNP>200pmol/L
NYHA class III+, JVP>3, HJR
present, Ankle oedema

NT-proBNP
<200pmol/L

NT-proBNP
>200pmol/L

Uptitration of ACE inhibitor
and βB to target doses, may
decrease diuretic if
appropriate

Increase diuretic, increase
ACE inhibitor, May add
spironolactone, Do not
increase βB

NYHA, New York Heart Association; JVP, jugular venous pressure; HJR, hepatojugular reflex; ACE, angiotensin converting enzyme; βB, beta blocker

5.2.3. NT-proBNP measurements

Blood samples (5ml plain tube) were taken at each study visit. NT-proBNP level was measured in a commercial laboratory (LabPlus, Auckland, New Zealand) using the Roche Elecsys® platform. NT-proBNP results were available to the study investigators within 60 minutes of sampling and HF therapy was titrated accordingly.

5.2.4. Echocardiographic methods

Standard 2-D and M-mode images of the left ventricle were obtained according to a standard research protocol, using a Phillips HDi5000 ultrasound machine (Phillips, Bothell, USA). Measurements of LV volume, EF (Simpson's biplane summation of discs), and LA area were assessed from the apical four-chamber view. Detailed assessments of diastolic parameters were undertaken as follows: Doppler trans-mitral inflow velocities (E, A) were recorded by placing a 5mm pulsed wave sample volume at the tips of the mitral valve in the apical four chamber view, with the Doppler beam aligned parallel to the direction of blood flow. Images were recorded at the end of normal expiration and following a valsalva manoeuvre. IVRT was estimated with a 5mm pulsed wave sample volume in the LV outflow tract. Tissue Doppler Ea velocities were obtained by placing a 5mm pulsed wave sample volume at the medial and lateral aspects of the mitral annulus, the average of these two measurements was used for analysis.

All echocardiographic images were analysed off-line in random order using the Digiview® (Digisonics, Houston, Texas) dedicated cardiac measurement system by trained observers (GW and CW) who were blind to the NT-proBNP result. The average of three (or five if AF present) measurements for each variable was used for the analysis.

5.2.5. Post titration follow up

After the completion of the treatment phase of the study, patients were returned to the care of their family doctor. To assess the long term effects of treatment titration patients returned for a final late follow-up evaluation (FU) approximately one year after V5. All clinical, neurohormonal, and echocardiographic parameters were reassessed at that time.

5.2.6. Endpoints

The primary endpoint was change in E/Ea ratio from BL to V5. Additional pre-specified endpoints included change in mitral inflow Doppler filling pattern, and change in NYHA functional class. Changes in NT-proBNP and echocardiographic variables between BL-FU and V5-FU were also evaluated.

5.2.7. Statistics

This study was designed as a pilot study to provide preliminary data from which to develop further research protocols. The study was powered on the basis of providing sufficiently precise estimates for a variety of normally distributed parameters (95% confidence intervals of ± 50% of the standard deviation of the change, 80% power for a two tailed test). With at least 16 participants changes of at least two thirds of a standard deviation (i.e. a large effect) would be found to be statistically significant. Student's paired t-test was used to test the hypothesis that the change from baseline (BL) to V5 was not significantly different from zero. A second pre-planned comparison of the change from V5 to follow-up was also tested in the same way. These independent hypotheses for each of the variables listed were pre-planned so an overall significance level of 5% was pre-specified. Results presented as mean ± SD

All tests were performed using procedures of Statistical Analysis Software (SAS) (SAS Institute Inc V 9.2)

5.3. Results

5.3.1. Patient population

18 patients consented to participate in the study. One patient died in hospital prior to the BL visit. Fourteen patients were male (82%). Mean age was 67.1 ± 15.3 years. HF aetiology was ischaemic in 10 patients (59%) and non-ischaemic in 7 (41%). Most patients had severe symptoms with NYHA functional class II, III, and IV in 5, 10, and 2 patients respectively. Five patients were in AF (29%) and the remainder were in SR. Mean six minute walk distance was 268 ± 188m. Mean EF at BL was 29.1 ±13.9%. The mean treatment phase of the study (BL-V5) was 77.7 ± 9.4 days. Thirteen of the 17 study patients were able to be followed up 326 ± 43 days after V5,

of the others 3 patients died and 1 patient did not attend as he was awaiting coronary bypass surgery.

5.3.2. HF treatment titration phase

Changes in medications, clinical parameters and NT-proBNP are presented in Table 10. No correlation was observed between BL NT-proBNP and mean E/Ea (R=0.41, p=0.12). Significant increases in frusemide, ACE inhibitor/ARB, βB, and spironolactone doses were achieved. Up-titration of therapy was not associated with significant changes in weight or BP. NT-proBNP decreased in response to HF treatment titration (-265 ± 465 pmol/L, p=0.045) and a further reduction was observed at FU (-105 ± 151 pmol/L, p=0.027). Functional capacity improved with HF management (mean 6 minute walk distance at BL 267.9 ± 187.8m and FU 404 ± 118.8m, p=0.042).

There was a significant reduction in the primary endpoint (change in E/Ea ratio between BL and V5); E/Ea ratio 17.6 ± 6.8 to 13.7 ± 5.0, p=0.018. Accompanying the reductions in E/Ea ratio from BL-V5, changes in conventional Doppler indices of diastolic filling were observed (mitral E velocity and deceleration time) with a trend towards lower E/A ratio. No significant change was observed in Ea velocity or LA area between BL and V5. From BL to V5 there was a significant improvement in LV stroke volume (SV) (BL 43.7 ± 18.2mL vs. V5 52.2 ± 18.6mL, p=0.047). No change in LV volume or EF was observed.

5.3.3. Post titration follow up

Average duration of long term follow up (between V5 and FU visits) was 326 ± 43 days. There was a further reduction in NT-proBNP between V5 (311 ± 235pmol/L) and FU (175 ± 254 pmol/L), p=0.027 (Table 10) without a significant further reduction in E/Ea ratio (13.65 ± 4.96 to 12.87 ± 9.4, p=0.80) (Table 11). Similarly, conventional Doppler indices of diastolic function did not significantly change (Table 11). The improved SV was maintained from V5 to FU and in addition end systolic volume (ESV) was reduced (ESV 105.7 ± 46 to 80.2 ± 52.7, p=0.013) and EF increased (EF 34.3 ± 11.1% to 42.0 ± 9.3%, p=0.0056).

5.3.4. Responders and Non-Responders

During the treatment phase of the study (BL-V5), 8 patients responded to NT-proBNP guided treatment titration (reduction in NT-proBNP of $\geq$ 50%) and 9 did not. At BL NT-proBNP levels were 758 ± 699 vs. 353 ± 222 (p=0.14) and E/Ea ratio 19.5 ± 7.1 vs. 15.9 ± 6.5 (p=0.28) in responders and non-responders respectively. During the treatment phase of the study a significant reduction in E/Ea ratio was observed in the responders, which did not occur in the non-responders (responders 19.5 ± 7.1 to 11.8 ± 5.6, p=0.0019; non-responders 15.8 ± 6.5 to 15.5 ± 3.8, p=0.88). The overall change in E/Ea ratio was similar to the changes observed in NT-proBNP in each group (responders 758 ± 699 to 239 ± 206, p=0.022; non-responders 353 ± 222 to 383 ± 253, p=0.80), Figure 15. Between V1 and V4 the mean E/Ea remained elevated in both patient groups (responders and non-responders) and this is consistent with the substantially elevated mean NT-proBNP level. However, at V5 the E/Ea fell in the responders but remained elevated in the non-responders.

Both NT-proBNP level and E/Ea ratio remained stable during the follow up phase of the study in both groups. Although the study was not powered to assess the predictive power of a response to treatment, the three deaths that occurred in the study population all occurred in non-responders.

Table 10: Changes in clinical parameters during HF treatment titration

	Baseline N=17	Visit 5 N=17	Follow Up N=13	P value BL-V5	P value V5-FU
Medications					
Frusemide, mg/day	63.5 (35.5)	125 (79.8)	96.7 (49.6)	0.0006	0.027
ACEi*, mg/day	16.8 (13.8)	30.3 (14.0)	25.6 (13.5)	0.0072	0.40
Beta blocker#, mg/day	3.7 (7.3)	16.4 (18.5)	37.5 (26.7)	0.013	0.089
Spironolactone, mg/day	4.4 (8.8)	14.8 (12.2)	13.5 (13.0)	0.0082	0.77
Digoxin, μg/day	18.4 (42.9)	19.5 (44.6)	21.2 (45.6)	0.94	0.92
NYHA class, n					
I/II/III/IV	0/5/10/2	2/11/3/0	6/6/1/0	0.02	0.38
Weight, kg	80.3 (22.8)	83.3 (22.1)	86.9 (27.9)	0.71	0.64
Heart rate, bpm	80 (21)	71 (14)	71 (14)	0.062	0.97
SBP, mmHg	130.4 (33.9)	124.3 (21.6)	140.6 (26.4)	0.38	0.071
DBP, mmHg	72.0 (18.7)	68.2 (11.2)	73.5 (13.6)	0.32	0.27
NT-proBNP, pmol/L	603 (561)	311 (235)	175 (254)	0.045	0.027

*ACE inhibitor doses converted to enalapril equivalents (mg/day)

#Beta blocker doses converted to carvedilol equivalents (mg/day)

Table 11: Changes in echocardiographic parameters

	Baseline N=17	Visit 5 N=17	Follow Up N=13	P value BL-V5	P value V5-FU
2D variables					
LA area, cm²	28.7 (7.4)	29.1 (7.7)	26.3 (7.7)	0.96	0.15
LVEDV, mL	169.7 (67.1)	157.7 (49.8)	131.3 (70.8)	0.25	0.077
LVESV, mL	124.0 (62.2)	105.7 (46.0)	80.2 (52.7)	0.083	0.013
EF, %	29.1 (13.9)	34.3 (11.1)	42.0 (9.3)	0.10	0.0056
SV, mL	43.7 (18.2)	52.2 (18.6)	50.7 (19.5)	0.047	0.72
Doppler variables					
E, cm/sec	92.6 (25.8)	76.1 (24.2)	67.3 (30.4)	0.03	0.58
A, cm/sec	60.0 (24.5	72.9 (17.1)	78.8 (18.7)	0.38	0.33
E/A	1.79 (1.16)	0.96 (0.41)	0.8 (0.37)	0.073	0.43
Deceleration time, msec	158.3 (60.2)	211.9 (82.4)	230.3 (77.0)	0.12	0.84
Tissue Doppler indices					
Ea mean	6.3 (1.6)	6.7 (1.9)	6.7 (1.94)	0.44	0.15
E/Ea mean	17.6 (6.83)	13.65 (4.96)	12.87 (9.4)	0.018	0.80

LA, left atrial; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular

end systolic volume; EF, ejection fraction; SV, stroke volume

Figure 15: Visit by visit NT-proBNP and Doppler parameters
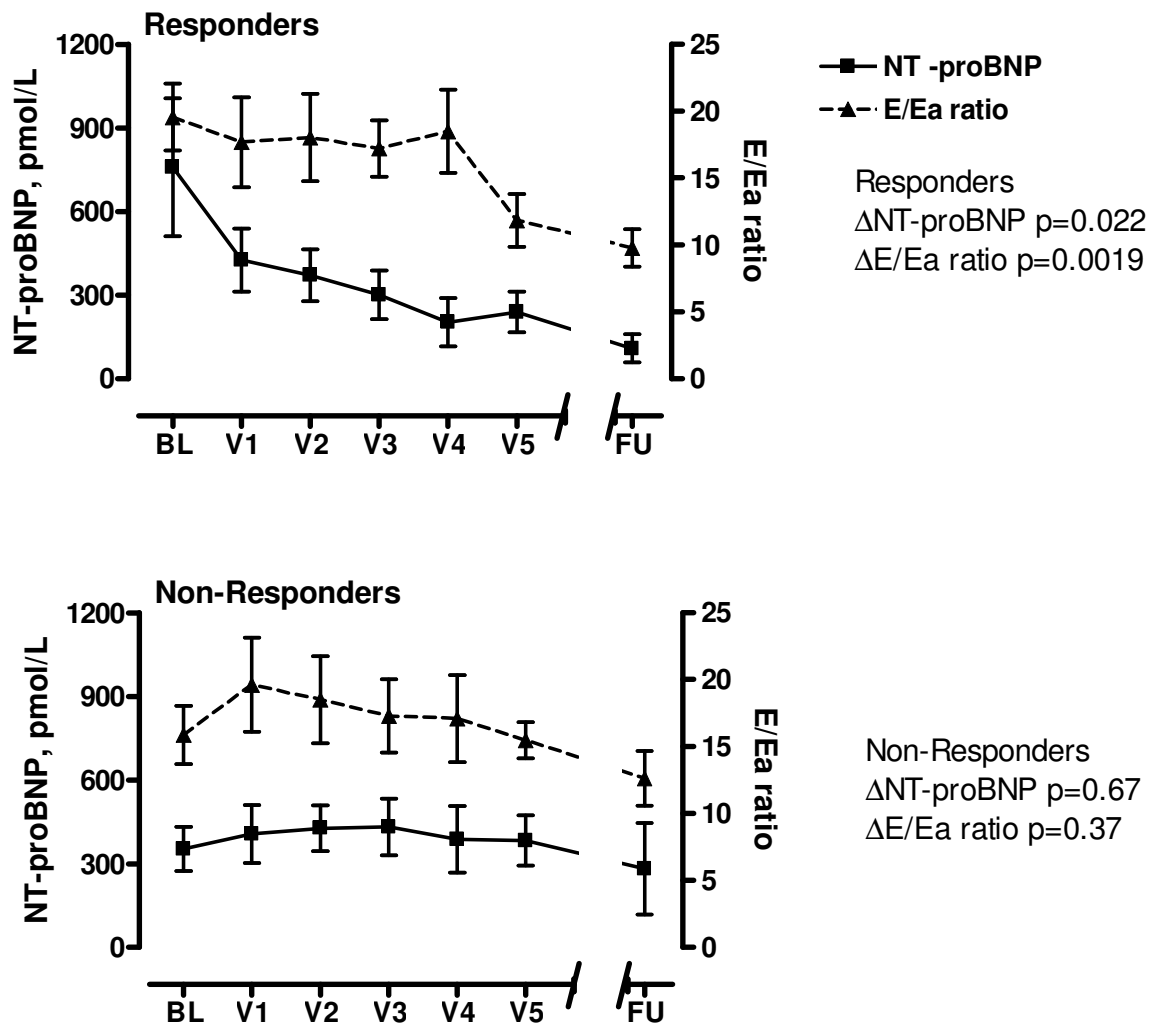
P values are comparisons between BL and V5

5.4. Discussion

This pilot study has demonstrated that HF therapy targeted to reducing NT-proBNP level was accompanied by a reduction in a simple echocardiographic correlate of LVFP, the E/Ea ratio over a ten week period. Our data suggests that the E/Ea ratio may provide a potential target for HF treatment optimisation.

The difficulty of using traditional methods to guide treatment titration was highlighted by the observation that weight did not change and that symptoms and NYHA functional class are crude measures when applied to individual patients. The relationship between NT-proBNP and E/Ea was consistent in those who responded to treatment optimisation (patients with a reduction of >50% in NT-proBNP levels also had a significant reduction in E/Ea ratio) and those who did not suggesting that these two variables respond in similar ways to HF treatment titration.

While the overall mean change in NT-proBNP and E/Ea was similar, there appeared to be temporal differences between the response of NT-proBNP and E/Ea ratio during therapy optimisation. Similarly to NT-proBNP, a reduction in E/Ea was observed between BL and V5 but no further reduction was observed over longer term follow up. The reasons for this are unclear but may not be unexpected. E is a volume dependent echocardiographic variable and therefore likely to change significantly with optimisation of HF therapy in the short term whereas the Ea velocity closely relates to both LV β receptor density and the extent of myocardial fibrosis [288]. Changes in these structural properties of the heart are likely to occur over weeks to months rather than days. In addition, the absolute E/Ea ratio remained markedly abnormal during the titration phase of the study and as such if E/Ea were used as a treatment target this consistently elevated level would have resulted in an increase in therapy.

The observation that HF therapy optimisation directed toward a reduction in LVFP may be beneficial is not new. Early studies suggested that therapy targeted toward reducing invasively measured PCWP improved both haemodynamics [154] and patient outcomes [153]. BNP-32 and NT-proBNP have emerged as potential targets for HF therapy titration with early data suggesting that outcomes are improved with this approach [156, 157]. However, there remains some uncertainty regarding the role of BNP-guided HF therapy titration in the current era of contemporary HF treatment, at least three large randomised studies are currently underway addressing this issue.

The concept of titrating HF treatment to normalisation of LVFP was evaluated by the recently published ESCAPE study[279]. This study randomised patients with severe symptomatic HF to inpatient treatment with placement of a PAC or to inpatient treatment guided by clinical assessment only. The primary end point of days alive out of hospital during six months following randomisation was neutral suggesting that simply placing a PAC and measuring LVFP directly was not beneficial in most HF patients. This study did not provide a specific treatment algorithm to guide treatment in patients with a PAC and no specific differences between clinical and laboratory parameters with HF treatment were observed. The ESCAPE study suggests that the knowledge of LVFP during HF hospitalisation does not necessarily equate to improved outcomes. The ESCAPE study did not examine the role of repeated measures of LVFP over prolonged treatment titration in ambulatory HF patients (an impractical approach due to the invasive nature of PAC). Our current data are consistent with early studies assessing the role of BNP-guided HF treatment[156, 157] suggesting that a non-invasive assessment of LVFP may help guide outpatient HF treatment titration.

In clinical practice patients with HF are often elderly, they have multiple co-morbidities, and polypharmacy is common [10, 289, 290]. Consequently, tools that allow individualisation of HF therapies such as natriuretic peptides and echocardiographic measures of LVFP are of clinical relevance [291]. The relationship between natriuretic peptides and E/Ea is well established: both are abnormal in patients with symptomatic HF [120], and in HF patients with both systolic [94] and diastolic [261, 292] dysfunction. In addition, early studies suggest that TDI, in particular E/Ea, appears to have similar diagnostic [120] and prognostic [217] utility in HF. Furthermore, in certain populations the E/Ea ratio may be more closely related to LVFP than BNP-32 [265]. The E/Ea ratio is an appealing echocardiographic tool for non-invasive assessment of LVFP. This parameter is easily measured in a clinical echocardiographic laboratory [202], is well validated (with an E/Ea ratio of greater than 15 indicating increased LVFP) [204], and recent data in normal subjects confirm the relative load independence of this measure[287].

Use of hand-carried echocardiography in the clinic setting may obviate some of the practical obstacles to the use of echo guided HF therapy optimisation in day-to-day patient management. Doppler echocardiography is one of the most reproducible echocardiographic measures and may be ideally suited for this application in HF patients. A trans-mitral traditional Doppler in conjunction with the TDI assessment could potentially be performed easily in a clinic setting using hand-carried ultrasound.

5.4.1. Limitations

This small study included patients with systolic dysfunction only. The applicability of these results to patients who have HFNEF is unclear. Similarly, this study excluded patients with HF due to valve disease and those with permanent pacemakers and so the results may not be applicable to these patient groups.

The small sample size of this study limited statistical power and precluded exploration of the detailed relationships between NT-proBNP and echocardiographic variables, and of factors predicting a response to therapy or assessment of the prognostic implications of being a "responder". However for a measure such as E/Ea to be useful in guiding therapy in individual patients (rather than groups of patients) a result should be apparent with a small sample size. In addition the definition of a responder was based on an arbitrary change in NT-proBNP.

5.5. Conclusion

This pilot study demonstrates that the E/Ea decreases after NT-proBNP guided HF therapy optimisation in patients with HF and reduced LVEF and may provide a simple echocardiographic measure to guide HF therapy. The temporal course of change in E/Ea ratio may differ to that of NT-proBNP during the early weeks of treatment optimisation and this needs further study. E/Ea may be a complementary target for HF therapy optimisation and should be further evaluated in larger scale randomised trials.

Chapter 6. Atrial fibrillation and the risk of death in patients with heart failure: a literature-based meta-analysis

6.1. Background

HF is a common condition which contributes to significant impairment in quality of life and is associated with high mortality and morbidity [16, 293]. AF is the most common arrhythmia in the general population and is associated with increased mortality and morbidity even when adjusted for multiple factors; such as age, hypertension, and ischemic heart disease [294]. AF commonly co-exists with HF and the prevalence of AF in patients with HF appears to increase as the severity of HF increases [31]. HF and AF share many of the same predisposing conditions such as hypertension, coronary artery disease, valvular heart disease, and diabetes. The presence of HF leads to electrical and structural changes within the left atrium which predispose to the development and maintenance of AF [295, 296]. In addition, recent data suggests that genetic polymorphisms may increase the likelihood of AF in HF patients [297]. AF may lead to adverse haemodynamic consequences, particularly important in patients with HF, such as abnormalities of diastolic function (including shortened diastole due to high heart rates and loss of atrial "kick"), impaired LV systolic function due to heart rate irregularity and loss of atrio-ventricular synchrony, and tachycardia associated ventricular impairment [298].

Despite the known adverse effects of AF, it is uncertain from published data whether the presence of AF in the context of a diagnosis of HF is associated with an adverse outcome compared with patients with SR. Studies that have evaluated the prognostic effect of AF in HF populations are heterogeneous, with wide ranging inclusion criteria, markedly different sample size, and variable length of follow up.

The aim of this literature-based meta-analysis was to combine the results of all studies investigating the prognosis for patients with HF and co-existing AF compared to those in SR to gain a more accurate assessment of the mortality risk associated with this arrhythmia. The hypothesis was that survival would be worse among patients with HF and AF compared with those with SR.

6.2. Methods

6.2.1. Search strategy

The literature search used the following search terms: congestive heart failure OR HF.mp OR heart failure.mp OR ventricular dysfunction AND atrial fibrillation OR atrial flutter OR sinus rhythm AND prognosis OR outcome.mp OR mortality OR death OR morbidity OR hospitalisation. Databases were searched from inception until December 2006. Online databases, including Biological Abstracts, Current Contents, EMBASE, Medline, Medline In-progress, PubMed and Scopus were searched using Ovid Technologies, Inc software. Hand searching reference lists of obtained articles and previously identified reviews was carried out. Abstracts, unpublished studies, and articles published in languages other than English were not excluded. Authors of included studies were invited to provide details of any additional studies, unpublished data and ongoing trials. An initial pool of 3380 potential publications was identified.

6.2.2. Criteria for study inclusion

Each study was reviewed according to a pre-determined protocol, which included information about patients' recruitment and follow-up (prospective, retrospective, consecutive recruitment, exclusions and reason), co-morbidity, loss to follow-up and completeness of data. RCTs and observational studies were included in this analysis. Two investigators initially screened the titles and abstracts of all studies identified from the search of online databases. Studies were evaluated in more detail if they were HF populations and if rhythm (AF or SR) and outcome had been recorded. Any studies that clearly did not meet the selection criteria were discarded. In addition studies that excluded patients on the basis of rhythm or recruited only patients with AF or SR were excluded. Two investigators then screened the abstracts of the remaining studies. Studies were retained or excluded at this stage if they appeared to meet the pre-specified study inclusion criteria. The full-text of all retained studies were obtained, citation lists were checked for additional studies, and the two investigators agreed on potential publications in which patient outcome (mortality) was reported according to cardiac rhythm. The final inclusion of studies was determined when consensus was reached by both reviewers and other listed authors. Included studies were required to enrol HF patients with both AF and SR at baseline and to report outcome (death) according to cardiac rhythm.

6.2.3. Data extraction

Data were extracted from included studies and recorded in an electronic database. Data collected included: duration of follow-up, number of patients with AF and SR at the start of the study, number of deaths in each group, mean age and gender. The corresponding or senior authors of all included studies were contacted by email and asked to confirm the data extracted or provide data where the paper's content was insufficient. In the case of potential duplicate publications clarification was sought from the authors and the largest single published data set was used for the meta-analysis. At the same time, additional references to either published or unpublished studies were sought (Figure 16).

Figure 16: Review process for identification of suitable studies

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│ 3380 publications identified by electronic search of     │
│ Biological Abstracts, Current Contents, EMBASE, Medline, │
│ Medline In-progress, PubMed and Scopus                   │
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                          │
                          │        ┌──────────────────────────┐
                          ├───────▶│ 2676 excluded after      │
                          │        │ review of title          │
                          ▼        └──────────────────────────┘
┌─────────────────────────────────────────────────────────┐
│ 704 Abstracts reviewed                                   │
└─────────────────────────────────────────────────────────┘
                          │
                          │        ┌──────────────────────────┐
                          ├───────▶│ 678 not relevant         │
                          ▼        └──────────────────────────┘
┌─────────────────────────────────────────────────────────┐
│ 26 publications potentially eligible                     │
│ Heart failure population, cardiac rhythm identified at    │
│ study entry, patients with both AF and SR included in     │
│ study population, mortality reported according to AF/SR   │
└─────────────────────────────────────────────────────────┘
                          │
                          │        ┌──────────────────────────┐
                          ├───────▶│ 6 excluded               │
                          │        │ 2 duplicate publications,│
                          │        │ 4 data insufficient in   │
                          │        │ original paper and could │
                          │        │ not be confirmed         │
                          ▼        └──────────────────────────┘
┌─────────────────────────────────────────────────────────┐
│ 20 publications (24 cohorts) included in final analysis  │
│ 9 RCT's (7 publications)                                 │
│ 11 Prospective Observational Studies (9 publications)    │
│ 2 Retrospective Observational Studies                    │
│ 1 Prospective Registry, 1 Case-Control Study             │
│ 32946 patients, 10819 deaths                             │
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6.2.4. Statistical methods

For all studies, patients were stratified according to cardiac rhythm (SR or AF) and the number of patients and events allocated to each group were recorded. The OR comparing all-cause mortality in SR and AF were calculated for each study then combined using a DerSimonian and Laird random effects model [299] to obtain a pooled OR for each of RCTs and observational studies. Statistical heterogeneity (differences in the reported effects) and methodological heterogeneity (differences between studies according to characteristics of participants, interventions or outcome measures) were assessed using I^2 [300] and Cochran's Q statistic [301]. Funnel plots [302] were visually assessed for bias. Analyses were performed using the Cochrane Collaboration Program Review Manager v 4.2.1 [303].

This meta-analysis is of a clinically diverse patient population from differing study designs. Heterogeneity between included studies was expected as the search criteria was designed to include studies that reported outcome stratified by the presence or absence of AF in patients with HF. These studies were not necessarily prospectively designed to evaluate the prognostic effect of AF in a HF population and therefore were expected to differ in methodology. It was decided *a priori* to address a primary source of heterogeneity by stratifying analysis by study design (RCT or observational). Further exploratory analysis of factors contributing to residual heterogeneity within strata were then investigated by sensitivity analysis of the mean I^2 value to assess the effects of study quality using the method of Hayden [304], and potential confounders (pharmacotherapy versus non-pharmacotherapy RCTs; studies from the pre-ACE inhibitor era; very severe HF (pre-transplant cohorts); HFNEF; studies with very long follow up).

All-cause mortality was the primary endpoint. When available, pooled mean age and LVEF were calculated within each category. Duration of follow up was variably reported between studies and is presented as reported in each publication.

6.3. Results

We identified 3,380 publications from our literature search of published work. We excluded 2,676 (Figure 16) after review of the title, and a further 678 after review of the abstract. Thus, 26 potential publications were identified [305-330] involving 24

patient cohorts. In two studies there was patient overlap between other included studies [305, 306] and thus these were excluded. Of the retained studies, nine were RCTs [323-329], 11 prospective observational studies [311, 313, 315, 318-322, 330], two retrospective observational studies [314, 316], one registry [317], and one case-control study [312]) (Table 12). Four studies were excluded as there was insufficient information in the original paper and further confirmation could not be obtained from the authors; these studies involved 2,018 patients, representing 5.8% of potentially available patients [307-310]. Thus, 20 studies describing the association between the presence of AF or SR and mortality in patients with HF were included in this meta-analysis (32,946 patients, 10,819 deaths). Study data (number of patients and events) was confirmed by 12 of the 20 original authors.

Table 12: Characteristics of included studies

Study, Year Published Randomised Controlled Trials	Origin	Data confirmed	Study design	HF population	Follow up years	AF Deaths/N	SR Deaths/N
Carson (V-HeFT-I), 1993[329]	USA	Numbers in paper	Clinical Trial	Males, chronic HF (Class II-III)	Mean 2.5	39/99	237/533
Carson (V-HeFT-II), 1993[329]	USA	Numbers in paper	Clinical Trial	Males, chronic HF Class II-III	Mean 2.5	36/107	243/688
Dries (SOLVD), 1998[328]	USA	Numbers in paper	Clinical Trial	Chronic HF (Class I-II), EF<35%	4	144/419	1395/6098
Crijns (PRIME-II), 2000[327]	Netherlands	Numbers in paper	Clinical Trial	Chronic HF (Class III-IV), LV dysfunction (EF<35%)	Mean 0.97	50/84	153/325
Swedberg (COMET), 2005[326]	Europe	Yes	Clinical Trial	Chronic HF (Class II-IV), EF≤35%	5	255/600	857/2429
Olsson (CHARM), 2006[325]	USA/Europe	Yes	Clinical Trial	Chronic HF (Class II-IV), EF≤40%	Median 3.14	248/670	1102/3906
Olsson (CHARM-P), 2006[325]	USA/Europe	Yes	Clinical Trial	Chronic HF (Class II-IV), EF>40%	Median 3.14	117/478	364/2545
Pedersen (Diamond), 2006[324]	Denmark	Numbers in paper	Clinical Trial	Patients admitted with HF, EF≤35%	10	634/818	1951/2661
Wasywich, 2006[323]	New Zealand	Yes	Clinical Trial	Patients admitted with HF	3	26/62	69/129
Observational Studies							
Convert, 1980[322]	France +	Yes	Prospective	Consecutive patients admitted with HF	Mean 3.37	6/32	38/100
Unverferth, 1984[321]	USA	Yes	Prospective	Patients admitted with HF, EF<50%	1	8/12	16/57
Takarada, 1993[320]	Japan	Numbers in paper	Prospective	Consecutive patients admitted with HF, FS<25%	Mean 3.8	3/36	31/111
Stevenson 1, 1996[319]	USA	Numbers in paper	Prospective	Consecutive HF patients, transplant assessment, EF<40% (1985-1989)	2	45/73	129/286
Stevenson 2, 1996[319]	USA	Numbers in paper	Prospective	Consecutive HF patients, transplant assessment, EF<40% (1990-1993)	2	41/93	75/298
Mahoney, 1999[318]	USA	Numbers in paper	Prospective	Consecutive HF patients, transplant assessment, severe LV dysfunction	2	14/63	26/171

Aronow EF <50%, 2001[330]	USA	Numbers in paper	Prospective	Chronic HF due to myocardial infarction, EF<50%	3.08	129/132	200/223
Aronow EF >50%, 2001[330]	USA	Numbers in paper	Prospective	Chronic HF due to myocardial infarction, EF>50%	3.08	91/98	146/198
Baldasseroni (In-CHF), 2002[317]	Italy	Yes	Prospective	Consecutive patients admitted with HF (Registry)	1	166/983	493/4534
Ahmed, 2004[316]	USA	Yes	Retrospective	Medicare discharges with primary diagnosis of HF	4	166/233	439/711
Sosin, 2004[315]	UK	Yes	Prospective	Patients admitted with HF	8	63/65	129/149
Koitabashi, 2005[314]	Japan	Yes	Retrospective	Consecutive patients admitted with HF	2.83	31/188	45/239
Zysko, 2005[313]	Poland +	Yes	Prospective	Consecutive patients admitted with HF	7	18/33	25/38
Wojtkowska, 2006[312]	Poland	Yes	Case-control study	Consecutive men admitted with HF, EF<30%	3	33/60	26/60
Corell, 2007[311]	Denmark	Yes	Prospective	Chronic HF	5.33	88/269	179/750

HF, heart failure; EF, ejection fraction; +, published in language other than English

6.3.1. Randomised Controlled Trials

The RCTs involved 22,651 patients: the prevalence of AF in this cohort was 15% (3,337/22,651 patients); and 7,920 (35%) patients died during follow-up, which ranged from 1 to 10 years. Pooled mean age was 69 years for patients with AF and 64 years for those in SR. Pooled mean LVEF was 33% and 32% in patients with AF and SR respectively. Crude mortality rates were 46% in those with AF and 33% in those with SR. The overall OR for death was 1.33 (95% CI 1.12 - 1.59) for those with AF compared with SR (Figure 17). Significant heterogeneity was observed between these studies (I^2 = 73.7%, Cochran's Q statistic p=0.0002). The asymmetry of the funnel plot suggests that bias may be present. The 'missing studies' are those that would favour SR, so if present, would support the findings of this meta-analysis (Figure 18)

6.3.2. Observational Studies:

10,295 patients were included from observational studies: the prevalence of AF in this cohort was 23% (2,370/10,275 patients); and 2,899 (28%) patients died during follow-up, which ranged from 1 to 8 years. Pooled mean age was 68 years for patients with AF and 75 years for those in SR. Pooled mean LVEF was 31% and 28% in patients with AF and SR respectively. Crude mortality rates were 38% in those with AF and 25% in those with SR. The OR for death was 1.57 (95% CI 1.20-2.05) for those in AF compared to SR (Figure 19). Significant heterogeneity was observed between these studies (I^2 = 68.9%, Cochran's Q statistic p<0.0001). The funnel plot does not suggest significant bias in the studies available for inclusion (Figure 20).

Figure 17: Meta-analysis of the effect of the presence of AF or SR on mortality in patients with HF (randomised controlled trials)

Study, year published	Atrial fibrillation deaths/number at risk	Sinus rhythm deaths/number at risk	Odds Ratio 95% CI	Weight %	OR (95% CI)
					(random effects)
Carson I, 1993	39/99	237/533		8.27	0.81 [0.52, 1.26]
Carson II, 1993	36/107	243/688		8.42	0.93 [0.60, 1.43]
Dries, 1998	144/419	1395/6098		13.75	1.77 [1.43, 2.18]
Crijns, 2000	50/84	153/325		7.36	1.65 [1.02, 2.69]
Swedberg, 2005	255/600	857/2429		14.47	1.36 [1.13, 1.63]
Olsson, 2006	248/670	1102/3906		14.73	1.50 [1.26, 1.78]
Olsson-P, 2006	117/478	364/2545		13.07	1.94 [1.53, 2.46]
Pedersen, 2006	634/818	1951/2661		14.39	1.25 [1.04, 1.51]
Wasywich, 2006	26/62	69/129		5.54	0.63 [0.34, 1.16]
Events/number at risk:	**1549/3337**	**6371/19314**		**100.00**	**1.33 [1.12, 1.59]**

Test for heterogeneity: Chi² = 30.46, df = 8 (P = 0.0002), I² = 73.7%

Test for overall effect: Z = 3.23 (P = 0.001)

0.1   0.2   0.5   1   2   5   10

Atrial fibrillation better   Atrial fibrillation worse

Figure 18: Funnel Plot (randomised controlled trials)
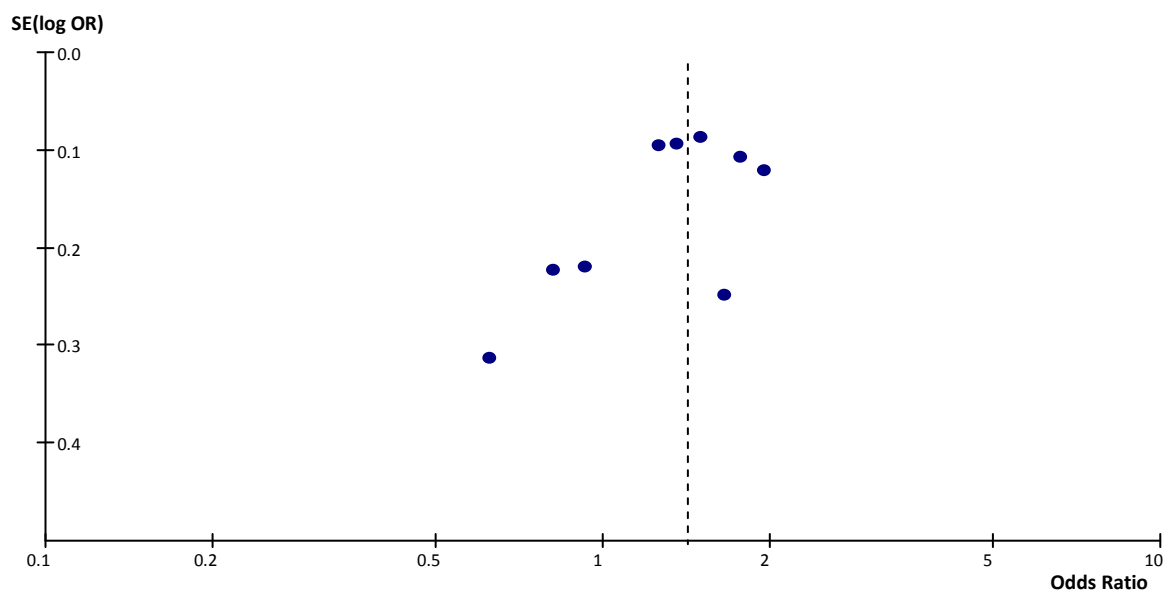
Figure 19: Meta-analysis of the effect of the presence of AF or SR on mortality in patients with HF (observational studies)

Study, year published	Atrial fibrillation deaths/number at risk	Sinus rhythm deaths/number at risk	Weight %	OR (95% CI)
				(random effects)
Carson I, 1993	39/99	237/533	8.27	0.81 [0.52, 1.26]
Carson II, 1993	36/107	243/688	8.42	0.93 [0.60, 1.43]
Dries, 1998	144/419	1395/6098	13.75	1.77 [1.43, 2.18]
Crijns, 2000	50/84	153/325	7.36	1.65 [1.02, 2.69]
Swedberg, 2005	255/600	857/2429	14.47	1.36 [1.13, 1.63]
Olsson, 2006	248/670	1102/3906	14.73	1.50 [1.26, 1.78]
Olsson-P, 2006	117/478	364/2545	13.07	1.94 [1.53, 2.46]
Pedersen, 2006	634/818	1951/2661	14.39	1.25 [1.04, 1.51]
Wasywich, 2006	26/62	69/129	5.54	0.63 [0.34, 1.16]
Events/number at risk:	**1549/3337**	**6371/19314**	**100.00**	**1.33 [1.12, 1.59]**

Test for heterogeneity: Chi² = 30.46, df = 8 (P = 0.0002), I² = 73.7%

Test for overall effect: Z = 3.23 (P = 0.001)

Figure 20: Funnel Plot (Observational Studies)

6.3.3. Approach to heterogeneity

Significant residual heterogeneity remained within each of the RCT and observational analyses. The I^2 in the RCT analysis was 73.7%. No studies were identified as low quality. Exclusion of studies according to additional criteria specified above did not significantly reduce heterogeneity further (Table 13). The I^2 value in the analysis of observational studies was 68.9%. The greatest source of heterogeneity in the observational studies appears to relate to studies published before the ACE-inhibitor era, exclusion of these studies [320-322] reduced the I^2 to 55.1%. Exclusion of the three studies identified as low quality [313, 321, 322] also significantly improved heterogeneity (I^2 reduced to 63.1%). Exclusion of other observational studies according to additional specified criteria did not significantly change the I^2 (Table 13). Importantly, none of these approaches affected the direction or significance of the OR associated with AF.

Table 13: Sensitivity analysis of sources of heterogeneity

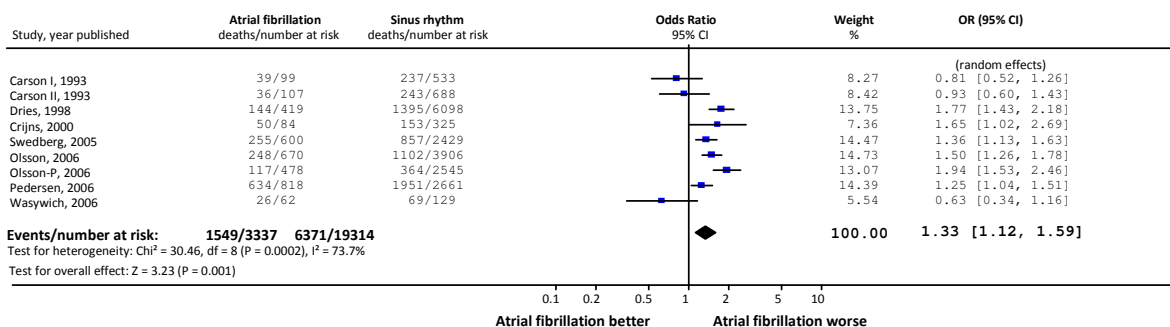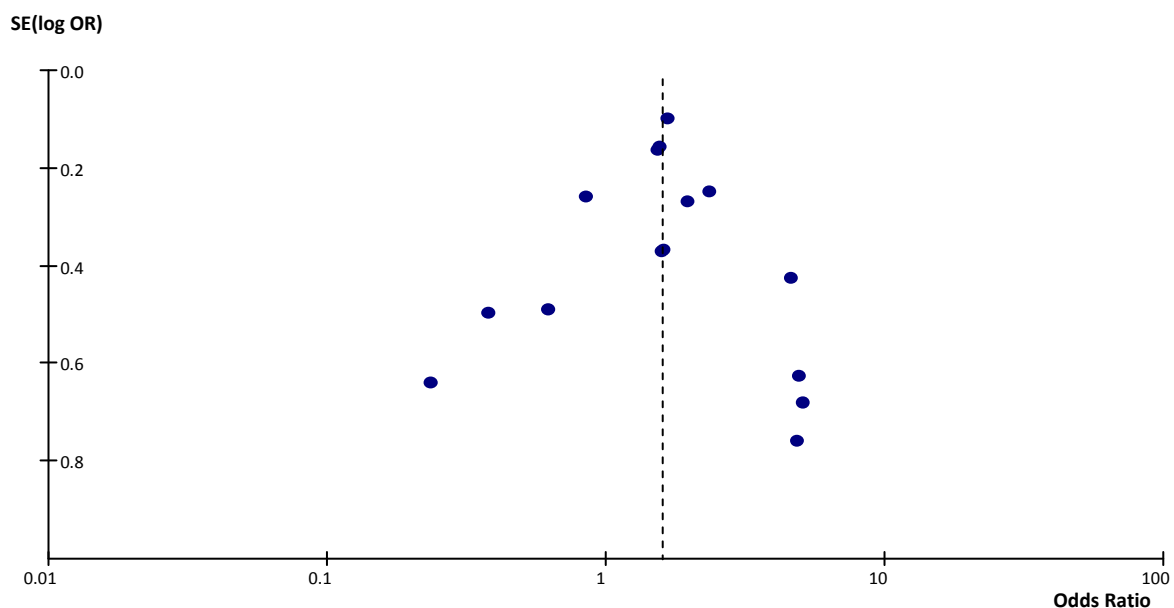| Reason for Exclusion	I^2	OR (95% CI)
Randomised controlled trials	73.7	1.33 (1.12-1.59)
Non pharmacotherapy study [323]	70.1	1.4 (1.19-1.65)
Pre ACE inhibitor era studies [329]	69.3	1.46 (1.24-1.73)
HFNEF [325]	69.5	1.27 (1.06-1.15)
Prolonged follow up [324]	75.2	1.34 (1.09-1.64)
Observational studies	68.9	1.57 (1.20-2.05)
Pre ACE inhibitor era studies [320-322]	55.1	1.7 (1.36-2.13)
Advanced HF studies [318, 319]	73.7	1.46 (1.05-2.03)
HFNEF [330]	66.4	1.47 (1.13-1.91)
Prolonged follow up [313, 315]	69.4	1.59 (1.22-2.08)
Low quality studies [313, 321, 322]	63.1	1.65 (1.46, 1.86)

ACE, angiotensin converting enzyme; HF, heart failure; EF, ejection fraction;

HFNEF, heart failure with normal ejection fraction

6.4. Discussion

Previous individual studies have reported conflicting evidence of the prognostic impact of co-existing AF among patients with HF [290, 318, 327, 328, 330-332]. This literature-based meta-analysis, including 20 studies (representing 32,946 patients and 10,819 deaths), has shown that patients with HF and co-existing AF have higher total mortality than for patients with SR. The importance of this increase in odds of mortality is highlighted by the differences in the crude mortality rates of patients with AF and SR respectively (RCTs 46.4% vs. 33.0%, observational studies 38.1% vs. 25.2%).

The association between HF and AF is well described; both conditions are common, prevalence increases with increasing age, and both share similar risk factors such as IHD, hypertension, and valvular heart disease. Data from the Framingham study show that the development of new HF in those with AF or conversely the development of new AF in those with HF is associated with increased mortality [332]. While this meta-analysis has provided evidence that AF is associated with higher mortality than SR in patients with HF the mechanisms underlying this higher mortality are uncertain. HF is a clinical syndrome and patients with HF have a wide range of underlying risk factors, co-existing diseases and cardiac abnormalities. There are many potential reasons why the presence of AF may worsen HF outcomes such as; abnormalities of diastolic function (including shortened diastole due to high heart rates and loss of atrial "kick"), impaired left ventricular systolic function due to heart rate irregularity and loss of A-V synchrony, and tachycardia associated ventricular impairment [298, 333]. In addition the presence of AF significantly increases the risk of thromboembolic complications [334]. It is likely that different mechanisms will contribute to AF and subsequent poor outcome despite all patients having the syndrome of HF.

Patients with AF in the RCT cohort were older compared to those with SR however the reverse was true for the patients in the cohort of observational studies. This suggests that the increased mortality associated with AF is not likely to be simply related to patient age.

Previous studies have proposed that the effect of AF on prognosis in patients with HF may be different depending on the severity of HF [335, 336]. While there is no universally accepted definition of severity potential candidates include patient symptoms, hospital admission for HF, LVEF, or "advanced/stage D HF [131]". Most RCTs select HF patients on the basis of LVEF. Although it is acknowledged that EF is a crude measure of HF severity within the

current meta-analysis pooled mean EF was similar in patients with AF and SR in both the RCT and observational study cohorts. Studies included in this meta-analysis included a wide range of HF severity, although most used low EF as a criteria for HF diagnosis [312, 318-320, 324-328]. In this analysis the presence of AF in cohorts of advanced HF patients was associated with increased odds of death [318, 319]. Studies which included outpatients with less severe disease suggest that the presence of AF is associated with a neutral effect [329] or increased mortality [325, 326, 328]. Similarly, the vast majority of studies enrolling patients at the time of hospital admission suggested that the presence of AF was associated with increased mortality [311, 312, 315-317, 321, 324, 327] with only studies enrolling small numbers of patients suggesting a neutral or beneficial effect of AF on outcome [313, 320, 322, 323]. The CHARM-Preserved cohort provides insight into the effect of AF in patients with mild, moderate, and severe HF who have relatively preserved EF. In this group of patients the presence of AF was clearly associated with increased mortality [325]. This result is consistent with a smaller observational cohort with preserved EF [330] and with the results of a recently published study not included in our meta-analysis although in this study the adverse effect of AF on mortality was not independent of covariates [337]. These combined data suggest that the adverse prognostic effect of AF is not simply a function of patient age, HF severity, or EF.

The overall adverse prognostic effect of AF in this meta-analysis (OR 1.33 in the RCT cohort, OR 1.57 in the observational study cohort) is very similar to that reported in unselected individuals from the Framingham population [294] which reported a 1.5 (men)-1.9 (women) increase in mortality risk associated with the presence of AF after adjustment for multiple variables. The recognition of this adverse prognostic effect of AF in the general population led to the "rhythm control" approach to therapy in the hope that the achievement and maintenance of SR in patients with AF would lead to an improvement in outcomes. The publication of the AFFIRM [32] and European [33] studies of rate control compared to rhythm control confirmed that the strategy of rhythm control in patients with AF did not improve their outcomes. Our data confirm that the presence of AF in patients with HF is associated with a similar increase in the odds of death compared to the general population. This translates to a more significant increase in risk because of the poor prognosis of HF patients in general (crude mortality rates in our study increase from 33% to 46% (RCTs) and 25% to 38% (Observational studies) for HF patients in SR and AF respectively). The recent publication of the AF-CHF study [34] evaluated whether a rhythm control approach to AF in

patients with HF was superior to rate control. The strategy of rhythm control did not improve outcomes (no difference in the rates of cardiovascular death) in this patient population. It is possible that the lack of superiority of a rhythm control approach is due in part to the adverse effects of antiarrhythmic drugs. To further evaluate whether return of SR is superior in patients with HF who have coexisting AF a randomised study comparing catheter ablation of AF to a rate control strategy would be required.

6.5. Limitations

There are several limitations of this meta-analysis. One important factor is that most of the studies included in this meta-analysis were not designed to specifically address the prognostic effect of AF in patients with HF. All studies in the RCT cohort except one [323] were retrospective analyses of pharmacotherapy trials which enrolled a HF population. These data are inherently limited by the selection bias that occurs with recruitment for these studies. The observational cohort may provide a more "real world" assessment of the prognostic effect of AF in HF patients. This data set also included several studies, which were designed specifically to address the question posed by this meta-analysis (drawing patients from multiple sources: HF clinics [311], hospital inpatients [312, 316], a HF registry [317], and pre-transplant populations [318, 319]). The prognostic effect of AF was at least as important in the observational cohort. By design, the inclusion criteria of this study means the question of the prognostic impact of the development of AF in patients with HF is not addressed by this study although other published data suggests this is associated with an adverse prognosis [332].

Heterogeneity is another important limitation of this meta-analysis and was expected. To explore reasons for heterogeneity sensitivity analysis was undertaken. Exclusion of studies according to multiple criteria (study quality, pharmacotherapy versus non-pharmacotherapy RCTs, studies from the pre-ACE inhibitor era, very severe HF (pre-transplant cohorts), HFNEF, and studies with very long follow up) attempted to address statistical and methodological heterogeneity. Attempts to address heterogeneity strengthened the results of this meta-analysis (Table 13).

By design, literature-based meta-analyses have many inherent limitations including publication bias, duplication of published data, and the inability to assess the independent impact of possible confounding factors. To minimise publication bias we contacted all

corresponding authors of included studies and asked for any unpublished data. Examination of the funnel plots does not suggest important publication bias. Duplication of patients in this meta-analysis is unlikely given the rigorous methodology adopted; two studies were specifically excluded for this reason [305, 306]. Although our study confirms that the presence of AF in patients with HF is associated with an adverse prognosis, we are unable to assess the impact that confounding factors such as age, gender, aetiology of HF, severity of HF, and duration of HF may have on our results. Our data are unable to confirm that the presence of AF is independently associated with an adverse prognosis.

6.6. Conclusion

This meta-analysis, including all available data, has demonstrated that the presence of AF is associated with worse outcomes for patients with HF compared to those with SR. Further research is required to determine the specific factors associated with the worse outcome associated with the combination of HF and AF, and to subsequently design appropriate interventions to improve outcomes for these patients.

Chapter 7. Myocardial aldosterone release in aortic stenosis and in coronary artery disease with normal left ventricular systolic function

7.1. Introduction

Treatment with an ARA improves outcomes in patients with severe HF and in patients with reduced LVEF after myocardial infarction [35, 36]. However it is not known whether the adverse effects of aldosterone, which include vascular [37] and myocardial inflammation and fibrosis [38, 39], are due to increased circulating aldosterone alone. Some animal [40, 41, 338, 339] and human studies [41-43, 45] suggest aldosterone can be synthesised within the myocardium as well as from the adrenal gland. It is therefore possible aldosterone could have pathophysiological roles in cardiovascular disease which are independent of the systemic renin-angiotensin-aldosterone system [44].

A small number of studies have evaluated trans-myocardial aldosterone metabolism by comparing plasma levels in samples taken from the aorta and coronary sinus [42, 43, 45, 46]. Mizuno and colleagues reported a step-up in coronary sinus aldosterone, implying myocardial synthesis, in patients with LV systolic and diastolic dysfunction [42, 43] and in patients with essential hypertension [45] but not in normal controls. In contrast Tsutamoto reported trans-cardiac extraction of aldosterone both in normal subjects and patients with HF [46]. Results of these studies are therefore inconsistent and there is a need for further research to determine both whether aldosterone is released by myocardium and whether the magnitude of this release is greater in specific cardiac diseases.

AS is characterised by progressive LV hypertrophy and fibrosis. Angiotensin II and aldosterone promote myocardial fibrosis in experimental models and activation of myocardial angiotensin synthesis has been demonstrated in patients with aortic valve disease [47]. However it is not known whether aldosterone has a role in the adverse LV remodelling of AS. In experimental studies aldosterone can cause vascular dysfunction [48] and promote atherosclerosis [49], suggesting a pathophysiological role in coronary artery disease [50].

The aim of this study was to determine whether myocardial release of aldosterone, detected as a step-up in coronary sinus levels, occurs in patients with severe AS and/or in patients with stable coronary artery disease who have a normal LVEF and no clinical evidence of HF.

7.2. Methods

Two groups of patients were studied; 19 patients with severe AS undergoing cardiac catheterisation prior to aortic valve replacement and 18 patients undergoing elective coronary angiography for investigation of stable angina. Patients were excluded if they had suffered an acute coronary syndrome within the last three months, abnormal LV systolic function (EF <50% by echocardiography or LV angiogram), a history of HF or other significant cardiac disease (including AF, pulmonary hypertension, and valvular heart disease other than AS), renal impairment (serum creatinine >0.14mmol/L), current treatment with an ARA, and the presence of important non-cardiac disease.

A diagnostic catheter was advanced to the ascending aorta from the femoral artery and a second catheter (usually 6 French AL2 or multi-purpose catheter) advanced at least 2cm into the coronary sinus from the femoral vein. The position of the catheter tip was confirmed by contrast injection and then blood samples were drawn from the aortic root, coronary sinus (slowly to reduce the chance of sampling from the right atrium) and femoral vein, with less than 2 minutes difference between sampling sites. Diagnostic coronary angiography was then performed using standard methods. Coronary angiograms were analysed later by an expert angiographer blind to clinical and hormone data. The coronary tree was divided into 14 segments using the CASS criteria [340]. The extent of coronary artery disease was estimated for each patient by determining the number of segments with stenoses ≥20% and ≥50% of vessel diameter. Echocardiograms were performed for all patients with AS and analysed blind to other clinical and hormone data using standard methods [175, 341].

Blood samples for pro-collagen type III amino terminal peptide (PIIINP) were collected in plain tubes, for aldosterone and BNP-32 in tubes containing ethylene diamine tetra-acetic acid (EDTA), and for angiotensin II in pre-chilled tubes containing 0.15 ml of an angiotensin inhibitor solution. All samples were immediately centrifuged and plasma stored at -70°C for later analysis in a single batch at study end. Plasma levels of aldosterone [342], angiotensin II [343], and BNP-32 [344] were analysed by the Christchurch Cardioendocrine Laboratory using radioimmunoassays developed in-house. Cross reactivity of the aldosterone assay with

other steroids has been assessed previously at 0.1% for deoxycorticosterone, 0.0017% for cortisol, and 0.02% for corticosterone [342]. Inter-assay coefficients of variation are 6-7% for aldosterone, 4-8% for angiotensin II, and 11-14% for BNP-32 respectively. To convert results reported in pmol/l to pg/ml multiply by 3.47 for BNP-32, 1.05 for angiotensin II and 0.36 for aldosterone. PIIINP samples were analysed using a commercially available radioimmunoassay (Orion Diagnostica, Finland) with an inter-assay coefficient of variation <7%.

Results are reported as mean ± standard deviation or median (and inter-quartile range) for BNP because the distribution of values was skewed. The difference between the aortic root and coronary sinus samples was assessed using a paired t-test. Differences between groups were compared using an unpaired t-test. Spearman's correlation coefficients (r) were used to assess associations between variables. All analysis was performed using SAS statistical software and a p-value <0.05 was considered statistically significant.

7.3. Results

Demographic and clinical information are presented for the study population in Table 14. Systolic BP was higher in patients with AS and patients with IHD were more likely to be treated with aspirin. Other clinical variables were similar for the two patient groups. No patients had clinical or radiographic evidence of HF. Patients with AS had a mean peak aortic velocity of 4.8 ± 0.7m/s, aortic valve area mean of 0.8cm2 ± 0.3 cm^2 and mean LV wall posterior wall thickness 1.4cm ± 0.2cm.

Plasma aldosterone, angiotensin II, BNP, and PIIINP levels in the aortic root and coronary sinus are presented in Table 15 and Figure 21. Plasma aldosterone was on average about 20% higher in the coronary sinus than the aortic root respectively in both patient groups (AS: 120 versus 102 pmol/L, p<0.001; IHD: 94 versus 77 pmol/L, p<0.001) and was consistent with myocardial aldosterone production. Although both aortic and coronary sinus aldosterone appeared to be higher in patients with AS compared to those with IHD, this difference was not statistically significant. The mixed venous plasma levels of aldosterone were below the upper limit of the normal reference range for both patients with AS and IHD.

Table 14: Demographic and clinical variables

|	Aortic stenosis	Ischemic heart disease	P
Number of subjects	19	18	
Age in years, median (IQR)	76 (62, 79)	69 (64, 75)	0.25
Male, number (%)	13 (68%)	14 (78%)	0.71
Clinical Information			
Systolic BP, mmHg	142 ± 17	130 ± 16	0.05
Diastolic BP, mmHg	72 ± 12	71 ± 11	0.82
Creatinine, mmol/L	0.10 ± 0.02	0.10 ± 0.02	0.78
Medications, number (%)			
Beta blocker	9 (47%)	13 (72%)	0.12
ACE inhibitor	7 (37%)	10 (56%)	0.25
Frusemide	4 (21%)	1 (6%)	0.34
Thiazide	2 (11%)	2 (11%)	1.0
Aspirin	10 (53%)	16 (89%)	0.02
Statin	13 (72%)	16 (89%)	0.23
Angiographic score			
Number of segments>=20%	7.2 ± 4.4	8.3 ± 3.2	0.42
Number of segments >=50%	2.5 ± 2.7	3.5 ± 2.5	0.24

IQR, interquartile range; BP, blood pressure; ACE, angiotensin converting enzyme

Table 15: Comparison of plasma levels of aldosterone, angiotensin II, B-type natriuretic peptide and pro-collagen type III amino terminal peptide in the ascending aorta and coronary sinus

	Normal range	Aortic root	Coronary sinus	Difference	P	P#
Aldosterone (pmol/L)	100-200					
AS		102 (93)	120 (91)	18 (3)	<0.001	0.18
IHD		77 (40)	94 (47)	17 (14)	<0.001	
Angiotensin II (pmol/L)	6-26					
AS		11 (6)	16 (7)	5 (4)	<0.001	0.94
IHD		9 (4)	12 (4)	3 (3)	<0.001	
BNP-32 (pmol/L)*	3-12					
AS		29 (20, 43)	58 (39, 73)	27 (12, 38)	<0.001	0.04
IHD		13 (10, 15)	27 (20, 41)	15 (7, 24)	<0.001	
PIIINP (µg/L)	1.5-4.5					
AS		3.3 (1.3)	3.5 (1.3)	0.2 (0.6)	0.16	0.16
IHD		3.3 (0.9)	3.2 (0.8)	0 (0.4)	0.69	

Normal range = reference laboratory range for a peripheral venous sample; Difference = plasma level in coronary sinus-aortic root; * Results are reported as mean and (standard deviation) except for BNP-32 which is reported and median (interquartile range); AS, aortic stenosis; IHD, ischaemic heart disease.

Figure 21: Coronary sinus/aortic root ratio of peptides
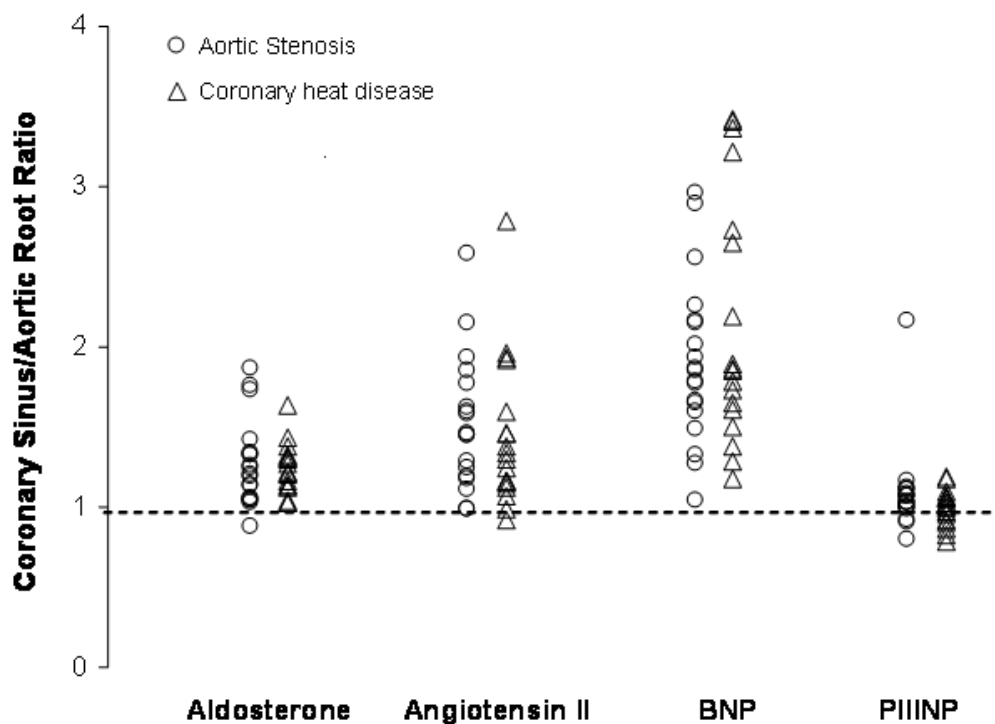
The ratio of the plasma level of each hormone or peptide in the coronary sinus compared with the aorta is presented for individual study participants. For most subjects this ratio was >1 for aldosterone, angiotensin II and BNP-32 indicating the plasma level was higher in the coronary sinus than the aorta. For pro-collagen type III amino terminal peptide (PIIINP) this ratio was about 1 for most subjects.

Plasma angiotensin II was also approximately 20% higher in the coronary sinus compared with the aortic root respectively in both patient groups (AS: 16 versus 11 pmol/L, p<0.001; IHD: 12 versus 9 pmol/L, p<0.001) consistent with myocardial angiotensin II release. Mixed venous plasma levels of angiotensin II were within the normal reference range for both patients with AS and IHD and were similar for the two patient groups. Plasma levels of BNP-32 approximately doubled between the aorta and coronary sinus in both groups of patients. Plasma levels of BNP-32 were higher in the patients with AS than those with IHD, both in the aorta and the coronary sinus, and the step-up across the myocardium was also greater (27 versus 13 pmol/L respectively, p=0.043).

There was no association between mixed venous levels of aldosterone (r=0.06, p=0.74) or angiotensin II (r=0.04, p=0.80) and the trans-myocardial gradient of these hormones. In contrast the mixed venous plasma BNP-32 level increased with the size of the trans-myocardial BNP-32 gradient (r=0.47, p=0.003) consistent with the myocardium being the predominant source of circulating BNP-32.

There was no significant association between either the mixed venous or the trans-myocardial gradient in aldosterone and mixed venous or trans-myocardial measures of angiotensin II or BNP-32 or between BNP-32 and angiotensin II. The magnitude of the myocardial step-up of aldosterone, angiotensin II, and BNP-32 were not related to the extent of coronary disease, severity of AS, or LV wall thickness for patients with AS (r<0.2, p >0.05 for all).

Mixed venous plasma levels of PIIINP were within the normal range for both groups of patients (Table 15). There was no difference in the plasma level of PIIINP between the aortic root and coronary sinus in either patient group. In addition there was no evidence for an association between plasma levels of PIIINP and the myocardial step-up in aldosterone, angiotensin II, or BNP-32 (r<0.2, p >0.05 for all).

7.4. Discussion

This study confirms aldosterone is released by the human heart in patients with severe AS and in stable IHD even when LVEF is within the normal range and there is no clinical HF. These observations are consistent with Mizuno and colleagues who also reported that myocardial aldosterone was about 20% higher in the coronary sinus compared to aorta in patients with LV systolic and diastolic dysfunction [42] and in patients with essential hypertension [45]. Tsybouleva recently reported increased myocardial aldosterone and

increased expression of CYP11B2 mRNA (aldosterone synthase) in a small cohort of patients with hypertrophic cardiomyopathy [41]. The current study extends evidence for myocardial aldosterone release to patients with AS and coronary artery disease. There was no evidence for extraction of aldosterone by the heart, as reported by Tsutamoto [46]. It is noteworthy that aortic and mixed venous plasma levels of aldosterone and angiotensin II were below the upper limit of the normal reference range in both groups of patients studied and there was no association between mixed venous plasma levels of these hormones and the step-up in coronary sinus aldosterone or angiotensin II. This implies myocardial angiotensin II and aldosterone synthesis may be independent of the systemic renin-angiotensin-aldosterone system.

Peripheral venous plasma levels of PIIINP increase after myocardial infarction and with HF. In these conditions higher levels are associated with a poorer prognosis [345-347]. In a sub-study of the RALES study patients with elevated peripheral venous plasma levels of PIIINP had a greater reduction in mortality on spironolactone [348] suggesting the ARA may act in part by decreasing myocardial collagen turnover. However these studies did not directly measure myocardial release of PIIINP by coronary sinus sampling. Querejeta has reported an increase in coronary sinus levels of the carboxy-terminal pro-peptide of procollagen type I in patients with hypertensive HF, associated with elevated peripheral venous levels [349]. In the current study peripheral venous levels of PIIINP were within the normal range and there was no evidence of myocardial release of PIIINP in patients with a normal LVEF and AS or coronary artery disease.

In this study there was no clear association between the amount of LV hypertrophy by echocardiography or the extent of coronary artery disease on angiography and myocardial aldosterone release. In addition there was no statistically significant difference in the myocardial release of aldosterone or angiotensin II between patients with AS and those with coronary artery disease. These observations do not support the hypothesis that myocardial aldosterone synthesis is increased by pressure overload LV hypertrophy or is higher in patients with more extensive coronary artery disease. In contrast Mizuno [42] reported an association between myocardial aldosterone production and the severity of LV dysfunction. In the current study the coronary sinus step-up in plasma levels of aldosterone and angiotensin II, although modest was observed in almost all subjects, and the observation that plasma levels are higher in the coronary sinus than the aorta is unlikely to be due to chance alone ($p<0.001$ for all). However a larger cohort of patients and more precise measures of

disease severity are needed to more reliably evaluate possible associations between the size of these step-ups and the severity of coronary or myocardial disease.

7.5. Limitations

One limitation of the current study is lack of data from subjects with no cardiac disease. In patients with normal coronary arteries or vaso-spastic angina Yamamoto [45] reported myocardial aldosterone release in subjects with hypertension but not those with a normal BP. In contrast Tsutamoto reported trans-cardiac extraction of aldosterone in normal subjects [46]. Additional investigations are therefore needed to confirm normal levels of myocardial aldosterone release or extraction.

Angiotensin II is an important stimulus for aldosterone synthesis [350] but in this study there was no association between the size of the trans-cardiac step-up of aldosterone and that of angiotensin II. Almost half of study patients were taking an ACE inhibitor, which may decrease both aldosterone and angiotensin II synthesis. In a randomised study perindopril for one week decreased coronary sinus levels of aldosterone and ACE in patients with congestive HF, with no change in peripheral blood levels of aldosterone [43]. In contrast Kutada reported that genetic knockout of the angiotensin II type 1A receptor fails to arrest cardiac aldosterone synthesis in mice after myocardial infarction [339]. The influence of ACE inhibitors and other medications on myocardial aldosterone and angiotensin II production could not be reliably evaluated from the current observational study.

7.6. Conclusion

This study demonstrates myocardial aldosterone release in patients with severe AS and in patients with stable coronary disease who have a normal LVEF and no clinical HF. The clinical benefits of ACE inhibitors have been demonstrated in cardiovascular disease without systemic renin-angiotensin system activation [351, 352]. Findings from the current study strengthen the rationale for evaluating ARAs in clinical situations not characterised by increased circulating aldosterone.

Chapter 8. Conclusions

This thesis has drawn together the several studies linked by the theme of contemporary HF management. Management of this complex syndrome requires a multifaceted, evidence based approach linking accurate diagnosis, multi-drug pharmacotherapy, consideration of devices in appropriate patient groups, out-reach of care into the community, and in the end stages of this chronic disease implementation of palliative care strategies [7, 54]. Despite major advances in all of these facets, the prognosis for patients with HF remains poor with high mortality rates after diagnosis [9, 11, 12, 19]. It is also clear from recent negative trials in both acute [353, 354] and chronic HF [355-357] that further neurohormonal manipulation (on a background of ACE inhibitor, βB, and ARA or ARB therapy) is not likely to improve outcomes for HF patients. The focus of care becomes sharpened on the individual patient and therapy is tailored to specific individual's circumstances to improve their outcomes.

Chapter 2 of this thesis is a population study that collates two decades of hospitalisation and mortality data. Major changes in the epidemiology of HF have occurred over this time. We have seen an initial rise and then fall in the age standardised incidence of first HF hospitalisation. Important improvements in survival after a HF admission were seen, particularly in the 1990's, likely driven in part by evidence based pharmacotherapy in particular ACE inhibition. No further improvements in survival were seen after 2000. To understand the influences of changes in both hospitalisation and mortality the number of days alive and out of hospital from the time of the initial HF admission were calculated. Days alive and out of hospital have progressively increased over two decades in New Zealand. At one year patients are living in the community for an extra month in 2008, compared to 1988, and this has increased to two months at two years. The improvements in days alive and out of hospital after 2000 are driven by a reduction in the total days spent in hospital after a HF admission (mortality rates are unchanged between 2000 and 2008). This data tells us that, in the current era, patients are living in the community longer after a hospital admission for HF. Understanding the shifting burden of HF will help clinicians and health care systems deliver optimal care.

A theme of much HF research over the last decade has been the identification of biomarkers, which have the potential to assist in the management of HF patients. Natriuretic peptides (particularly BNP-32 and NT-proBNP) have emerged as biomarkers that provide important

diagnostic and prognostic information in HF patients. Echocardiography is a widely utilised imaging modality in patients with HF. It is the commonest means of identifying cardiac dysfunction (a requirement for making a diagnosis of HF). Echocardiography may also be used as a biomarker in HF management and the severity of both systolic and diastolic dysfunction provide important prognostic information in this patient group. Accurate assessment of LVFP is fundamental in the management of HF; elevated LVFP is responsible for symptoms of breathlessness and the cause of most hospitalisations for HF [358]. High LVFP predicts rehospitalisation and death and the magnitude to which pressure can be reduced predicts survival [359]. An accurate non-invasive method of assessing LVFP would be of great benefit in the management of patients with decompensated HF. Many studies have evaluated the relationship of both BNP and of echocardiographic measures of diastolic function (in particular the tissue Doppler E/Ea) to left sided filling pressure (LVEDP, PCWP, LA pressure) and to each other. BNP and E/Ea appear to be related to each other and to left sided filling pressure assessed in a variety of ways, and so are appealing non-invasive biomarkers in the assessment of left sided filling pressure. The literature review presented in Chapter 3 of this thesis backgrounds this information.

Recognising this relationship between BNP, E/Ea and left sided filling pressure; the studies presented in Chapters 4 and 5 were designed to explore this relationship further.

Although BNP and E/Ea are complementary diagnostic and prognostic biomarkers in HF patients little information existed on the relationship between BNP and E/Ea during a hospital admission for HF. Abnormal levels of both measures, in part, reflect abnormal haemodynamics. The study presented in Chapter 4 was conducted to explore the relationship between these two biomarkers further; the hypothesis was that both parameters would change during inpatient treatment for decompensated HF and that those changes would be related. After an average hospital stay of 5.5 days patients had improved sufficiently to be discharged. At discharge there was a significant reduction in BNP-32 level (although this remained markedly elevated); and E/Ea which was increased at the time of hospital admission did not decrease by discharge. Interestingly, while patient symptoms were significantly improved, no reduction in patient weight or improvement in heart rate or blood pressure was observed. It is likely that at the time of hospital discharge most patients remained decompensated. This data suggests that the temporal response of E/Ea during a short hospitalisation does not mirror changes in BNP-32. Although E/Ea and BNP provide similar diagnostic and prognostic information in HF patients they do not respond in the same way during treatment

for acute decompensated HF. These variables are complementary rather than interchangeable.

When the study presented in Chapter 5 of this thesis was conceived the concept of titrating HF therapy to a particular biomarker (BNP level) held great promise based on the results of several small studies [93, 156, 157]. BNP-guided HF therapy was associated with a significant reduction in death or hospitalisation for HF without significant adverse effects [157]. This observational study explored the response of E/Ea during outpatient BNP-guided HF treatment titration. Treatment was titrated according to a standardised protocol aiming to reduce the NT-proBNP level to <200pmol/L. At each titration, echocardiographic variables were also assessed. Treatment titration was associated with a significant reduction in NT-proBNP level (per protocol) and significant improvements in patient symptoms and functional capacity. Doses of ACE inhibitor, βB, and aldosterone antagonist medications were significantly increased. Treatment titration was associated with a significant reduction in E/Ea and this relationship held true in those patients who responded to treatment (>50% reduction in NT-proBNP during treatment titration) and those who did not. This data suggest that during outpatient HF treatment titration both NT-proBNP and E/Ea respond in a similar way (although examination of week by week changes in both variables suggest that the response of E/Ea may lag behind that of NT-proBNP).

The role of BNP-guided HF therapy is less clear with the subsequent publication of several large studies evaluating this approach in the current era of modern HF pharmacotherapy (including βB therapy) [161-164]. The STARS-BNP study [162] randomised patients, thought to be optimally treated, to guideline based therapy or to a goal of reducing BNP-32 to <100pmol/L. This study showed a reduction in death related to HF or hospitalisation in the BNP-guided group. All cause mortality was not reduced. The TIME-CHF study [161] was very similar in design. This study showed improvements in survival free of HF hospitalisation in the BNP guided group (restricted to patients under the age of 75 years) but no improvements in all cause mortality. Preliminary data from two other studies, the STARBRITE study [163] and the BATTLESCARRED study [164] are consistent with these results; suggesting that BNP-guided therapy is associated with a reduction in HF hospitalisation. The benefits in the BATTLESCARRED study were also restricted to those patients aged <75 years. It is clear therefore that "one size does not fit all" and BNP-guided HF therapy may be only beneficial in younger HF patients. It is likely that the lack of benefit in older patients (who have increased as a proportion of the HF population) may relate to

adverse effects experienced by the progressive up-titration of multiple medications. The ultimate role of BNP-guided therapy needs to be further explored in larger studies targeting specific populations.

It has become aparrent, that similarly to BNP, when studied in multiple populations E/Ea is not simply a non-invasive surrogate for left sided filling pressure. Initial data described a close relationship between E/Ea and LVFP in a variety of clinical situations including HF, tachycardia, AF, hypertrophic cardiomyopathy and cardiac transplantation [203, 205, 360, 361] and that E/Ea tracked changes in PCWP in patients with acute decompensated HF [265]. Recently published data from a large group of patients with advanced HF (NYHA class III and IV) who underwent simultaneous haemodynamic and echocardiographic assessment suggest that the relationship between E/Ea and measured PCWP is much less clear [362]. This study found that the predictive value of E/Ea to identify an elevated PCWP was poor (sensitivity 66%, specificity 50%) and that there was no correlation between E/Ea and PCWP. Unlike previous reports no correlation was observed between absolute changes in E/Ea and PCWP. This data highlights the complex relationship between left sided filling pressure, cardiac structure and function, and non-invasive measures such as E/Ea and BNP, all of which are influenced by multiple factors. Although these biomarkers are related to each other in many clinical situations and may provide similar and complementary diagnostic and prognostic information they are not surrogates for each other and are not simply interchangeable.

The issues raised above highlight the complexity of managing HF in individual patients who frequently would not have been eligible for clinical trials in which a particular disease modifying therapy was tested [363]. Co-morbid disease is very common in patients with HF and adds to the complexity of patient management. AF commonly co-exists with HF, the prevalence of AF increases as severity of HF increases [31], and the presence of AF in a patient with HF may lead to adverse haemodynamic consequences [298]. Despite the known adverse effects of AF, it has been uncertain from published data if the presence of AF in patients with a diagnosis of HF is associated with an adverse outcome compared to HF patients in SR (rather than simply a bystander of disease severity).

Chapter 6 of this thesis describes a meta-analysis combining the results of all studies investigating the prognosis of patients with HF and co-existing AF compare to those with SR. This study combined the results of 20 studies (32,946 patients, 10,819 deaths). Observational

studies and RCT's were analysed separately because heterogeneity was expected. Eight RCTs were included (22,651 patients, 7,920 deaths). In this population the prevalence of AF was 15%. Crude mortality rates were higher in those with AF (46%) compared to SR (33%) and the odds of death was 1.33 (1.12-1.59) for those with AF compared to SR. Twelve observational studies were included (10,295 patients, 2,899 deaths). In this population the prevalence of AF in this population was 23%. Crude mortality rates were higher in those with AF (38%) compared to SR (25) and the odds of death was 1.57 (1.20-2.05) for those with AF compared to SR. This data confirms that the presence of AF in patients with HF is associated with an adverse effect on mortality, although this study (because of the inherent limitations of literature-based meta-analysis) does not confirm the independence of this adverse affect on mortality from other confounding variables such as patient age, gender, and severity of HF.

Strategies of "rhythm control" in patients with HF have been disappointing. The AF-CHF trial [34] randomised patients with reduced LVEF to an aggressive rhythm control approach (including cardioversion and the use of antiarrhythmic drug therapy) or rate control (aiming for a target heart rate of <80bpm at rest or <110bpm with exercise). This study showed no difference in the rates of cardiovascular death (the primary end point) between the two treatment arms. Potential reasons for this lack of effect include; the fact that the adverse effect of AF in HF patients may not be independent of other negative prognostic features such as worse ventricular function and neurohormonal activation, and that the potential benefit of maintenance of SR in HF patients was outweighed by the adverse effects of antiarrhythmic drugs. To further evaluate the question of whether the return to SR is superior in patients with HF and AF, randomised studies comparing catheter ablation of AF in this patient group are required. One small study has been recently published comparing pulmonary vein isolation (catheter ablation of AF) to AV node ablation and CRT in patients with symptomatic, drug-resistant AF, an EF of 40% or less, and NYHA class II or III HF [364]. This study showed that pulmonary vein isolation was associated with significant improvements in quality of life and functional capacity. This data needs to be confirmed in other larger studies and it is unclear whether these benefits will translate to the broader population of HF patients who may not meet the entry criteria for this study.

Neurohormonal manipulation remains the cornerstone of HF pharmacotherapy based on the results of seminal studies confirming the benefits of ace inhibition [280, 281, 365] or angiotensin receptor blockade [366], beta blockade [283-285, 367], and aldosterone

antagonism [35, 36]. The recognition of the importance of neurohormonal manipulation in HF management has lead to the use of neurohormones as biomarkers as discussed above. Cardiovascular diseases such as IHD and valvular heart disease are important risk factors for the development of HF. Neurohormones clearly play a role in the pathophysiology of these diseases; treatment with an ARA improves outcomes in patients with severe HF and in patients with impaired LV systolic function after myocardial infarction [35, 36]. However it is not known whether the adverse effects of aldosterone are due to increased circulating aldosterone alone. Some animal [40, 41, 338, 339] and human studies [41-43, 45] suggest aldosterone can be synthesised within the myocardium as well as from the adrenal gland. It is therefore possible aldosterone could have pathophysiological roles in cardiovascular disease which are independent of the systemic renin-angiotensin-aldosterone system [44].

The study described in Chapter 7 evaluated whether aldosterone released from the myocardium in patients with severe AS and patients with IHD and normal EF. This study demonstrated that in this patient population, a step-up in plasma concentration occurred between the aortic root and coronary sinus despite normal circulating plasma levels of aldosterone, indicating myocardial release of aldosterone, as well as angiotensin II. No association was noted between mixed venous plasma levels of these hormones and the magnitude of the coronary sinus step-up, suggesting that synthesis of these hormones may be independent of the systemic renin-angiotensin system. The data presented in this chapter expands current knowledge of the role of these cardiac neurohormones in cardiovascular disease and strengthens the rationale for evaluating ARAs in clinical situations not characterised by increased circulating aldosterone.

The themes of research presented in this thesis are linked by the wish add to current knowledge regarding various facets of contemporary HF management. The focus of this body of work has been firstly to quantify the extent of the HF burden in New Zealand, and to identify changes in epidemiology which have occurred on the background of changing HF treatment, and secondly to evaluate and understand the roles of biomarkers (neurohormones, echocardiographic measures of diastolic function), and co-morbid disease on HF management with a focus on the individual patient. These aims have been achieved with the execution and publication of the studies described in the chapters contained within this thesis.

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