Microvolt T-Wave Alternans in Chronic Heart Failure: A Study of Prevalence and Incremental Prognostic Value

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Declaration

The work described in this thesis was carried out while I was employed as a Clinical Research Fellow in the University Division of Cardiovascular and Medical Sciences at the British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow. Supervision was provided by Professor John McMurray, Professor Stuart Cobbe and Dr Mark Petrie.

Recruitment of patients from Glasgow Royal Infirmary was undertaken by me. Dr Yannis Tsorlalis recruited patients from the Western Infirmary, under my supervision (Dr Tsorlalis is currently performing a separate study of corticosteroids in heart failure using samples from the patients involved in this study). Patients from the Royal Alexandra Hospital were recruited by myself and research nurses from the Glasgow Clinical Research Facility.

I conducted all of the follow-up study visits. Echocardiography at the study visit was performed by me and offline calculations of ejection fraction were performed by Mr Tony Cunningham. All MTWA tests were carried out by me with assistance from the research nurses. All automated computer-generated MTWA test results were interpreted by Dr Rachel Myles. Biochemical and haematological analyses were carried out in the local hospital laboratories. Measurement of BNP was provided by Dr Richard Spooner. Construction of the database was performed by me and several database managers at the Robertson Centre for Biostatistics, University of Glasgow. The more complex statistical analyses were performed by Dr Vladimir Bezylak and Ms Nicola Greenlaw, under the supervision of Professor Ian Ford.

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Table of Contents

Index of Tables

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

Index of Figures

Chapter 5

Chapter 6

Abbreviations

ABCD	Alternans Before Cardioverter Defibrillator
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
AF	Atrial fibrillation
ALPHA	Microvolt T-wave Alternans in Patients with Heart Failure
ALT	Alanine transaminase
ANOVA	Analysis of variance
AR	Aortic regurgitation
ARB	Angiotensin-receptor blocker
AS	Aortic stenosis
AST	Aspartate transaminase
AV	Atrioventricular
β-blocker	Beta-blocker
BHF	British Heart Foundation
BMI	Body mass index
BNP	B-type natriuretic peptide
BPM	Beats per minute
CABG	Coronary artery bypass graft
CARISMA	Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction
CHARM	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease

CRP	C-reactive protein
CRT	Cardiac resynchronisation therapy
CRT-D	Cardiac resynchronisation therapy with defibrillator
CRT-P	Cardiac resynchronisation therapy with pacemaker only
CVA	Cerebrovascular accident
CXR	Chest X-ray
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra acetic acid
EGFR	Estimated glomerular filtration rate
EF	Ejection fraction
EPS	Electrophysiological study
ESC	European Society of Cardiology
FBC	Full blood count
GGT	Gamma glutamyl transpeptidase
HBA1c	Glycosylated haemoglobin
HDL	High density lipoprotein
HF	Heart failure
HF-PEF	Heart failure with preserved ejection fraction
HR	Hazard ratio
HF-REF	Heart failure with reduced ejection fraction
ICD	Implantable cardioverter-defibrillator
ICD-10	International classification of diseases (version 10) coding system
IQR	Inter-quartile range
ISD	Information services division
JVP	Jugular venous pressure

LBBB	Left bundle branch block
LV	Left ventricle/ventricular
LVEF	Left ventricular ejection fraction
LFT	Liver function tests
LVH	Left ventricular hypertrophy
LVSD	Left ventricular systolic dysfunction
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MASTER	Microvolt T-Wave AlternanS Testing for Risk Stratification of Post MI Patients
MDRD	Modification of Diet in Renal Disease
MET	Metabolic equivalent value
MR	Mitral regurgitation
MS	Mitral stenosis
MTWA	Microvolt T-wave alternans
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NPV	Negative predictive value
NSAID	Non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal-proBNP
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PND	Paroxysmal nocturnal dyspnoea
QTc	QT interval corrected for heart rate
RBBB	Right bundle branch block
RDW	Red cell distribution width

RR	Relative risk
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SCD-HeFT	Sudden cardiac death in Heart Failure Trial
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SpO_2	Saturation of oxygen
SPSS	Statistical package for the social sciences
SSS	Sick sinus syndrome
SVT	Supraventricular tachycardia
T4	Thyroxine
TIA	Transient ischaemic attack
TFT	Thyroid function test
TR	Tricuspid regurgitation
TSH	Thyroid stimulating hormone
U&E	Urea and electrolytes
UK	United Kingdom
VO_2	Oxygen consumption
VF	Ventricular fibrillation
VT	Ventricular tachycardia
VTE	Ventricular tachyarrhythmic events
WBC	White blood cell
WHO	World Health Organization

Summary

Heart failure (HF) is a major health concern internationally and associated with considerable mortality and morbidity. Patients with HF are at risk of sudden cardiac death (SCD). Most SCD is caused by ventricular tachyarrhythmic events (VTE) that can be treated with an implantable cardioverter-defibrillator (ICD). Identifying patients at risk of VTE remains a clinical challenge.

Microvolt T-wave alternans (MTWA) examines beat-to-beat fluctuations in the morphology of the electrocardiographic T-wave. The presence of significant alternans is thought to reflect dynamic instability of repolarisation and be mechanistically linked to VTE. MTWA testing can be performed clinically using a commercially available system. Patients must be in sinus rhythm and the heart rate is increased up to a maximum of 110 beats per minute by using sub maximal treadmill exercise. Observational studies in highly selected populations have suggested that MTWA testing may be used as a non-invasive tool for identifying patients at risk of VTE who, by implication, may benefit from primary prevention ICD therapy. However, to date, no study has investigated the use of MTWA testing in a real-life population of patients with HF.

The main aims of this study were to evaluate the applicability of MTWA testing in an unselected cohort of patients recently hospitalised with decompensated HF and determine the prevalence and incremental prognostic value of this test.

Of 2361 patients with suspected decompensated HF screened for inclusion in the study, 1003 were recruited. Of those recruited, 648 patients attended the study visit for MTWA testing one month following hospital discharge. The most common reason for failing to attend the study visit was refusal to participate; other reasons were deteriorating health and death before the study visit appointment.

The mean age of those returning for MTWA testing was 71 years (SD 11) and 58% were male. Of 648 patients who completed the study visit, 330 (51%) were eligible for MTWA testing. Almost half were ineligible for MTWA testing due to atrial fibrillation (AF), pacemaker-dependency or physical inability to undertake the treadmill test. AF accounted for three-quarters of those who were ineligible in this study, i.e. 38% of all patients. Although only a small proportion of patients (7%) overall were ineligible because of physical inability to attempt the sub-maximal treadmill test, this is an underestimate of this problem as many patients simply did not attend for the test because of poor health.

Many of the characteristics of the ineligible patients in this study suggested they had a poor prognosis, including the highest log (BNP) concentration. BNP is also an independent predictor of sudden cardiac death, suggesting that the patients at the highest arrhythmic risk may in fact not be eligible for MTWA testing. These findings suggest the utility of the MTWA test as a means of detecting those at highest risk of sudden death is likely to be limited as many such patients are ineligible for the test. Patients ineligible for MTWA testing were older than patients eligible for testing and a higher proportion had a history of pre-admission heart failure. Ineligible patients also had more evidence of persisting or advanced heart failure, with a higher proportion having NYHA functional class III or IV symptoms and a greater frequency of peripheral oedema. Those ineligible for MTWA testing also had a greater prevalence of renal dysfunction, liver enzyme abnormalities, hyperuricaemia and lymphopenia.

The clinical data collected at the study visit was analysed according to whether patients had HF with preserved ejection fraction (HF-PEF) or reduced ejection fraction (HF-REF). The majority of clinical characteristics were similar between the two groups although there were some notable differences. Patients with HF-PEF were older, more likely to be female, more likely to have hypertension and less likely to have had a myocardial infarction (MI), in comparison to those with HF-REF. These findings are consistent with previous studies of HF-PEF. Prescribing of HF pharmacological therapies was greater amongst patients with HF-REF. Patients with HF-REF had median BNP concentrations almost twice that of those with HF-PEF, both on admission to hospital and at the study visit.

Of 330 patients who underwent MTWA treadmill testing, 100 (30%) were positive, 78 (24%) were negative and 152 (46%) were indeterminate (unable to be classified as positive or negative). The majority of indeterminate tests (75%) occurred because of failure to achieve the target heart rate due to chronotropic incompetence, secondary to beta-blocker therapy, or physical limitations. There were more abnormal clinical characteristics associated with an indeterminate result, than a positive or negative result. Patients with an indeterminate result were older and more likely to have a history of HF, diabetes, AF, anaemia and renal dysfunction, as well as a higher log (BNP). Patients with positive and indeterminate MTWA tests were quite different, in terms of clinical characteristics, questioning the contemporary way of classifying these results as 'non-negative'.

The mean follow-up was 18 months (SD 8.1) and 131 deaths occurred during this period. There were proportionately more deaths amongst the patients ineligible for MTWA testing than those eligible. There was no significant difference in mortality rates between patients with HF-PEF and HF-REF. There was no significant difference in crude all-cause mortality rates between the three MTWA groups. Unexpectedly, patients with negative and indeterminate results had proportionately similar mortality rates whilst those with positive results had proportionately fewest events overall. MTWA was analysed in the accepted way of 'non-negative' (positive and indeterminate) and negative, but this did not alter the results. Indeed, the very different mortality for those patients with positive and indeterminate results challenges the use of this 'non-negative' classification.

MTWA had no incremental prognostic value when added to a multivariable model containing the strongest predictors of mortality in this study. The independent predictors of all-cause mortality following stepwise multivariable modelling were; lower body mass index, New York Heart Association class III-IV, previous myocardial infarction, elevated BNP concentration and elevated troponin levels.

In summary, MTWA treadmill-testing was not widely applicable in typical patients with HF and failed to predict mortality risk. At present MTWA cannot be endorsed as a tool for improving risk stratification in HF.

CHAPTER ONE

INTRODUCTION

1.1 Epidemiology and pathophysiology of heart failure

1.1.1 Definition of heart failure

Heart failure (HF) is the clinical syndrome that occurs when the ventricle fails to properly fill with or eject blood. It commonly presents with symptoms of breathlessness and fatigue and clinical signs of fluid retention. Depending on the timing of symptoms and signs, HF may present in one of three ways; acute '*de novo*' HF, chronic HF or acute decompensation of chronic HF. Acute '*de novo'* HF may present as acute pulmonary oedema or cardiogenic shock, often in the context of an acute coronary syndrome.

1.1.2 Global burden of heart failure

HF is a significant public health problem internationally. In Europe the overall prevalence is 2-3% (1). The prevalence of HF correlates with age and increases exponentially, rising to 10-20% for septuagenarians. Younger patients with HF are more likely to be men with reduced systolic function secondary to myocardial infarction, predominantly because coronary heart disease occurs earlier in men. On the other hand, elderly patients with HF are more likely to be women with HF with preserved systolic function, secondary to established hypertension (2). Overall the prevalence of HF is rising, particularly in developed countries as life expectancy improves. Thus the burden this health problem has on society is increasing. The incidence of HF is also age-related. In the United Kingdom (UK), a population-based study found that the majority of new diagnoses of HF occur in the elderly with an incidence rate of 0.2 cases per 1000 population per year for 45-55 year olds, rising to 11.6 in those 85 years and over (3). In this study the incidence was greater in males and the median age at presentation was 76 years.

The financial burden of HF is huge and growing. The cause of this is multifactorial and includes the increasing prevalence of HF, an ageing population, a rising rate of hospital admissions for HF and the availability of expensive therapies that are revolutionising treatment of this condition. The implications for healthcare systems are substantial. Between

1-2% of the National Health Service (NHS) budget is spent on HF (4), whilst in the United States a recent estimate for annual expenditure for HF was 27.9 billion dollars (5). In the UK, HF accounts for around 5% of all hospital admissions (3) and readmission rates are high, almost one-third of patients hospitalised with HF may be readmitted within one year of discharge (6). Unsurprisingly, hospitalisation costs account for the majority of the budget spent on HF.

1.1.3 Aetiology of heart failure

HF may result from a broad spectrum of structural or functional cardiac and non-cardiac disorders and is often the end-stage of many forms of cardiovascular disease. The common causes of HF and their clinical presentations are outlined in Table 1-1. Causes of HF can be categorised into disorders of the pericardium, myocardium, endocardium or great vessels. Myocardial disorders are the most common causes of HF and are often classified according to ejection fraction (EF), namely HF with reduced ejection fraction (HF-REF) or HF with preserved ejection fraction (HF-PEF). HF-PEF is discussed in more detail below (section 1.1.5). HF-REF is also commonly classed as ischaemic or non-ischaemic HF. Common causes of non-ischaemic HF-REF include hypertension, valvular heart disease, arrhythmias, alcohol and dilated cardiomyopathy. The cardiomyopathies are a collection of myocardial diseases that are often, but not exclusively, familial in which the diagnosis can only be made after the exclusion of other causes of heart failure. The different types of cardiomyopathy are hypertrophic, dilated, restrictive, arrhythmogenic right ventricular and unclassified (7). Hypertension is also a common cause of HF-PEF. Other causes of HF-PEF include hypertrophic, restrictive and infiltrative cardiomyopathies. HF-PEF often occurs in association with atrial fibrillation (AF). Other causes of HF are presented in Table 1-2.

Aetiology and risk factors for HF exhibit geographical variation. Coronary heart disease is undoubtedly the most common cause of HF in developed countries, accounting for approximately 70% of cases (8). Hypertension is the next commonest cause in Western countries, followed by valvular heart disease (particularly degenerative) and cardiomyopathies. Arrhythmias and alcohol are also frequent precursors of HF in developed countries. In

Africans and African Americans, hypertension is a common cause of HF (9), whilst in South America Chagas disease is often implicated (10). In developing countries, rheumatic valvular heart disease and nutritional deficiencies are more common causes of HF (11).

Coronary heart disease has not always been the commonest cause of HF in Western societies. Hypertension was the most common cause in the original Framingham study (12). However the proportion of cases of HF caused by hypertension has decreased over the follow-up period, whilst those attributed to coronary heart disease have risen. The reasons for the changing aetiology of HF are likely multifactorial and include improvements in survival after a myocardial infarction (13) as well as increasing accessibility to techniques for diagnosing coronary heart disease. Hypertension may be responsible for fewer cases of HF owing to pharmacological advances in antihypertensive therapy preventing the longer term complications such as HF (14).

Table 1-1: Common causes of heart failure and their common modes of presentation

Cause	Examples of presentations
Coronary heart disease	Myocardial infarction
	Chronic ischaemia
	Arrhythmias
Hypertension	Heart failure with preserved systolic function
	'Burnt out' hypertensive cardiomyopathy
	Malignant hypertension with acute pulmonary oedema
Valvular heart disease	Degenerative
	Rheumatic fever
	Endocarditis
	Congenital valve disease
Arrhythmias	Atrial fibrillation
Cardiomyopathies	Idiopathic
	Alcohol

Table 1-2: Other causes of heart failure and their modes of presentation

Cause	Examples of presentations
Cardiomyopathies	Familial
	Peripartum
	Toxins (cocaine, iron, copper)
Congenital heart disease	Corrected transposition of great arteries
	Repaired tetralogy of Fallot
	Ebstein's anomaly
Infective	Viral myocarditis
	Chagas disease
	Human immunodeficiency virus
	Lyme disease
Iatrogenic	Anthracyclines
	Abstruzimab
	Steroids
Infiltrative	Amyloid
	Sarcoid
	Neoplastic
Storage disorders	Haemachromatosis
	Fabry disease
	Glycogen storage diseases
Endomyocardial disease	Radiotherapy
	Endomyocardial fibrosis
	Carcinoid
Pericardial disease	Calcification
	Infiltrative
Metabolic	Endocrine (e.g. acromegaly, thyroid disease)
	Nutritional (e.g. deficiency of thiamine, selenium)
	Autoimmune (e.g. scleroderma)
Neuromuscular disease	Friedreich's ataxia
	Muscular dystrophy
High-output	Anaemia
	Thyrotoxicosis
	Arteriovenous fistulae
	Paget's disease

1.1.4 Diagnosis of heart failure

The Heart Failure Association of the European Society of Cardiology (ESC) specify that three diagnostic criteria must be met in order to make the diagnosis of HF (1). Firstly, the patient must experience symptoms characteristic of this condition. These include breathlessness, fatigue and ankle swelling. Secondly the patient should have clinical signs indicative of HF, including amongst others; tachypnoea, tachycardia, raised jugular venous pressure, pulmonary crepitations, pleural effusions and peripheral oedema. Finally, there must be objective evidence of structural or functional cardiac disease. This may be verified by evidence of cardiomegaly, a third heart sound, echocardiographic abnormalities or a raised natriuretic peptide level.

1.1.5 Heart failure with preserved ejection fraction

Myocardial disorders account for the vast majority of cases of HF, caused by either systolic or diastolic dysfunction. Systolic dysfunction leads to a low left ventricular ejection fraction (LVEF). Diastolic dysfunction impairs left ventricular (LV) distensibility, filling and relaxation, irrespective of LVEF. Yet, patients with HF are often subdivided according to their EF; HF-REF or HF-PEF. One possible explanation for this is because of the difficulties measuring diastolic dysfunction. HF-PEF diagnosed solely by LVEF may encompass patients without diastolic dysfunction. Indeed, the major clinical trials of pharmacological therapy in HF-PEF enrolled patients solely on the basis of an echocardiographically assessed LVEF (15-17). HF-REF may also include patients with diastolic dysfunction. Unlike HF-REF, HF-PEF remains a diagnosis of exclusion. Non-cardiac causes of signs and symptoms of HF must be excluded before HF-PEF can be accurately diagnosed.

The LVEF cut-off criterion for HF-PEF varies in different guidelines and studies. A recent ESC consensus statement includes more than just LVEF in the diagnostic criteria of HF-PEF (18). In addition to the presence of signs or symptoms of HF and normal or mild LVSD, these guidelines recommend that there should be evidence of diastolic dysfunction, obtained invasively or non-invasively. Normal or mild LVSD is defined as LVEF > 50% (18).

HF-PEF and HF-REF may be considered as two ends of a spectrum. Both lead to reductions in exercise tolerance and activation of neurohormonal systems with different myocardial remodelling processes. HF-PEF is recognised as a precursor to HF-REF in several causes of HF, for example hypertension and the cardiomyopathies. Epidemiological studies have revealed that as many as 50% of HF patients with acute decompensation have HF-PEF (19-23). HF-PEF is the principal cause of HF in the elderly and in women (23;24). Although previously considered to have a more favourable prognosis than HF-REF, HF-PEF is now considered to be associated with significant mortality risk. The mortality rates of HF-PEF vary between clinical studies. This variation may be explained by the heterogeneity of the populations studied and the diagnostic criteria used for HF-PEF. Recent large population studies have reported one year mortality rates of 22% and 29% in patients with HF-PEF (19;23), comparable to one year mortality rates of 21% observed in a recent local study (25). Yet, despite the poor prognosis associated with this condition, treatment of HF-PEF remains challenging and largely symptomatic based. This is in stark contrast to HF-REF, for which a large evidence-base exists.

1.1.6 Treatment of heart failure

The treatment of HF-REF consists of pharmacological, device and surgical therapy. Advances in pharmacological therapy over the last three decades have significantly improved the prognosis for many patients with HF-REF. The first step of managing HF-REF should involve initiating diuretic therapy and an angiotensin-converting enzyme (ACE) inhibitor. There is a large evidence-base for the use of ACE inhibitors in HF-REF for improving both mortality and morbidity (26;27). For patients hospitalised with decompensated HF, an ACE inhibitor should be initiated prior to discharge from hospital. Patients intolerant of ACE inhibitors may be prescribed an angiotensin-receptor blocker (ARB) (28). All patients with HF-REF should also be treated with a beta-blocker, unless contraindicated. There is significant evidence of improved mortality and morbidity with the use of beta-blockers in addition to ACE inhibitor therapy (29-31). Patients hospitalised with decompensated HF may be commenced on beta-blocker therapy prior to discharge, once they are stable and euvolaemic (31). Following ACE inhibitor and beta-blocker therapy, patients with HF-REF and persistent symptoms should be started on an aldosterone antagonist (32;33).

The introduction of device therapy, in the form of the implantable cardioverter defibrillator (ICD) and, more recently, cardiac synchronisation therapy (CRT), has revolutionised the treatment of HF-REF. ICDs have been demonstrated to reduce the risk of sudden cardiac death in patients with HF-REF. The majority of evidence for this comes from trials involving patients with coronary heart disease (34-36) although there is evidence of survival benefit in patients with non-ischaemic HF-REF (37). CRT with pacemaker function (CRT-P) should be considered for patients with moderate-severe HF (New York Heart Association [NYHA] III-IV) with left ventricular ejection fraction (LVEF) $\leq$ 35% and QRS duration $\geq$ 120ms that remain symptomatic despite optimal medical therapy (38). Patients who fulfil criteria for CRT-P and who have a life expectancy exceeding 1 year should be considered for CRT-D (39). Patients with mild HF (NYHA I-II, LVEF $\leq$ 30% and QRS duration $\geq$ 130ms) (40) and those with mild-moderate HF (NYHA II-III, LVEF $\leq$ 30% and QRS duration $\geq$ 120ms) (41) should also now be considered for CRT-D.

Surgical treatment for advanced HF-REF is available in the form of cardiac transplantation, ventricular assist devices and artificial hearts. These are therapies of limited resource, for financial and availability reasons, and therefore must be targeted to those at highest risk of dying and greatest potential for benefit. Patients with HF, LVEF $\leq$ 35% and coronary artery disease amenable to coronary artery bypass grafting (CABG) may be considered for CABG, although a recent trial showed no difference in all-cause mortality compared with medical therapy alone (42).

The evidence-base for the treatment of HF-PEF is less clear. Diuretics are used for symptomatic control and fluid balance. There is evidence that ARBs reduce hospital admissions in patients with HF and preserved systolic function (15). However there is no evidence of mortality benefit with modulation of the renin angiotensin system (15-17). Results are awaited for the effect of aldosterone antagonist therapy in HF-PEF (43).

1.1.7 Prognosis in heart failure

Although advances in the modalities of treatment have greatly improved the prognosis for patients with HF, the outlook for many remains poor. The mortality rate is high and comparable with rates seen in many common cancers (44). Around 50% of patients with heart failure will be dead at 4 years (1). The morbidity and mortality associated with hospitalisation for HF is dire; 40% of patients will be readmitted or dead within 1 year (1). The mortality rate for new cases of HF admitted to hospital is highest within the first few weeks with a 30 day mortality rate approximately 10-20% (2).

1.2 Prognostication in heart failure

1.2.1 Importance of assessing prognosis

Determining whether a patient with HF is at high risk of mortality is important for several reasons. Optimal tolerated doses of evidence-based medical therapies are indicated regardless of risk status. However, other therapies for which there are limited resources, such as ICDs, CRT and cardiac transplantation should be targeted to those at highest risk of dying and greatest chance of benefit. Those at particularly high risk of dying can be considered for appropriate end-of life care. Benefits can also come from identifying those at low risk of dying. Patients at lower risk could be reassured that invasive therapies (e.g. ICDs or transplantation) are unlikely to be in their interests.

Accurate assessments of prognosis can also confer economic benefits. This is particularly important given the financial burden associated with HF. The majority of this expenditure is incurred in the provision of inpatient care. Identifying low risk patients in hospital may allow appropriate early discharge, thus improving hospital efficiency and targeting intensive monitoring and longer hospital stays to high risk patients. Furthermore, identifying patients at high risk of admission or readmission to hospital might allow targeted interventions to lower hospitalisation rates.

A universal approach to defining prognosis in HF is complicated for several reasons. HF is a clinical syndrome with a range of aetiologies and mechanisms and is associated with both reduced and preserved LV systolic function. Patients with HF often have co-morbidities which also influence prognosis. For these reasons, many individual predictors of morbidity and mortality do not have independent predictive power when incorporated into multivariable models. Moreover, patients with HF face competing risks of progressive pump failure and sudden cardiac death (SCD). Thus predicting prognosis for patients with HF is extremely challenging.

Yet despite the recognised importance of prognostication in HF, accurate determination of individual risk within this large and heterogeneous population is a major challenge. It has recently been demonstrated that physicians often fail to accurately predict mortality for patients with advanced HF (45).

1.2.2 Traditional predictors of prognosis in heart failure

Many individual markers have been associated with an increased risk of mortality and morbidity in HF. These include a spectrum of demographic data, past medical history, physical examination findings, comorbidity, aetiology of HF, electrocardiographic parameters, echocardiographic variables, exercise-related parameters, laboratory blood results and haemodynamic variables. Some of these markers, for example the natriuretic peptides, have been identified to be independently predictive in comprehensive multivariable analyses undertaken in large cohorts of HF patients. However, many markers have limited prognostic ability having been identified in small cohorts after only univariate or limited multivariable analyses. Few markers have been evaluated in the prediction of cause-specific death. The established prognostic markers in HF are displayed in Table 1-3.

The use of individual risk markers in isolation has limited prognostic utility. The absence or presence of a single risk marker does not necessarily convey a good or bad prognosis. Multiple individual risk markers may be present in any given patient. Combining these to predict an individual's prognosis is a challenge that has not yet been adequately met.

Table 1-3: Established prognostic markers in heart failure

Category	Prognostic Marker
Demographics	Age
	Male sex
Comorbidity	Coronary artery disease
	Resuscitated sudden cardiac death
	Chronic renal failure
	Diabetes mellitus
	Anaemia
	Chronic obstructive pulmonary disease
Clinical parameters	Low blood pressure
	Increasing heart rate
	NYHA class III-IV
	Prior HF hospitalisation
Laboratory tests	B-type natriuretic peptides
	Sodium
	Creatinine/Urea/eGFR
	Haemoglobin
Electrophysiological	QRS duration
Imaging	LVEF
	LV end-diastolic dimensions
Haemodynamics	Peak VO_2
	6 minute walk test

eGFR = estimated glomerular filtration rate; VO_2 = oxygen consumption

1.2.3 The B-type natriuretic peptides

The natriuretic peptides consist of a group of 4 hormones (A, B, C and D). The principal role of these hormones is to regulate sodium and water homeostasis via natriuresis, diuresis and vasodilatation. The B-type natriuretic peptides (BNPs) have been most widely studied in HF and their name derives from the site of origin of their discovery - porcine brain (46). However it has since become apparent that the major secretory source of these neurohormones in humans is the left ventricle (LV). ProBNP is the precursor from which the biologically active BNP and inactive N-terminal-proBNP (NT-proBNP) are derived. ProBNP is produced predominantly by ventricular myocytes, and to a lesser extent in the atria, and synthesis increases in response to stretch and dilatation of the LV. The biological half-life of BNP is approximately 20 minutes whilst NT-proBNP, partially excreted by the kidneys, has a half-life of between 1-2 hours. In addition to natriuresis, diuresis and vasodilatation, the physiological actions of BNP also include inhibition of the sympathetic and renin-angiotensin-aldosterone systems and reduction in myocardial fibrosis and vascular smooth muscle proliferation.

Over the last 5-10 years, BNP and NT-proBNP have increasingly been used in HF for diagnostic and prognostic purposes. One of the strengths of this test as a diagnostic tool is its high negative predictive value (47). Clinical use of this biomarker has been endorsed by the ESC guidelines for HF and features in the diagnostic pathway. These guidelines state that a diagnosis of chronic HF is unlikely in untreated patients with normal BNP or NT-proBNP levels (1).

In recent years, BNP has become established as a powerful predictor of prognosis in chronic HF, independent of many other markers of risk. Independent prognostic power for mortality has been demonstrated across the HF spectrum encompassing asymptomatic LVSD (48), mild to moderate severity (49;50) and advanced HF (51). It has also been demonstrated that patients with BNP levels that decrease significantly have a more favourable prognosis. On the other hand, elevated BNP levels that fail to fall or rise over serial measurements confer highest mortality risk (52). Studies evaluating the link between BNP and prognosis have largely concentrated on all-cause mortality or cardiac mortality, incorporating both modes of death in HF; pump failure and SCD. However, one study has established BNP to be the only independent predictor of SCD in chronic HF in a

multivariable analysis including systolic blood pressure (SBP), LVEF, NYHA, coronary heart disease, diabetes, heart rate and HF medications (53).

BNP and NT-proBNP have also been demonstrated to be beneficial in the diagnosis of acute HF. These biomarkers have high negative predictive values for patients presenting to Accident and Emergency departments with breathlessness (54-56). The diagnostic accuracy of BNP has incremental benefit, after multivariable adjustment for standard clinical variables, in the identification of patients with acute HF (55). Akin to its role in chronic HF, BNP has also been shown to be a powerful determinant of prognosis in acute HF (57). BNP levels that rise during an admission with acute HF are predictive of an increased risk of both mortality and readmission with decompensated HF (58). Moreover, one study found a high pre-discharge BNP to be the only significant variable for predicting risk of death or readmission with HF. This followed multivariable adjustment including clinical variables, echocardiographic parameters and percentage change in BNP levels during admission (59).

BNP and NT-proBNP are simple, non-invasive biomarkers with powerful prognostic utility in HF, independent of many established predictors of risk. The BNPs should be incorporated into the management of all patients with HF to guide prognostication.

1.2.4 Cardiac troponin

Cardiac troponins are emerging as potentially powerful biomarkers for prognostication in HF. Troponin is a complex of three integrated proteins (troponin C, troponin I and troponin T), integral to muscle contraction and relaxation and under the regulation of intracellular calcium concentration (60). Cardiac troponin I and troponin T are cardiac specific, levels are not raised following noncardiac injury or disease. Cardiac troponin has become established as the gold standard biomarker for the diagnosis of acute myocardial infarction (61). Acute myocardial ischaemia and necrosis destroys the myocyte structure, resulting in large elevations of the troponin proteins in the bloodstream. Modern troponin assays are able to detect small elevations in cardiac troponin, representative of minor myocardial injury in acute coronary syndromes. These biomarkers provide prognostic information and

are used in the risk stratification process for patients with an acute coronary syndrome (62-64).

Troponin elevation reflects myocardial damage but is not indicative of a specific pathological process. Elevated levels of troponin are detectable in the absence of myocardial ischaemia in a wide range of clinical conditions, including HF. The majority of cardiac troponin is located within the complex involved in the contractile process with the remainder existing in the cytoplasm. The mechanisms of nonischaemic troponin elevations are unclear but are probably related to disruption of the cell membrane and release of cytoplasmic troponin, leading to small rises of troponin concentration in the bloodstream. Possible mechanisms in HF include; ongoing myocyte necrosis in ischaemic LVSD (65), cellular stretch in dilated cardiomyopathy (66-68), ventricular remodelling (69) and chronic activation of the neuroendocrine and inflammatory pathways (70).

Several studies over the last decade have identified an elevated troponin in 10-50% of patients with chronic HF (71-73). Troponin elevation in patients with stable HF may reflect pathophysiological mechanisms such as continual 'cytosolic leakage'. Elevation of this biomarker has been linked with adverse clinical outcomes, including mortality, hospitalisation with HF and cardiac transplantation (71-75). A multimarker approach with BNP and other established biomarkers has recently been shown to improve risk stratification in two modest-sized studies of patients with advanced HF (71;75). Only one study published to date has included troponin in a prognostic risk score for chronic HF (76). This large study stratified patients into risk categories using ten non-invasive variables, including troponin and NT-proBNP. A high score corresponded with a four-fold risk of the primary outcome of cardiac mortality. This risk tool is yet to be validated in an external cohort to determine its applicability to a general HF population.

More recently, troponin elevation has been identified in patients with acute decompensated HF. Unsurprisingly, these studies have found high proportions of patients to have raised troponin levels in the decompensated state (69;70;77-82). Elevation of troponin has also been linked to adverse clinical events in these studies. Although many of these studies have evaluated the incremental prognostic value of an elevated troponin, albeit some in limited multivariable analyses, the incorporation of troponin into a prognostic risk tool is currently lacking for acute HF.

Troponin elevation is common in chronic and acute HF, the prognostic significance of which is emerging. Many studies to date have evaluated the impact of a raised troponin in univariate or limited multivariable analyses. More recent analyses have shown an incremental prognostic value for troponin over the natriuretic peptides. No studies have evaluated the significance of elevated troponin in prediction of cause-specific death in HF. The combination of troponin with other established biomarkers in the form of a prognostic scoring tool may improve risk stratification in HF.

1.2.5 Rationale for improving prognostication

There remains a real need for improving prognostication in order to improve the management of patients with heart failure. This is essential in an era in which complex therapies are improving outcomes but are limited by resources and financial restraints. Accurate targeting of these therapies is required to optimise their use. An accurate means of predicting an individual's risk will facilitate the efficient allocation of therapies and provide physicians with an objective assessment of their patient's prognosis. The latter may enable medical staff to have more honest and informative discussions with their patients regarding prognosis. In a wider sense, improving risk assessment in HF may further knowledge of the pathophysiology of this condition. Identification of novel biomarkers and determining the combinations of variables which identify those at greatest risk are likely to provide avenues for further research and new targets for potential therapeutic intervention.

1.2.6 Identifying cause-specific mortality in heart failure

Many established and novel biomarkers are predictive of an increased risk of all-cause mortality. Few biomarkers have demonstrated a capability to determine cause-specific mortality. This is particularly relevant in HF where many deaths may be attributed to SCD caused by ventricular tachyarrhythmic events (VTE) and better selection of candidates for primary prevention ICD devices is warranted. Many guidelines advocate the use of LVEF to select candidates who would most benefit from device implantation (1;83;84), as this was what gated the clinical trials inclusion criteria. However, in the largest randomised controlled trial evaluating primary prevention ICD therapy in patients with reduced LVEF

HF, 79% of patients in the ICD arm did not use their device (37). Moreover the absolute risk reduction in the group randomised to ICD therapy was modest at 7.2% over 5 years follow-up. Although this landmark study clearly demonstrated the mortality benefit associated with reducing SCD in HF, it also highlighted the limitation of LVEF in isolation for identifying those at risk of SCD.

Other non-invasive tests have been scrutinised as potential biomarkers for predicting the risk of SCD in HF. These include electrocardiographic parameters, markers of autonomic dysfunction, imaging modalities and serum biomarkers.

A prolonged QRS duration is associated with a poor prognosis in patients with HF and is currently part of the selection criteria for implantation of CRT devices (83;84). However, patients with HF and a normal QRS duration remain at high risk of SCD (37;85). This highlights the difficulty of using QRS duration as a tool for predicting risk and ICD requirement. The presence of nonsustained arrhythmias does not predict risk of SCD in HF (86). Markers of ventricular repolarisation, such as QT dispersion, QT dynamics (ratio of QT to RR interval) and QT interval rate dependence have been linked to increased risk of arrhythmias. Many of these markers have been predictive for all-cause mortality rather than SCD or have been predictive for SCD after limited multivariable analyses and in patients on sub-optimal medical therapy (87). Other electrophysiological markers, such as signal-averaged electrocardiogram (ECG), are also limited predictors of SCD due to their low sensitivity (88). Markers of autonomic dysfunction, such as baroreflex sensitivity and heart rate variability, have limited clinical utility due to their low sensitivity (88). The clinical utility of BNP as an independent predictor of SCD in chronic HF has already been discussed in section 1.2.3. Markers of collagen turnover, such as procollagen type 1 aminoterminal peptide (PINP) and PIIINP have been demonstrated to be elevated in HF and may have a role in predicting SCD (89). The role of nuclear imaging with single-photon emission computed tomography (SPECT) is expanding in HF and may be used to risk stratify patients for SCD in the future (90).

Microvolt T-wave alternans (MTWA) has recently been proposed as a potential tool for identifying patients at risk of sudden cardiac death and assisting in the selection of patients for primary prevention ICD therapy.

1.3 Microvolt T-wave alternans in heart failure

1.3.1 Definition and clinical application

T-wave alternans describes beat-to-beat fluctuations in the morphology of the electrocardiographic T-wave. Experimentally, it has been suggested that T-wave alternans is caused by cellular repolarisation alternans, which can cause dynamic instability in cardiac repolarisation and has been mechanistically linked to a predisposition to ventricular arrhythmias (91). Repolarisation alternans is thought to be due to action potential duration alternans and abnormal intracellular calcium handling (92). Repolarisation alternans normally develops in a concordant way with all myocytes alternating in phase. The presence of repolarisation alternans may cause arrhythmias if discordant repolarisation alternans develops. In early clinical studies, MTWA during atrial pacing was associated with ventricular arrhythmia (93). MTWA testing is now performed clinically using a commercially available system (CH2000 or HearTwave II, Cambridge Heart, Bedford, Mass). MTWA testing is undertaken using proprietary low-noise ECG electrodes. Patients must be in sinus rhythm and the heart rate is increased up to a maximum of 110 beats per minute (bpm) by using sub maximal treadmill exercise. A series of beats recorded at a stable heart rate are lined up and the amplitude of each T-wave at the same time with respect to the QRS complex is plotted. These data then undergo spectral analysis using fast Fourier transformation, a computer mathematical process that transforms a waveform into the components of its frequency spectrum. This determines the magnitude, at the microvolt level, of T-wave fluctuations occurring on alternate beats. If sufficient alternans is sustained at heart rates <110 bpm, the test is classified as positive. Absence of alternans activity at 110 bpm constitutes a negative test. Alternans is a heart rate dependent phenomenon and the presence of alternans at heart rates >110 bpm is considered normal. A test that satisfies neither set of criteria is classified as indeterminate. An indeterminate test may occur when analysis is not possible due to artifact, ectopic beats, nonsustained alternans or inability to raise the heart rate to 110 bpm. The latter may occur either due to chronotropic incompetence or if the patient is physically incapable of exercising long enough to raise their heart rate. The computer system generates a report and an automatic classification of the MTWA results. MTWA tests are reported as positive, negative or indeterminate. Patients in AF are ineligible for MTWA testing by the spectral method as unequal R-R intervals confound the frequency analysis. MTWA can also be determined

with time-domain methods, which are applicable to AF and Holter data. This method has been evaluated during pacing (94), in patients undergoing routine exercise tolerance testing (95) and in post myocardial infarction studies (96;97), but at present no prospective data are available regarding the prognostic value of Holter-based MTWA testing in patients with HF.

1.3.2 Predictive value of microvolt T-wave alternans

The published studies that have assessed the predictive value of MTWA testing during exercise are summarised in Table 1-4.

1.3.2.1 Known or suspected arrhythmia

In a population of 313 patients referred for cardiac electrophysiological study (EPS), a positive MTWA test predicted the primary endpoint of VTE (VTE: SCD, ventricular fibrillation [VF], sustained ventricular tachycardia [VT] or appropriate ICD therapy) better than EPS (relative risk [RR] 10.9 vs.7.1) (98). However, this was a heterogeneous population; some patients were referred for EPS because of prior cardiac arrest, while others were undergoing assessment of supraventricular tachycardia.

1.3.2.2 Myocardial infarction

Three studies have investigated the prognostic utility of MTWA following myocardial infarction (MI) regardless of LVEF. Only one has suggested that MTWA may predict SCD. This study enrolled 850 consecutive patients who underwent MTWA testing after MI (mean 2.7 months post-MI). A positive MTWA test predicted SCD or resuscitated VF, although the event rate was only 3% in this population (99). The proportion of patients prescribed a beta-blocker was low (30%). Two other studies have suggested that MTWA is not prognostically useful in this population. In one, 140 consecutive patients were investigated in the first 30 days following MI. Only three endpoints, death or VTE, occurred over 15 months of follow-up (100). A positive MTWA test did not predict events in this low-risk population. The second study examined the predictive value of MTWA for

all-cause mortality in patients early after MI (mean 8 days post-MI) (101). Of 323 consecutive patients, only 56 (17%) had a positive MTWA result. None of the 26 deaths occurred in this group. Notably, these patients were receiving optimal medical therapy, including a beta-blocker in 97%, at the time of MTWA testing.

In a cohort of 1041 patients with preserved LVEF after MI (mean 48 days post-MI), a positive MTWA test did predict VTE, although the number of endpoints was extremely low over a long period of follow-up (18 over 34 months) (102).

Two small studies have enrolled patients meeting Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II entry criteria (previous MI, LVEF $\leq$ 30% and no history of ventricular arrhythmia) from other cohorts. In 129 such patients, none of the twelve who experienced SCD or resuscitated VF had a negative MTWA result (103). In a subgroup analysis of a larger study, 177 patients meeting MADIT-II criteria were studied. MTWA tests were classified as abnormal (positive or indeterminate) in 68% and normal (negative) in 32% (85). The hazard ratio (HR) associated with an abnormal test was 4.8 (95% Confidence Interval [CI]: 1.1-20.7), but this was only adjusted for QRS duration, and therefore does not reflect incremental prognostic value.

Results from two larger studies were published after my study commenced. The Microvolt T-Wave AlternanS Testing for Risk Stratification of Post MI Patients (MASTER) study (104) study examined MTWA in 575 MADIT-II-indicated ICD-treated patients. MTWA tests were classified as non-negative (positive 51% and indeterminate 12%) and negative (37%). After multivariable adjustment (including age, LVEF, beta-blocker medications, QRS duration and NYHA class), a non-negative MTWA result did not predict VTE. The Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study (105) examined MTWA in 312 patients. Patients were tested six weeks post-MI, all had LVEF $\leq$ 40% and all received an implantable ECG loop-recorder. In addition to MTWA testing, heart rate variability measures, signal-averaged ECG and electrophysiological studies were also performed. MTWA was not predictive of the primary endpoint of VF/VT, all-cause mortality or cardiac death. The strongest predictors of the primary endpoint were measures of heart rate variability. MTWA does not appear to have clinical benefit early after MI in patients with LVSD.

The evidence for the use of MTWA in the risk stratification of patients post-MI is not robust. The negative predictive value (NPV) may be high in selected patients, but the results are conflicting in more representative cohorts.

1.3.2.3 Ischaemic left ventricular systolic dysfunction

Three studies have examined the prognostic value of MTWA in patients with ischaemic LVSD. The first performed MTWA testing in 144 non-consecutive patients referred for EPS (106). The cohort was separated into primary (n = 88) and secondary (n = 56) prevention subgroups and 111 patients received an ICD, because of a prior history or induction of sustained ventricular arrhythmia. A positive MTWA test did not predict the primary endpoint, death or VTE, in the primary prevention subgroup.

The second study evaluated 768 consecutive patients with coronary heart disease and LVSD (107). The authors analysed positive and indeterminate tests together and separately, addressed cause-specific death as a secondary endpoint, and performed a more extensive multivariable analysis than previous studies. However, the follow-up was relatively short (mean 18±10 months) and the event rate (n=99) was low for this type of population, limiting the power of the study. A non-negative MTWA test independently predicted all-cause mortality (HR 2.24; 95% CI, 1.34 to 3.75) and arrhythmic mortality (HR 2.29; 95% CI, 1.0 to 5.24) in the whole population. However, when positive and indeterminate results were analysed separately, positive results failed to predict arrhythmic mortality, whereas indeterminate results predicted both all-cause and arrhythmic death. Therefore, indeterminate rather than positive tests accounted for the majority of the predictive value for arrhythmia in this study, which contradicts the proposition that MTWA identifies a specific proarrhythmic substrate.

The Alternans Before Cardioverter Defibrillator (ABCD) study published results as my study was closing (108). This interventional study recruited 566 patients with ischaemic LVSD and nonsustained VT and compared the ability of MTWA and EPS to predict VTE. The 1-year event rate was lowest (2.3%) when both tests were negative and highest (11.1%) when both were positive. The event rate was intermediate and similar when only 1 test was positive (MTWA positive, 6.5%; EPS positive, 7.8%). However, the 1-year event rate was

highest when MTWA was indeterminate and EPS was positive (14.8%). Use of an ICD (shock or pacing) accounted for the majority of end points (85%). However, ICD implantation was not compulsory if both tests were normal, and so patients in this group (n=99) may have been less likely to reach an end point. Moreover, because ICD therapies occur more frequently than SCD in patients without ICDs, a significant proportion of the end points in this study may have been attributable to non clinical arrhythmias.

1.3.2.4 Left ventricular systolic dysfunction irrespective of aetiology

One study recruited 549 patients with LVSD and no history of sustained ventricular arrhythmia, including patients with both ischaemic (n = 267) and non-ischaemic (n = 282) cardiomyopathy (109). The primary endpoint was a composite of death and VTE. Over 20 months, there were 2 deaths and 2 ICD discharges in the normal (negative) MTWA group (n = 189) compared with 38 deaths and 9 ICD discharges in the abnormal (positive or indeterminate) MTWA group (n = 360). The proportion with an ICD in each group was the same. After multivariable adjustment, an abnormal MTWA test was associated with an increased risk of VTE.

Results were published from an electrophysiological MTWA study shortly after my study began. This study investigated the predictive value of MTWA in patients with both ischaemic and nonischaemic cardiomyopathy, referred for EPS for evaluation of non-sustained VT and/or syncope (110). MTWA was performed during atrial pacing at the time of EPS. Over 38 months, the primary endpoint of arrhythmia-free survival (defined as freedom from death or sustained ventricular arrhythmias) was higher in MTWA negative patients (88%) than MTWA non-negative patients (66%). However, the two-year event rate for death or sustained ventricular arrhythmias was 19% among the MTWA negative patients. This suggests MTWA alone may be insufficient for identifying a low-risk population who, by implication, do not need ICD implantation.

1.3.2.5 Nonischaemic left ventricular systolic dysfunction

Three studies have examined the prognostic utility of MTWA in non-ischaemic cardiomyopathy. The first study performed MTWA testing in 104 patients and found that a

positive MTWA test was independently associated with VTE (111). However, this study has many limitations. The actual number of endpoints was very small (n=12), as was the sample size, limiting the multivariable analysis. Many screened patients were ineligible because of AF, but no information was given regarding the number or characteristics of the patients screened. No patient was prescribed an ACE inhibitor or beta-blocker prior to entry into the study and thus MTWA testing was carried out on sub-optimal medical therapy. The mean NYHA functional class was less than II and more than half of the patients were not prescribed a diuretic, suggesting the majority had asymptomatic LVSD, not symptomatic heart failure. The second recruited 137 patients and compared MTWA with other arrhythmic markers (112). A positive MTWA test was the only independent predictor of VTE after a mean of 14 months follow-up. This study again has many limitations. The multivariable model did not include age or LVEF. The cohort included patients with an ICD (27%), mostly for prior sustained ventricular arrhythmia, and 11 of 18 endpoints occurred in those patients. This restricts extrapolation of these results to a primary prevention population. The third and largest study (n = 263) excluded patients with prior VF/VT and had a longer duration of follow-up (52 months) (113). In this study a positive MTWA test was not associated with the occurrence of VTE. In this study an indeterminate test was associated with the primary outcome on univariate analysis.

The available evidence suggests that MTWA is not a reliable indicator of arrhythmia in patients with non-ischaemic LVSD. There appears to be little to recommend a strategy of using MTWA in this population to determine which patients should or should not have an ICD.

1.3.2.6 Symptomatic heart failure with low left ventricular ejection fraction

The evidence for the prognostic utility of MTWA in LVSD cannot simply be extrapolated to patients with symptomatic chronic HF, which is a clinically distinct entity. When my study began, only three small studies (n=73, n=46, n=107) had assessed the predictive value of MTWA testing in patients with HF-REF (114-116). On initial review these studies suggest that MTWA predicts clinical outcome in this population. However, they do have several limitations beyond their size.

The first study selected 73 patients with NYHA II chronic HF after excluding those with LVEF ≤ 20% “because of high risk of death”. An additional 17 patients with indeterminate results were excluded, leaving a small and highly selected group in which a positive MTWA test was associated with an increased risk of VTE over 17 months (114). In another study, of 46 patients with NYHA II-III chronic HF, MTWA predicted cardiac death (n=7) but not SCD (n=1) (115). In the third study, of 107 patients with chronic HF, none of the 13 end points occurred in MTWA-negative patients and MTWA was the only independent predictor of VTE (116). However, this multivariable analysis included only 7 arrhythmia markers.

These studies are small, appear to be highly selected, and lack proper multivariable adjustment. Their limited relevance to real-life populations with chronic HF is exemplified by the mean ages of the patients enrolled (64 years, 59 years, and 56 years, respectively). The average age of unselected HF populations is 75 years (117). This evidence certainly does not support the routine use of MTWA testing to risk stratify patients with chronic HF.

Results were published from two larger studies of MTWA in chronic HF after my study began. The Microvolt T-Wave Alternans in Patients with Heart Failure (ALPHA) study recruited 446 patients with non-ischaemic cardiomyopathy (LVEF ≤ 40%) and stable NYHA II-III chronic HF on optimal medical therapy (118). A non-negative MTWA test was associated with an increased risk of cardiac death or VTE over 18 - 24 months. However, these patients were older, more symptomatic, and had lower mean LVEF, imbalances that highlight the need for careful multivariable adjustment in such studies. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) T-wave alternans sub-study, MTWA testing was performed in 490 patients with LVEF ≤ 35% and NYHA II-III chronic HF (119). In this study 41% of tests were indeterminate and over 35 months there was no difference in the rate of VTE between MTWA groups for patients who received either ICD or placebo. These studies are larger than those published to date and their contradictory results means that doubt remains regarding the value of MTWA for predicting arrhythmic risk in chronic HF.

Table 1-4: Published observational studies of MTWA exercise testing

Study	N	Mean age (yrs)	Mean LVEF (%)	Prior VTE (%)	BB stopped pre-MTWA	MTWA result (%)			Primary end-point			Predictive value		
						Pos	Indet	Neg	Event	Mean FU (mths)	N	RR/HR (95% CI)	PPV (%)	NPV (%)
Suspected arrhythmia														
Gold (98)	313	56	44	19	>24 hrs	31	24§	45	VTE‡	10	22	RR 10.9	NA	NA
Post-MI														
Ikeda (99)	850	63	NA	0	NA	36	13§	51	SCD/ VF	25	25	RR† 5.9 (1.6-21)	7	99
Schwab (100)	140	60	56	0	1 dose	20	27§	53	Death/ VTE	15	3	NS	4	97
Tapanainen (101)	323	62	45	0	No	17	38	45	ACM	14	26	NS	0	99
Ikeda (102)	1041	64	55	0	No	17	9	74	VTE	32	18	19.7†	9	99
Post-MI LVSD														
Hohnloser (103)	129	63	26	0	NA	60	13	27	SCD/ VF	17	12	RR 5.5	13	100
Chow (104)	575	65	24	0	NA	51	12	37	VTE	25	70	NS	NA	NA
Bloomfield (85)	177	61	23	0	No	27	41	32	ACM	20	20	HR 4.8 (1.1-20)	NA	NA
Huikuri (105)	312	65	35	0	NA	NA	NA	NA	VF/VT	22	25	NS	NA	NA
LVSD (ischaemic)														
Rashba (106)	144	64	28	39	>24hr	49	25	26	ACM/ VTE‡	17	50	HR 2.2† (1.1-4.7)	40	84
Chow (107)	768	~67	~27	0	>24hr	46	21	33	ACM	18	99	HR 2.2† (1.3-3.8)	15	92
Costantini (108)	566	65	28	0	>24hr	46	25	26	SCD/ ICD	19	65	HR 2.1	9	95
LVSD (ischaemic and nonischaemic)														
Bloomfield (109)	549	56	25	0	No	29	35	36	ACM/ VTE‡	20	51	HR 6.5† (2.4-18)	13	98

Study	N	Mean age (yrs)	Mean LVEF (%)	Prior VTE (%)	BB stopped pre-MTWA	MTWA result (%)			Primary end-point			Predictive value		
						Pos	Indet	Neg	Event	Mean FU (mths)	N	RR/HR (95% CI)	PPV (%)	NPV (%)
LVSD (nonischaemic)														
Kitamura (111)	104	52	41	0	NA	44	20§	36	VTE	21	12	RR 8.9† (2-34)	38	95
Hohnloser (112)	137	55	29	20	NA	48	27§	25	VTE‡	14	18	RR 3.4†	22	94
Grimm (113)	263	~49	~30	0	>24hr	52	21	27	VTE	52	38	NS	13	90
Chronic HF and LVSD														
Baravelli (114)	73	64	36	10	>48hr	41	23§	36	VTE‡	17	8	∞	24	100
Sarzi (115)	46	59	29	0	NA	52	20§	28	Cardiac death	19	7	NA	30	100
Klingenheben (116)	107	56	28	0	NA	49	20	31	VTE	14	13	∞	21	100
Gold (119)	490	59	24	0	>24hr	37	41	22	SCD/ VTE‡	30	75	NS	NA	NA
Chronic HF and nonischaemic LVSD														
Salerno-Uriarte (118)	446	59	29.5	0	No	45	20	35	Cardiac death/ VTE	19	33	3.98	9	97

N = number; BB = beta-blocker; Pos = positive; Indet = indeterminate; Neg = negative; FU = follow-up; RR = relative risk; HR = hazard ratio; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; hr = hours; NA = not applicable; NS = not significant; ICD = appropriate ICD discharge; † = multivariable HR/RR; ‡ = VTE including ICD discharges; § = excluded from predictive analyses; ∞ = infinity

1.3.3 Unresolved issues in Microvolt T-wave alternans testing

1.3.3.1 Does MTWA have incremental prognostic value?

There are, at present, few data regarding the true incremental prognostic value of MTWA testing, due to the lack of detailed multivariable analysis undertaken in the studies to date. The parameters that have been included in these limited multivariable analyses are displayed in Table 1-5. A number of powerful predictors of outcome in chronic HF have been identified including BNP, as outlined in section 1.2.3. BNP has also been found to be an independent predictor of SCD (53). The prognostic value of MTWA testing has not been compared with that of BNP. It is certainly conceivable that a low BNP could confer as good a prognosis as a negative MTWA test. If this were the case, then the cost and small risk to the patient associated with MTWA testing would be unjustified. Although BNP may be considered unsuitable for risk stratification because concentrations may vary over short periods of time, there is no evidence regarding the reproducibility of MTWA results over timescales greater than a few hours (120). MTWA testing should be investigated as an independent predictor of outcome over and above already established indicators in chronic HF.

1.3.3.2 Atrial fibrillation

MTWA exercise testing cannot be performed in patients with AF. Only 2 studies have reported the proportion of screened patients ineligible due to AF [23% (113) and 22% (118)]. In the MADIT-II study 9% of patients had AF (36), and in populations with chronic HF approximately 25-30% have concurrent AF (121). If sufficient evidence was obtained to allow MTWA to be used to identify appropriate candidates for ICD therapy in populations with sinus rhythm, alternative strategies will have to be found for the large population ineligible for testing. Other methods of MTWA analysis, which may be applicable to patients with AF, are available, but there are as yet no published data regarding their prognostic value.

Table 1-5: Parameters included in MTWA observational studies multivariable analyses

	Age	Gender	LVEF	NYHA class	BNP	β-Blocker	ACE inhibitor	QRS duration
Suspected arrhythmia								
Gold (98)	√	√	√	x	x	x	x	x
Post-MI								
Ikeda (99)	√	√	√	x	x	√	x	x
Tapanainen (101)	√	√	√	√	x	x	x	√
Ikeda (102)	√	√	√	x	x	√	x	x
Post-MI LVSD								
Bloomfield (85)	x	x	x	x	x	x	x	√
LVSD (ischaemic)								
Rashba (106)	√	√	√	√	x	x	x	x
Chow (107)	√	√	√	x	x	√	√	√
LVSD (ischaemic and nonischaemic)								
Bloomfield (109)	√	√	√	√	x	x	x	x
LVSD (nonischaemic)								

	Age	Gender	LVEF	NYHA class	BNP	β-Blocker	ACE inhibitor	QRS duration
Kitamura (111)	x	x	√	x	x	x	x	x
Hohnloser (112)	x	x	√	x	x	x	x	√
Grimm (113)	√	√	√	√	x	√	√	x
Chronic HF and LVSD								
Baravelli (114)	√	√	√	x	x	x	x	x
Klingenheben (116)	x	x	√	x	x	x	x	x
Chronic HF and nonischaemic LVSD								
Salerno-Uriarte (118)	√	√	√	√	x	√	√	√

1.3.3.3 Inability to exercise

One post-MI study reported that 15% of 379 consecutive patients in sinus rhythm could not exercise due to co-morbidity or physical frailty (101). Although a positive MTWA test did not predict all-cause mortality, inability to perform the exercise test was found to be an independent predictor of death (RR 5.62; 95% CI, 1.76 to 15.99). Implementation of a risk stratification tool which requires exercise is likely to be problematic in populations such as chronic HF and LVSD, where the incidence of frailty and co-morbidity is high.

1.3.3.4 Medical therapy

Pharmacological therapy can reduce SCD. Yet optimal medical therapy was mandatory inclusion criteria in only one of the studies described. Less than half of patients were prescribed a beta-blocker in one post-MI study (99) and two chronic HF studies (115;116). Most studies have discontinued beta-blockers for at least 24 hours, to facilitate elevation in heart rate and reduce indeterminate tests. This practice is not suitable for many HF patients, but whether beta-blocker continuation would then prevent a significant portion of patients achieving the heart rate required for a valid test is uncertain but clearly important. Aside from the impact on heart rate, there is also evidence that acute beta-blockade reduces the magnitude of MTWA, potentially converting a positive to a negative test (122). Omission of beta-blockers may not only reduce the number of indeterminate tests but may also increase the number of positive tests. I believe that MTWA testing is only clinically valuable, if shown to be independently predictive of outcome in patients on optimal tolerated medical therapy, including a beta-blocker.

1.3.3.5 Indeterminate MTWA results

MTWA tests are classified as indeterminate in the following circumstances: if there is significant noise or ventricular ectopy; if alternans is unsustained; or if the patient is able to exercise but cannot attain a heart rate of 110bpm for one minute. In early studies, indeterminate MTWA tests were believed to be of no significance to arrhythmic events and were excluded from predictive analyses. However, in a study of 177 patients post-MI, indeterminate MTWA tests accounted for the majority of non-negative tests. The authors

grouped indeterminate and positive tests together as abnormal (85), which has now become common practice in MTWA studies. Table 1-6 shows outcomes in MTWA positive and indeterminate groups from studies which have examined all-cause mortality. For each study, mortality was higher in the MTWA indeterminate group than in the MTWA positive group. Clearly, an indeterminate test result indicates a poor prognosis, but the nature of this risk is unclear. Only one study, in patients with ischaemic LVSD, enrolled a sufficiently large cohort to examine cause-specific mortality (Table 1-7). Indeterminate tests accounted for 159 of 514 non-negative MTWA tests and an indeterminate test predicted both arrhythmic and non-arrhythmic death, whereas a positive test only predicted all-cause mortality (107). Moreover, in another study, the rate of major arrhythmic events was higher in the indeterminate group (24%) than either the MTWA positive (13%) or negative (10%) groups (113).

This suggests that an indeterminate test may actually predict both non-arrhythmic and arrhythmic risk. While this may seem counter-intuitive, it is possible that patients with unsustained alternans or ectopy on exercise are prone to ventricular arrhythmia. Recent analyses of indeterminate tests concluded that such patients were at high risk, distinct from the tests categorised as indeterminate due to noise, artifact or a sharp rise in heart rate (123;124). This suggests that the classification of MTWA tests may require re-evaluation and the prognostic value of MTWA may be improved by reclassification of indeterminate tests.

Table 1-6: Distribution of all-cause mortality rates *per* MTWA result

Study	Number	Population	Mean FU (months)	All-cause mortality, %		
				Positive	Indeterminate	Negative
Chow (107)	768	Ischaemic LVSD	18	12	21	8
Bloomfield (85)	177	Ischaemic LVSD	2-year mortality rate	14.5	20.1	3.8
Bloomfield (109)	549	LVSD	2-year event rate (mortality & ICD discharges)	12.3 (5 ICD discharges)	17.8 (4 ICD discharges)	2.4 (2 ICD discharges)
Tapanainen (101)	323	Post-MI	14	0	15	<1

Table 1-7: Adjusted comparisons of mortality *per* MTWA result in 768 patients with ischaemic cardiomyopathy (107)

	MTWA Result		
	Non-negative (n=514)	**Positive (n=355)**	**Indeterminate (n=159)**
All deaths HR (95% CI)	2.24 (1.34 – 3.75)	2.08 (1.18 – 3.66)	2.78 (1.55 – 4.99)
Arrhythmic deaths HR (95% CI)	2.29 (1.00 – 5.24)	NS	3.62 (1.44 – 9.13)
Nonarrhythmic deaths HR (95% CI)	NS	NS	2.47 (1.17 – 5.22)

CI = confidence interval; HR = hazard ratio; NS = not significant

1.3.4 Extrapolation to primary prevention ICD therapy

There has been much speculation that MTWA could improve risk stratification for the primary prevention of SCD, including patients with HF. It has been argued that the current evidence regarding the favourable prognosis conferred by a negative test is sufficient to justify using MTWA to identify a subgroup of primary prevention ICD candidates who would not benefit (85;125). This could reduce the number of primary prevention implants and thereby reduce the cost of therapy.

However, the current evidence is lacking in many respects. Most of the studies are limited by small sample size or by low event rates, which reduces power, and there is a lack of detailed multivariable analysis. We cannot, at present, extrapolate the prevalence data for a negative test to unselected populations, because the proportion of patients who would be ineligible for testing because of AF, demand ventricular pacing or an inability to exercise is unknown. In addition, a high NPV has only been demonstrated over relatively short time scales, and because the arrhythmic substrate changes over time it is likely that serial MTWA testing would be required. This is difficult to address when little is known regarding reproducibility of this test. The corollary of not implanting in MTWA negative patients would be to implant in all non-negative patients, including those with indeterminate tests. Given the lack of proven incremental prognostic value of MTWA and the conflicting results in some studies, there are serious doubts regarding the benefit of this strategy.

1.4 Aims of this study

MTWA has been proposed as a novel method of predicting risk of sudden cardiac death and recommended as a solution to the conundrum of decision making for ICD implantation. Yet as outlined above, there are many gaps in the literature surrounding MTWA and HF. The clinical utility of MTWA testing in HF remains to be fully evaluated. The proportion of patients eligible for MTWA testing in a representative HF population is unknown, but clearly has major implications for the widespread use of MTWA testing. The tolerability of the exercise protocol and the prevalence of determinate MTWA results have not been assessed prospectively in such a population. In particular, the prevalence of abnormal MTWA results in patients with HF and preserved LVEF is not known. Little is known about the clinical characteristics associated with a specific MTWA result. The incremental predictive value of MTWA over LVEF in an unselected HF population has yet to be conclusively demonstrated. The incremental value of MTWA over other prognostic markers such as BNP has not been assessed in any type of HF. In particular, patients with HF-PEF have not been studied. It is necessary to have this information before considering implementing MTWA as a routine clinical tool.

This study intends to provide a comprehensive evaluation of the use of MTWA in patients with HF and evaluate if this test will improve risk stratification for these patients. The hypotheses of the study of MTWA are twofold.

Firstly, in an unselected population of patients recently hospitalised for HF, the presence of an abnormal MTWA test (positive or indeterminate) provides prognostic information over and above that obtained from clinical data, LVEF or natriuretic peptide levels in the prediction of all-cause mortality, SCD and cardiovascular death.

Secondly, not withstanding the first hypothesis, the inability or ineligibility to perform an MTWA test will identify a group of patients at highest risk of all-cause mortality, SCD and cardiovascular death.

This aims of this study are:

1. Define eligibility for MTWA testing in a cohort of patients with stable HF.
2. Determine the prevalence of positive, negative and indeterminate results in a representative, well-defined population of patients with HF on optimal medical therapy, accounting for aetiology and LVEF.
3. Determine the tolerability of the exercise protocol in patients with HF.
4. Describe the clinical characteristics associated with a specific MTWA result.
5. Examine the predictive value of MTWA testing for all-cause mortality, SCD and cardiovascular mortality in HF.
6. Clarify the incremental prognostic utility of MTWA by evaluating MTWA alongside established predictors of mortality, including BNP, and more novel biomarkers, such as cardiac troponin.
7. Describe the characteristics and outcomes of those ineligible for MTWA testing.

Ultimately this study endeavours to determine if MTWA testing has a role in the risk stratification of patients with HF.

CHAPTER TWO

METHODS

2.1 Introduction

This chapter will explain the methods behind this prospective observational study. The study design, patient identification methods, and data collection techniques will be illustrated. Application of the MTWA test to this cohort will be described. The methods of collecting and storing data will be outlined, and the statistical analyses used will be described. An overview of the study design is presented in Figure 2.1.

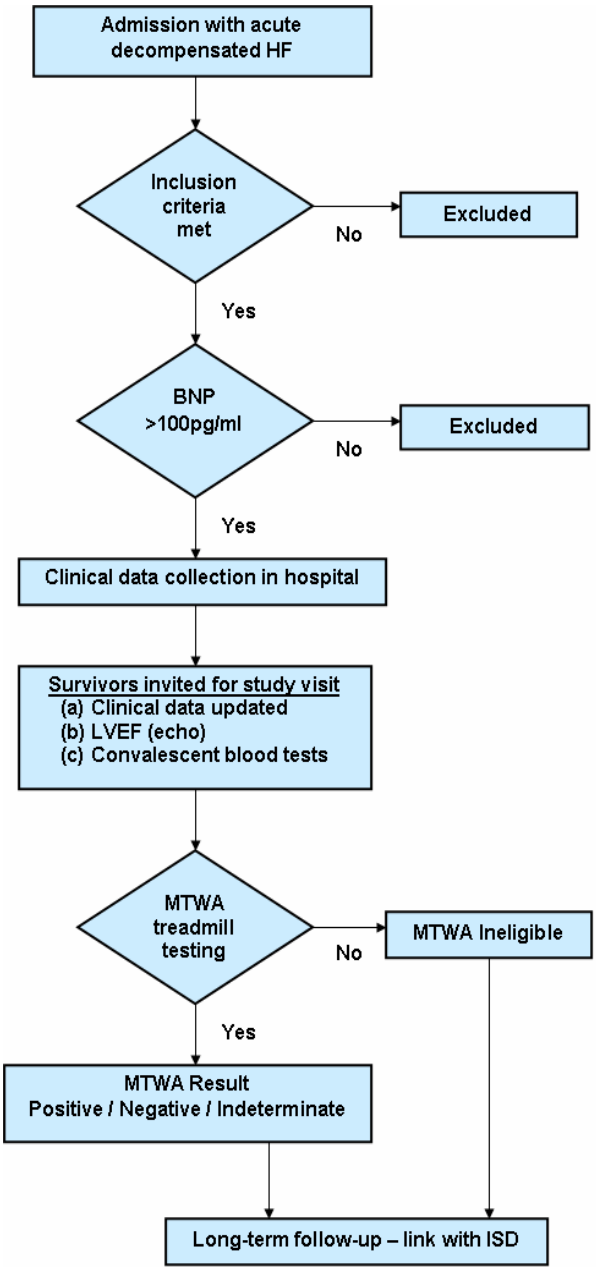


Figure 2.1: Outline of the study design

2.2 The hospitalised heart failure cohort

2.2.1 Patient population and recruitment

All patients were recruited from the Royal and Western Infirmaries in Glasgow, and the Royal Alexandra Hospital in Paisley. The Royal Infirmary in Glasgow is a city hospital covering a catchment area of over 250,000 for the north and east of Glasgow. The Western Infirmary covers north-west Glasgow, with a catchment area of approximately 250,000. The Royal Alexandra Hospital is a district general hospital with a large catchment area, approximately 200,000 from Renfrewshire and also serving areas as far away as Oban and Argyll.

Patients recruited into this study were admitted to these hospitals by self referral to the Accident and Emergency Department or referral from their General Practitioner. All patients recruited were admitted to the Medical Receiving Units, Coronary Care Units or directly to general medical wards. Near-consecutive admissions were screened daily in both Glasgow hospitals between 1st December 2006 and 10th January 2009, and in the Royal Alexandra Hospital in Paisley from 22nd April 2008 to 10th January 2009. Recruitment of patients from the third site, the Royal Alexandra Hospital, began after it became apparent that a significant proportion of enrolled patients failed to return for the follow-up study visit and that additional recruitment was needed to achieve an adequate number of patients attending the follow-up visit.

Identifying potential study patients

All admissions to the three hospitals were screened for evidence of decompensated HF (appendix I, page 326). This involved reviewing the case records for all new admissions for documentation of the following:

- Symptoms and clinical signs of HF
- Radiological evidence suggestive of HF
- Clinical response to intravenous diuretics

Symptoms of HF included shortness of breath and peripheral oedema. Clinical signs of HF included a raised jugular venous pressure (JVP), lung crepitations and pitting peripheral oedema. Radiological evidence of HF included cardiomegaly (defined as a cardiothoracic ratio >0.5) and signs of pulmonary oedema. The latter comprised vascular redistribution (upper lobe venous diversion), raised pulmonary pressure (Kerley B lines), pulmonary venous congestion (interstitial or alveolar oedema) and pleural effusions. A clinical response to intravenous diuretics was defined as an improvement in the signs of HF (documented in the case notes) or a symptomatic improvement (reported by the patient).

Inclusion criteria

Patients were invited to participate in the study if they met all of the following criteria:

- Primary reason for admission to hospital was decompensated HF
- Symptoms and signs of HF **plus** radiological evidence of HF **or** clinical response to intravenous diuretics
- No exclusion criteria (see below)

Exclusion criteria

Patients were not approached for participation if they met any of the following exclusion criteria:

- Cognitive impairment
- Serious concurrent systemic disease resulting in reduced life expectancy (such as advanced malignancy)
- Acute coronary syndromes complicated by pulmonary oedema
- Geographical or social factors making participation or follow-up impractical

Recruitment into the study involved a two stage consent process (see below). Written information was provided for both stages (appendices II, page 327, and III, page 329). Patients who agreed to participate in the study provided written informed consent for both

stages (appendix IV, page 334). Copies of the consent form were given to the patient and filed in their medical case records. The study was approved by the Local Research Ethics Committee.

Consent - Stage One

Stage one involved providing informed consent to blood sampling to measure plasma BNP concentration. Information for medical staff explaining the BNP test was placed in the patient's case notes (appendix V, page 336). The BNP test result was available within 24 hours. All patients were informed the following day of their result. Those with a BNP level within the normal reference range, below the ESC guidelines "rule-out" threshold for HF (<100pg/ml) (1), were not recruited into stage two. No further participation in the study was asked of these patients. Patients providing consent at this stage also gave permission to be "flagged" for follow-up with Information Services Division (ISD) of NHS Scotland, allowing identification of deaths and readmissions to hospital.

Thus, all patients enrolled in the study fulfilled the three ESC diagnostic criteria for HF (1). All enrolled patients had both symptoms and signs of HF, the first and second criteria of these guidelines. The third criteria requires evidence of structural or functional cardiac disease, namely; evidence of cardiomegaly, a third heart sound, echocardiographic abnormalities or a raised natriuretic peptide level. Thus, an elevated BNP concentration satisfied the third criteria of these guidelines.

Consent – Stage Two

This involved obtaining consent from patients with an elevated BNP concentration to participate in the follow-up study visit. The study visit was scheduled for approximately 4-6 weeks after the patients were discharged from hospital. Details of the study visit were provided verbally and by written means. A letter explaining the study was issued to every participant's general practitioner and filed in the patient's case notes (appendix VI, page 337).

An appointment card was issued to each patient prior to their discharge from hospital, detailing the date and location of the study visit (appendix VII, page 339).

2.2.2 Data collection

Every patient recruited into the study had an extensive amount of clinical data collected during their hospital admission. This was contained in a case record form (appendix VIII, pages 340-355). Each patient was allocated a unique and anonymous study identification number. Completing the case record form involved a forty-five minute consultation with each patient during their hospital admission. Data were obtained by a thorough review of the patient's medical case notes as well as a clinical assessment of each patient. The latter comprised taking a detailed account of their medical history and examining their cardiovascular system. Other methods of obtaining data included searching hospital database systems for echocardiography, coronary angiography and radiological reports.

The types of data recorded were chosen for several reasons. A precise record of the past medical history and results of any previous angiography allowed accurate determination of the aetiology of HF. Data used in recently validated models of mortality prediction in HF (126) were collected, both from hospitalisation and study visit, to evaluate the incremental prognostic value of MTWA to these models.

Data were recorded under the following headings; demographics, clinical HF assessment, past medical history and family medical history. Medications prescribed pre-admission and heart failure medical therapy administered during the first 24 hours of admission were noted. ECG results, chest X-ray (CXR) findings and echocardiogram analysis pre- and during admission were also recorded. Finally, results from blood tests carried out on admission to hospital were noted.

Demographic data included date of birth, gender and race. Dates of admission, recruitment and discharge, or death in hospital, were recorded.

The clinical HF assessment included a detailed history recording the presence or absence of typical symptoms of HF prior to admission. An assessment of symptom severity in the days prior to admission was made using the NYHA classification system, an established objective method of recording HF symptom status (Table 2-1). This classification system relates symptoms to activities of daily life and allows an assessment of quality of life. This classification is also commonly used by medical professionals to guide therapeutic decisions. If the patient already had an established diagnosis of chronic HF in their medical case notes, this was recorded as a previous history of HF. For those with a history of HF, the duration was documented and whether or not there had been a previous hospitalisation for HF. This information has prognostic relevance in HF (126). The clinical HF assessment also included a clinical examination. This examination involved: the vital signs on admission, the presence or absence of common signs of HF and a complete cardiovascular system examination. The severity of the HF clinical examination findings were summarised by assigning each patient a Killip score (Table 2-2). In addition to the clinical examination, every patient had their weight, height and waist measurement recorded whilst in hospital.

Table 2-1: New York Heart Association (NYHA) classification of heart failure

NYHA Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations or breathlessness.
II	Mild limitation of physical activity. Comfortable at rest or with mild exertion but ordinary activity results in fatigue, palpitations or breathlessness.
III	Marked limitation of physical activity. Comfortable at rest but any ordinary activity causes fatigue, palpitations or breathlessness.
IV	Symptoms of HF at rest and any physical activity cause exacerbation of symptoms.

Table 2-2: Killip classification of heart failure

Killip Score	Description of Signs
I	No clinical signs of heart failure.
II	Basal lung crepitations, S3 gallop rhythm, elevated jugular venous pressure.
III	Frank pulmonary oedema.
IV	Cardiogenic shock – hypotension and evidence of peripheral vasoconstriction.

Every patient in this study had a 12-lead ECG performed during their hospital admission. ECG abnormalities occur frequently in patients with HF. This is particularly evident in LVSD (127;128). The ECG can also allude to the primary aetiology, for example previous myocardial infarction (MI). Arrhythmias can be the cause or effect of decompensated HF and may also be evident on the 12-lead ECG. There are many other ECG abnormalities suggestive of potential causes of HF (1). The ECG can also confer prognostic information in HF. AF and bundle branch block have been shown to be independent predictors of mortality in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) study (126). Left bundle branch block (LBBB) has been demonstrated to be an independent predictor of sudden cardiac death, as well as all-cause mortality, in the Italian Network Congestive HF registry (129). Specific ECG parameters were recorded in each patient's case record form (appendix VIII, page 352). These included rhythm, QRS duration and the QT interval corrected for heart rate (QTc). QTc was calculated using Bazett's formula (130). The presence or absence of the following parameters were also recorded; bundle branch block, paced rhythm, pathological Q waves, left ventricular hypertrophy (LVH) and ischaemic ST depression. LVH was defined using the Sokolow and Lyon criteria (S V_1 + R V_5 or V_6 > 35 mm) (131).

The CXR frequently assists in the diagnosis of acute HF, although a normal CXR does not exclude this diagnosis. The majority of patients enrolled in this study had a CXR performed on admission to hospital. The presence of radiological signs suggestive of HF, as detailed in the ESC HF guidelines (1), were recorded in the case record form (appendix VIII, page 352). These radiological signs were outlined earlier in Section 2.2.1. Cardiomegaly has prognostic significance in HF and has been shown to be predictive of all-cause mortality (126), as well as sudden death (132).

Echocardiography is an established investigation in patients with suspected HF. It enables a non-invasive assessment of pericardial, myocardial and valvular function. LV systolic function, as measured by ejection fraction, is an independent predictor of mortality in patients with HF (126). Many patients in the study had an echocardiogram performed prior to enrolment in this study. Data from this was recorded in the case record form (appendix VIII, page 353). If multiple echocardiograms had previously been performed, data from the most recent one was recorded. If an echocardiogram was performed during the index hospital admission then these data were also recorded in the case record form. Often patients were discharged from hospital with an appointment for an early outpatient echocardiogram; in these instances the data from these scans were also obtained. Specific information from the echocardiogram report was recorded. The LV internal dimension in diastole was recorded and whether or not the ventricle was dilated. The presence or absence of LVSD and LVH was noted. LVSD was recorded as documented on the report; mild, mild to moderate, moderate, moderate to severe or severe. This classification system is a subjective measure of dysfunction. Unfortunately LVEF is not routinely calculated. The presence of absence of valvular heart disease was recorded. The valve type and lesion (stenosis or incompetence) was recorded as well as the severity, using the same classification system as that of LVSD.

2.2.3 Biochemical and haematological tests

Blood sampling is informative in heart failure. It provides prognostic information and can assist with determining the aetiology of HF and reason for decompensation. Many routine laboratory investigations are recommended in the evaluation of patients with HF (1).

All patients had the following blood tests taken during hospitalisation; BNP, urea and electrolytes (U&E), liver function tests (LFT) and full blood count (FBC). The majority of patients had troponin I measured. The results of the following blood tests were also recorded in the case record form if they were carried out during the hospital admission; thyroid function (TFT), glycosylated haemoglobin (HBA1c), urate, phosphate, C-reactive protein (CRP), glucose and lipid profile. All routine biochemical and haematological tests were performed at the time of admission and analysed in the hospital biochemistry and haematology laboratories within four hours of venesection.

Plasma BNP was an essential test in this study, an elevated level being mandatory for recruitment to stage two of the study. Blood sampling for BNP was performed within 24 hours of admission to hospital. Blood samples were collected in potassium ethylene diamine tetra acetic acid (EDTA) tubes and sent to the department of biochemistry at Gartnavel General Hospital in Glasgow for testing. Results were available on the same day of sampling. Plasma BNP was measured using the Architect Assay (Abbott Laboratories, Abbott Park, IL, USA). The Architect Assay has a range 0-5000 pg/ml. BNP values exceeding 5000pg/ml are recorded as >5000pg/ml. The cut-off for BNP in this study was 100 pg/ml and patients with values <100pg/ml were not recruited into stage two. This level was determined by consideration of several factors. Firstly, work carried out previously on a local healthy population identified the 95^{th} percentile at 67.6pg/ml for those aged 70 years and over (133). Abbott Laboratories evaluated their assay in non-hospitalised patients with renal disease, diabetes mellitus, chronic obstructive pulmonary disease and hypertension. In non-HF patients over 75 years old, mean and median values were 31pg/ml and 67pg/ml, respectively. Furthermore, 83.3% of these patients had results <100pg/ml. A previous study of the utility of BNP in diagnosing HF in the emergency setting also used 100pg/ml as the cut-off level (55). This yielded a diagnostic accuracy of 83%, with 90% sensitivity and 76% specificity, for differentiating HF from other causes of breathlessness. Finally, according to ESC guidelines, a diagnosis of HF is unlikely for patients presenting to hospital with breathlessness and a BNP level <100pg/ml (1).

Cardiac troponin is commonly measured in patients admitted to hospital with decompensated HF. This was of particular interest in our study to evaluate the prognostic significance of this novel biomarker in HF. In the Royal and Western Infirmaries troponin I is measured using the

Architect assay (Abbott Laboratories, Abbott Park, IL, USA). This assay reports negative results as <0.04ng/ml, the level that achieves 10% coefficient of variance. Elevated troponin I results are reported as ≥ 0.04ng/ml. In the Royal Alexandra Hospital troponin T is measured using the Roche assay (Roche Diagnostics, Basel, Switzerland). This assay reports negative results as <0.05ng/ml the level that achieves 10% coefficient of variance. Elevated troponin T results are reported as ≥ 0.05ng/ml.

All patients had U&E measured on admission. Serum creatinine concentration alone is a poor indicator of renal function (134). Thus, renal function was assessed by estimation of the glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equations (135). The MDRD equations have been validated in patients with severe chronic HF (136). The four-variable MDRD equation was calculated for all patients. This formula calculates eGFR as follows:

eGFR (ml/min/1.73m^2) = 32788 x (Serum Creatinine in μmol/l)$^{-1.154}$ x (Age)$^{-0.203}$ x [1.210 if Black] x [0.742 if Female]

Renal function, represented by eGFR concentration, was then classified using the National Kidney Foundation classification (137). This guideline classifies renal function as normal if the eGFR is ≥ 90 ml/min/1.73m^2. Mild renal impairment is eGFR 60 - < 90 ml/min/1.73m^2. Moderate and severe renal impairment are defined as eGFR of ≥ 30 – 59 ml/min/1.73m^2 and < 30 ml/min/1.73m^2, respectively.

All patients had a FBC measured on admission. This haematological test includes several parameters that are useful in HF. These are haemoglobin, white blood cell (WBC) count, lymphocytes and red cell distribution width (RDW). Anaemia may be a cause or a consequence of HF and has prognostic importance regardless of systolic function (138). In this study, anaemia was defined according to the World Health Organization (WHO) criteria (139). These criteria define anaemia as a haemoglobin < 12g/dl in women and < 13g/dl in men. A raised total WBC count may indicate infection as a cause of decompensated HF. Lymphopenia is common in HF (138). Red cell distribution width is a novel prognostic marker in patients with chronic HF (140).

2.3 The post-discharge heart failure cohort

2.3.1 Study visit

All enrolled patients were invited to attend the British Heart Foundation (BHF) Glasgow Cardiovascular Research Centre to complete the follow-up study visit. This visit was arranged approximately 4-6 weeks after the patients were discharged from hospital. All surviving patients were telephoned one week prior to their allocated appointment to confirm attendance for study visit and organise taxi transport to the BHF Glasgow Cardiovascular Research Centre. The local online patient record database was checked prior to telephoning patients to ensure they were still alive. The study visits took place between 17th January 2007 and 12th March 2009.

2.3.2 Data collection

Every patient had a second case record form completed for their study visit using the same unique, anonymous study identification number allocated during their hospital admission (appendix IX, pages 356-368). Data collected in hospital were updated and recorded. This included current HF symptom status and current medications. New medical conditions were noted. Further admissions to hospital with HF, since enrolment in this study, were documented. Routine physiological measurements, body composition measurements and a cardiovascular system examination were performed for all patients. A 12-lead ECG was recorded and the same parameters described in section 2.2.2 were noted. The aetiology of HF was detailed for every patient. Biochemical and haematological blood tests results, LVEF by echocardiography and MTWA results, were also recorded in the case record form (appendix IX). The reasons patients failed to attend the study visit were noted. These were recorded as; refusal to attend, unable to attend due to deteriorating health, or deceased. If the patient was deceased, the date of the death was obtained from the local online patient record database.

2.3.3 Aetiology of heart failure

The primary aetiology of HF was recorded for all enrolled patients. Contributing aetiologies were also noted. The primary aetiology was defined as “ischaemic” if there was evidence of prior myocardial infarction, coronary revascularisation or angiographically significant coronary artery disease. Significant coronary artery disease was defined as >50% stenosis in at least one major epicardial coronary artery branch. “Non-ischaemic” aetiology was assumed only when significant coronary artery disease had been excluded by angiography. Patients who did not fit into either group were deemed to have “unknown” aetiology. Patients with non-ischaemic aetiology of HF were categorised into one of the following categories; idiopathic dilated cardiomyopathy, hypertension, alcohol or valvular heart disease. Valvular heart disease was only considered causative if at least moderate in severity. Patients with a non-ischaemic cause who did not fit into one of the aforementioned categories were classified as ‘other’ and the specific cause recorded. Assigning the aetiology of HF was performed at the time of the study visit, rather than during the hospital visit. This allowed use of information from investigations performed after recruitment, and improved the chances of determining the primary aetiology. For example, investigations like coronary angiography may have been performed late in the hospital admission or following discharge from hospital. Results of angiograms were obtained by interrogation of the local angiography database.

Other aetiologies potentially contributing to HF were also recorded for all patients. These largely fell into the following categories; valvular heart disease, diabetes mellitus, atrial fibrillation, hypertension and alcohol. Valvular heart disease was only considered a potential contributor if the severity was at least moderate. The valve(s) involved were also recorded. Atrial fibrillation was only considered a contributing aetiology if persistent or permanent. The aetiology of HF was also recorded for patients who did not complete the study visit.

2.3.4 Biochemical and haematological tests

Several biochemical and haematological tests were performed at the study visit. The blood tests were selected either because they are already established biomarkers in HF or to

potentially allow identification of new variables that may be prognostically important in HF. The blood tests carried out at the study visit included all the laboratory parameters that were part of the final multivariable model for cardiovascular death or chronic heart failure hospitalisation for the CHARM cohort (126). These are red cell distribution width, bilirubin, lymphocytes, urate, glycosylated haemoglobin, haemoglobin, creatinine and phosphate. This would allow testing of the CHARM model in this cohort. In addition to the aforementioned tests the following biochemical and haematological tests were performed at the study visit; BNP, troponin I, U&E, LFT, TFT, cholesterol profile and FBC. The same assays (section 2.2.3) were used to measure BNP and troponin I. Renal function was assessed by eGFR in the same way as described earlier (section 2.2.3).

2.3.5 Echocardiography

All patients attending the study visit underwent echocardiographic assessment of LVEF using the biplane method of discs (modified Simpson's rule). This method relies on accurate tracing of the endocardial borders to calculate left ventricular volume. Apical four-chamber and two-chamber views were used. LVEF was then calculated from the left ventricular volumes recorded in systole and diastole. This would allow dichotomising of patients into HF-REF and HF-PEF groups. Images were recorded on an Acuson Sequoia C512 machine, the machine used for all studies in the BHF Glasgow Cardiovascular Research Centre. All images were recorded by myself. Patients were positioned in the left lateral decubitus position. The calculations of LVEF were carried out offline by a single operator, who is an accredited cardiac technician of the British Society of Echocardiography. The images were stored using the anonymous study identification number and the operator calculating the LVEFs was blinded to all patient details. HF-PEF was defined as LVEF > 50% (18). Simpson's Biplane method cannot be used if the quality of echocardiographic images is sub-optimal, as this leads to poor identification of endocardial borders. This is usually due to patient body habitus or poor echocardiographic windows. In these cases, a qualitative assessment of overall left ventricular systolic function was made (reduced or preserved function).

2.3.6 Microvolt T-Wave Alternans

2.3.6.1 Application of the Microvolt T-Wave Alternans test

MTWA testing was performed on eligible patients using the commercially available HearTWave^{TM} system (Cambridge Heart) (Figure 2.2). This uses the spectral analysis method to measure the magnitude of MTWA at a threshold heart rate. Seven proprietary noise-reducing electrodes (Figure 2.3) and seven standard electrodes were placed on the praecordium and limbs. The proprietary electrodes are designed to detect alternans, even in the presence of the noise that is usually present during exercise stress testing. Noise was further minimised by careful preparation of the skin using abrasive gel prior to electrode placement. Detailed ECG recordings were taken at rest, during exercise on the treadmill and in recovery (Figure 2.4). The treadmill exercise was tailored to produce a gradual elevation in heart rate. The test requires elevation of the heart rate to at least 110bpm for approximately 2-3 minutes. The HearTWave^{TM} system then analyses the data by measuring the amplitude of the corresponding points of 128 consecutive T waves (Figure 2.5) (141). Each T-wave is measured at the same time point relative to the start of the QRS complex. Beat-to-beat fluctuations in amplitude are plotted and fast Fourier transformation performed to quantify the variation in frequency (Figure 2.5) (141). The HearTWave^{TM} system provides an automatic interpretation of the test results, as positive, negative or indeterminate. Indeterminate results are most commonly due to an inability to raise the heart rate sufficiently (due to chronotropic incompetence or if the patient is physically incapable of exercising long enough to raise their heart rate), the presence of ventricular ectopy or excessive signal noise due to motion or respiration (141). Indeterminate tests due to noise may become determinate when re-tested immediately. There is evidence that indeterminate results due to noise are not prognostically significant (123) and for this reason, those patients with an indeterminate result due to excessive noise were re-tested once. Whether or not a patient was prescribed optimal HF therapy at the time of MTWA testing was also documented. Patients were not asked to discontinue beta-blockers prior to MTWA testing; previous studies have done this in order to improve the likelihood of a determinate test. A fundamental objective of this study was to determine the predictive role of MTWA testing while taking optimal individualised therapy. Overall the MTWA test takes less than 30 minutes to perform, including preparation time.

Figure 2.2: HearTWave™ system (Cambridge Heart)

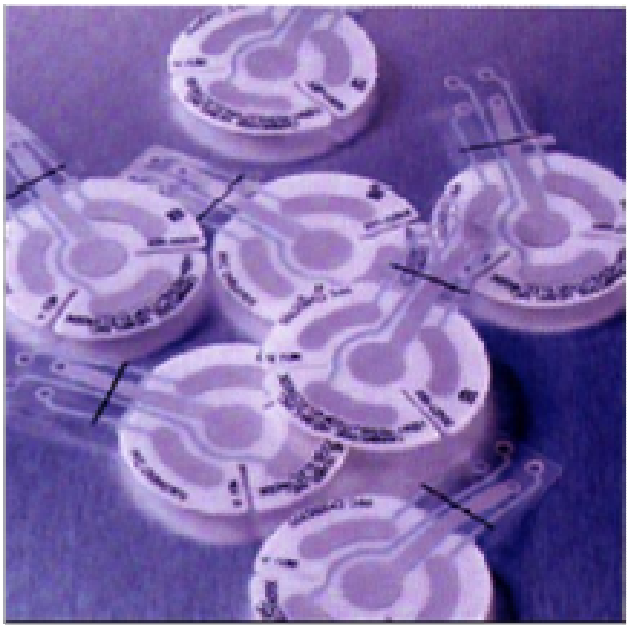


Figure 2.3: Proprietary ECG electrodes

Figure 2.4: MTWA testing in the BHF Glasgow Cardiovascular Research Centre

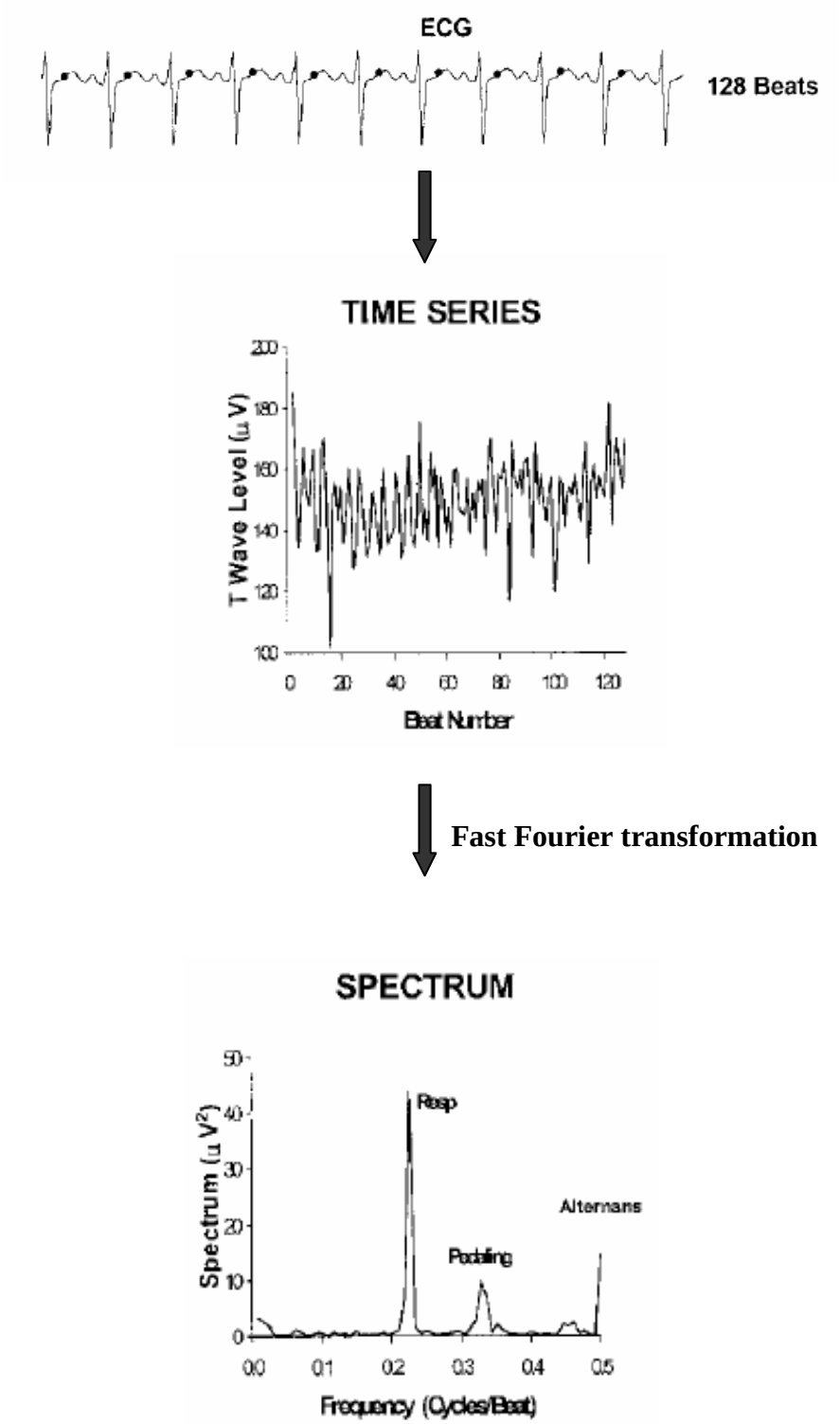


Figure 2.5: Spectral method of measuring T-wave alternans (141)

2.3.6.2 Microvolt T-Wave Alternans Prevalence Study

Eligibility for MTWA testing was recorded for all patients attending the study visit. Reasons for ineligibility were documented (AF, demand ventricular pacing or inability to exercise). Differences in clinical characteristics according to eligibility for MTWA testing were analysed. Potential eligibility for MTWA treadmill testing was recorded for patients who did not attend and was derived from clinical data collected during the hospital admission. This was to enable an assessment of whether or not the patients attending the study visit were representative of an unselected cohort of patients with HF.

The results of MTWA testing and the prevalence of positive, negative and indeterminate results in our study population were recorded. The reasons for an indeterminate test were outlined. The functional capacity of the patients was recorded. This included a description of the reason for terminating exercise, duration of exercise and metabolic equivalent values (METs) expended. This would allow an evaluation of the practicality of MTWA testing in patients with HF. For patients unable to exercise, MTWA testing at rest was described.

All automated computer-generated MTWA test results were reviewed by myself and subsequently interpreted by a single clinician (Dr Rachel Myles) experienced in reviewing MTWA reports. The clinician was blinded to both the patient details and the automated computer-generated result. This would enable an assessment of the correlation between the automatic result and a clinician's interpretation.

Differences in the clinical characteristics between the three MTWA groups were analysed to determine the clinical associates of a particular MTWA result. Particular attention was paid to LVEF, aetiology of HF (ischaemic or non-ischaemic), QRS duration, BNP levels, as well as many clinical and demographic variables.

2.3.6.3 Microvolt T-Wave Alternans Prognostic Study

The prognostic value of MTWA testing was examined after a period of follow-up (section 2.5). The statistical analysis of the prognostic study is described later (section 2.6). The incremental prognostic value of MTWA over established predictors of outcome in HF was determined. These included LVEF, BNP, clinical variables and biochemical and haematological indices. These analyses were carried out in all patients completing MTWA testing.

2.4 Database Construction

All paper copies of the hospital and study visit case record forms were kept in a locked filing system at the BHF Glasgow Cardiovascular Research Centre. An electronic database was created in the Robertson Centre for Biostatistics at the University of Glasgow to store these data. Data were manually entered into the electronic database and verified by two independent database managers working in the Robertson Centre. No patient identifying material was entered into the electronic database; patients were anonymised and identified by their unique study identification number. All data were subject to manual and prespecified electronic data validation checks which resulted in the production of a large number of queries. All queries were rectified and data appropriately amended in the central database. This robust system ensured quality control of the data processed.

2.5 Long-Term Follow Up

All enrolled patients consented to be “flagged” with the Information Services Division (ISD) of the Scottish Health Service. This allowed mortality follow-up data to be obtained. Patient identifying information was sent to ISD for all patients once recruitment was complete. ISD linked the study database to information on in-hospital and out-of hospital deaths, held by the General Register Office for Scotland. The database was also linked to the Scottish Morbidity Register which provides details of dates and causes of hospital readmission. Data on cause,

location and date of death were obtained. ISD classifies causes of death using the WHO International Classification of Diseases (ICD-10) coding system.

The final follow-up visit was 12th March 2009. Linkage data were requested in January 2010. Data provided by ISD has a lag time of approximately six months. Thus, survival time was calculated from the date of attendance at the study visit until death or censoring at 31st July 2009.

2.6 Statistical methodology

2.6.1 Statistical Analyses

Statistical Package for the Social Sciences (SPSS) (version 18) software was used for basic statistical analyses. S-Plus (version 8.1) was used for analysis of variance (ANOVA), Student's t-test, χ^2 test logistic regression and mortality analyses.

Inter-group comparisons were made for continuous variables using ANOVA F-test (for comparisons involving more than 2 groups) and Student's t-test (for 2 group comparisons), and for categorical variables using χ^2 test. Logistic regression analysis was used to identify predictors of each MTWA result. A probability value of $p<0.1$ was used for selecting variables for the logistic regression analyses. A probability value of $p<0.05$ was considered significant for all other analyses. All continuous variables were transformed as appropriate to normalize their distributions.

Survival time was calculated from the date of attendance at the study visit until death or censoring at 31st July 2009. Kaplan-Meier survival curves were constructed to illustrate survival of the patients according to MTWA result. Curves were compared using the log rank test. The incremental prognostic value of MTWA testing was evaluated using Cox proportional hazard models. A three stage prognostic model (Table 2-3) was used with

variable selection based on the clinical model derived by the CHARM investigators (126). Stage one, the basic model, incorporated the strongest predictors of outcome from the CHARM model in a multivariable Cox proportional hazard model. Stage two included the variables from stage one plus routine haematological and biochemical variables predictive of outcome in the subsequent CHARM analyses (140;142). Stage three included the variables from stages one and two plus the novel biomarkers BNP and troponin I. For the multivariable models variables were removed using backwards elimination, removing the largest p values first until all p values were significant (< 0.05). Finally, the MTWA result was added to each of the three stages to assess for incremental prognostic value.

Table 2-3: Three stage model for evaluating the incremental prognostic value of MTWA

Stage	Variables
1	Age
	Ejection fraction
	Diabetes – insulin treated
	BMI (kg/m^2)
	Sex (Female)
	NYHA class III and IV
	Bundle branch block
	Cardiomegaly
	SBP
	Diagnosis of chronic HF over 2 years ago
	Previous myocardial infarction
	Dependent oedema
	Heart rate
	AF
2	eGFR
	RDW
	Bilirubin
	Haemoglobin
	Lymphocytes
	Urate
	Phosphate
	Glycosylated haemoglobin
3	BNP
	Troponin I

BMI = body mass index; RDW = red cell distribution width

2.6.2 Power Calculation

It was assumed that if 600 subjects were recalled for MTWA testing then 400 would actually undergo evaluation, after excluding those ineligible for testing. Based on recent studies (107;109), it was assumed that these would split one third MTWA negative and two thirds MTWA non-negative (positive or indeterminate). Power calculations were based on the all-cause mortality data estimating the hazard ratio of MTWA (non-negative / negative) with adjustment for other prognostic factors. Assuming crude 1 year mortality rates of 21% in the preserved ejection fraction group and 32% in the reduced ejection fraction group, as observed in a recent study in Glasgow (25), the study would have 84% power at the 5% level of significance to detect a MTWA non-negative/ MTWA negative hazard ratio of 1.78.

2.6.3 Defining events and outcomes

The primary outcome measure of this study was all-cause mortality. Secondary outcome measures of interest were (i) SCD or resuscitated cardiac arrest, and (ii) cardiovascular death (excluding sudden). All outcome data were obtained from linkage data provided by ISD. Causes of death were classified according to the ICD-10 classification as documented on the death certificates. Causes of death were not adjudicated. Although the secondary outcome measures were of interest in this study, it was recognised at study conception that, due to the limitations of the ISD data, only all-cause mortality would be a robust and definitive outcome.

All-cause mortality was defined as death from any cause. Cardiac transplantation was also censored as death. Much has been written on the problems of defining and identifying SCD, particularly in patients with HF (143;144). Not all sudden deaths are arrhythmic, and not all arrhythmic deaths are sudden. The majority of SCD occurs outside hospital, and is commonly certified as acute myocardial infarction. A small proportion of patients undergo a resuscitation attempt by the ambulance service, while others may suffer sudden and unexpected death during their hospital admission. Some classification systems, such as that proposed by Hinkle and Thaler (145), require detailed information to be obtained from relatives or medical attendants on the exact sequence of events immediately prior to death. Such an approach was

beyond the scope of this study. A recent clinical trial in patients with acute HF defined SCD as death occurring unexpectedly in a previously stable patient and including any of the following deaths: (i) witnessed and instantaneous without new or worsening symptoms and also in the absence of progressive circulatory failure lasting for 1 hour or more, (ii) witnessed within 1 hour of the onset of new or worsening symptoms unless a cause other than cardiac is obvious, (iii) death witnessed and attributed to an identified arrhythmia, (iv) death during an attempted resuscitation for cardiac arrest or death within 24 hours of resuscitation, or without gaining consciousness, from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death, and (v) unwitnessed death in the absence of pre-existing progressive circulatory failure or other causes of death, only where the stability of the patient in the week prior to death was known (146). Clinical trials are supported by endpoint adjudication committees who are provided with detailed information regarding deaths, allowing the clinical expertise of the committee to appropriately adjudicate the cause of deaths. Some MTWA studies have included SCD as a clinical endpoint (103;104;111-115;119). These studies have defined SCD as death within an hour of symptom onset or during sleep without another identifiable cause.

The detailed information and infrastructure required for adjudicating sudden cardiac death, as outlined above, was not available for this study. Thus, a pragmatic definition of SCD for this study was adopted as being: (i) death occurring outside hospital and certified as due to acute MI, (ii) death certified as cardiac arrest (ICD-10 code I46) or (iii) death certified as VF (ICD-10 code I490) or VT (ICD-10 code I472).

The secondary outcome ‘SCD or resuscitated cardiac arrest’ therefore included successful in- and out-of-hospital resuscitations of cardiac arrest (ICD-10 code I460), in addition to SCD as defined above. Information regarding appropriate ICD discharges for documented ventricular arrhythmia is not provided by ICD-10 codes and was therefore unavailable and not included in outcome measures for this study. Cardiovascular death (excluding sudden) was defined as death from any cardiovascular disease (ICD-10 codes I00-I99) and not meeting the criteria for sudden cardiac death, as outlined above. The latter was included to evaluate if MTWA was predictive of general cardiovascular mortality, rather than arrhythmic mortality.

CHAPTER THREE

CLINICAL CHARACTERISTICS
OF
HOSPITALISED COHORT

3.1 Introduction

This chapter will outline the recruitment of patients into the study and detail the reasons for exclusion from participation. The main focus of this chapter is to describe in detail the clinical characteristics of the hospitalised patients recruited into the study. This will include basic demographic details, signs and symptoms prior to admission, medical history, medications prescribed pre-admission, medical therapies administered during the first 24 hours after admission and examination findings. Electrocardiographic, radiological, blood test and echocardiographic results will also be described.

3.2 Results

3.2.1 Selection of study cohort

An overview of the patients screened for participation in the study and the subsequent involvement of recruited patients in the follow-up study visit is shown in Figure 3.1. Recruitment into the study took place between 1.12.06 and 10.01.09 at the Royal and Western Infirmaries in Glasgow and between 22.04.08 and 10.01.09 at the Royal Alexandra Hospital in Paisley. During these periods, 2361 patients admitted with suspected decompensated HF were screened for participation in the study. A total of 1003 patients were recruited; the breakdown per hospital and rate of recruitment is displayed in Figure 3.2. Recruitment stopped once the 600th patient had completed the study visit. This was the original target number of patients (section 2.6.2, page 89).

More than half (n=1358) of all patients with suspected decompensated HF were excluded from recruitment. Figure 3.3 illustrates the reasons for exclusion. The most common reason was readmission of patients already enrolled in the study, confirming the high readmission rates that occur for patients with HF. The next most common reasons for exclusion were cognitive impairment and a normal BNP level (<100pg/ml). Analysis *per* hospital revealed consistency for most reasons of exclusion (Figure 3.3). Notable exceptions to this were the following

categories; BNP level <100pg/ml, pulmonary oedema secondary to ACS (acute coronary syndrome) and refusal to take part in the study. A greater proportion of patients screened in Glasgow Royal Infirmary had a normal BNP level than the other two hospitals. This may be due to variation in operator screening techniques at the three hospitals. Alternatively, more patients with suspected HF may have been admitted to Glasgow Royal Infirmary. The proportions of patients excluded due to pulmonary oedema secondary to ACS were similar at the two Glasgow hospitals but lower at the Royal Alexandra Hospital. The reasons for this are unclear but may reflect less frequent screening at the Royal Alexandra Hospital or variations in investigator screening technique at that site. Finally, considerable variation in the number of patients who refused to take part in the study was observed across all three sites. The reasons for this are likely multifactorial and may include the communication skills of the investigators at each hospital, the patients response to whether a doctor or research nurse approached them and the distance the patient would have to travel for the follow-up visit. The majority of patients in the category 'Other' would have required ambulance transportation to the study visit. This included nursing home residents, patients dependent on domiciliary oxygen and those who were housebound. Patients who subsequently had alternative diagnoses and explanations for an elevated BNP, such as pulmonary embolism, were also included in the category 'Other'.

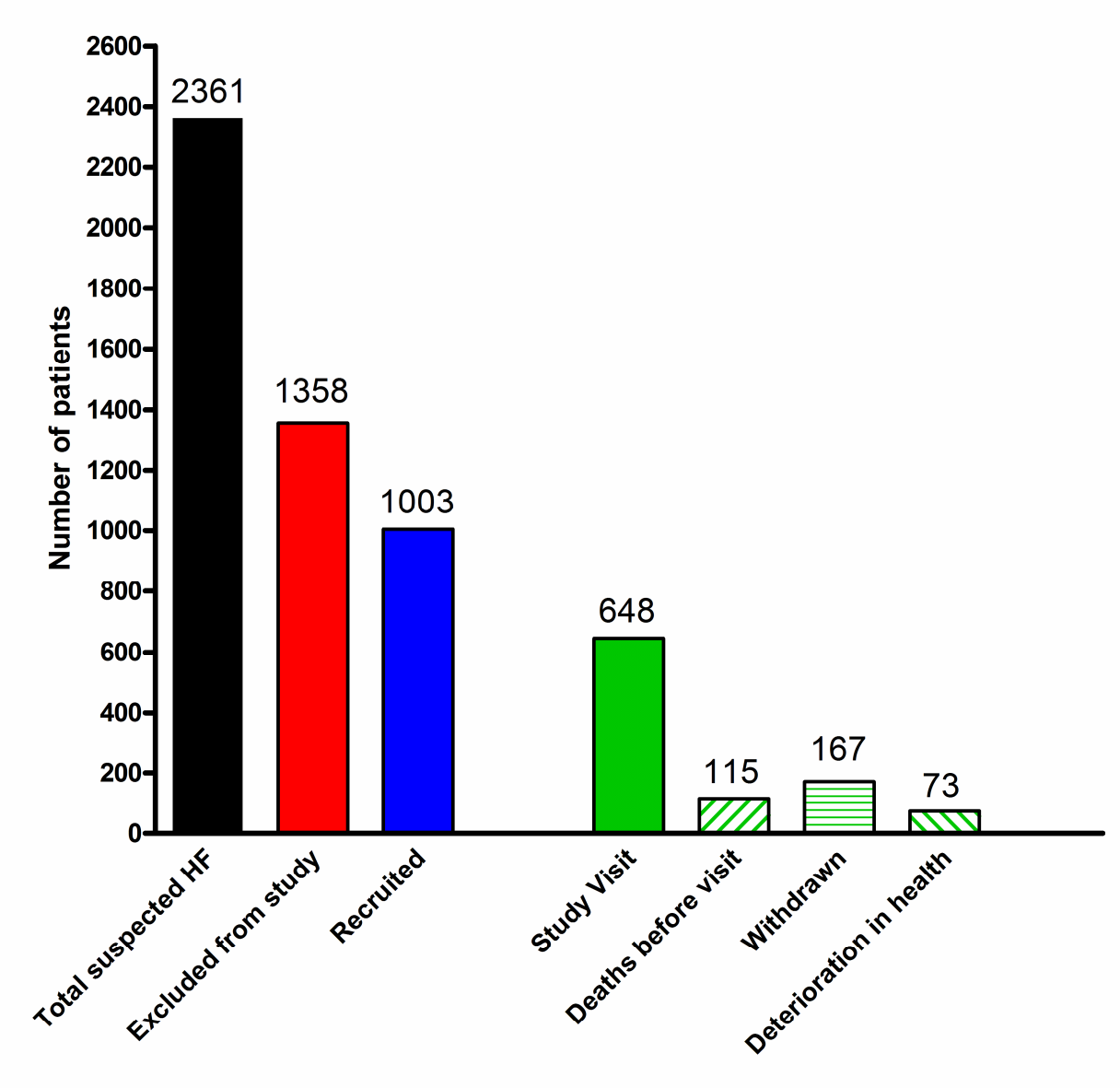


Figure 3.1: Overview of all the patients screened from the three hospitals and final composition of the recruited study cohort

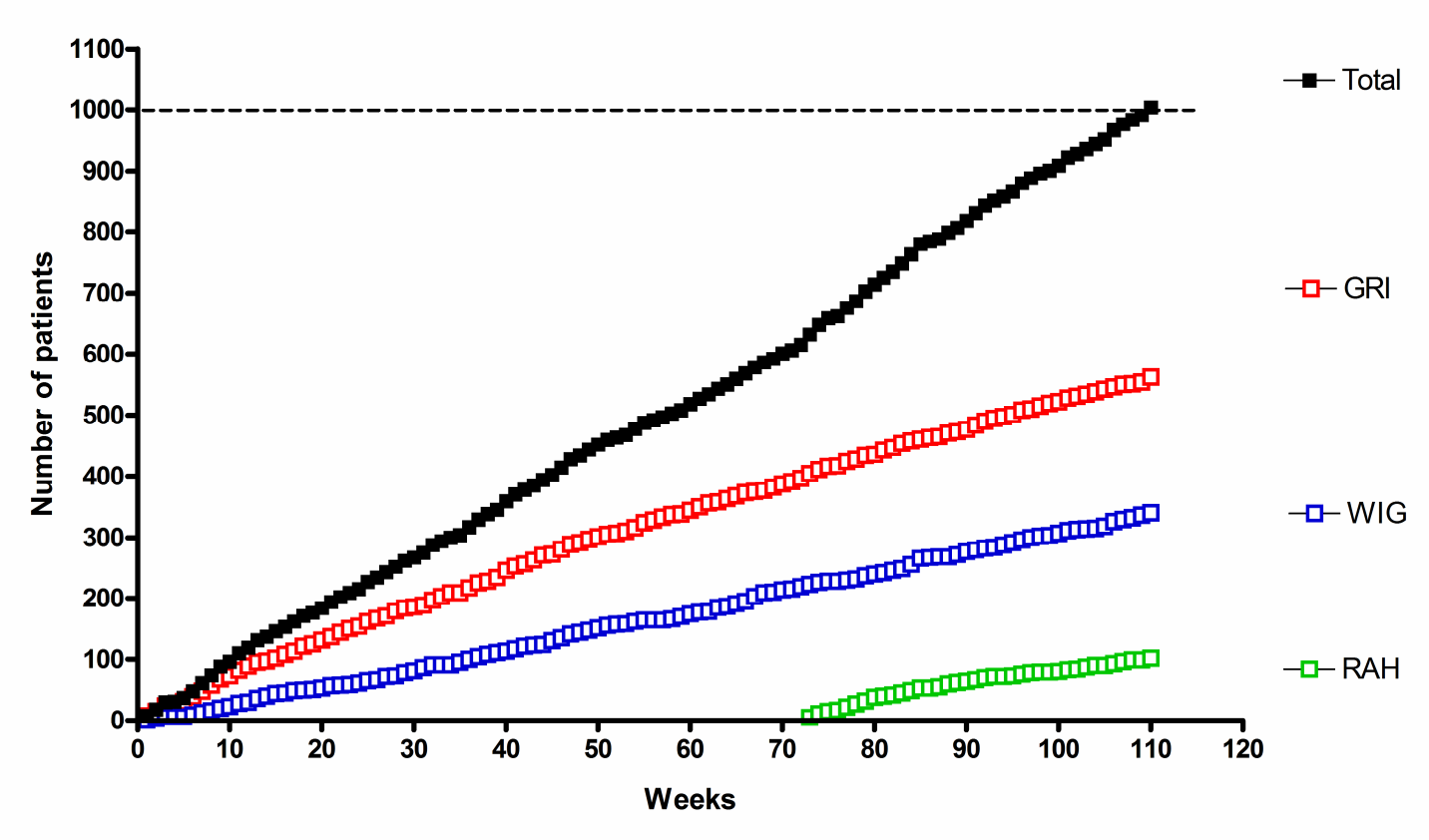


Figure 3.2: Recruitment into the study; overall and *per* hospital. This figure details the rate of recruitment at each of the 3 hospitals, from 1st December 2006 for Royal and Western Infirmaries in Glasgow (GRI and WIG, respectively) and from the 22nd April 2008 from the Royal Alexandra Hospital (RAH). Recruitment finished on 10th January 2009.

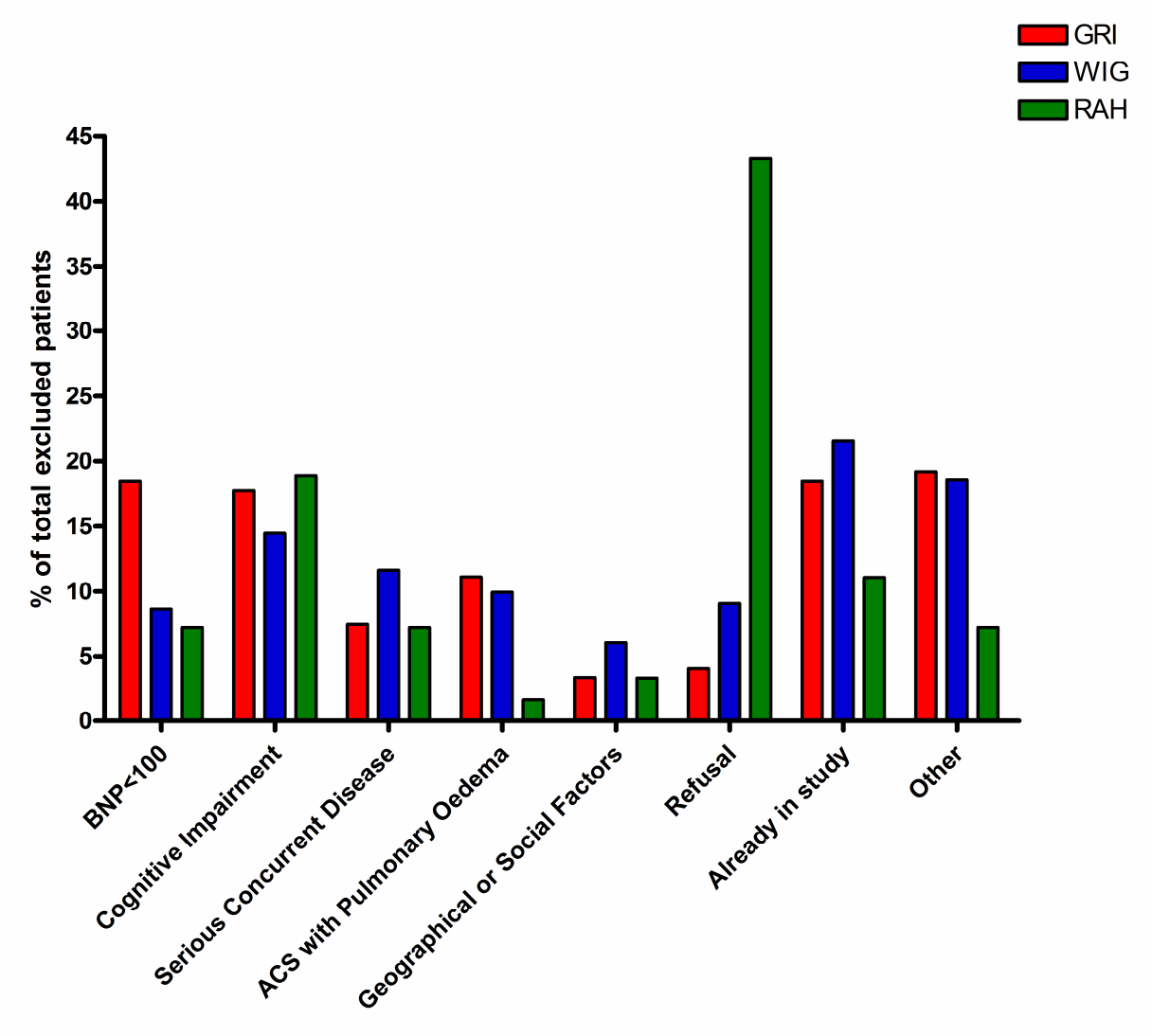


Figure 3.3: Breakdown of the major reasons for exclusion from recruitment into the study, *per* hospital.

3.2.2 Demographics

The demographics of the hospitalised cohort are displayed in Table 3-1. The majority of patients were male (53%). The mean (SD) age was 73 years (10.5), with a wide overall range from 19 to 99 years. Almost half of the cohort was more than 75 years old. The vast majority of patients were Caucasian (98.7%). The mean (SD) duration of admission was 12 days (14), with a wide overall range from 1-141 days. Many patients died during the index admission (6.8%).

Table 3-1: Demographics of the hospitalised cohort

Variable	n (%), mean (SD) or median [IQR]
Male	532 (53.0)
Female	471 (47.0)
Mean age (years)	73 (10.5)
Median age (years)	74 [67-81]
Age range	18 – 99
≥ 75 years old	458 (45.7)
Race	
Caucasian	990 (98.7)
Black	2 (0.2)
South Asian	10 (1.0)
Oriental	1 (0.1)
Mean duration of admission (days)	12 (14)
Median duration of admission (days)	8 [5-14]
Death during index admission	68 (6.8)

3.2.3 History of heart failure

Many patients hospitalised with decompensated HF have a history of chronic HF and previous hospital admissions. In this study, almost half of the patients had a history of chronic HF. The majority of these patients had previous hospitalisations with decompensated HF (76.5%). Most patients with a history of HF had this diagnosis established more than two years before enrolment into this study (71.4%).

Various healthcare professionals were involved in the care of those patients with a history of HF (Figure 3.4). The majority of these patients had regular cardiology follow-up, attending either general cardiology clinics (50.5%) or HF specialist clinics (22.1%). A small proportion of patients were looked after by a general physician (14.4%), whilst a similar proportion was cared for by their general practitioner alone (13.0%). Many patients were also under the care of HF liaison nurse services (22.3%).

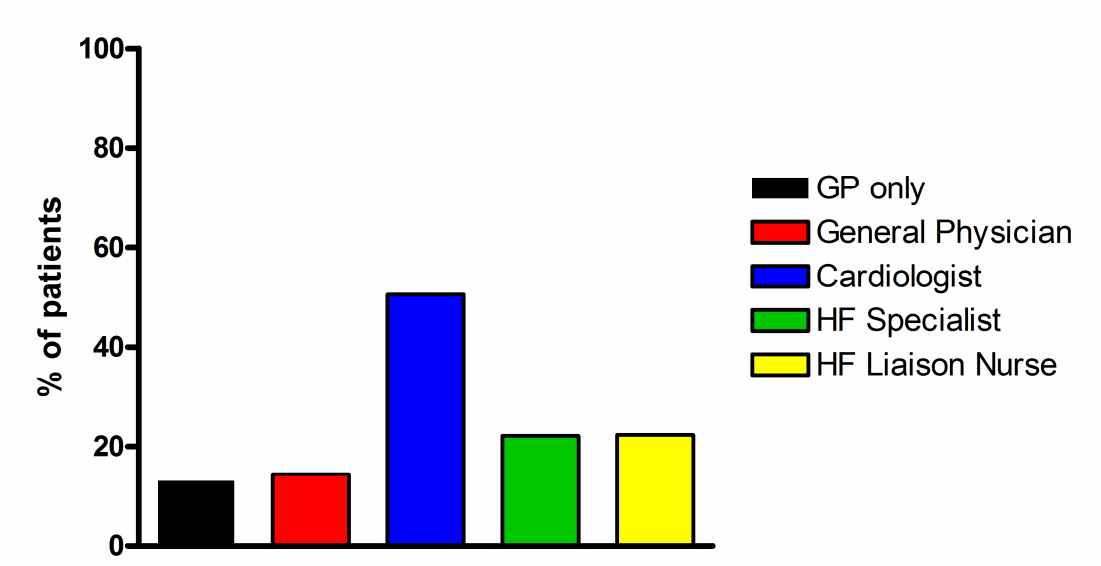


Figure 3.4: Healthcare professionals involved in the management of patients with a diagnosis of HF prior to recruitment into the study

3.2.4 Symptoms prior to admission

Symptoms of decompensated HF in the days prior to admission were recorded for every patient. Each patient was asked if they had experienced any of the following symptoms: paroxysmal nocturnal dyspnoea, orthopnoea, ankle swelling, palpitations, wheeze and chest pain. Table 3-2 displays the frequencies of these symptoms. Orthopnoea and ankle swelling were the commonest symptoms, affecting more than two-thirds of the cohort. Most patients had NYHA functional class III symptoms at the time of admission (59.2%). Similar proportions of patients had NYHA functional classes II or IV symptoms (22.4% and 18.4%, respectively). More than half of all patients recruited had a history of angina.

Table 3-2: Symptoms of heart failure prior to admission

Symptoms	Number of patients	% of cohort (n=1003)
NYHA Class		
II	225	22.4
III	594	59.2
IV	184	18.4
Paroxysmal nocturnal dyspnoea	484	48.3
Orthopnoea	761	75.9
Ankle swelling	698	69.6
Palpitations	204	20.3
Wheeze	291	29.0
History of angina	548	54.6
Current angina	296	29.5

3.2.5 Medical history

Table 3-3 shows the common cardiovascular conditions and their prevalences in the hospitalised cohort. The risk factors for cardiovascular disease are displayed in Table 3-4.

Coronary heart disease is the commonest cause of HF. Of 1003 patients enrolled in the study, 443 patients (44.2%) had a history of a previously reported MI. Many patients had evidence of significant coronary artery disease on angiography (defined as at least 50% stenosis in at least 1 major epicardial artery). The results of coronary angiograms performed prior to enrolment in the study are displayed in Figure 3.5. Percutaneous coronary intervention (PCI) had been performed in 122 patients (12.2%) and 170 patients (17.0%) had previous coronary artery bypass grafting (CABG), at the time of enrolment.

Hypertension is a frequent cause of HF, particularly in elderly patients, and was particularly common in this study with almost two-thirds of the cohort treated for hypertension prior to recruitment. A significant proportion had hypercholesterolemia (36.0%). Cerebrovascular disease, defined as a cerebrovascular accident (CVA) or transient ischaemic attack (TIA), was also common (23.0%).

Atrial fibrillation (AF) is a common comorbidity in HF, especially in this study. Over half of all patients had a history of AF (53.5%), with the majority of these patients experiencing permanent AF (28.5%). Few patients had a past history of AF but were in sinus rhythm at the time of recruitment (3.2%). A similar proportion of patients had paroxysmal AF (11.2%) or persistent AF (10.7%).

Arrhythmias are a common cause of morbidity and mortality in HF. Of 1003 enrolled patients, 108 patients (10.8%) had documented evidence of a prior arrhythmia. A similar proportion of patients had a history of syncope (12.2%). The documented arrhythmias included supraventricular tachycardia (SVT) (1.7%) ventricular tachycardia (VT) (2.6%), ventricular fibrillation (VF) (1.6%), sick sinus syndrome (SSS) (1.7%) and atrioventricular (AV) block

(3.2%). Of the small number of patients with a documented history of VT, the majority was nonsustained VT (73.1%). Of the patients with a history of AV block; the majority had either second or third degree (40.6% and 43.8%, respectively). The low prevalence of first-degree AV block may simply reflect this arrhythmia not being recorded in the medical case-notes.

Only 5 patients (0.5%) had a primary prevention ICD and 8 patients (0.8%) a secondary prevention ICD. Conventional pacemakers were more common (6.1%), but few patients had cardiac resynchronisation therapy with a defibrillator device (CRT-D) (0.5%). No patients had cardiac resynchronisation therapy without a defibrillator device (CRT-P) at the time of enrolment into the study.

Many patients had a history of valvular heart disease (44.3%). A subset of these patients had a history of rheumatic valvular heart disease (7.2%) or a valve replacement prior to enrolment into the study (8.0%).

Diabetes mellitus is an established risk factor for coronary heart disease and has recently emerged as a risk factor for HF. Almost one third of the cohort had a history of diabetes mellitus (31.2%). This was managed in the following ways; dietary modification alone (5.8%), oral hypoglycaemic therapy (14.4%), insulin (8.0%), and oral hypoglycaemic and insulin combination therapy (3.1%).

Alcohol is another important risk factor for HF and the majority of patients in this study acknowledged alcohol consumption prior to admission (62.0%). Of these patients, few admitted to alcohol intake in excess of the recommended safe limits (7.0%). A similar proportion of patients admitted to a previous history of alcohol excess (9.6%) and almost half of the cohort consumed alcohol within the recommended limits (45.5%). Few patients admitted to a past history of alcohol excess but drank within recommended limits at the time of admission (1.1%).

Over two-thirds of the cohort reported a history of cigarette smoking, the majority being ex-smokers. Of the ex-smokers, most had stopped smoking more than 12 months before recruitment into the study. Approximately one fifth of the cohort were cigarette smokers prior to admission.

A family history of cardiac disease was recorded for every patient enrolled in the study. The majority had no family history (61.0%). Around one third of the cohort described details of a family history of coronary heart disease, with few patients aware of family members with a diagnosis of a cardiomyopathy (0.7%). A small proportion could give an account of family members having a history of cardiac disease but did not know the specific diagnoses (5.1%).

Table 3-3: Common cardiovascular conditions present in the hospitalised cohort

Medical condition	Number of patients	% of cohort (n=1003)
MI	443	44.2
Angiographic CAD	323 /436	74.1
PCI	122	12.2
CABG	170	17.0
Cerebrovascular disease (TIA/CVA)	231	23.0
Atrial fibrillation		
Past	32	3.2
Paroxysmal	112	11.2
Persistent	107	10.7
Permanent	286	28.5
Prior arrhythmia		
SVT	17	1.7
SSS	17	1.7
1st degree AV block	5	0.5
2nd degree AV block	13	1.3
3rd degree AV block	14	1.4
Sustained VT	7	0.7
Nonsustained VT	19	1.9
VF	16	1.6
Conventional pacemaker	61	6.1
CRT-D	5	0.5
Primary prevention ICD	5	0.5
Secondary prevention ICD	8	0.8
Valvular heart disease	444	44.3
Rheumatic heart disease	72	7.2
Valve replacement	80	8.0
Peripheral arterial disease	180	18.0

CAD = coronary artery disease (defined as > 50% stenosis in ≥ 1 major epicardial vessel, denominator is number of patients who had an angiogram)

Table 3-4: Prevalence of major risk factors for cardiovascular disease in the hospitalised cohort

Cardiovascular risk factor	Number of patients	% of cohort (n=1003)
Treated hypertension	660	65.8
Hypercholesterolemia	361	36.0
Diabetes mellitus	313	31.2
Diet controlled	58	5.8
Oral therapy	144	14.4
Insulin	80	8.0
Oral therapy & insulin	31	3.1
Smoking history		
Ex-smoker >1 year	427	42.6
Ex-smoker <1 year	46	4.6
Current smoker	208	20.7
Alcohol history		
Within recommended limits	456	45.5
Previous or current excess	166	16.6
Family history of cardiac disease		
No history	612	61.0
Unknown cardiac conditions	51	5.1
Coronary heart disease	333	33.2
Cardiomyopathy	7	0.7

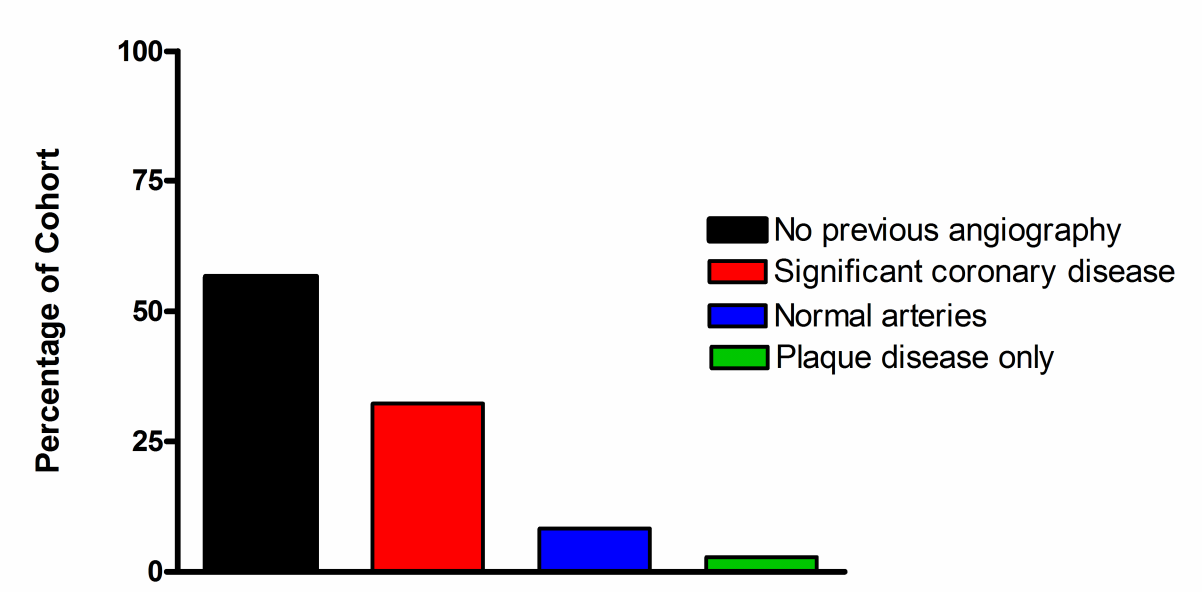


Figure 3.5: Coronary angiography results for the hospitalised cohort. This figure displays the results of angiograms performed prior to recruitment into the study.

Table 3-5 shows the common non-cardiovascular medical comorbidities and their prevalences in the hospitalised cohort. Chronic obstructive pulmonary disease (COPD), anaemia and depression are common comorbidities with HF. In particular, HF and COPD often coexist and almost one-third of the cohort had a diagnosis of COPD at the time of enrolment into the study. Anaemia has also been demonstrated to be frequently present in HF. Anaemia, as defined by the WHO criteria (139), affected almost half of the hospitalised cohort. A significant proportion of patients with HF have depression. This was observed in this study with one fifth of all patients having a history of depression and the majority of these patients were experiencing ongoing symptoms prior to their admission to hospital. Weight loss is associated with a poor prognosis in HF. Involuntary weight loss, defined as a loss of at least 5% of body weight, was experienced prior to admission in a significant proportion of the hospitalised cohort. Other common comorbidities recorded in the hospitalised cohort are displayed in Table 3-5. Finally, only 12 patients (1%) had no significant medical history at the time of recruitment into the study. This was defined as no cardiovascular disease, cardiovascular risk factor or other medical comorbidity.

Table 3-5: Frequencies of common non-cardiovascular medical comorbidities in the hospitalised cohort

Medical condition	Number of patients	% of cohort (n=1003)
Depression	208	20.7
Current	139	13.9
Cancer		
Previous	121	12.1
Current	24	2.4
COPD	297	29.6
Asthma	48	4.8
Anaemia	454	45.3
Hypothyroidism	102	10.2
Hyperthyroidism	22	2.2
Osteoarthritis	255	25.4
Rheumatoid arthritis	35	3.5
Connective tissue disease	20	2.0
Neuropathy	58	5.8
Urinary incontinence	112	11.2
Involuntary weight loss (≥ 5% body weight)	164	16.4

3.2.6 Medications pre-admission

Table 3-6 displays the frequencies of prescribing of HF medications prior to admission. More than two-thirds of the cohort was prescribed diuretics prior to admission. This was more than the number of patients with an established previous diagnosis of HF. This may be explained

by General Practitioners suspecting a diagnosis of HF in the weeks preceding admission, and initiating diuretic therapy. Half of the cohort was prescribed an ACE inhibitor prior to admission, with almost the same proportion of patients prescribed a beta blocker. Fewer patients were prescribed an ARB or an aldosterone blocker prior to admission.

Table 3-6: Frequency of heart failure medication prescribing prior to admission to hospital

Heart failure medication	Number of patients	% of cohort (n=1003)
Diuretics	696	69.4
Furosemide & other loop diuretics	641	63.9
ACE inhibitor	507	50.6
ARB	140	14.0
ACE or ARB	613	61.1
ACE and ARB	34	3.4
Beta-blocker	478	47.7
Aldosterone blocker	66	6.6
Digoxin	167	16.7

Table 3-7 outlines the frequencies of prescribing of other common cardiovascular medications. A large proportion of patients were taking statins and aspirin prior to admission, reflective of the high prevalence of coronary heart disease in this cohort. A significant number of patients were prescribed calcium channel blockers, warfarin, oral hypoglycaemic agents or long-acting nitrates. Smaller proportions of patients were taking digoxin, nicorandil, clopidogrel, insulin or anti-arrhythmic medications.

Table 3-7: Frequency of cardiovascular medication use prior to admission to hospital

Cardiovascular medication	Number of patients	% of cohort (n=1003)
Statins	657	65.5
Aspirin	543	54.1
Clopidogrel	118	11.8
Aspirin or clopidogrel	602	60.0
Calcium channel blockers	272	27.1
Warfarin	264	26.3
Oral hypoglycaemic agents	244	24.3
Long-acting nitrates	196	19.5
Nicorandil	147	14.7
Insulin	109	10.9
Anti-arrhythmic	38	3.8

Many patients were taking non-cardiovascular medications prior to their admission to hospital, reflective of the many comorbidities associated with HF (Table 3-8). Almost 40% of the cohort was prescribed proton pump inhibitors. A significant number of patients were prescribed bronchial inhalers, consistent with the high prevalence of chronic obstructive airways disease in this cohort. Few patients were prescribed non-steroidal anti-inflammatory drugs (NSAIDs).

Table 3-8: Frequency of non-cardiovascular medication use prior to admission to hospital

Non-cardiovascular medication	Number of patients	% of cohort (n=1003)
Proton pump inhibitors	396	39.5
Inhalers	283	28.2
Antidepressants	146	14.6
Ferrous sulphate	105	10.5
Allopurinol	76	7.6
Alendronate	58	5.8
Vitamins (B1 & B-complex)	54	5.4
NSAIDs	37	3.7
Antihistamines	30	3.0
H_2-receptor antagonists	26	2.6
Incontinence meds	20	2.0

3.2.7 Heart failure medical therapy during first 24 hours of admission

The medical therapy administered during the first 24 hours of admission was recorded for every patient in the study (Table 3-9). Medical therapies prescribed beyond the first 24 hours of hospitalisation and on discharge from hospital were not recorded. Medications prescribed on discharge from hospital were likely similar to the medical therapy recorded at the follow-up study visit, albeit smaller doses of HF therapies may have been prescribed on discharge.

Nearly all patients in the study were treated with diuretics immediately on admission to hospital. The most commonly used diuretic was furosemide (95.7%). Of the patients treated with furosemide on admission, the majority were given this medication intravenously (71.2%). More than half of the patients treated with intravenous furosemide received this more than

once during their admission. Almost one quarter of the cohort received oral diuretic therapy on admission to hospital.

A small number of patients were treated with intravenous nitrates (8.9%) or inotropes (1.7%) on admission to hospital. Most patients receiving these therapies are critically unwell. Approaching such patients for consent to participate in a research study could be ethically inappropriate. This may explain why few patients treated with these therapies were enrolled in this study.

Table 3-9: Heart failure medications administered during the first 24 hours of hospitalisation

Heart failure therapy	Number of patients	% of cohort (n=1003)
Diuretics	975	97.2
Furosemide	960	95.7
i) Intravenous furosemide	714	71.2
Single dose	333	33.2
Regular	381	38.0
ii) Oral furosemide	247	24.6
Intravenous nitrate	89	8.9
Inotropes (dopamine or dobutamine)	17	1.7

3.2.8 Clinical examination findings on admission

3.2.8.1 Routine physiological measurements

Routine physiological measurements were recorded for all patients enrolled in the study (Table 3-10). The first recording on arrival to hospital was used. The mean pulse rate was 90 bpm, with approximately one-third of patients having a tachycardia on admission (defined as pulse >100 bpm). Of those patients with a tachycardia on admission, almost half were in AF on their admission ECG. The majority of patients had a pulse between 60-100 bpm on arrival to hospital, with few patients having a bradycardia (defined as pulse <60 bpm). The mean (standard deviation [SD]) blood pressure was 136/76 mmHg (27.3/18.0), with an elevated pulse pressure of 60mmHg. Many patients had a systolic blood pressure (SBP) greater than 140 mmHg (41.8%), with a significant proportion of these patients having stage 2 hypertension (defined as SBP ≥ 160 mmHg) on admission (16.4%). Few patients had systolic hypotension (defined as SBP <90 mmHg) on admission. Over one fifth of patients presented with diastolic hypertension (defined as diastolic blood pressure [DBP] ≥ 90 mmHg). A similar proportion of patients presented with diastolic hypotension (defined as DBP <60 mmHg). The mean temperature was 36.5°C with the majority of patients having a temperature within the normal range (defined as 36.1-37.8°C). The mean respiratory rate was slightly elevated and most patients were tachypnoeic (defined as respiratory rate ≥ 20 breaths per minute) on admission to hospital (66.2%). The median oxygen saturation (SpO_2) on admission to hospital was 96%. Almost one third of all patients had SpO_2 recordings less than 95% on admission to hospital.

Table 3-10: Physiological measurements on admission to hospital.

Variable	n (%), mean (SD) or median [IQR]	Units
Mean pulse rate	90 (24.2)	bpm
Median pulse rate	86 [71-105]	bpm
Pulse rate > 100	324 (32.3)	bpm
Pulse rate > 100 & AF on ECG	149/324 (46)	bpm
Pulse rate < 60	67 (6.7)	bpm
Mean SBP	135.6 (27.3)	mmHg
Median SBP	134 [115-152]	mmHg
SBP > 140	419 (41.8)	mmHg
SBP ≥ 160	164 (16.4)	mmHg
SBP < 90	27 (2.7)	mmHg
Mean DBP	76.1 (18.0)	mmHg
Median DBP	75 [63-88]	mmHg
DBP ≥ 90	228 (22.7)	mmHg
DBP < 60	215 (21.4)	mmHg
Mean pulse pressure	59.5 (21.3)	mmHg
Median pulse pressure	56 (45-71)	mmHg
Mean temperature	36.5 (0.7)	° Celsius
Median temperature	36.6 [36.1-36.9]	° Celsius
Temperature < 36.1	254 (25.3)	° Celsius
Temperature > 37.8	35 (3.5)	° Celsius
Mean respiratory rate	22 (5.1)	breaths / min
Median respiratory rate	20 [18-24]	breaths / min
Respiratory rate ≤ 12	3 (0.3)	breaths / min
Respiratory rate ≥ 20	664 (66.2)	breaths / min
Mean SpO_2	95 (4.2)	%
Median SpO_2	96 [94-97]	%
SpO_2 < 95%	314 (31.3)	%

3.2.8.2 Body mass index and waist circumference measurements

Table 3-11 displays the body composition measurements recorded on admission to hospital. Height, waist and weight measurements were recorded for all patients enrolled into the study. Body mass index (BMI) was calculated from these measurements. Over two-thirds of all patients were either overweight or obese on admission (defined as BMI 25-30 kg/m^2 or >30 kg/m^2, respectively). Few patients were underweight on admission (defined as BMI <18.5 kg/m^2). In terms of waist circumference, over half of all patients had a waist circumference exceeding the sex-specific recommendations (defined as ≥ 102 cm in men and ≥ 88 cm in women). Approximately one quarter of patients had a waist circumference below the sex-specific recommendations (defined as <94 cm in men and <80 in women).

Table 3-11: BMI and waist circumference measurements on admission to hospital

Measurement	n (%), mean (SD) or median [IQR]	Units
Mean height	163.5 (10.4)	cm
Median height	163.0 [156-171]	cm
Mean height (men)	170.2 (8.1)	cm
Mean height (women)	155.9 (7.2)	cm
Mean weight	77.7 (20.4)	kg
Median weight	75.0 [63-89]	kg
Mean weight (men)	84.4 (20)	kg
Mean weight (women)	70.2 (18.3)	kg
Mean BMI	29.0 (6.9)	kg/m^2
Median BMI	27.8 [24.1-32.8]	kg/m^2
Mean BMI (men)	29.1 (6.5)	kg/m^2
Mean BMI (women)	28.9 (7.3)	kg/m^2
BMI calculation missing	10 (1.0)	-
BMI < 18.5 (underweight)	23 (2.3)	kg/m^2
BMI 18.5–24.9 (normal weight)	285 (28.7)	kg/m^2
BMI 25–30 (overweight)	307 (30.9)	kg/m^2
BMI >30 (obese)	378 (38.1)	kg/m^2
Mean waist	98.7 (17.1)	cm
Median waist	97.0 [87-109]	cm
Waist measurement missing	31 (3.1)	-
Waist < 94 males; < 80 females	240 (24.7)	cm
Waist 94–102 males; 80–88 females	195 (20.1)	cm
Waist ≥ 102 males; ≥ 88 females	537 (55.2)	cm

3.2.8.3 Cardiovascular examination signs

A full cardiovascular examination was performed for all patients enrolled into the study (Table 3-12). The cardiovascular signs on examination were consistent with expected findings for patients with decompensated HF. The majority of patients had a raised jugular venous pressure (JVP), pulmonary crackles and peripheral oedema. Almost one quarter of patients had a palpable displaced apex beat. Nearly all patients were in Killip class II or III. The small number of patients in Killip class IV likely reflects the high mortality associated with this clinical state, and the unsuitability of approaching such unstable patients for inclusion in a research study. The small number of patients with a third heart sound is unexpected for a cohort of patients with decompensated HF. One explanation may be the variation in an individual's ability to detect and record this clinical sign. Furthermore, this sign may have been no longer present by the time of enrolment if the patient had already received HF treatment. More than one-third of all patients recruited had a detectable murmur recorded, consistent with the notable prevalence of valvular heart disease.

Table 3-12: Cardiovascular examination findings on admission to hospital

Clinical Sign	Number of patients	% of cohort (n=1003)
Elevated JVP (>4cm)	680	67.8
JVP not elevated	210	20.9
JVP not seen	113	11.3
Palpable apex	661	65.9
Displaced apex	241	24.0
Third heart sound	66	6.6
Murmur	367	36.6
Pulmonary crackles (any)	942	93.9
Pulmonary crackles – basal only	706	70.4
Pulmonary crackles – mid-zones	223	22.2
Pulmonary crackles - apices	13	1.3
Pleural effusion(s)	150	15.0
Peripheral oedema (any)	725	72.3
Peripheral oedema – ankle	715	71.3
Peripheral oedema – knee	295	29.4
Peripheral oedema – thigh	97	9.7
Peripheral oedema – sacrum	45	4.5
Peripheral oedema – abdomen	19	1.9
Ascites	40	4.0
Carotid bruit	38	3.8
Killip class I	46	4.6
Killip class II	706	70.4
Killip class III	247	24.6
Killip class IV	4	0.4

3.2.9 Electrocardiography

A 12-lead ECG was performed routinely on admission to hospital for the majority of patients in this study. This was usually performed as part of the work-up to determine the cause of decompensated HF, for example ischaemia or arrhythmias, or to investigate possible consequences of the decompensation, for example arrhythmias. The first ECG performed during the admission was analysed, the parameters and their frequencies are shown in Table 3-13. More than half of all patients were in sinus rhythm. A significant number of patients were in AF (41.3%). A small proportion was in a paced rhythm (4.3%). More than one fifth of patients had ECG evidence of LVH. A quarter of patients had a bundle branch block, the majority being LBBB. The mean (SD) QRS duration for the hospitalised cohort was 109ms (27.8), within normal limits. A prolonged QRS duration (defined as greater than 120ms) was evident in almost one third of patients, many of these having a major prolongation (defined as >150ms). The mean (SD) corrected QT (QTc) interval for the whole cohort was 448ms (39.8), slightly higher than the upper limit of normal (defined as 440ms).

Table 3-13: Admission ECG findings and their frequencies within the cohort

Variable	n (%), mean (SD) or median [IQR]	Units
Sinus rhythm	549 (54.7)	-
AF	414 (41.3)	-
Paced rhythm	43 (4.3)	-
LBBB	190 (18.9)	-
RBBB	69 (6.9)	-
Pathological Q waves	62 (6.2)	-
LVH	214 (21.3)	-
Ischaemic ST depression	42 (4.2)	-
Mean QRS duration	109 (27.8)	ms
Median QRS duration	102 [88-126]	ms
QRS duration >120	296 (29.5)	-
QRS duration 120 – 150	184 (18.3)	-
QRS duration >150	112 (11.2)	-
Mean QTc interval	448 (39.9)	ms
Median QTc interval (IQR)	447 [422-471]	ms
QTc interval <440	417 (41.6)	-
QTc interval ≥ 440	585 (58.3)	-

3.2.10 Chest X-Ray

Of 1003 patients in the study, 1000 patients had a CXR performed on admission to hospital. The findings are displayed in Figure 3.6. The majority of patients had radiological evidence of cardiomegaly (70.5%). Similar proportions of patients had signs of pulmonary oedema reported on CXR, namely upper lobe venous diversion (68.5%) and alveolar oedema (73.8%). Over half of patients (54.2%) had evidence of pulmonary congestion in the form of interstitial oedema. Pleural effusions were also a common radiological finding, reported in a third of the cohort.

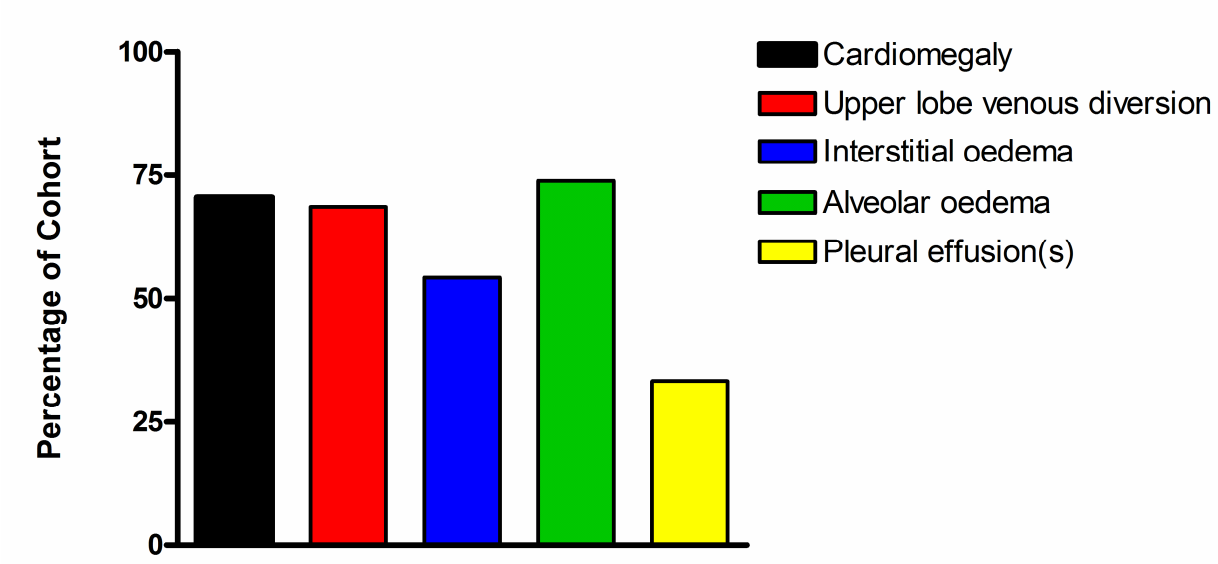


Figure 3.6: Radiological findings on the admission CXR for the hospitalised cohort

3.2.11 Echocardiography

3.2.11.1 Previous echocardiographic findings

An echocardiogram was performed prior to hospitalisation in 761 patients (Table 3-14). The majority of these scans were performed more than a year before the admission, thus a repeat study was performed in many of these cases. The previous echocardiographic findings revealed many abnormalities. Many patients had a dilated LV or LVH (29.5% and 43.3%, respectively). LVEF is not calculated on a routine echocardiogram. More than half had LVSD (55.3%), the majority of which was at least moderate in severity. Almost half of patients with a previous echocardiogram had preserved LV systolic function (44.7%). Many patients had at least moderate valvular heart disease. This included aortic stenosis (AS), aortic regurgitation (AR), mitral stenosis (MS), mitral regurgitation (MR) or tricuspid regurgitation (TR).

Table 3-14: Echocardiographic findings for the 761 patients with an echocardiogram performed prior to enrolment in the study

Echocardiographic parameter	Number of patients	% of cohort (n=761)
Dilated LV	223	29.3
LVH	327	43.0
Preserved LV systolic function	340	44.7
Mild LVSD	128	16.8
Moderate LVSD	161	21.2
Severe LVSD	131	17.2
At least moderate AS	53	7.0
At least moderate AR	25	3.3
At least moderate MS	13	1.7
At least moderate MR	147	19.3
At least moderate TR	66	8.7

3.2.11.2 Current echocardiographic findings

An echocardiogram was performed after enrolment into the study for 727 patients (Table 3-15). The majority of these were carried out during the index admission (81.2%), with the remainder being performed in the weeks following discharge from hospital. The predominant reason an echocardiogram was not performed following enrolment in the study was that the scan had been performed recently. The proportions of patients with a dilated LV or LVH were similar to the previous echocardiographic studies (35.5% and 43.1%, respectively). LVEF was not calculated routinely on the current echocardiograms, thus preventing dichotomisation of patients into HF-REF or HF-PEF groups. A qualitative assessment of LVSD was recorded as documented on the echocardiogram report; mild, mild to moderate, moderate, moderate to severe or severe. Figure 3.7 displays the distribution of severity of LVSD. The majority of patients had LVSD (65.9%), proportionately more than the previous echocardiogram findings. The high prevalence of LVSD is an expected finding in a cohort of patients with decompensated HF. Many of those with preserved LV systolic function may have had diastolic dysfunction. Unfortunately, parameters of diastolic dysfunction were not routinely recorded. The proportions of patients with significant valvular heart disease (defined as at least moderate in severity) were similar to those in the previous echocardiogram studies. The exception to this was higher proportions of MR and TR, possibly due to more patients having functional MR and TR in the decompensated state.

Table 3-15: Current echocardiographic findings for the 727 patients with an echocardiogram performed after enrolment in the study

Echocardiographic parameter	Number of Patients	Percentage of cohort (n=727)
Dilated LV	258	35.5
LVH	313	43.1
Preserved LV systolic function	249	34.3
LVSD	479	65.9
At least moderate AS	57	7.8
At least moderate AR	29	4.0
At least moderate MS	14	1.9
At least moderate MR	211	29.0
At least moderate TR	116	16.0

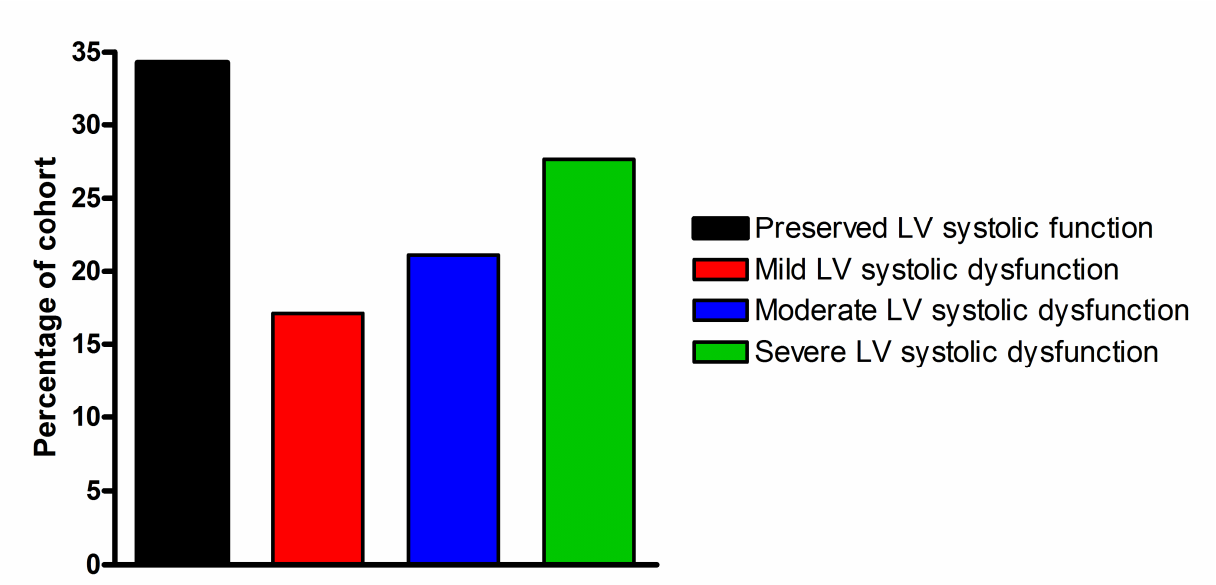


Figure 3.7: Distribution of LV systolic function for the 727 patients with an echocardiogram performed after enrolment in the study

3.2.12 Haematology

All patients enrolled in the study had a full blood count performed routinely on admission to hospital; the results are displayed in Table 3-16. The mean haemoglobin for the hospitalised patients was 12.1g/dl. More than half of all patients were anaemic by WHO standards (defined as haemoglobin <12g/dl for females and <13g/dl for males) and many of these met criteria for severe anaemia (defined as haemoglobin <11.5g/dl for both sexes). The mean WBC count for the whole cohort was within normal limits, with almost a quarter of patients having a raised count. The mean lymphocyte count for the cohort was within normal limits but over one-fifth of patients had a low lymphocyte count (<1 $x10^9$/l). The mean RDW concentration was 15.4%, higher than the upper limit of normal (defined as >15%).

Table 3-16: Full blood count profile on admission for all patients (n=1003)

FBC parameter	n (%), mean (SD) or median [IQR]	Units
Mean WBC count	9.4 (3.7)	$x10^9$/l
Median WBC count	8.7 [6.9-10.9]	$x10^9$/l
WBC count >11	250 (24.9)	-
Mean haemoglobin	12.1 (2.2)	g/dl
Median haemoglobin	12.1 [10.6-13.6]	g/dl
Haemoglobin <13 males; <12 females	568 (56.6)	-
Haemoglobin <11.5	398 (39.7)	-
Mean RDW	15.4 (2.3)	%
Median RDW	15 [13.9-16.3]	%
RDW >15	503 (50.2)	-
Mean lymphocytes	1.64 (1.37)	$x10^9$/l
Median lymphocytes	1.4 [1.0-1.88]	$x10^9$/l
Lymphocytes <1	236 (23.5)	-

3.2.13 Biochemistry

There was considerable variation in the number of biochemical tests performed for each patient during their admission, as displayed in Table 3-17. The results of the biochemical tests are shown in Tables 3-18-20. All patients had BNP measured within 24 hours of admission to hospital, an elevated result being mandatory for inclusion in the study. All patients had U&E measured on admission to hospital. The majority of patients had troponin I, LFT, CRP, phosphate and glucose measured routinely during their hospital stay. Approximately half of the cohort had their cholesterol level checked. A small proportion of patients had TFT, urate and HbA1c measured.

Table 3-17: Frequencies of biochemical tests performed in the hospitalised cohort

Biochemical test	Number of patients	% of cohort (n=1003)
BNP	1003	100
U&E	1003	100
LFT	998	99.5
CRP	983	98.0
Glucose	945	94.2
Phosphate	892	88.9
Troponin*	875	87.2
TFT	706	70.4
Lipid profile	527	52.5
HbA1c	85	8.5
Urate	48	4.8

* Troponin I measured at Royal and Western Infirmaries, troponin T measured at Royal Alexandra Hospital

The BNP and U&E results are displayed in Table 3-18. The median BNP for the hospitalised cohort was significantly raised at 880pg/ml [IQR 394-1811]. A small proportion of the cohort had a major elevation of BNP, exceeding the upper limit of the assay (>5000pg/ml). The distribution of BNP results for the entire cohort is displayed in Figure 3.8. The mean sodium and potassium levels for the whole cohort were within the normal ranges (138mmol/l and 4.2mmol/l, respectively). Many patients were hyponatraemic (defined as sodium <135mmol/l) on admission (17.9%). The majority of patients had an elevated urea concentration (defined as ≥ 7.5mmol/l) on admission (62.3%). The mean creatinine level was elevated at 122µmol/l. eGFR was calculated using the 4-variable MDRD formula, as outlined in Chapter 2. The mean eGFR for the entire cohort was reduced at 55.6 ml/min/1.73m^2. Only 5.5% of patients had a normal eGFR (defined as >90 ml/min/1.73m^2). The distribution of GFR per 30 ml/min/1.73m^2 is shown in Figure 3.9.

Table 3-18: BNP and renal function results on admission for all patients (n=1003)

Biochemical Test	n (%), mean (SD) or median [IQR]	Units
Mean BNP	1308 (1234)	pg/ml
Median BNP	880 [394-1812]	pg/ml
BNP >5000	32 (3.2)	pg/ml
Mean sodium	137.8 (4.5)	mmol/l
Median sodium	138 [136-141]	mmol/l
Sodium <135	179 (17.8)	mmol/l
Mean potassium	4.2 (0.6)	mmol/l
Median potassium	4.1 [3.8-4.5]	mmol/l
Mean urea	10.1 (5.8)	mmol/l
Median urea	8.6 [6.3-11.8]	mmol/l
Urea ≥ 7.5	625 (62.3)	mmol/l
Mean creatinine	121.7 (54.0)	µmol/l
Median creatinine	109 [87-138]	µmol/l
Mean eGFR	55.6 (21.1)	ml/min/1.73m^2
Median eGFR	54.5 [40.8-68.5]	ml/min/1.73m^2

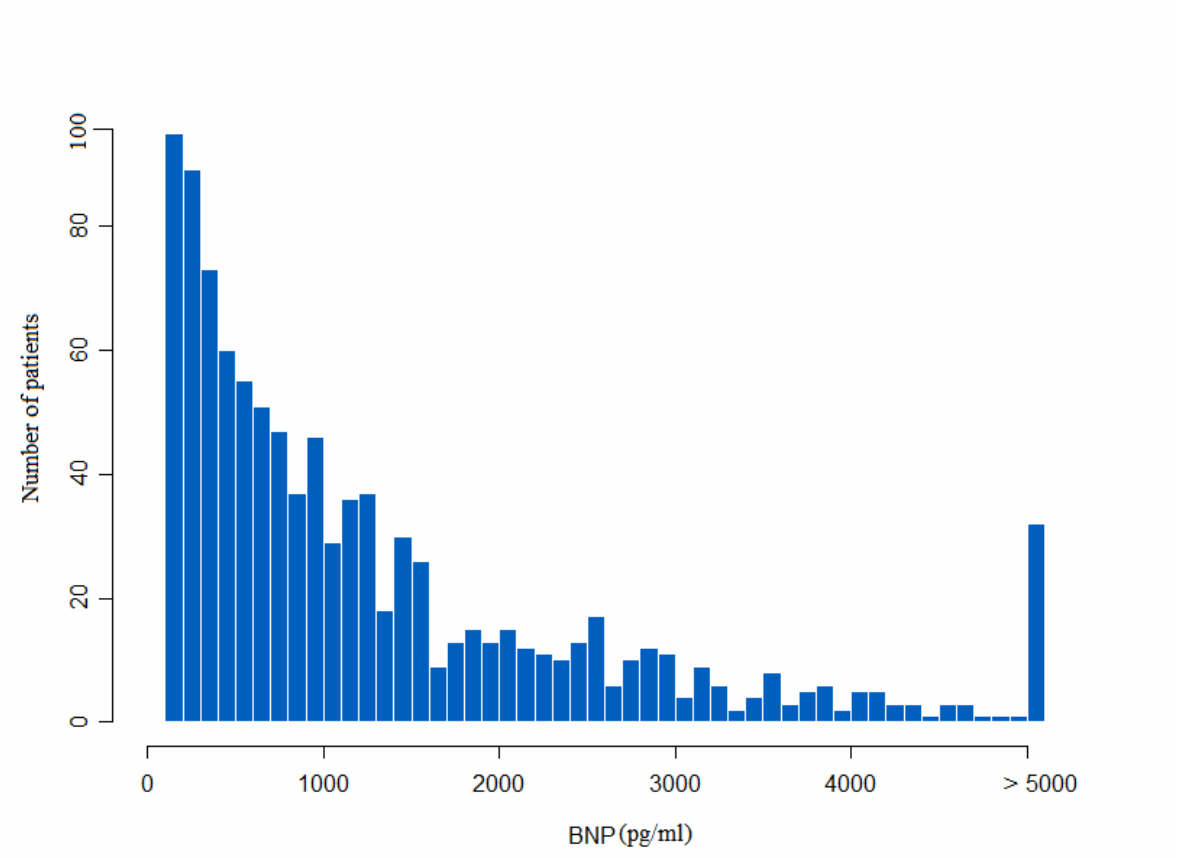


Figure 3.8: Distribution of BNP levels for all enrolled patients

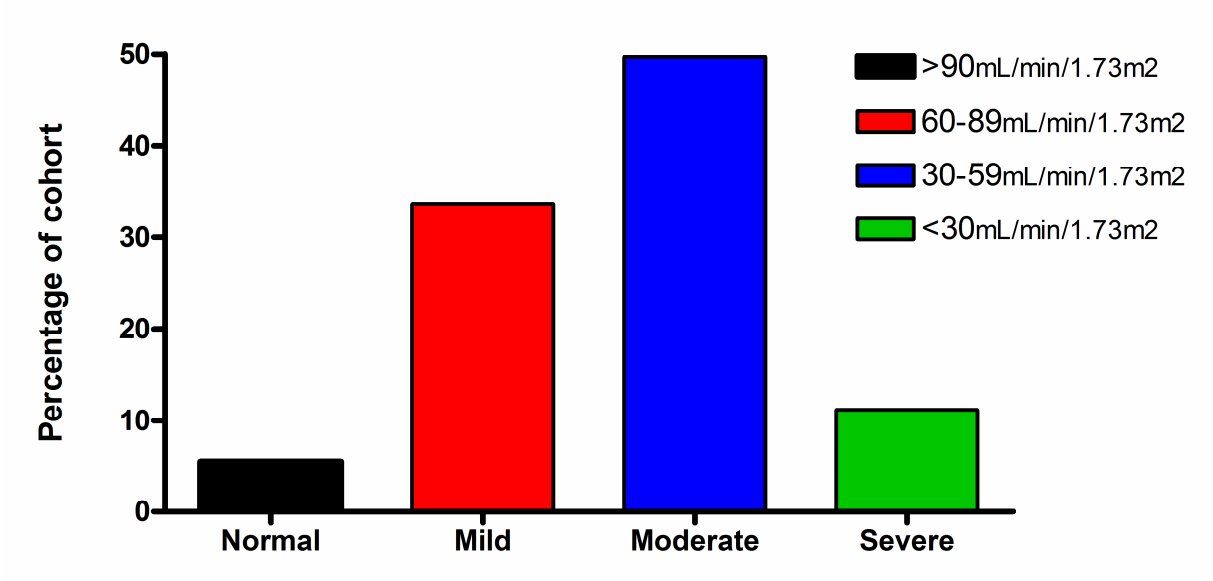


Figure 3.9: Distribution of eGFR on admission for all enrolled patients

Most patients enrolled in the study had LFT measured during their admission (Table 3-19). The mean bilirubin level was within normal limits. Almost one fifth of patients had an elevated bilirubin (defined as >22 µmol/l). The mean concentration of liver enzymes aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase were within the local reference ranges. The mean gamma glutamyl transpeptidase (GGT) was elevated at 86.6U/l, the upper limit of normal being 55U/l. The mean albumin level was at the lower end of the normal range at 35.5g/l and over one-third of patients had hypoalbuminaemia (defined as <35g/l).

Table 3-19: Liver function tests during hospital admission for 998 patients

Biochemical Test	n (%), mean (SD) or median [IQR]	Units
Mean Bilirubin	15.8 (11.9)	µmol/l
Median bilirubin	13.0 [8-19]	µmol/l
Bilirubin ≥ 22	182 (18.2)	U/l
Mean AST	35.8 (49.5)	U/l
Median AST	25.0 [19-36]	U/l
Mean ALT	33.7 (57.3)	U/l
Median ALT	20.0 [14-32]	U/l
Mean GGT	86.6 (94.7)	U/l
Median GGT	57.0 [32-103]	U/l
Mean Alkaline Phosphatase	109.0 (58.5)	U/l
Median Alkaline Phosphatase	95.0 [75-123]	U/l
Mean albumin	35.5 (4.5)	g/l
Median albumin	36.0 [33-39]	g/l
Albumin <35	369 (37.0)	g/l

The remaining biochemical tests recorded during the admission for subsets of the cohort are shown in Table 3-20. The mean CRP was significantly raised at 28.4mg/l and three-quarters of patients had an elevated CRP level (defined as ≥ 6mg/l). Of 901 patients recruited from the Royal and Western Infirmaries, 844 patients had troponin I measured. More than half of these patients had an elevated result (defined by the local biochemistry laboratory as ≥ 0.04 µg/l). Of 102 patients recruited from the Royal Alexandra Hospital, 31 had troponin T measured and approximately one quarter of these patients had an elevated result (defined by the local biochemistry laboratory as ≥ 0.05 µg/l). The mean phosphate, thyroid stimulating hormone (TSH), thyroxine (T4), urate, cholesterol and HbA1c levels were within normal reference ranges.

Table 3-20: Other biochemical tests measured during the hospital admission

Biochemical Test	n (%), mean (SD) or median [IQR]	Units
Mean CRP	28.4 (42.5)	mg/l
Median CRP	14.0 [6-31]	mg/l
CRP ≥ 6	743 (75.6)	mg/l
Mean glucose	8.0 (4.6)	mmol/l
Median glucose	6.6 [5.6-8.5]	mmol/l
Troponin I ≥ 0.04	465 (55.1)	µg/l
Troponin T ≥ 0.05	8 (25.8)	µg/l
Mean phosphate	1.21 (0.32)	mmol/l
Median phosphate	1.16 [1.03-1.33]	mmol/l
Mean TSH	2.54 (3.2)	mU/l
Median TSH	1.7 [1-2.8]	mU/l
Mean T4	15.3 (4.0)	pmol/l
Median T4	15 [13-17]	mmol/l
Mean cholesterol	4.1 (1.1)	mmol/l
Median cholesterol	3.9 [3.2-4.7]	mmol/l
Mean HbA1c	7.7 (1.9)	%
Median HbA1c	7.4 [6-8.9]	%
Mean urate	0.47 (0.16)	mmol/l
Median urate	0.49 [0.36-0.57]	mmol/l

3.2.14 Aetiology of heart failure

The primary aetiologies of heart failure for the entire hospitalised cohort are displayed in Table 3-21. Coronary heart disease was the primary aetiology for the majority of patients. Over 40% of the entire cohort had documented evidence of a prior MI. Approximately one-third of patients had angiographic evidence of coronary heart disease (defined as >50% stenosis in at least one major epicardial vessel). Over a third of patients had an 'unknown' primary aetiology of HF. These were patients with no previous MI or angiogram performed by the time of aetiology assessment. The non-ischaemic primary causes of HF are also displayed in Table 3-21. A non-ischaemic primary aetiology was only assigned when ischaemia had been excluded (no previous MI and coronary angiography demonstrating no significant stenoses) and no other clear causes of HF were present. The majority of non-ischaemic causes were valvular heart disease. As outlined in the methods, valvular heart disease was only considered causative if it was at least moderate in severity. The cardiomyopathies were the primary cause of HF for a small number of patients (see Table 3-21). Few patients had hypertension and alcohol as the primary reason for their HF. It is likely that more patients had hypertension, alcohol or valvular heart disease as the primary cause of HF. However if these patients had not had coronary angiography, to exclude ischaemia as the cause, then the primary aetiology was classified 'unknown'. In these instances all potential causes were recorded as 'contributing aetiologies', as detailed in the following paragraph.

Table 3-21: Primary aetiology of heart failure for the hospitalised cohort

Primary Aetiology	Number of patients	% of cohort (n=1003)
Ischaemic	**544**	**54.2**
a) Definite previous MI	447	44.6
b) Angiographic evidence (>50% stenosis in ≥ 1 vessel)	324	32.3
Non-ischaemic	**114**	**11.4**
Valvular	60	6.0
Cardiomyopathies	26	2.6
a) Idiopathic dilated cardiomyopathy	17	1.7
b) Hypertrophic cardiomyopathy	4	0.4
c) Peripartum cardiomyopathy	3	0.3
d) Restrictive cardiomyopathy	2	0.2
Hypertension	16	1.6
Alcohol	12	1.2
Unknown (no previous MI or angiography)	**345**	**34.4**

Regardless of whether or not the patient had a primary aetiology assigned, the presence of any potential contributing aetiologies were also documented, the results are shown in Table 3-22. Two-thirds of all patients had hypertension as a contributing cause of HF. Almost 40% of the entire cohort had valvular heart disease as a contributing cause of HF. The majority of these were mitral regurgitation, many cases being functional regurgitation secondary to LVSD rather than primary valve disease. Aortic stenosis was also a significant contributing cause for many patients. AF was a potential contributing cause of HF when persistent or permanent in duration, this applied to almost half of the entire cohort. Epidemiological studies have recently demonstrated an increased risk of HF amongst patients with diabetes. In this study the

prevalence of diabetes was high, affecting almost a third of all patients. Excess alcohol consumption was also a significant contributor, in at least 16% of all patients. A small proportion of the cohort had other contributing causes of HF identified, including; previous chemotherapy, thyrotoxicosis and long-term right ventricular pacing.

Table 3-22: Potential contributing aetiologies of heart failure in the hospitalised cohort

Contributing aetiology	Number of patients	% of cohort (n=1003)
Hypertension	663	66.1
Valvular heart disease	396	39.5
Atrial fibrillation	445	44.4
Diabetes mellitus	314	31.3
Alcohol	166	16.6
Other	68	6.8

3.3 Summary

This chapter outlined the process of recruitment and described in detail the clinical characteristics from the hospital admission for the cohort of patients hospitalised with decompensated HF. Of 2361 patients with suspected decompensated HF screened for inclusion in the study, 1003 patients were recruited. The mean age was 73 years, consistent with established epidemiological studies of HF. The majority of patients were male. A significant proportion of the cohort was elderly with multiple medical co-morbidity and polypharmacy. Only 1% of the entire cohort had no known medical conditions prior to enrolment into the study, reflecting the high levels of co-morbidity associated with HF. Survivors were discharged from hospital after approximately 12 days.

Almost half of the cohort had a prior diagnosis of HF. Three-quarters of these patients had experienced a previous hospitalisation with decompensated HF, highlighting the high rates of

hospitalisation associated with this condition. The primary aetiology of HF was ischaemia for the majority of patients, but over one-third had an unknown primary aetiology. The majority of patients were already taking oral diuretics prior to admission. Many were already prescribed HF disease-modifying therapies. Nearly all of the patients recruited into the study received diuretic therapy on admission to hospital, approximately three-quarters of the cohort received this therapy intravenously. Less than 3% of all patients in the study were not treated with diuretic therapy on admission to hospital, most likely reflecting younger patients presenting with progressive pump failure rather than fluid overload. Most physiological measurements were stable on admission, indicative of the inability of more unstable patients to be approached to consent to participate in the study. The majority of patients had a raised JVP, lung crepitations, peripheral oedema and were in Killip class II.

There were a significant number of patients in AF on admission to hospital and many had left bundle branch block on their ECG. The presence of radiological signs of pulmonary oedema was common on the admission CXR. Most patients had an echocardiogram performed following enrolment into the study. This revealed LVSD for the majority of cases. Routine blood sampling on admission to hospital revealed many biochemical and haematological abnormalities in this cohort. All patients had an elevated BNP, an essential component of the study inclusion criteria, and the median was significantly elevated. More than half of all patients were anaemic by WHO criteria, almost two-thirds had an elevated serum urea concentration and >90% had a reduction in their GFR. More than half of all patients with troponin I measured on admission to hospital had an elevated result.

In summary the hospitalised cohort was made up of 1003 patients, the majority of whom were elderly with multiple medical co-morbidity and LVSD.

CHAPTER FOUR

CLINICAL CHARACTERISTICS OF HOSPITALISED COHORT STRATIFIED BY STUDY VISIT ATTENDANCE

4.1 Introduction

This chapter will compare the clinical characteristics of the hospital cohort of patients according to whether or not they attended the post-discharge study visit. The data described will be similar to the previous chapter but stratified by subsequent attendance at the study visit or not. Non-attendance will be subdivided into the reasons for failure to complete the study visit. The data described will comprise basic demographic details, symptoms prior to admission, medical history, medications pre-admission and during the first 24 hours of admission, and examination findings on admission. Electrocardiographic, radiological, blood test and echocardiographic results will also be stratified by attendance at the study visit. The main aim of this chapter will be to ascertain whether or not there were any major clinical differences in the cohort of patients who returned to complete the study visit compared to those who did not attend. Ultimately, these comparisons will allow an objective assessment of whether or not the patients returning for the study visit were truly representative of the entire cohort.

4.2 Comparison of hospital data for study visit attendees and non-attendees

4.2.1 Outcome of hospitalised cohort

Of 1003 patients enrolled in the study, 648 patients (64.6%) completed the study visit. The reasons why the remaining patients failed to attend are outlined in Figure 4.1. The most common reason for failure to attend the study visit was refusal to participate, 167 patients (16.7%) withdrew from the study for this reason following discharge from hospital. 115 patients (11.5%) died prior to the study visit appointment. More than half of these deaths, 68 deaths (59.1%), occurred during the index admission. The remaining 47 deaths (40.9% of deaths) occurred after discharge from hospital and before the study visit. Finally, 73 patients (7.3%) were unable to attend the study visit appointment because of deterioration in their health.

For the remainder of this chapter patients who completed the post-discharge study visit will be referred to as ‘attendees’ and those who withdrew from participating in the study visit will be referred to as ‘withdrawn’. Patients who failed to complete the study visit because of deterioration in their health will be referred to as ‘deteriorating health’ and those who died before their study visit appointment will be referred to as ‘deceased’ or ‘died before the study visit’.

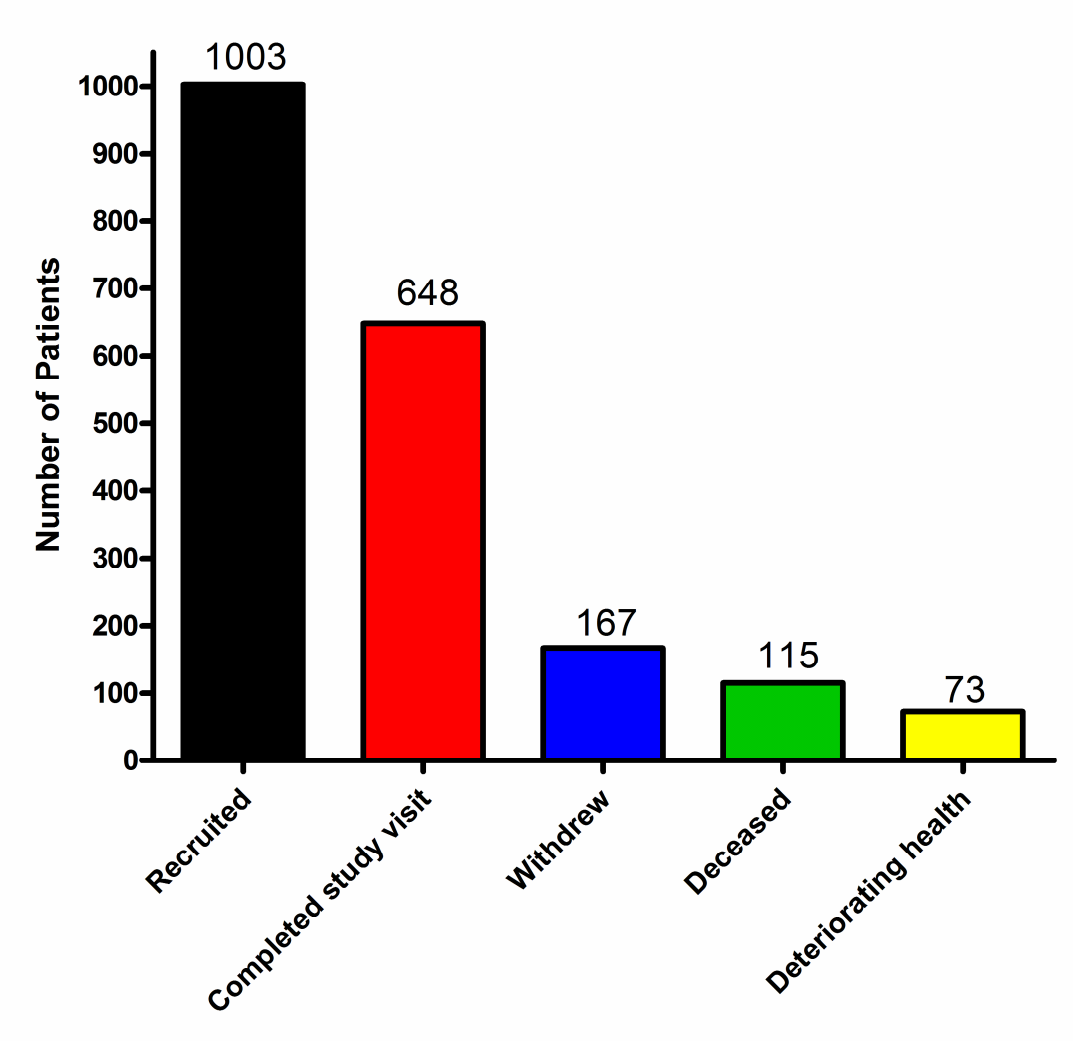


Figure 4.1: Overview of the 1003 patients recruited into the study and the breakdown of reasons for failure to attend the study visit

4.2.2 Demographics

Table 4-1 shows the demographics of the hospitalised cohort, stratified by whether or not they subsequently attended the study visit. Attendees had proportionately more male patients than the other three groups, whilst patients who died before the study visit had more female patients than the other three groups ($p=0.00015$).

Patients attending the study visit were younger than the other three groups ($p<0.0001$), with fewest patients over 75 years of age ($p<0.0001$). Patients with deteriorating health had the highest mean age, with almost three-quarters of this group over 75 years of age.

The average length of hospitalisation was significantly longer for patients with deteriorating health and those who died before their study visit appointment ($p<0.0001$).

Table 4-1: Basic demographics of the hospitalised cohort, stratified by whether or not they subsequently attended the study visit. Data are expressed as number (%), mean (SD) or median [IQR].

Variable	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
Male	377 (58.2)	73 (43.7)	35 (48.0)	47 (40.9)	532 (53.0)	0.00015
Age (years)	70.8 (10.6)	77.1 (8.2)	80.0 (8.0)	75.1 (10.3)	73.0 (10.5)	<0.0001
≥ 75 years of age	232 (35.8)	107 (64.1)	54 (74.0)	65 (56.5)	458 (45.7)	<0.0001
Mean duration of admission (days)	9.7 (8.1)	10.3 (10.3)	21.9 (23.4)	20.9 (23.8)	11.9 (13.6)	<0.0001
Median duration of admission (days)	7 [4-12]	7 [5-12]	13 [8-31]	13 [6-24.5]	8 [5-14]	<0.0001

* Inter-group comparisons using ANOVA F-test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the four groups.

4.2.3 History of heart failure

A history of HF was defined as a previous admission with decompensated HF or a diagnosis of HF established in an outpatient clinic. Almost half of the overall cohort had a history of HF prior to enrolment in this study. A history of HF was more common amongst patients with deteriorating health and those who were deceased (p=0.00047) [Table 4-2]. Consequently, more patients who subsequently attended the study visit or withdrew from participation were *de novo* presentations of HF at the time of enrolment in this study. The proportion of patients with a diagnosis of chronic HF for more than 2 years was similar in all four groups. The proportion of patients with a previous hospital admission with decompensated HF did not significantly differ between the groups, although the proportion was greatest for those who died before the study visit.

Table 4-2: History of heart failure, stratified by study visit attendance. Data are expressed as number (%).

	Attendee (n=648)	**Withdrawn (n=167)**	**Deteriorating health (n=73)**	**Deceased (n=115)**	**Overall (n=1003)**	**p value***
1	283 (43.7)	69 (41.3)	44 (60.3)	69 (60.0)	465 (46.4)	0.00047
2	203 (71.7)	45 (65.2)	33 (75.0)	51 (73.9)	332 / 465 (71.4)	0.62
3	216 (76.3)	48 (69.6)	33 (75.0)	58 (84.1)	355 / 465 (76.3)	0.31

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the four groups.

1 = Previous diagnosis of heart failure

2 = Diagnosis of heart failure > 2 years ago

3 = Previous admission with decompensated heart failure

4.2.4 Heart failure symptoms prior to admission

The presence of HF symptoms prior to hospitalisation varied between the four groups, as displayed in Table 4-3.

Severity of HF symptoms, as defined by the NYHA classes, differed between the groups ($p=0.00067$). Those who attended the study visit or withdrew from participation had more patients with milder HF symptoms (NYHA class II) than the other two groups. The prevalence of moderate HF symptoms (NYHA class III) was similar amongst all four groups. Those who died prior to the study visit had the greatest proportion of patients with severe HF symptoms (NYHA class IV).

Patients who died before the study visit were more likely to experience paroxysmal nocturnal dyspnoea (PND) ($p=0.022$).

Ankle swelling affected the majority of all patients, although was more common amongst patients with deteriorating health and those who died before the study visit ($p<0.0001$).

There was no significant difference between the four groups in the prevalence of the following symptoms; orthopnoea, palpitations, wheeze and angina.

Table 4-3: Heart failure symptom status prior to admission, stratified by study visit participation. Data are expressed as number (%).

Symptom	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
NYHA II	160 (24.7)	42 (25.1)	13 (17.8)	11 (9.6)	225 (22.4)	
III	374 (57.7)	104 (62.3)	47 (64.4)	69 (60.0)	594 (59.2)	0.00067
IV	114 (17.6)	21 (12.6)	13 (17.8)	35 (30.4)	184 (18.3)	
PND	311 (48.0)	69 (41.3)	35 (47.9)	69 (60.0)	484 (48.3)	0.022
Orthopnoea	488 (75.3)	121 (72.5)	54 (74.0)	98 (85.2)	761 (75.9)	0.078
Ankle swelling	412 (63.6)	126 (75.4)	61 (83.6)	99 (86.1)	698 (69.6)	<0.0001
Palpitations	146 (22.5)	25 (15.0)	14 (19.2)	19 (16.5)	204 (20.3)	0.11
Wheeze	189 (29.2)	43 (25.7)	24 (32.9)	35 (30.4)	291 (29.0)	0.68
Angina	356 (54.9)	86 (51.5)	40 (54.8)	66 (57.4)	548 (54.6)	0.79

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the four groups.

4.2.5 Medical history

The prevalences of common medical comorbidities varied between the groups (Table 4-4). A history of a previously reported MI was similar in all four groups, affecting a large proportion of all patients. On the other hand, the prevalence of major angiographic coronary heart disease differed between the groups (p=0.012). This was defined as previous angiographic evidence of at least 50% stenosis in at least 1 major epicardial vessel. Angiographic coronary heart disease was more prevalent amongst patients who withdrew and those with deteriorating health. A higher proportion of attendees had undergone PCI compared to the non-attendees, a difference of borderline statistical significance (p=0.057).

AF was proportionately more common amongst patients who withdrew from the study visit or had deteriorating health (p=0.045). Surprisingly, the lowest prevalence of AF was amongst the patients who died before the study visit.

Patients with deteriorating health or death before the study visit were more likely to have experienced major weight loss in the 6 months prior to enrolment in the study (p=0.019).

A history of cancer was more common in those with deteriorating health than the other three groups (p=0.0034). Surprisingly, there were similar proportions of this comorbidity amongst attendees and patients who died before the study visit.

Peripheral arterial disease was most common amongst patients who died before the study visit and least common amongst attendees (p=0.041). One possible explanation for the higher prevalence of this condition amongst patients who withdrew or cited deteriorating health as the reason for non-attendance may be the MTWA treadmill test. Patients experiencing pain from walking due to peripheral arterial disease may have been more inclined to withdraw from participation in the study visit.

Hypothyroidism was most common amongst patients with deteriorating health and least common amongst attendees, although this was of borderline statistical significance

(p=0.051). Those who subsequently died or withdrew from the study visit had similar proportions of patients affected by this condition.

Osteoarthritis was more common in patients with deteriorating health, affecting over 40% of this group (p=0.0062). Although fewer patients in the other three groups suffered from osteoarthritis, it was still common and affected around a quarter of these patients. Physical disabilities may have been a reason why many patients withdrew from participation because of difficulties travelling to the study visit or anxiety regarding the treadmill test.

Patients who did not complete the study visit due to deteriorating health or death were more likely to be anaemic (p<0.0001). However this comorbidity was common in the overall cohort and many patients in all four groups met the WHO criteria for the diagnosis of anaemia.

Urinary incontinence was more prevalent amongst patients who failed to complete the study visit, irrespective of cause (p=0.0016). Those unable to attend due to declining health were most likely to suffer from this comorbidity.

There was no difference between the groups in the prevalence of the following medical conditions; hypertension, cerebrovascular disease (as defined by prior TIA or CVA), prior arrhythmia, diabetes mellitus, depression, COPD, asthma, hyperthyroidism and rheumatoid arthritis.

Table 4-4: Prevalence of common medical conditions, stratified by study visit attendance. Data are expressed as number (%).

Condition	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
MI	278 (42.9)	70 (41.9)	39 (53.4)	56 (48.7)	443 (44.2)	0.23
Angiographic CAD	224 / 307 (73.0)	48 / 59 (81.4)	15 / 19 (78.9)	36 / 51 (70.6)	323 / 436 (74.1)	0.012
PCI	92 (14.2)	16 (9.6)	6 (8.2)	8 (7.0)	122 (12.2)	0.057
CABG	112 (17.3)	27 (16.2)	9 (12.3)	22 (19.1)	170 (16.9)	0.65
Hypertension	420 (64.8)	116 (69.5)	49 (67.1)	75 (65.2)	660 (65.8)	0.72
TIA/CVA	146 (22.5)	36 (21.6)	25 (34.2)	24 (20.9)	231 (23.0)	0.12
History of AF	344 (53.1)	95 (56.9)	43 (58.9)	55 (47.8)	537 (53.5)	0.045
Prior arrhythmia	53 (8.2)	15 (9.0)	6 (8.2)	9 (7.8)	83 (8.3)	0.99
Diabetes	203 (31.3)	48 (28.7)	25 (34.2)	37 (32.2)	313 (31.2)	0.84
Weight loss†	94 (14.5)	26 (15.6)	19 (26.0)	26 (22.6)	165 (16.5)	0.019
Depression	137 (21.1)	31 (18.6)	17 (23.3)	23 (20.0)	208 (20.7)	0.83
History of cancer	87 (13.4)	28 (16.8)	15 (20.5)	15 (13.0)	145 (14.5)	0.0034

Condition	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
COPD	181 (27.9)	50 (29.9)	23 (31.5)	43 (37.4)	297 (29.6)	0.23
PAD	104 (16.0)	30 (18.0)	15 (20.5)	31 (27.0)	180 (17.9)	0.041
Asthma	34 (5.2)	7 (4.2)	2 (2.7)	5 (4.3)	48 (4.8)	0.76
Hypothyroidism	55 (8.5)	20 (12.0)	13 (17.8)	14 (12.2)	102 (10.2)	0.051
Hyperthyroidism	12 (1.9)	6 (3.6)	1 (1.4)	3 (2.6)	22 (2.2)	0.53
RA	18 (2.8)	5 (3.0)	5 (6.8)	7 (6.1)	35 (3.5)	0.12
OA	154 (23.8)	43 (25.7)	31 (42.5)	27 (23.5)	255 (25.4)	0.0062
Anaemia	276 (42.6)	64 (38.3)	46 (63.0)	68 (59.1)	454 (45.3)	<0.0001
Urinary incontinence	58 (9.0)	21 (12.6)	17 (23.3)	16 (13.9)	112 (11.2)	0.0016

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the four groups.

CAD = coronary artery disease (defined as > 50% stenosis in ≥ 1 major epicardial vessel, denominator is number of patients who had an angiogram); OA = osteoarthritis; PAD = peripheral arterial disease; RA = rheumatoid arthritis

† >5% body weight in previous 6 months

4.2.6 Cardiovascular medications pre-admission

The pre-admission use of certain cardiovascular medications varied between the four groups (Table 4-5). The majority of these differences were in HF medications. The majority of patients in all groups were prescribed a diuretic. However, patients with deteriorating health and those who died before the study visit were most likely to be taking diuretics prior to the index admission (p=0.027).

Patients attending the study visit were more likely to be prescribed beta-blockers before hospitalisation (p=0.0018). Patients who died before the study visit and those with deteriorating health had fewest patients on this drug. The use of ACE inhibitors was similar in all 4 groups.

In comparison to ACE inhibitors and beta-blockers, the overall number of patients prescribed ARBs pre-admission was small. Only 14% of the entire cohort was prescribed ARBs before the index admission. Patients who withdrew from the study visit were most likely to be prescribed ARBs whilst those with deteriorating health or death had fewest patients prescribed this drug (p=0.025). The overall prescribing of aldosterone antagonists prior to admission was also small. However, the use of this medication was most common amongst those who died before the study visit (p=0.029).

Although there was no statistically significant difference between the groups in the proportion of patients prescribed aspirin, there was a trend towards more prescribing amongst the group who died before the study visit (p=0.057). Two-thirds of deceased patients were prescribed aspirin compared to approximately half of patients in the other three groups. Statin prescribing was more common amongst attendees and least common amongst patients who did not attend the study visit due to deteriorating health (p=0.043).

The use of the following medications was similar in all four groups; digoxin, clopidogrel, warfarin, nicorandil, calcium channel blockers, anti-arrhythmic therapies, long-acting nitrates and non-statin lipid lowering agents.

Table 4-5: Prevalence of cardiovascular medication prescribing pre-admission, stratified by study visit attendance. Data are expressed as number (%).

Medication	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
Diuretics	432 (66.7)	117 (70.1)	57 (78.1)	90 (78.3)	696 (69.4)	0.027
Beta-blockers	337 (52.0)	71 (42.5)	26 (35.6)	44 (38.3)	478 (47.7)	0.0018
ACE inhibitors	340 (52.5)	74 (44.3)	33 (45.2)	60 (52.2)	507 (50.5)	0.21
ARBs	92 (14.2)	32 (19.2)	4 (5.5)	12 (10.4)	140 (14.0)	0.025
Aldosterone antagonists	36 (5.6)	10 (6.0)	5 (6.8)	15 (13.0)	66 (6.6)	0.029
Aspirin	341 (52.6)	87 (52.1)	39 (53.4)	76 (66.1)	543 (54.1)	0.057
Clopidogrel	82 (12.7)	16 (9.6)	9 (12.3)	11 (9.6)	118 (11.8)	0.61
Aspirin or clopidogrel	382 (59.0)	99 (59.3)	42 (57.5)	79 (68.7)	602 (60.0)	0.13
Digoxin	104 (16.0)	27 (16.2)	15 (20.5)	22 (19.1)	168 (16.7)	0.68
Warfarin	186 (28.7)	39 (23.4)	16 (21.9)	23 (20.0)	264 (26.3)	0.12
Nicorandil	90 (13.9)	26 (15.6)	15 (20.5)	16 (13.9)	147 (14.7)	0.48
Calcium channel blockers	166 (25.6)	58 (34.7)	17 (23.3)	31 (27.0)	272 (27.1)	0.1
Anti-arrhythmic	22 (3.4)	8 (4.8)	3 (4.1)	5 (4.3)	38 (3.8)	0.84
Long-acting nitrates	120 (18.5)	29 (17.4)	19 (26.0)	28 (24.3)	196 (19.5)	0.21
Statin	443 (68.4)	101 (60.5)	40 (54.8)	73 (63.5)	657 (65.5)	0.043
Other lipid lowering agents	16 (2.5)	9 (5.4)	2 (2.7)	7 (6.1)	34 (3.4)	0.095

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the four groups.

4.2.7 Heart failure medical therapy during first 24 hours of admission

The pharmacological treatment of HF during the first 24 hours of admission is shown in Table 4-6. More than 95% of the overall cohort was prescribed furosemide on admission. The use of furosemide and loop diuretics was similar in all four groups.

The use of intravenous nitrate therapy during the first 24 hours of admission differed between the groups of patients. Those who died before the study visit were most likely to be treated with intravenous nitrate therapy, more than double the prescribing rate of the other three groups ($p=0.0055$).

Few patients were prescribed inotrope therapy (dobutamine or dopamine). However the use of this therapy was more common amongst those who died before the study visit ($p<0.0001$).

Table 4-6: Heart failure medical therapy during the first 24 hours of admission, stratified by study visit attendance. Data are expressed as number (%).

Medication	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
Furosemide	615 (94.9)	161 (96.4)	71 (97.3)	113 (98.3)	960 (95.7)	0.33
Other loop diuretic	28 (4.3)	5 (3.0)	3 (4.1)	9 (7.8)	45 (4.5)	0.27
Intravenous nitrate	54 (8.3)	10 (6.0)	5 (6.8)	20 (17.4)	89 (8.9)	0.0055
Inotrope (dobutamine or dopamine)	5 (0.8)	0 (0)	3 (4.1)	9 (7.8)	17 (1.7)	<0.0001

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the four groups.

4.2.8 Clinical examination findings on admission

4.2.8.1 Routine physiological measurements

There were several differences between the four groups of patients in the routine physiological measurements recorded on admission to hospital (Table 4-7). Patients who died before the study visit had lower SBP than the other three groups ($p<0.0001$). When the range of SBP was divided into 5 cut-off points there were other differences between the groups ($p<0.0001$). Patients who did not attend the study visit because of death or deteriorating health had proportionately more patients in the lower two categories of SBP (<80mmHg and 80-100mmHg). Attendees and those who withdrew from participating had more patients in the middle categories of SBP (100-140mmHg and 140-180mmHg).

Patients who did not attend the study visit because of death or deteriorating health had lower DBP than the other two groups ($p<0.0001$). Attendees had a similar DBP to those who withdrew from the study visit. When the range of DBP was divided into three cut-off points, other differences existed between the groups ($p=0.00013$). Patients who subsequently did not participate in the study visit because of deteriorating health or death had proportionately more patients with DBP <65mmHg. In contrast, attendees and those who withdrew from the study visit had proportionately more patients with diastolic hypertension (defined as $\geq$ 90mmHg).

The first peripheral SpO_2 reading, on either air or oxygen, was recorded for every patient enrolled in the study. Patients who subsequently did not participate in the study visit because of deteriorating health or death had a lower SpO_2 reading on air than the other two groups of patients ($p<0.0001$). Unsurprisingly, there was no difference between the groups for patients with an initial SpO_2 reading on oxygen.

There were no differences between the groups of patients in the following physiological parameters; mean heart rate, temperature and respiratory rate.

Table 4-7: Routine physiological measurements on admission to hospital, stratified by study visit attendance. Data are expressed as number (%) or mean (SD).

Physiological measurement (units)	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
Heart rate (bpm)	89 (25)	90 (25)	89 (21)	92 (22)	90 (24)	0.68
SBP (mmHg)	137 (27)	139 (29)	134 (27)	122 (26)	136 (27)	<0.0001
SBP levels (mmHg)						
< 80	0 (0)	0 (0)	0 (0)	3 (2.6)	3 (0.3)	
80-100	41 (6.3)	9 (5.4)	6 (8.2)	17 (14.8)	73 (7.3)	<0.0001
100-140	312 (48.2)	83 (49.7)	41 (56.2)	72 (62.6)	508 (50.6)	
140-180	250 (38.6)	56 (33.5)	19 (26.0)	18 (15.7)	343 (34.2)	
≥ 180	45 (6.9)	19 (11.4)	7 (9.6)	5 (4.3)	76 (7.6)	
DBP (mmHg)	78 (18)	76 (19)	73 (17)	69 (16)	76 (18)	<0.0001

Physiological measurement (units)	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
DBP levels (mmHg)						
< 65	157 (24.2)	43 (25.7)	30 (41.1)	42 (36.5)	272 (27.1)	0.00013
65-90	329 (50.8)	82 (49.1)	28 (38.4)	64 (55.7)	503 (50.2)	
≥ 90	162 (25.0)	42 (25.2)	15 (20.5)	9 (7.8)	228 (22.7)	
Pulse pressure (mmHg)	59.6 (20.6)	62.4 (22.7)	61.6 (21.7)	52.6 (21.8)	59.4 (21.3)	0.0012
Temperature (°C)	36.5 (0.6)	36.5 (0.7)	36.6 (0.6)	36.5 (0.8)	36.5 (0.7)	0.4
Respiratory rate (breaths per min)	22 (5.1)	21 (5.4)	22 (4.9)	23 (4.9)	22 (5.1)	0.16
SpO2 on air (%) †	95 (3.8)	95 (2.9)	93 (5.6)	93 (6.0)	95 (4.2)	<0.0001
SpO2 on oxygen (%)†	96 (4.1)	95 (4.5)	96 (4.1)	96 (4.1)	96 (4.2)	0.37

* Inter-group comparisons using ANOVA F test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the four groups.

† SpO2 measurement as per first recording on observation chart on air or oxygen

4.2.8.2 Body mass index and waist circumference measurements

BMI and waist circumference measurements recorded on admission to hospital differed between the four groups (Tables 4-8 to 4-10). For the male patients, attendees and those who withdrew from the study visit were taller than the patients in the other two groups (p=0.0036). Attendees and patients who withdrew from the study visit were also heavier than the other two groups (p=0.0017). A similar trend was seen amongst the female patients, although the difference was not statistically significant for weight.

Consequently the BMI differed between the four groups, with male attendees having a larger BMI than men in the other three groups (p=0.0029). There was no significant difference between the four groups in the mean BMI for the female patients. Interestingly the mean BMI for all four groups, regardless of sex, was in the pre-obese range. BMI levels were analysed in the categories that are used clinically; underweight (<18.5), ideal weight (18.5-25), pre-obese / overweight (>25-30) and obese (≥ 30). The proportions of patients in each of the BMI categories differed. Those who died before the study visit had more underweight patients than the other three groups, particularly amongst the female patients. Attendees had most obese patients whilst those who died before the study visit had the fewest.

Attendees had the largest waist circumference of all four groups, over 7cm greater than the mean circumference of patients who died before the study visit (p<0.0001). Waist circumference was analysed in the sex-specific categories that are used clinically; low waist circumference (<94cm for men and <80cm for women), normal waist circumference (94-102cm for men and 80-88cm for women) and high waist circumference (>102cm for men and >88cm for women). The proportions in each of the categories differed between the four groups (p=0.0056). Attendees had most patients with high waist circumference and fewest patients with low waist circumference. Patients who withdrew from the study visit or died before the study visit had the greatest proportion of patients with low waist circumference.

Table 4-8: BMI and waist circumference measurements for men on admission to hospital, stratified by study visit attendance. Data are expressed as number (%) or mean (SD).

Measurement (units)	Attendee (n=377)	Withdrawn (n=73)	Deteriorating health (n=35)	Deceased (n=47)	Overall (n=532)	p value*
Missing value	0	1	4	1	6	-
Height (cm)	170.0 (8)	172.8 (7.6)	167.0 (9.3)	169.1 (7.3)	170.2 (8.1)	0.0036
Weight (kg)	86.2 (20.3)	83.3 (19.7)	77.7 (20.7)	76.0 (13.3)	84.4 (20.0)	0.0017
BMI (kg/m^2)	29.8 (6.7)	27.9 (6.6)	27.7 (5.8)	26.7 (4.9)	29.1 (6.5)	0.0029
BMI levels <18.5	1 (0.3)	3 (4.2)	1 (3.3)	2 (4.4)	7 (1.3)	
18.5-25	88 (23.3)	22 (30.5)	9 (29.0)	14 (30.4)	133 (25.3)	0.023
25-30	133 (35.3)	26 (36.1)	9 (29.0)	19 (41.3)	187 (35.6)	
>30	155 (41.1)	21 (29.2)	12 (38.7)	11 (23.9)	199 (37.8)	

* Inter-group comparisons using ANOVA F test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the four groups.

Table 4-9: BMI and waist circumference measurements for women on admission to hospital, stratified by study visit attendance. Data are expressed as number (%) or mean (SD).

Measurement (units)	Attendee (n=271)	Withdrawn (n=94)	Deteriorating health (n=38)	Deceased (n=68)	Overall (n=471)	p value*
Missing value	0	4	0	0	4	-
Height (cm)	155.8 (6.4)	157.9 (6.5)	154.7 (7.0)	154.8 (10.0)	155.9 (7.2)	0.023
Weight (kg)	71.6 (18.4)	69.6 (17.2)	67.1 (18.7)	67.3 (18.6)	70.2 (18.3)	0.21
BMI (kg/m^2)	29.5 (7.3)	27.7 (6.7)	28.2 (8.2)	28.2 (7.7)	28.9 (7.3)	0.17
BMI levels <18.5	6 (2.2)	3 (3.3)	0 (0)	7 (10.3)	16 (3.4)	
18.5-25	79 (29.2)	37 (41.1)	19 (50.0)	17 (25.0)	152 (32.6)	0.0037
25-30	74 (27.3)	21 (23.3)	5 (13.2)	20 (29.4)	120 (25.7)	
>30	112 (41.3)	29 (32.3)	14 (36.8)	24 (35.3)	179 (38.3)	

* Inter-group comparisons using ANOVA F test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the four groups.

Table 4-10: Waist circumference measurements on admission to hospital, stratified by study visit attendance. Data are expressed as mean (SD) or number (%).

Measurement (units)		Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
Missing value		0	20	8	3	31	-
Waist (cm)		100.7 (17.0)	95.1 (17.5)	96.5 (16.5)	93.4 (15.5)	98.7 (17.1)	<0.0001
Waist levels	<94 M / <80 F	137 (21.1)	50 (34.0)	16 (24.6)	37 (33.0)	240 (24.7)	
	94-102 M / 80-88 F	134 (20.7)	24 (16.3)	18 (27.7)	19 (17.0)	195 (20.1)	0.0056
	>102 M / >88 F	377 (58.2)	73 (49.7)	31 (47.7)	56 (50.0)	537 (55.2)	

* Inter-group comparisons using ANOVA F test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the four groups.

4.2.8.3 Clinical signs of heart failure

There were several differences between the four groups of patients in the signs of HF recorded on admission to hospital. The results are displayed in Table 4-11.

Few patients had an audible third heart sound. However, the prevalence of this clinical sign was more common amongst patients who died before the study visit than the other three groups (p=0.037). The level of pulmonary oedema differed between the groups (p=0.0019). Few patients in all four groups had no crackles auscultated. The absence of pulmonary crackles was more common amongst attendees and patients who withdrew from the study visit. These groups also had more patients with only basal crackles whilst those unable to participate in the study visit due to deteriorating health or death had more patients with crackles extending to the mid-zones and apices. The presence of a pleural effusion (unilateral or bilateral) showed a similar pattern to pulmonary crackles, although the prevalence was much less in all four groups and the difference less striking (p=0.042).

Peripheral oedema was a common clinical sign, affecting the majority of patients in all groups. However, there were differences between the four groups in the proportions of patients with peripheral oedema (p=<0.0001). Patients who died before the study visit or had deteriorating health had more patients with peripheral oedema, than the other two groups. The level of peripheral oedema also differed between the groups. Those unable to complete the study visit due to death or deteriorating health had proportionately more patients with oedema at all levels (ankle, knee, thigh, sacrum and abdomen), than the other two groups.

Few patients in the overall cohort had ascites. There was no significant difference between the groups in the presence of this clinical sign, although it was proportionately more common amongst those who died before the study visit.

The majority of patients in all four groups were in Killip class II. The proportions in each of the four Killip classes differed between the groups (p<0.0001). Patients who died before the study visit were more likely to be in class III and IV, than the other three groups.

Table 4-11: Clinical signs of heart failure on admission to hospital, stratified by study visit attendance. Data are expressed as number (%) or mean (SD).

Clinical sign	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
Third heart sound	42 (6.5)	8 (4.8)	2 (2.7)	14 (12.2)	66 (6.6)	0.037
Pulmonary crackles						
None	42 (6.5)	12 (7.2)	3 (4.1)	4 (3.5)	61 (6.1)	
Basal	468 (72.2)	124 (74.3)	50 (68.5)	64 (55.7)	706 (70.4)	0.0019
Middle	130 (20.1)	30 (17.9)	18 (24.7)	45 (39.1)	223 (22.2)	
Apex	8 (1.2)	1 (0.6)	2 (2.7)	2 (1.7)	13 (1.3)	
Pleural effusion						
None	568 (87.6)	139 (83.2)	60 (82.2)	86 (74.8)	853 (85.0)	
Right	24 (3.7)	8 (4.8)	6 (8.2)	9 (7.8)	47 (4.7)	0.042
Left	14 (2.2)	4 (2.4)	3 (4.1)	4 (3.5)	25 (2.5)	
Bilateral	42 (6.5)	16 (9.6)	4 (5.5)	16 (13.9)	78 (7.8)	
Peripheral oedema (any)	436 (67.3)	129 (77.2)	62 (84.9)	98 (85.2)	725 (72.3)	<0.0001

Clinical sign	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
Peripheral oedema – ankle	432 (66.7)	127 (76.1)	61 (83.6)	95 (82.6)	715 (71.3)	<0.0001
Peripheral oedema – knee	155 (23.9)	48 (28.7)	35 (48.0)	57 (49.6)	295 (29.4)	<0.0001
Peripheral oedema – thigh	49 (7.6)	12 (7.2)	15 (20.6)	21 (18.3)	97 (9.7)	<0.0001
Peripheral oedema – sacrum	25 (3.9)	4 (2.4)	8 (11.0)	8 (7.0)	45 (4.5)	0.011
Peripheral oedema – abdomen	10 (1.5)	1 (0.6)	2 (2.7)	6 (5.2)	19 (1.9)	0.029
Ascites	26 (4.0)	4 (2.4)	1 (1.4)	9 (7.8)	40 (4.0)	0.077
Killip class						
I	39 (6.0)	6 (3.6)	1 (1.4)	0 (0)	46 (4.6)	
II	464 (71.6)	132 (79.0)	52 (71.2)	61 (53.0)	709 (70.7)	<0.0001
III	144 (22.2)	29 (17.4)	19 (26.0)	51 (44.4)	243 (24.2)	
IV	1 (0.2)	0 (0)	1 (1.4)	3 (2.6)	5 (0.5)	

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the four groups.

4.2.9 Electrocardiography

There were few differences between the four groups of patients in the electrocardiographic (ECG) parameters recorded on admission to hospital, as displayed in Table 4-12. The parameters that differed between the groups were; sinus rhythm, LBBB and prolonged QRS. There were no differences between the four groups for the following parameters; AF, paced rhythm, LVH, ischaemic ST depression, mean QRS duration, mean QTc interval and proportion with prolonged QTc.

Patients who died before the study visit and attendees were more likely to be in sinus rhythm than the other two groups (p=0.009). Less than half of patients who did not complete the study visit because of deteriorating health or withdrawal from participation were in sinus rhythm on admission.

LBBB was present on almost a fifth of the admission ECGs of all patients enrolled in the study. This ECG abnormality was more common amongst patients who died before the study visit (p=0.012). Patients who attended the study visit or were unable to because of deteriorating health had similar percentages of LBBB. Those who withdrew from participating in the study visit had fewest patients with this ECG abnormality.

The prevalence of a prolonged QRS differed between the four groups (p=0.024). The prevalence of a QRS duration 120-150ms amongst the four groups exhibited a similar pattern to that of LBBB. However a more prolonged QRS duration (>150ms) was more common amongst those with deteriorating health than the other three groups. Attendees and patients who died before the study visit had similar proportions with a QRS duration >150ms whilst those that withdrew from participation had fewest patients with this ECG abnormality.

Table 4-12: Electrocardiographic parameters on admission to hospital, stratified by study visit attendance. Data are number (%) or mean (SD).

ECG parameter (units)	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
Sinus rhythm	368 (56.8)	74 (44.3)	36 (49.3)	71 (61.7)	549 (54.7)	0.009
AF	258 (39.8)	81 (48.5)	34 (46.6)	41 (35.7)	414 (41.3)	0.089
LBBB	124 (19.1)	19 (11.4)	15 (20.5)	32 (27.8)	190 (18.9)	0.012
Paced	28 (4.3)	9 (5.4)	4 (5.5)	2 (1.7)	43 (4.3)	0.46
LVH	127 (19.6)	37 (22.2)	16 (21.9)	34 (29.6)	214 (21.3)	0.11
Ischaemic ST depression	29 (4.5)	3 (1.8)	4 (5.5)	6 (5.2)	42 (4.2)	0.37
Mean QRS (ms)	109.9 (27.9)	104.2 (26.2)	112.9 (31.9)	111.2 (26.4)	109.3 (27.8)	0.055
QRS duration >120	193 (29.8)	34 (20.4)	27 (37.0)	42 (36.5)	296 (29.5)	
QRS duration 120-150	121 (18.7)	22 (13.2)	13 (17.8)	28 (24.3)	184 (18.3)	0.024
QRS duration >150	72 (11.1)	12 (7.2)	14 (19.2)	14 (12.2)	112 (11.2)	
Mean QTc (ms)	449.4 (39.7)	448.2 (36.4)	444.3 (40.9)	439.7 (43.9)	447.7 (39.8)	0.097
QTc ≥440	388 (59.9)	96 (57.5)	39 (53.4)	62 (53.9)	585 (58.3)	0.51

* Inter-group comparisons using ANOVA F test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the four groups.

4.2.10 Chest X-Ray

Radiological features of pulmonary oedema differed between the four groups of patients, as shown in Table 4-13.

Many patients enrolled in the study had cardiomegaly present on their admission CXR, defined as a cardiothoracic ratio >50%. Patients with deteriorating health or who died before the study visit were more likely to have cardiomegaly on their CXR than the other two groups, albeit with only a trend towards statistical significance (p=0.056). Patients who withdrew from the study visit had fewest patients with this radiological sign.

The presence of alveolar oedema was more common in patients who died before the study visit (p<0.0001). Patients attending the study visit and those with deteriorating health had similar proportions with this radiological sign. Those who withdrew from the study visit had fewest patients with alveolar oedema.

Patients with deteriorating health or who died before the study visit were most likely to have a unilateral pleural effusion (p=0.0054). Bilateral pleural effusions were more common amongst those who died before the study visit, than the other three groups of patients.

Although there was no statistically significant difference between the groups in the proportions of patients with upper lobe venous diversion or interstitial oedema, there was a trend towards a greater prevalence of both of these parameters amongst patients who died before the study visit.

Table 4-13: CXR parameters on admission to hospital, stratified by study visit attendance. Data are expressed as number (%).

Parameter	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
CXR performed	646 (99.7)	166 (99.4)	73 (100)	115 (100)	1000 (99.7)	-
Cardiomegaly	463 (71.7)	103 (62.0)	54 (74.0)	85 (73.9)	705 (70.5)	0.056
Upper lobe venous diversion	433 (67.0)	112 (67.5)	48 (65.8)	91 (79.1)	684 (68.4)	0.068
Interstitial oedema	350 (54.2)	81 (48.8)	37 (50.7)	73 (63.5)	541 (54.1)	0.089
Alveolar oedema	165 (25.5)	31 (18.7)	20 (27.4)	49 (42.6)	265 (26.5)	<0.0001
Pleural effusion						
None	455 (70.5)	112 (67.5)	42 (57.5)	58 (50.4)	667 (66.7)	
Left	55 (8.5)	15 (9.0)	10 (13.7)	15 (13.0)	95 (9.5)	0.0054
Right	35 (5.4)	7 (4.2)	6 (8.2)	8 (7.0)	56 (5.6)	
Bilateral	101 (15.6)	32 (19.3)	15 (20.6)	34 (29.6)	182 (18.2)	

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the four groups.

4.2.11 Echocardiography

The majority of all patients had an echocardiogram performed after enrolment into the study (Table 4-14). Most of these echocardiograms were carried out during the index admission (81.2%), with the remainder being performed in the early weeks following discharge from hospital. The main reason for not performing echocardiography for the remaining 276 patients was that it had already been done.

Patients who died before the study visit were less likely to have an echocardiogram performed after enrolment, than the other three groups (p=0.0012). Most recorded echocardiographic parameters did not differ between the four groups. However a dilated LV was more common amongst patients who attended the study visit (p=0.0014). The prevalence of this abnormality was similar in the other three groups.

The presence of LVH and LVSD was similar in all four groups. As reported in chapter 3 (section 3.2.11.2), LVEF was not calculated routinely on the current echocardiograms, thus preventing dichotomisation of patients into HF-REF or HF-PEF groups. The majority of valvular abnormalities did not differ between the four groups. There was a trend towards AS being more common in patients who died before the study visit (p=0.064). MR and TR were the commonest recorded valvular abnormalities in all four groups of patients, likely reflecting functional rather than structural valve disease. The presence of TR was greatest amongst those who died before the study visit (0.044).

Table 4-14: Echocardiographic parameters following enrolment, stratified by study visit attendance. Data are expressed as number (%).

Parameter	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
Echo after enrolment	487 (75.2)	116 (69.5)	57 (78.1)	67 (58.3)	727 (72.5)	0.0012
Dilated LV	197 (40.5)	29 (25.0)	16 (28.1)	16 (23.9)	258 (35.5)	0.0014
LVH	197 (40.5)	58 (50.0)	29 (50.9)	28 (41.8)	312 (42.9)	0.12
LVSD	340 (69.8)	62 (53.4)	34 (59.6)	42 (62.7)	478 (65.7)	0.14
At least moderate AS	31 (6.4)	15 (12.9)	4 (7.0)	7 (10.4)	57 (7.8)	0.064
At least moderate AR	20 (4.1)	3 (2.6)	2 (3.5)	4 (6.0)	29 (4.0)	0.23
At least moderate MS	8 (1.6)	4 (3.4)	1 (1.8)	1 (1.5)	14 (1.9)	0.95
At least moderate MR	147 (30.2)	29 (25.0)	16 (28.1)	19 (28.4)	211 (29.0)	0.75
At least moderate TR	66 (13.6)	20 (17.2)	11 (19.3)	19 (28.4)	116 (16.0)	0.044

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the four groups.

4.2.12 Haematology

All patients enrolled in the study had a full blood count performed routinely on admission to hospital. The results of the individual parameters of the FBC, stratified by study visit attendance, are displayed in Table 4.15.

Patients unable to complete the study visit due to deteriorating health or death had a lower haemoglobin level than those who completed the study visit or withdrew from participation ($p=0.0028$). Moreover, patients with deteriorating health or who died before the study visit were more likely to be anaemic by WHO criteria (defined as haemoglobin <12g/dl for females and <13g/dl for males).

Half of all patients had an elevated RDW concentration with the mean value for all four groups above the normal range (>15%). However, RDW level was highest in patients who died before the study visit ($p=0.00024$).

Lymphocyte concentration displayed a similar pattern between the four groups to that of haemoglobin. Patients unable to complete the study visit due to deteriorating health or death had a lower lymphocyte concentration than those who completed the study visit or withdrew from participation ($p=0.0032$). Many patients in all four groups were lymphopenic on admission to hospital, but this was more common amongst those unable to complete the study visit due to deteriorating health or death ($p<0.0001$).

Total WBC count and platelet concentration was similar in all four groups.

Table 4-15: Full blood count parameters on admission, stratified by study visit attendance. Data are expressed as mean (SD) or number (%).

Parameter	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
WBC count ($x10^9$/l)	9.3 (3.7)	9.2 (3.4)	9.2 (4.0)	9.8 (4.1)	9.4 (3.7)	0.62
Haemoglobin (g/dl)	12.3 (2.2)	12.0 (2.1)	11.5 (2.0)	11.7 (2.2)	12.1 (2.2)	0.0028
Haemoglobin <13 males, <12 females	337 (52.0)	101 (60.5)	53 (72.6)	77 (67.0)	568 (56.6)	0.00025
RDW %	15.2 (2.1)	15.6 (2.5)	15.9 (3.2)	16.1 (2.6)	15.4 (2.3)	0.00024
RDW ≥ 15 %	305 (47.1)	91 (54.5)	35 (47.9)	72 (62.6)	503 (50.1)	0.045
Platelets ($x10^9$/l)	244.7 (90.0)	249.0 (89.7)	257.1 (109.0)	237.7 (97.6)	245.5 (91.7)	0.52
Lymphocytes ($x10^9$/l)	1.8 (1.6)	1.5 (0.9)	1.3 (0.8)	1.4 (1.0)	1.6 (1.4)	0.0032
Lymphocytes <1 $x10^9$/l	122 (18.8)	44 (26.3)	22 (30.1)	48 (41.7)	236 (23.5)	<0.0001

* Inter-group comparisons using ANOVA F test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the four groups.

4.2.13 Biochemistry

Many biochemical laboratory tests were performed on admission to hospital. All patients had BNP and U&E measured. The majority of patients also had LFT and CRP measured. Most patients recruited from Glasgow Royal Infirmary and Western Infirmary Glasgow had troponin I measured. The results of these tests, as stratified by study visit attendance, are presented in Tables 4-16 to 4-20.

BNP testing was part of the study protocol, a raised BNP (>100pg/ml) being mandatory for enrolment in the study. BNP concentration was highest amongst patients who died before the study visit ($p<0.0001$). Those who completed the study visit or withdrew from participation had the lowest levels.

Troponin I was raised (defined as $\geq 0.04\mu g/l$) on admission to hospital for more than half of all patients recruited from Western and Royal Infirmaries. Those who died before the study visit were more likely to have an elevation of this biomarker than the other three groups ($p<0.0001$). Patients who attended the study visit had fewest patients with a raised troponin I. Of 102 patients recruited from the Royal Alexandra Hospital, 31 had troponin T measured and only 8 patients had an elevation of this biomarker (defined as $\geq 0.05\mu g/l$). There was no difference between the 4 groups in the proportions of patients with a raised troponin T.

Table 4-16: BNP levels on admission, stratified by study visit attendance. Data are mean (SD) or median [IQR].

Parameter	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
Mean BNP (pg/ml)	1197 (1154)	1173 (1136)	1296 (1095)	2142 (1550)	1308 (1234)	<0.0001
Median BNP (pg/ml)	788 [366-1582]	774 [351-1438]	967 [577-1609]	1762 [856-3176]	880 [394-1812]	<0.0001

* Inter-group comparisons using ANOVA F test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the four groups.

Table 4-17: Troponin I levels on admission for Glasgow Royal Infirmary and Western Infirmary patients who had troponin I measured, stratified by study visit attendance. Data are expressed as number (%).

Parameter	Attendee (n=561)	Withdrawn (n=125)	Deteriorating health (n=57)	Deceased (n=101)	Overall (n=844)	p value*
Troponin I ≥ 0.04 µg/l	280 (49.9)	69 (55.2)	35 (61.4)	81 (80.2)	465 (55.1)	<0.0001

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the four groups.

U&E were measured on admission for all patients enrolled in the study. Nearly all the parameters differed between the four groups of patients (Table 4-18). Patients who died before the study visit or had deteriorating health had lower sodium concentrations than the other two groups ($p<0.0001$). Hyponatraemia (defined as sodium <135mmol/l) was more common amongst those who died before the study visit, than the other three groups ($p=0.0019$). Patients attending the study visit had fewest patients with this biochemical abnormality, almost half the prevalence of those who died before the study visit.

The majority of patients in each of the four groups had an elevated urea concentration. Patients who died before the study visit had higher concentrations than the other three groups ($p<0.0001$). Patients with deteriorating health and those who died before the study visit had proportionately more patients with an elevation above the normal range (defined as >7.5mmol/l) [$p<0.0001$].

Creatinine concentration also differed between the four groups. Consistent with the findings regarding serum urea, the highest concentrations of creatinine were amongst those who failed to complete the study visit due to deteriorating health or death ($p=0.00035$).

eGFR was calculated for all patients using the four-variable MDRD formula, as outlined in Chapter 2. This formula uses age, sex, race and creatinine to calculate the eGFR and provides a more accurate assessment of renal function than urea or creatinine alone. Consistent with the results of urea and creatinine concentrations, eGFR was lower in those who died before the study visit or had deteriorating health than the other two groups ($p<0.0001$). Although the majority of patients in all four groups had renal dysfunction (defined as eGFR <60ml/min/1.73m^2), this was more common in patients who died before the study visit or had deteriorating health. Severe renal dysfunction (defined as eGFR <30ml/min/1.73m^2) was more common amongst those who died before the study visit ($p<0.0001$).

Table 4-18: Renal function on admission for all patients, stratified by study visit attendance. Data are mean (SD), number (%) or median [IQR]

Parameter	Attendee (n=648)	Withdrawn (n=167)	Deteriorating health (n=73)	Deceased (n=115)	Overall (n=1003)	p value*
Sodium (mmol/l)	138.3 (4.3)	137.3 (4.1)	136.8 (5.2)	136.4 (5.5)	137.8 (4.5)	<0.0001
Sodium < 135mmol/l	98 (15.1)	31 (18.6)	16 (21.9)	34 (29.6)	179 (17.8)	0.0019
Potassium (mmol/l)	4.2 (0.6)	4.2 (0.5)	4.2 (0.6)	4.2 (0.7)	4.2 (0.6)	0.35
Urea (mmol/l)	9.4 (5.4)	10.2 (5.7)	11.6 (5.6)	13.2 (6.9)	10.1 (5.8)	<0.0001
Urea ≥ 7.5 mmol/l	368 (56.8)	108 (64.7)	58 (79.5)	91 (79.1)	625 (62.3)	<0.0001
Creatinine (µmol/l)	105.5	107	115	120	109	0.00035
	[86.0-135.0]	[85.5-136.5]	[94.0-155.0]	[91.5-162.0]	[87.0-138.0]	
eGFR (ml/min/1.73m^2)	58.0 (20.4)	54.0 (21.8)	50.2 (19.5)	47.9 (22.5)	55.6 (21.1)	<0.0001
eGFR levels (ml/min/1.73m^2)						
<30	55 (8.5)	22 (13.2)	8 (11)	27 (23.5)	112 (11.2)	
30-60	310 (47.8)	85 (50.9)	45 (61.6)	59 (51.3)	499 (49.7)	<0.0001
60-90	244 (37.7)	51 (30.5)	18 (24.7)	24 (20.8)	337 (33.6)	
≥ 90	39 (6.0)	9 (5.4)	2 (2.7)	5 (4.4)	55 (5.5)	

* Inter-group comparisons using ANOVA F test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the four groups.

LFT were measured on admission for the majority of patients enrolled in the study. The results, stratified by study visit attendance, are displayed in Table 4-19.

The proportion of patients with an elevated bilirubin concentration result (defined as >22µmol/l) differed between the four groups (p=0.036). Those who died before the study visit had more patients with a raised bilirubin concentration. Those with deteriorating health had, perhaps surprisingly, fewest patients with an elevated bilirubin with similar proportions for those who completed the study visit or withdrew from participation.

Patients with deteriorating health had higher levels of alkaline phosphatase than the other three groups (p=0.00024). Patients attending the study visit had the lowest levels of this liver test.

Albumin concentration was lowest amongst patients who died before the study visit than the other three groups (p<0.0001). Patients who withdrew from participating in the study visit had the highest levels of this biomarker. Those who died before the study visit had more patients with hypoalbuminaemia (defined as albumin <35g/l), whilst attendees and patients who withdrew from participating in the study visit had fewest patients with this abnormality (P<0.0001).

AST, ALT and GGT concentrations were similar in all four groups.

Table 4-19: Liver function parameters stratified by study visit attendance. Data are expressed as median [IQR], number (%) or mean (SD).

Parameter	Attendee (n=646)	Withdrawn (n=165)	Deteriorating health (n=72)	Deceased (n=115)	Overall (n=998)	p value*
Bilirubin (µmol/l)	12.0 [8.0-19.0]	13.0 [9.0-19.0]	11.0 [8.0-16.0]	14.0 [9.5-23.0]	13.0 [8.0-19.0]	0.14
Bilirubin ≥ 22 µmol/l	111 (17.2)	29 (17.6)	10 (13.9)	32 (27.8)	182 (18.2)	0.036
AST (U/l)	25.0 [19.0-35.0]	25.5 [19.0-35.0]	24.0 [19.0-35.0]	28.5 [20.0-44.0]	25.0 [19.0-36.0]	0.17
ALT (U/l)	21.0 [15.0-33.3]	19.5 [13.0-30.0]	18.0 [13.0-28.0]	21.0 [14.0-32.0]	20.0 [14.0-32.0]	0.33
GGT (U/l)	59.0 [33.0-109.5]	51.0 [29.0-88.0]	59.0 [25.8-97.0]	55.0 [34.0-98.0]	57.0 [32.0-103.0]	0.39
Alk Phos (U/l)	93.0 [73.0-121.0]	96.0 [78.0-122.0]	109.0 [87.3-141.3]	97.0 [77.0-136.5]	95.0 [75.0-123.0]	0.00024
Albumin (g/l)	35.9 (4.2)	36.0 (4.5)	35.2 (5.2)	33.1 (5.0)	35.5 (4.5)	<0.0001
Albumin <35g/l	212 (32.8)	54 (32.7)	32 (44.4)	71 (61.7)	369 (37.0)	<0.0001

* Inter-group comparisons using ANOVA F test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the four groups.

The majority of all enrolled patients had CRP measured on admission to hospital, the results of which are shown in Table 4-20. Patients who died before the study visit or had deteriorating health had higher CRP levels than the other two groups (p=0.00027). The majority of patients in all four groups had a CRP level elevated above the normal reference range (defined as >6mg/l). There was a trend towards a greater proportion of patients with an elevated CRP in the group who died before the study visit, although the difference was not statistically significant (p=0.057).

Table 4-20: CRP results, stratified by study visit attendance. Data are expressed as median [IQR] or number (%).

Parameter	Attendee (n=638)	Withdrawn (n=160)	Deteriorating health (n=71)	Deceased (n=114)	Overall (n=983)	p value*
CRP (mg/l)	12.0 [5.5-27.8]	15.0 [6.2-30.8]	18.0 [5.5-44.0]	19.5 [9.2-41.8]	14.0 [6.0-31.0]	0.00027
CRP ≥ 6mg/l	471 (73.8)	124 (77.5)	51 (71.8)	97 (85.1)	743 (75.6)	0.057

* Inter-group comparisons using ANOVA F test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the four groups.

4.3 Summary

Chapter 4 has compared the clinical characteristics of the patients in hospital according to whether or not they subsequently completed the study visit. Many differences in the clinical characteristics between these four groups of patients have been described. The attendees were more likely to be younger and male. Both attendees and those who withdrew from the study visit contained patients with milder symptoms, in terms of NYHA class, and significantly shorter durations of hospitalisation. The groups of patients who died or had deteriorating health preventing subsequent attendance at the study visit had more patients with a previous diagnosis of HF.

There was a high prevalence of medical comorbidity amongst patients in all groups, regardless of subsequent attendance at the study visit. The majority of common medical conditions did not differ in prevalence between the four groups. Peripheral arterial disease and weight loss were more common amongst those who died before the study visit or had deteriorating health. There was a high prevalence of anaemia in all four groups but this was significantly higher amongst those who died before the study visit or had deteriorating health. This is reflective of anaemia being a predictor of poor prognosis in HF. A history of cancer was more prevalent amongst patients with deteriorating health, perhaps a reason for subsequent non-attendance at the study visit. Certain physically disabling conditions, such as peripheral arterial disease, osteoarthritis and urinary incontinence, were also more prevalent in non-attendees. This may be reflective of the burden of attending an additional clinic and the apprehension of attempting the MTWA treadmill test. The prescribing of certain HF medications prior to hospitalisation differed between the groups. More patients who did not attend the study visit due to deteriorating health or death were prescribed diuretics, most likely explained by the higher prevalence of a previous diagnosis of HF amongst these groups. More patients who subsequently attended the study visit were prescribed beta-blockers prior to their admission; this may reflect the prognostic benefit of these therapies. The use of intravenous nitrates or inotrope therapy on admission was greatest amongst patients who died before the study visit, an expected finding given that patients necessitating these medications are usually critically unwell.

Patients who did not attend the study visit because of deteriorating health or death had more adverse clinical signs on admission to hospital. These signs included systolic and diastolic hypotension, and lower peripheral oxygen saturations. Men who did not attend the study visit because of deteriorating health or death had a lower average weight than those who attended or withdrew from the study visit. Men and women who died before the study visit had the largest proportion of patients in the underweight category whilst those who attended the study visit had the highest proportion of patients in the obese category, evidence of the reverse epidemiology paradox in HF. Clinical signs of fluid overload on admission were also greater amongst those with subsequent deteriorating health or death preventing study visit attendance.

There were differences between the four groups in the routine clinical investigations performed on admission to hospital. Patients who subsequently died had the highest proportion of LBBB present on the admission ECG, consistent with this parameter being a marker of poor prognosis. Those with deteriorating health or death had the highest prevalence of some radiological features of HF, including cardiomegaly and pleural effusions. Perhaps surprisingly, the proportion of patients with a dilated LV on current echocardiogram was greatest amongst the group of attendees. There were no other differences in echocardiographic parameters between the four groups, including LVSD. There were several differences between the four groups in haematological and biochemical parameters recorded on admission to hospital. Many of these parameters are established markers of adverse outcome in HF, abnormalities of which were proportionately more common in the groups who failed to attend the study visit due to deteriorating health or death. These parameters included haemoglobin, RDW, lymphocytes, BNP, troponin, sodium, urea, creatinine, eGFR, albumin and CRP. The majority of these parameters were also abnormal amongst patients in the groups who attended or withdrew from participating, but to a lesser extent than the other two groups.

In summary, patients attending the study visit were similar, in terms of clinical characteristics during hospitalisation, to the group of patients who withdrew from participating in the study visit. Both of these groups contained patients with proportionately fewer markers of an adverse prognosis in heart failure, than the patients in the groups who failed to complete the study visit due to deteriorating health or death.

CHAPTER FIVE

CLINICAL CHARACTERISTICS
OF
POST-DISCHARGE COHORT

5.1 Introduction

This chapter will describe the cohort of patients who completed the study visit at the BHF Glasgow Cardiovascular Research Centre; the post-discharge cohort. The main focus of this chapter will be a detailed description of the clinical characteristics of the patients who completed the study visit. This will be an update of the data recorded from the hospital admission. This data will comprise current HF symptomatology and status, current prescribed medications, physiological and body composition measurements, and cardiovascular examination findings. ECG findings, LVEF by echocardiography and blood test results will also be presented.

5.2 Results

5.2.1 Composition of post-discharge cohort

Of 1003 patients enrolled in the study, 648 patients attended the BHF Glasgow Cardiovascular Research Centre approximately 4-6 weeks following discharge from hospital. This represented 64.6% of the original hospitalised cohort. The reasons the remaining 35.4% failed to attend were outlined in Figure 4.1 (page 136).

5.2.2 Demographics

The demographics of the patients who completed the study visit are displayed in Table 5-1. Compared to the results for the overall hospitalised cohort, the post-discharge cohort contained more men (58.2% versus 53.0%), the mean age was slightly younger (70.8 versus 73.0) and a smaller proportion of patients were over 75 years of age (35.8% versus 45.7%). For those attending the study visit the average duration of hospitalisation was 2 days shorter. Over 40% of patients completing the study visit had a previous diagnosis of HF, prior to enrolment in this study. Only 6.8% of the post-discharge cohort been readmitted to hospital with decompensated HF since the index admission.

Table 5-1: Demographics of the post-discharge cohort.

Variable	n (%), mean (SD) or median [IQR]
Male	377 (58.2)
Female	271 (41.8)
Mean age (years)	70.8 (10.6)
Median age (years)	71.6 [64.7 -78.0]
Age range	18 – 96
≥ 75 years of age	232 (35.8)
Mean duration of admission (days)	9.7 (8.1)
Median duration of admission (days)	7 [4-12]
Diagnosis of HF prior to enrolment	283 (43.7)
Readmission with HF since enrolment	44 (6.8)

5.2.3 Symptoms of heart failure

Current HF symptoms were recorded for each patient attending the study visit (Table 5-2). The majority of patients experienced an overall improvement in their HF symptom status since discharge from hospital, with only 10% of patients experiencing deterioration. Almost two-thirds of all patients were NYHA class II, with less than one-third of patients NYHA class III. Few patients were NYHA class I or IV. This contrasts with the hospital admission where the majority of the study visit attendees were NYHA class III (Table 4-3, page 141). Fewer patients experienced nocturnal symptoms by the time of their study visit (Table 4-3, page 141). Approximately one quarter of patients had symptoms of orthopnoea, whilst three-quarters of the study visit attendees had this symptom during hospitalisation. Only 12% of attendees had symptoms of PND, whilst almost half of the same patients had this symptom during hospitalisation. Over a quarter of patients had symptoms of ankle swelling at the time of the

study visit, compared with almost two-thirds during hospital admission. Almost a quarter of patients had symptoms of palpitations and wheeze, similar proportions to hospitalisation.

Table 5-2: Current heart failure symptoms

Symptom	Number of patients	% of cohort (n=648)
Overall deterioration since discharge	70	10.8
NYHA Class		
I	25	3.9
II	409	63.1
III	207	31.9
IV	7	1.1
PND	79	12.2
Orthopnoea	163	25.2
Ankle swelling	185	28.5
Palpitations	157	24.2
Wheeze	153	23.6

5.2.4 Common medical comorbidity

Table 5-3 displays the prevalences of common medical comorbidities in the post-discharge cohort. There was a high prevalence of coronary heart disease. Over 40% of the cohort had documented evidence of a previous MI and many had previously undergone PCI or CABG. Hypertension was the commonest medical comorbidity, affecting almost two-thirds of patients. AF was also extremely prevalent, affecting over half of the patients. Anaemia was another common condition amongst the post-discharge cohort, as were diabetes mellitus and COPD. Other common conditions and their prevalences are shown in Table 5-3.

Table 5-3: Prevalences of common medical conditions

Condition	Number of patients	% of cohort (n=648)
MI	278	42.9
History of angina	356	54.9
Angiographic CAD	224 / 307	73.0
PCI	92	14.2
CABG	112	17.3
Hypertension	420	64.8
TIA/CVA	146	22.5
History of AF	344	53.1
Prosthetic heart valve	50	7.7
Pacemaker	41	6.3
Prior arrhythmia	53	8.2
Diabetes mellitus	203	31.3
Anaemia	276	42.6
Depression	137	21.1
History of cancer	87	13.4
COPD	181	27.9
Peripheral arterial disease	104	16.0
Osteoarthritis	154	23.8

CAD = coronary artery disease (defined as > 50% stenosis in ≥ 1 major epicardial vessel, denominator is number of patients who had an angiogram)

5.2.5 Medications

Table 5-4 displays the frequencies of HF medication prescribing for patients attending the study visit. The data are presented for the overall post-discharge cohort and dichotomised by LVEF. This is because the evidence base for HF treatment is largely confined to HF-REF. The significant differences in clinical characteristics, including medications, between the patients with HF-REF and HF-PEF are described later in this chapter (section 5.2.12).

Almost all patients were prescribed diuretic therapy at the time of study visit, the overwhelming majority being furosemide or an alternative loop diuretic. More than 70% of patients with HF-REF were prescribed an ACE inhibitor, with almost 20% having this therapy initiated since recruitment into the study. Over two-thirds of the post-discharge cohort with HF-REF was prescribed a beta-blocker, with 17.5% having this therapy initiated since recruitment into the study. ARB prescribing was less common, with few patients in the post-discharge cohort having these drugs prescribed since recruitment. Similar proportions were prescribed an aldosterone receptor blocker, the majority of which was initiated since recruitment into the study. Of those with HF-REF, 60% were prescribed the combination of either an ACE inhibitor or an ARB and a beta-blocker. Various combinations of the other HF disease-modifying therapies (ACE inhibitor, beta-blocker, ARB and aldosterone blocker) were prescribed in small proportions of the post-discharge cohort (Table 5-4). Proportionately more patients with HF-PEF were prescribed digoxin, than patients with HF-REF.

Table 5-4: Frequency of heart failure medication prescribing in the post-discharge cohort at the study visit, overall and stratified according to LVEF. Data are expressed as number (%)

Heart failure medication	HF-PEF (n=127)	HF-REF (n=521)	Overall (n=648)
Diuretics	116 (91.3)	505 (96.9)	621 (95.8)
Furosemide / loop diuretics	114 (89.8)	498 (95.6)	612 (94.4)
ACE inhibitor*	72 (56.7)	384 (73.7)	456 (70.4)
ACE inhibitor since recruitment	18 (14.2)	98 (18.8)	116 (17.9)
Beta-blocker*	70 (55.1)	360 (69.1)	430 (66.4)
Beta-blocker since recruitment	2 (1.6)	91 (17.5)	93 (14.4)
ARB*	12 (9.4)	70 (13.4)	82 (12.7)
ARB since recruitment	3 (2.4)	7 (1.3)	10 (1.5)
Aldosterone blocker*	12 (9.4)	73 (14.0)	85 (13.1)
Aldosterone blocker since recruitment	4 (3.1)	45 (8.6)	49 (7.6)
ACE inhibitor or ARB	79 (62.2)	435 (83.5)	514 (79.3)
ACE inhibitor or ARB & Beta-blocker	43 (33.9)	314 (60.3)	357 (55.1)
ACE inhibitor and ARB & Beta-blocker	4 (3.1)	14 (2.7)	18 (2.8)
ACE inhibitor & Beta-blocker & Aldosterone blocker	4 (3.1)	46 (8.8)	50 (7.7)
ARB & Beta-blocker & Aldosterone blocker	0 (0)	2 (0.4)	2 (0.3)
ACE inhibitor or ARB & Beta-blocker & Aldosterone blocker	4 (3.1)	48 (9.2)	52 (8)
Digoxin	37 (29.1)	126 (24.2)	163 (25.2)

* = total number of patients prescribed this medication, including those since recruitment

The frequencies of prescribing of other cardiovascular medications in the post-discharge cohort are outlined in Table 5-5. The prescribing rates of these medications were similar to pre-admission (Table 4-5, page 147). Statin therapy was prescribed for almost three-quarters of the post-discharge cohort. Over half of the cohort was prescribed aspirin, with almost one fifth prescribed clopidogrel and 10% prescribed dual antiplatelet therapy. Almost 40% of patients were warfarinised, reflecting the high prevalence of AF in the post-discharge cohort. Many patients were prescribed anti-anginal therapies (calcium channel blockers, long-acting nitrates and nicorandil) and diabetic medications, as outlined in Table 5-5. Anti-arrhythmic therapy was prescribed in a minority of patients.

Table 5-5: Frequency of cardiovascular medication prescribing in the post-discharge cohort at the study visit

Cardiovascular medication	Number of patients	% of cohort (n=648)
Statin	477	73.6
Aspirin	362	55.9
Clopidogrel	115	17.7
Aspirin or clopidogrel	409	63.1
Warfarin	253	39.0
Calcium channel blocker	117	18.1
Anti-arrhythmic	35	5.4
Long-acting nitrates	112	17.3
Nicorandil	97	15.0
Oral hypoglycaemic agents	157	24.2
Insulin	66	10.2

The frequencies of prescribing of other common non-cardiovascular medications in the post-discharge cohort are outlined in Table 5-6. Over a quarter of all patients were prescribed bronchial inhaler therapies. A considerable proportion of patients were prescribed antidepressant medications.

Table 5-6: Frequency of prescribing of common non-cardiovascular medications in the post-discharge cohort

Non-cardiovascular medication	Number of patients	% of cohort (n=648)
Bronchial inhalers	172	26.5
Antidepressants	94	14.5
Vitamins (B1 & B complex)	39	6.0
NSAIDs	30	4.6
Antihistamines	21	3.2
Incontinence meds	16	2.5

5.2.6 Clinical examination

5.2.6.1 Routine physiological measurements

Routine physiological measurements were recorded for all patients attending the study visit (Table 5-7). In contrast to the recordings from the hospital admission (Table 4-7, page 151), fewer patients had abnormal physiological measurements. The mean pulse was lower at 77.1 beats per minute (bpm), with only 50 patients (7.7%) having a tachycardia (defined as a pulse greater than 100 bpm). Of those patients with a tachycardia at the study visit, over half were in AF on their study visit ECG. Of 648 patients, 84 patients (13%) were bradycardic (defined as a pulse less than 60 bpm), likely reflective of treatment with beta-blockers. The mean blood pressure was normal at 131 / 68 mmHg. Over one third of patients had a SBP greater than 140 mmHg, with only 22 patients (3.4%) having severe hypertension (defined as SBP greater than

180 mmHg). During hospitalisation, 45 study visit attendees (6.9%) had severe hypertension (Table 4-7, page 151). Only 43 patients (6.6%) had systolic hypotension (defined as SBP less than 90 mmHg) at the study visit. Only 34 patients (5.2%) met criteria for diastolic hypertension (defined as DBP greater than 90 mmHg), in contrast to a quarter of the same patients during hospitalisation (Table 4-7, page 154). A significant proportion of the cohort (42.6%) had diastolic hypotension (defined as DBP less than 60 mmHg). The mean temperature, respiratory rate and SpO_2 were normal.

5.2.6.2 Body mass index and waist circumference measurements

Height, waist and weight measurements were recorded for all patients attending the study visit. BMI was calculated from these measurements. The results are displayed in Table 5-8. Over three-quarters of the post-discharge cohort lost weight from the hospital admission (Table 4-8, page 154) to the study visit. These declines in weight are most likely due to successful diuresis and establishing euvolaemic status after the decompensated episode in hospital. Despite this, most of the post-discharge patients were still overweight with an average BMI of 28.7 kg/m^2. Over two-thirds of all patients were either overweight or obese (defined as BMI 25-30 kg/m^2 or >30 kg/m^2, respectively). Less than one-third of the post-discharge cohort was normal weight (defined as BMI 18.5-24.9 kg/m^2). Only 16 patients (2.5%) were underweight (defined as BMI < 18.5 kg/m^2). Over half of patients had a waist circumference exceeding the sex-specific recommendations (defined as 94–102 cm in men and 80–88 cm in women). More than one-quarter of patients had a waist circumference below the sex-specific recommendations (defined as < 94 cm in men and < 80 in women).

Table 5-7: Physiological findings in the post-discharge cohort, recorded at the study visit.

Variable	Mean (SD), median [IQR] or n (%)	Units
Mean HR	77.1 (15.5)	bpm
Median HR	76 [67-88]	bpm
HR > 100	50 (7.7)	bpm
HR > 100 & AF on study visit ECG	27/50 (54)	bpm
HR < 60	84 (13.0)	bpm
HR < 50	12 (1.9)	bpm
Mean SBP	131 (23.5)	mmHg
Median SBP	129 [114-145]	mmHg
SBP > 140	225 (34.7)	mmHg
SBP ≥ 180	22 (3.4)	mmHg
SBP < 90	43 (6.6)	mmHg
Mean DBP	67.8 (13.2)	mmHg
Median DBP	67 [58-77]	mmHg
DBP ≥ 90	34 (5.2)	mmHg
DBP < 60	276 (42.6)	mmHg
Mean pulse pressure	63.2 (23.6)	mmHg
Median pulse pressure	56 [45-71]	mmHg
Mean temperature	36.2 (0.6)	° Celsius
Median temperature	36.2 [35.9-36.5]	° Celsius
Mean respiratory rate	19.1 (3.5)	breaths / min
Median respiratory rate	18 [17-20]	breaths / min
Mean SpO_2	97.5 (2.8)	%
Median SpO_2	98 [96-99]	%

Table 5-8: BMI and waist circumference measurements at the study visit.

Measurement	Mean (SD), median [IQR] or n (%)	Units
Mean height	163.9 (10.2)	cm
Median height	164 [156.8-171]	cm
Mean height (men)	169.9 (8.0)	cm
Mean height (women)	155.6 (6.5)	cm
Mean weight	77.5 (20.3)	kg
Median weight	75 [63-88.5]	kg
Mean weight (men)	83.3 (19.6)	kg
Mean weight (women)	69.4 (18.4)	kg
Study visit weight < hospital weight	503 (77.6)	-
Mean BMI	28.7 (6.7)	kg/m^2
Median BMI	27.6 [24.1-32.5]	kg/m^2
Mean BMI (men)	28.8 (6.3)	kg/m^2
Mean BMI (women)	28.6 (7.3)	kg/m^2
BMI < 18.5 (underweight)	16 (2.5)	kg/m^2
BMI 18.5 – 24.9 (normal weight)	189 (29.2)	kg/m^2
BMI 25 – 30 (overweight)	218 (33.6)	kg/m^2
BMI > 30 (obese)	225 (34.7)	kg/m^2
Mean waist	97.5 (17.0)	cm
Median waist	97 [87-107]	cm
Waist < 94 M; < 80 F	186 (28.7)	cm
Waist 94 – 102 M; 80 – 88 F	125 (19.3)	cm
Waist ≥ 102 M; ≥ 88 F	337 (52.0)	cm

5.2.6.3 Cardiovascular examination signs

A full cardiovascular examination was performed for all patients attending the study visit (Table 5-9). Few patients had a raised JVP, an expected finding in a cohort of patients with stable HF. Three quarters of patients had palpable apices and over a third of these were displaced. Detection of a third heart sound was less common at the study visit than during the hospital admission for the post-discharge cohort (Table 4-11, page 158), also an expected finding in a cohort of patients with stable HF. Only a quarter of the post-discharge cohort had pulmonary crackles on examination, the vast majority of which were confined to the lung bases. More than 90% of the post-discharge cohort had at least basal pulmonary crackles on admission to hospital (Table 4-11, page 158). Few patients had clinical signs of a pleural effusion (uni- or bilateral) at the study visit. Over a third of the post-discharge cohort had ankle oedema, with few patients having oedema extending beyond the ankles. A significant proportion of the post-discharge cohort had complete resolution of peripheral oedema, by the time of their study visit. Few patients had clinical evidence of ascites at the study visit.

Table 5-9: Cardiovascular examination findings at the study visit

Clinical sign	Number of patients	% of cohort (n=648)
Elevated JVP (>4cm)	67	10.3
JVP not elevated	505	77.9
JVP not seen	77	11.9
Palpable apex	494	76.2
Displaced apex	178	27.5
Third heart sound	6	0.9
Murmur	288	44.4
Pulmonary crackles (any)	168	25.9
Pulmonary crackles – basal only	162	25.0
Pulmonary crackles – mid-zones	6	0.9
Pulmonary crackles – apices	0	0
Complete resolution of pulmonary crackles from hospitalisation	440	67.9
Pleural effusion(s)	17	2.6
Peripheral oedema – ankle	238	36.7
Peripheral oedema – knee	43	6.6
Peripheral oedema – thigh	6	0.9
Peripheral oedema – sacrum	1	0.2
Peripheral oedema – abdomen	0	0
Complete resolution of peripheral oedema from hospitalisation	234	36.1
Ascites	6	0.9

5.2.7 Electrocardiography

All patients had a 12-lead ECG performed at the study visit; the results are displayed in Table 5-10. Of 648 patients attending the study visit, 379 patients were in sinus rhythm. Over one third of the patients were in AF. Only 34 patients (5.2%) were in a paced rhythm. A significant number of patients had ECG evidence of LVH (n=107, 16.5%). Over a quarter of patients had evidence of a bundle branch block on ECG, with 142 patients having LBBB (21.9%). The mean QRS duration for the post-discharge cohort was within normal limits at 112ms. A prolonged QRS duration (defined as >120ms) was common and evident in almost one-third of patients, with 81 patients (12.5%) having a major prolongation (defined as >150ms). The mean QTc interval for the post-discharge cohort was at the upper limit of the normal range and approximately half of the cohort had a prolonged QTc (defined as >440ms).

Table 5-10: ECG parameters at the study visit.

ECG parameter	n (%), mean (SD) or median [IQR]	Units
Sinus Rhythm	379 (58.5)	-
AF	240 (37.0)	-
Paced rhythm	34 (5.2)	-
LBBB	142 (21.9)	-
RBBB	34 (5.2)	-
Pathological Q waves	61 (9.4)	-
LVH	107 (16.5)	-
Ischaemic ST depression	13 (2.0)	-
Mean QRS duration	111.7 (27.5)	ms
Median QRS duration	104 [90-126]	ms
QRS duration ≥ 120	206 (31.8)	-
QRS duration 120 -150	125 (19.3)	-
QRS duration > 150	81 (12.5)	-
Mean QTc interval	439.4 (33.0)	ms
Median QTc interval	439 [414.8-462]	ms
QTc interval <440	326 (50.3)	-
QTc interval ≥440	322 (49.7)	-

5.2.8 Ejection fraction by echocardiography

All patients had a focused echocardiogram performed at the study visit to calculate LVEF. Of 648 patients attending the study visit, 622 patients (96.0%) had echocardiographic images of satisfactory quality to enable LVEF to be calculated using Simpson's biplane method. The mean (SD) LVEF was 40.2% (12.2). The median [IQR] LVEF was also 40% [32-48]. The minimum LVEF was 11% and the maximum 70%. The distribution of LVEF is shown in Figure 5-1. One fifth of the post-discharge cohort had severe LVSD (defined as LVEF <30%). Approximately one fifth had preserved left ventricular systolic function (defined as LVEF ≥ 50%). For the 26 patients whose echocardiographic images were inadequate to calculate an ejection fraction by Simpson's method, an estimate of whether left ventricular systolic function was reduced or preserved was made. Of these patients with an incalculable LVEF by Simpson's method, 18 patients were estimated to have reduced left ventricular systolic function.

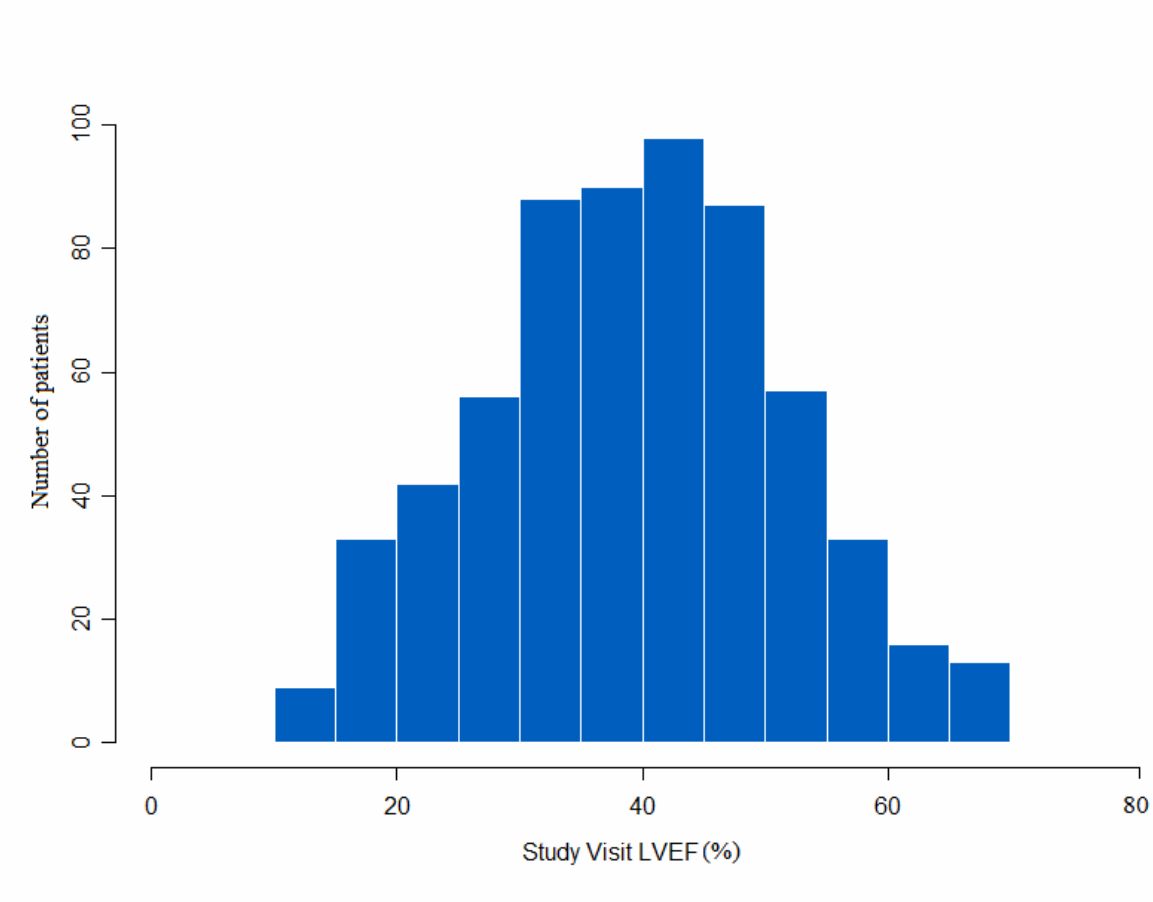


Figure 5-1: Distribution of LVEF at the study visit for 622 patients with calculable EF by Simpson's biplane method

5.2.9 Haematology

Table 5-11 displays the full blood count results for the post-discharge cohort. The mean WBC count was within normal limits, with only 54 patients (8.3%) having a raised count. The mean (SD) haemoglobin was 12.5g/dl (2.0). Almost half of the post-discharge cohort were anaemic, by WHO standards (defined as haemoglobin <12g/dl for females and <13g/dl for males). The mean lymphocyte count for the cohort was within normal limits and 79 patients (12.2%) had a low lymphocyte count (<1 $x10^9$/l). Over half of the cohort had an elevated RDW (defined as RDW ≥ 15%).

Table 5-11: Full blood count profile for the post-discharge cohort at the study visit

Parameter	Mean (SD), median [IQR] or n (%)	Units
Mean WBC count	7.9 (2.4)	$x10^9$/l
Median WBC count	7.6 [6.3-9.3]	$x10^9$/l
WBC count >11	54 (8.3)	-
Mean haemoglobin	12.5 (2.0)	g/dl
Median haemoglobin	12.4 [11.3-13.7]	g/dl
Haemoglobin <13 M; <12 F	318 (49.1)	-
Mean RDW	15.6 (2.5)	%
Median RDW (IQR)	15.0 [14-16.3]	%
RDW ≥ 15	333 (51.4)	-
Mean lymphocytes	1.9 (1.3)	$x10^9$/l
Median lymphocytes	1.8 [1.3-2.3]	$x10^9$/l
Lymphocytes <1	79 (12.2)	-

5.2.10 Biochemistry

All post-discharge patients attending the study visit had the following biochemical blood tests performed; BNP, troponin I, U&E, LFT, TFT, HBA1c, phosphate and urate.

The BNP and troponin I results are displayed in Table 5-12. The distribution of BNP results for the post-discharge cohort is displayed in Figure 5.2. The distribution of BNP was skewed and logarithmic (log) transformation of BNP was performed. The median BNP concentration was 395.5pg/ml [201.8-806.3]. This was considerably lower than the median BNP for the hospitalised cohort (880pg/ml, [394-1811]). As expected, there was a decline in BNP level for most patients from hospitalisation to the study visit. The median fall in BNP was 240.5pg/ml. Only 1 patient attending the study visit had a BNP in excess of the upper limit of the assay (>5000pg/ml), compared to 32 patients in the hospitalised cohort. Less than a quarter of the post-discharge cohort had an elevated troponin I (defined as ≥ 0.04 µg/l). Half of the post-discharge cohort had an elevated troponin I during the hospital admission (Table 4-17, page 169).

Table 5-12: BNP and troponin I results for the post-discharge cohort at the study visit

Parameter	Mean (SD), median [IQR] or n (%)	Units
Mean BNP	671.8 (775.9)	pg/ml
Median BNP	395.5 [201.8-806.3]	pg/ml
BNP >5000	1 (0.2)	pg/ml
Log (BNP)	5.9 (1.1)	-
Mean Δ BNP – hospital to study visit	525.2 (970.1)	pg/ml
Median Δ BNP – hospital to study visit	240.5 [17.8-771.3]	pg/ml
Troponin I ≥ 0.04	116 (17.9)	µg/l

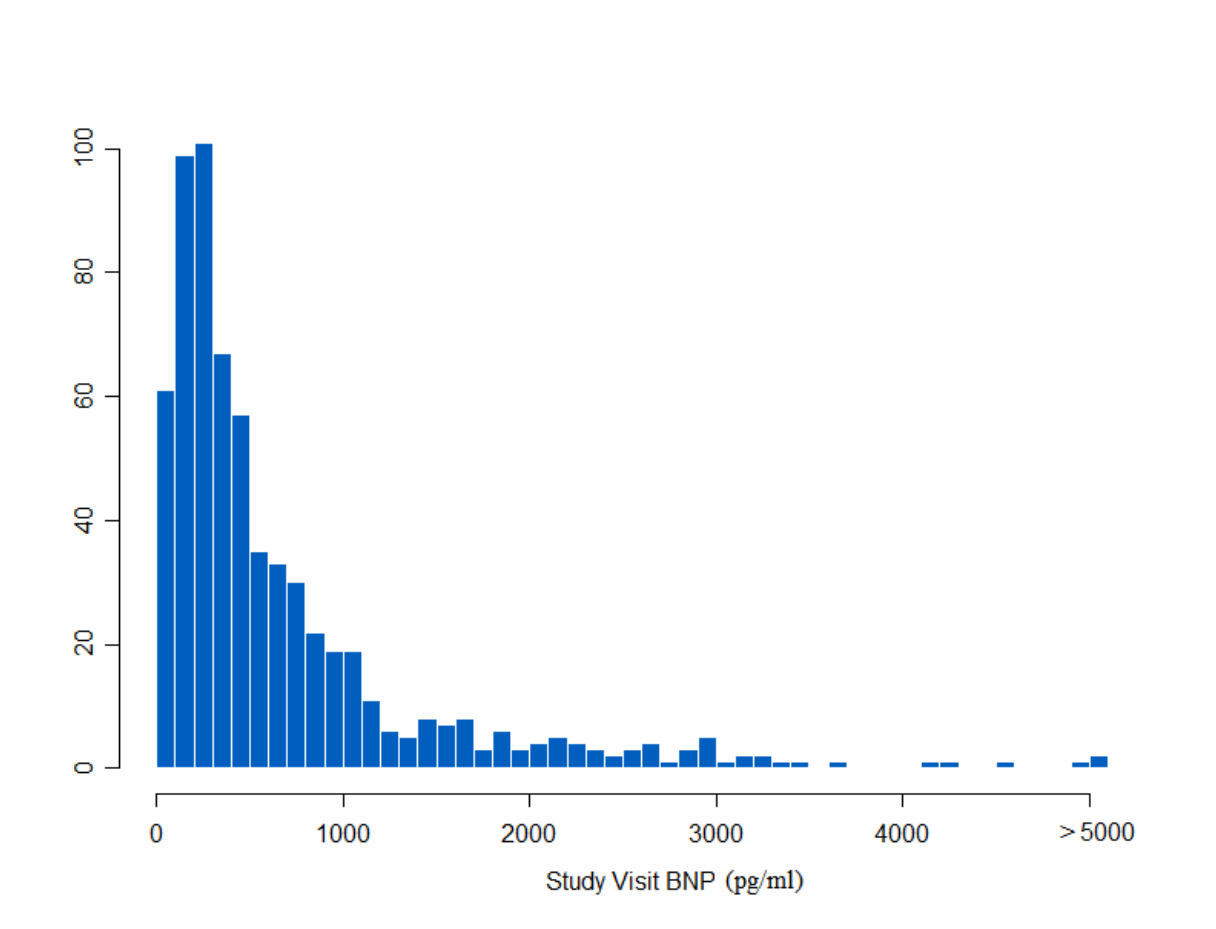


Figure 5.2: Distribution of BNP levels at the study visit

All patients had renal function measured at the study visit (Table 5-13). The mean sodium and potassium levels were within the normal ranges. Only 56 patients (8.6%) were hyponatraemic (defined as sodium <135mmol/l), approximately half the number of patients hyponatraemic during hospitalisation (Table 4-18, page 171). The mean urea concentration was raised at 9.8mmol/l and 390 patients (60.2%) had an elevated urea concentration (defined as urea ≥ 7.5mmol/l), similar to the proportion of this cohort with an elevated urea concentration during hospitalisation. The median creatinine concentration was 108µmol/l. The mean eGFR for the entire cohort was reduced at 56.7 ml/min/1.73m^2. Only 25 patients (3.9%) had a normal eGFR (defined as eGFR ≥ 90 ml/min/1.73m^2), fewer patients than during hospitalisation (Table 4-18, page 171). The distribution of GFR per 30 ml/min/1.73m^2 is shown in Figure 5.3.

Table 5-13: Renal function results for the post-discharge cohort at the study visit.

Parameter	Mean (SD), median [IQR] or n (%)	Units
Mean sodium	139.2 (3.4)	mmol/l
Median sodium	140 [137.8-141.3]	mmol/l
Sodium <135	56 (8.6)	mmol/l
Mean potassium	4.0 (0.5)	mmol/l
Median potassium	4.0 [3.7-4.3]	mmol/l
Mean urea	9.8 (5.1)	mmol/l
Median urea	8.3 [6.3-11.7]	mmol/l
Urea ≥ 7.5	390 (60.2)	mmol/l
Mean creatinine	117.8 (44.0)	µmol/l
Median creatinine	108 [89-132]	µmol/l
Mean eGFR	56.7 (19.3)	ml/min/1.73m^2
Median eGFR	55.4 [42.9-69.5]	ml/min/1.73m^2

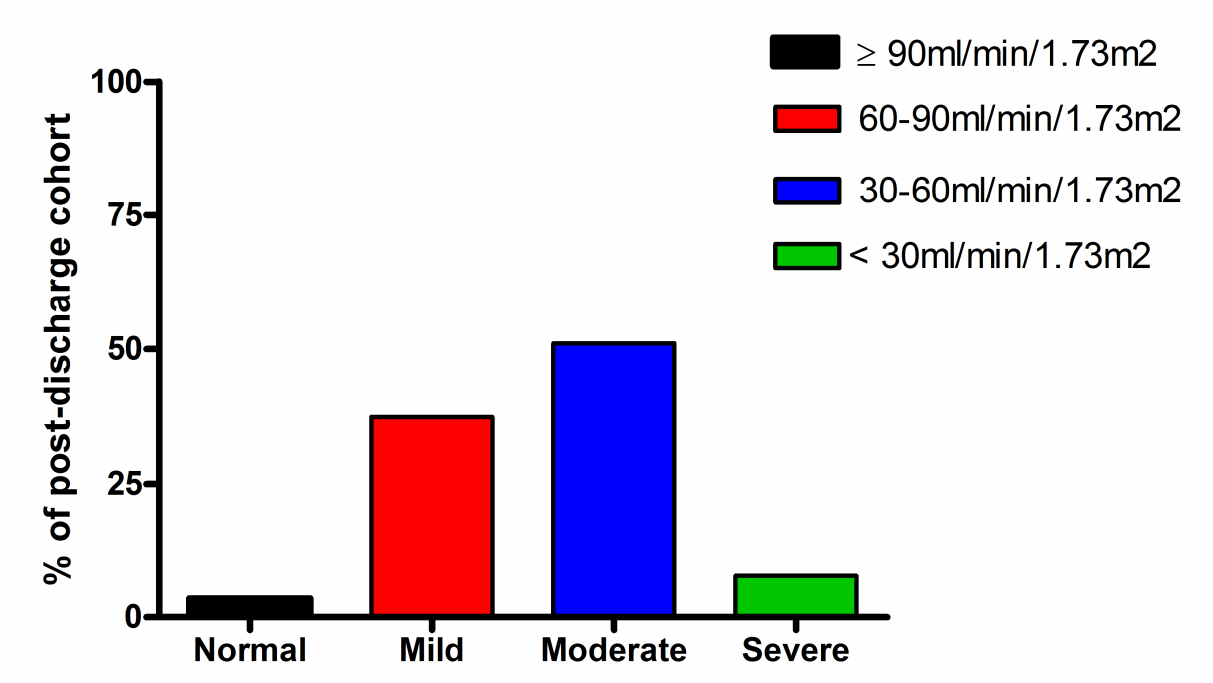


Figure 5.3: Distribution of eGFR for the post-discharge cohort

All patients had LFT measured at the study visit (Table 5-14). The mean bilirubin level was within the normal range. Only 55 patients (8.5%) had an elevated bilirubin (defined as >22 µmol/l). This was half the number of patients, in the post-discharge cohort, with a raised bilirubin in the decompensated state (Table 4-19, page 173). The mean AST, ALT and alkaline phosphatase levels were within the normal ranges. The mean GGT was elevated at 77.9U/l, the upper limit of normal is 55U/l. The mean albumin level was within the normal range at 38.7g/l, higher than the mean for the same patients during hospitalisation (Table 4-19, page 173). Only 86 patients (13.3%) were hypoalbuminaemic (defined as <35g/l), almost a third of the number of patients with this biochemical abnormality during hospital admission (Table 4-19, page 173).

The mean thyroid function, HbA1c, phosphate and urate levels were within the normal reference ranges. These results are displayed in Table 5-15.

Table 5-14: LFT results for the post-discharge cohort at the study visit.

Parameter	Mean (SD), median [IQR] or n (%)	Units
Mean bilirubin	11.6 (7.9)	µmol/l
Median bilirubin	9 [7-13]	µmol/l
Bilirubin ≥ 22	55 (8.5)	U/l
Mean AST	25.8 (41.3)	U/l
Median AST	21 [17-27]	U/l
Mean ALT	23.5 (49.0)	U/l
Median ALT	18 [13-25]	U/l
Mean GGT	77.9 (94.3)	U/l
Median GGT	45 [28-88.3]	U/l
Mean Alk Phos	104.6 (56.6)	U/l
Median Alk Phos	92 [74-118]	U/l
Mean albumin	38.7 (4.0)	g/l
Median albumin	39 [36-41]	g/l
Albumin <35	86 (13.3)	g/l

Table 5-15: Other biochemical tests recorded at study visit for the post-discharge cohort.

Parameter	Mean (SD), median [IQR] or number (%)	Units
Mean TSH	2.3 (3.5)	mU/l
Median TSH	1.6 [0.9-2.4]	mU/l
Mean T4	14.3 (3.0)	pmol/l
Median T4	14.0 [13.0-16.0]	pmol/l
Mean HbA1c	6.3 (1.3)	%
Median HbA1c	5.9 [5.6-6.7]	%
Mean phosphate	1.16 (0.22)	mmol/l
Median phosphate	1.16 [1.01-1.29]	mmol/l
Mean urate	0.47 (0.14)	mmol/l
Median urate	0.46 [0.37-0.55]	mmol/l
Mean cholesterol (total)	4.3 (1.3)	mmol/l
Median cholesterol (total)	4.1 [3.4-4.9]	mmol/l
Mean HDL	1.1 (0.4)	mmol/l
Median HDL	1.1 [0.9-1.4]	mmol/l

5.2.11 Aetiology of heart failure

The primary aetiologies of HF for the post-discharge cohort are displayed in Table 5-16. The primary aetiology for the majority of patients was ischaemic heart disease. Over 40% of the post-discharge cohort had documented evidence of a previously reported MI. More than one-third of patients had angiographic evidence of coronary heart disease (defined as >50% stenosis in at least 1 major epicardial vessel). Almost one-third of patients had an 'unknown' primary aetiology of HF. These patients had no history of a MI or a coronary angiogram performed by the time of the study visit. The non-ischaemic primary causes of HF are also detailed in Table 5-16. A non-ischaemic primary aetiology was only assigned where ischaemia

had been excluded (no previous MI and coronary angiography demonstrating no lesions ≥ 50% in ≥ 1 major epicardial artery). The majority of non-ischaemic causes of HF were valvular heart disease. As outlined in the methods section, valvular heart disease was only considered causative if it was at least moderate in severity. The cardiomyopathies were the cause of HF for a small number of patients, as outlined in Table 5-16. Fewer patients had hypertension and alcohol as the primary reason for their HF. It is likely that more patients had hypertension, alcohol or valvular heart disease as the primary cause of their HF but in the absence of coronary angiography these patients were categorised as 'unknown' primary aetiology and any potential primary causes were recorded as 'contributing aetiologies', as detailed in the following paragraph.

Table 5-16: Primary aetiology of heart failure for the post-discharge cohort

Primary aetiology	Number	% of cohort (n=648)
Ischaemic	**353**	**54.5**
a) Definite previous MI	278	42.9
b) Angiographic evidence (>50% stenosis in ≥ 1 vessel)	224	34.6
Non-ischaemic	**91**	**14.0**
Valvular	39	6.0
Cardiomyopathies	25	3.9
a) Idiopathic dilated cardiomyopathy	16	2.5
b) Hypertrophic cardiomyopathy	4	0.6
c) Peripartum cardiomyopathy	3	0.5
d) Restrictive cardiomyopathy	2	0.3
Hypertension	15	2.3
Alcohol	12	1.9
Unknown (no previous MI or angiography)	**204**	**31.5**

The prevalences of contributing aetiologies are displayed in Table 5-17. Almost two-thirds of the post-discharge cohort had a history of hypertension as a contributing cause of HF. AF was recorded as a potential contributing cause of HF in cases where the arrhythmia was persistent or permanent in duration, this was the case in 44% of the entire cohort. More than one-third had valvular heart disease as a contributing cause of their HF. Many of these were functional MR. The prevalence of diabetes mellitus was high in the post-discharge cohort, affecting almost a third of all patients. Excess alcohol consumption was also a significant contributor, in at least 18% of all patients.

Table 5-17: Contributing aetiologies of heart failure in the post-discharge cohort

Contributing aetiology	Number of patients	Percentage of cohort (n=648)
Hypertension	420	64.8
Valvular heart disease	286	44.1
AF (paroxysmal, persistent or permanent)	319	49.2
Diabetes mellitus	203	31.3
Alcohol (previous or current excess)	119	18.4

5.2.12 Heart failure with reduced versus preserved ejection fraction (HF-REF v HF-PEF)

Overall, the majority of the post-discharge cohort had HF-REF. Less than 20% had HF-PEF, defined as LVEF > 50% (Figure 5-4). The mean (SD) LVEF for patients with HF-REF was 36.0% (9.4) and for patients with HF-PEF was 57.6% (5.1). All of the clinical characteristics of the post-discharge cohort, described in this chapter, were analysed according to LVEF to determine if there were significant differences in the characteristics of the patients with HF-REF compared to those with HF-PEF. All characteristics with a significant difference (defined as a p-value <0.05) are presented in Tables 5-18 and 5-19.

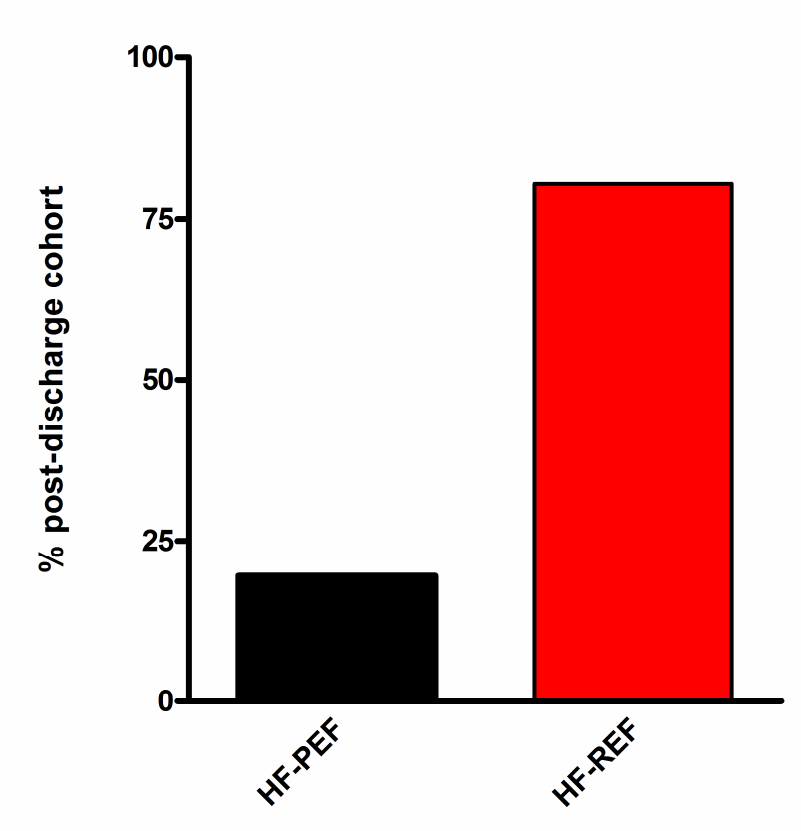


Figure 5.4: HF-PEF versus HF-REF for the post-discharge cohort

Patients with HF-REF were younger (p=0.025), by an average of more than 2 years, and were more often men (p<0.0001) than those with HF-PEF. A diagnosis of HF prior to enrolment into this study was more common amongst those with HF-REF (p=0.00049), although there was no difference in HF symptoms between the two groups. Coronary heart disease was more common amongst those with HF-REF, with proportionately more of these patients having a

history of MI (p=0.00011), angina (p=0.0017), angiographic coronary heart disease (p=0.006), PCI (p=0.023) and CABG (p=0.0007). Hypertension was more common amongst those with HF-PEF (p=0.00054), whilst COPD tended to be more common amongst those with HF-PEF (p=0.06), compared with patients with HF-REF. The prevalences of the other medical comorbidities (outlined in Table 5-3) were similar between the two groups.

The prescribing of diuretics (p=0.0047), ACE inhibitors (p=0.00017), beta-blockers (p=0.0028) and combinations of HF disease-modifying therapies was more common amongst patients with HF-REF (compared with patients with HF-PEF). Calcium channel blockers prescribing were more common amongst patients with HF-PEF. The prescribing of other cardiovascular medications was similar between the two groups.

There were few differences in clinical examination findings between the two groups. Patients with HF-PEF had higher SBP (p=0.006) and greater pulse pressure (p=0.0008), than those with HF-REF. There were no differences in the proportions of patients in sinus rhythm or AF, stratified by reduced or preserved LVEF. Among patients with HF-REF, LBBB was five times more common than in those with HF-PEF (p<0.0001). Median QRS duration was greater for patients with HF-REF (p<0.0001), and proportionately more HF-REF patients (than HF-PEF patients) had a prolonged QRS duration (p<0.0001). Mean QTc interval was longer for patients with HF-REF (p=0.00043) and more HF-REF patients had prolonged QTc intervals (p<0.0001), compared with patients with HF-PEF. The prevalence of radiological pulmonary oedema during hospitalisation did not differ between the two groups.

There were differences in biochemical and haematological findings between the two groups of patients. Patients with HF-REF had higher BNP concentrations during hospitalisation and at the study visit (both p<0.0001), with median values almost twice those of patients with HF-PEF on both occasions. Patients with HF-REF also had higher urea concentrations (p=0.049), more hypoalbuminaemia (0.046) and lower HDL concentrations p=0.0042). Mean haemoglobin concentration was lower amongst patients with HF-PEF (p=0.0019), and consequently anaemia was more prevalent amongst those patients (p<0.0001).

Table 5-18: Demographics, medical history and current medications, stratified by LVEF (significant results only). Data are expressed as number (%) or mean (SD).

Variable	HF-PEF (n=127)	HF-REF (n=521)	Overall (n=648)	p value*
Male	50 (39.4)	327 (62.8)	377 (58.2)	<0.0001
Age	72.7 (9.2)	70.3 (10.9)	70.8 (10.6)	0.025
Previous diagnosis HF	38 (29.9)	245 (47)	283 (43.7)	0.00049
MI	38 (29.9)	255 (48.9)	293 (45.2)	0.00011
History of angina	54 (42.5)	302 (58)	356 (54.9)	0.0017
Angiographic CAD	26/44 (59)	199/262 (76)	225/307 (73)	0.006
PCI	10 (7.9)	82 (15.7)	92 (14.2)	0.023
CABG	9 (7.1)	103 (19.8)	112 (17.3)	0.0007
Hypertension	99 (78)	321 (61.6)	420 (64.8)	0.00054
Diuretics	116 (91.3)	505 (96.9)	621 (95.8)	0.0047
ACE inhibitors	72 (56.7)	384 (73.7)	456 (70.4)	0.00017
Beta-blockers	70 (55.1)	360 (69.1)	430 (66.4)	0.0028
ACE inhibitor or ARB	79 (62.2)	435 (83.5)	514 (79.3)	<0.0001
ACE inhibitor or ARB & Beta-blocker	43 (33.9)	314 (60.3)	357 (55.1)	<0.0001
ACE inhibitor or ARB & Beta-blocker & Aldosterone blocker	4 (3.1)	48 (9.2)	52 (8)	0.038
Calcium channel blockers	37 (29.1)	80 (15.4)	117 (18.1)	0.00029

* Inter-group comparisons using Student's t-test (continuous variables) and χ^2 test (categorical variables), p value <0.05 indicates a significant difference between the two groups.

CAD = coronary artery disease (defined as > 50% stenosis in ≥ 1 major epicardial vessel, denominator is number of patients who had an angiogram)

Table 5-19: Clinical examination, ECG and blood parameters, stratified by LVEF (significant results only). Data are expressed as number (%), mean (SD) or median [IQR].

Variable	HF-PEF (n=127)	HF-REF (n=521)	Overall (n=648)	p value*
SBP	136.1 (22)	129.8 (23.7)	131 (23.5)	0.006
Pulse pressure	69.2 (23.3)	61.7 (22.2)	63.2 (22.6)	0.0008
LBBB	7 (5.5)	135 (25.9)	142 (21.9)	<0.0001
QRS (ms)	92 [86-104]	110 [94-134]	104 [90-126]	<0.0001
QRS duration				
≥ 120	11 (8.7)	195 (37.4)	206 (31.8)	
120-150	8 (6.3)	117 (22.5)	125 (19.3)	<0.0001
> 150	3 (2.4)	78 (15.0)	81 (12.5)	
QTc (ms)	430.2 (32.5)	441.6 (32.8)	439.4 (33.0)	0.00043
QTc ≥ 440	43 (33.9)	279 (53.6)	322 (49.7)	<0.0001
BNP - hospital (pg/ml)	435 [240-952]	918 [407-1866]	788 [366-1582]	<0.0001
BNP - study visit (pg/ml)	237 [129-426]	453 [225-920]	396 [202-806]	<0.0001
Troponin I ≥ 0.04 µg/l	8 (6.3)	97 (18.6)	105 (16.2)	0.0011
Urea (mmol/l)	9 (4.5)	9.9 (5.2)	9.8 (5.1)	0.049
Albumin <35 (g/l)	10 (7.9)	76 (14.6)	86 (13.3)	0.046
HDL (mmol/l)	1.2 (0.4)	1.1 (0.4)	1.1 (0.4)	0.0042
Haemoglobin (g/dl)	12.1 (2)	12.7 (1.9)	12.5 (2)	0.0019
Haemoglobin <13M; <12F	83 (65.4)	235 (45.1)	318 (49.1)	<0.0001

* Inter-group comparisons using Student's t-test (continuous variables) and χ^2 test (categorical variables), p value <0.05 indicates a significant difference between the two groups.

5.3 Discussion

Chapter 5 has described the clinical data obtained from the study visit for the post-discharge cohort. The study visit occurred approximately 4-6 weeks after hospitalisation. The post-discharge cohort comprised 648 patients of the original 1003 patients enrolled during hospitalisation. A significant proportion of the original cohort was deceased by 4-6 weeks, consistent with the high early mortality rate following hospitalisation for HF (147).

The post-discharge cohort was, expectedly, a cohort of patients with stable HF. The majority of these patients were NYHA class II, having been NYHA class III at the time of hospital admission. The majority of patients experienced a reduction in weight from the hospital admission to study visit attendance, consistent with achieving euvolaemic status following their admission with decompensated HF. There was also an expected reduction in the numbers of patients with signs of fluid overload by the time of the study visit. The significance of worsening signs and symptoms of HF following an admission for HF and subsequent rehospitalisation and mortality has recently been recognised (148).

The frequency of diuretic prescribing was high amongst the post-discharge cohort (> 95%), with modest prescribing of HF disease-modifying therapies (70% prescribed an ACE inhibitor; 66% prescribed a beta-blocker).

A large proportion of the post-discharge cohort was in AF at the time of the study visit (37%), consistent with the prevalence of 10-50% reported by clinical studies of AF in LVSD (149) and the recognition of AF as a common finding in patients with heart failure and preserved systolic function (150). Over a quarter of the post-discharge cohort had evidence of bundle branch block on the ECG performed at the study visit. The prevalence of this finding is similar to other chronic HF cohorts containing patients with both reduced and preserved systolic function (151). Many patients had electrocardiographic evidence of LVH, this prevalence is also similar to other chronic HF cohorts containing patients with both reduced and preserved systolic function (152).

The mean LVEF for the post-discharge cohort was 40%, consistent with the mean LVEF reported by other chronic HF cohorts containing patients with both reduced and preserved systolic function (121). Approximately one-fifth of the post-discharge cohort had preserved systolic function, defined as LVEF ≥ 50% (18).

There was an improvement in most of the haematological and biochemical parameters measured in the post-discharge cohort, compared to measurements performed whilst in hospital. There was a significant reduction in BNP levels for the majority of the post-discharge cohort and a sizeable reduction in the proportion of the cohort with an elevated troponin concentration. The prognostic importance of persistent troponin elevation in both chronic HF and during admission for acute decompensated HF has been recently demonstrated (153;154). Fewer patients were hyponatraemic, hyperbilirubinaemic or hypoalbuminaemic, than during the hospital admission. The post-discharge cohort had similar proportions of patients with an elevated urea concentration and reduced eGFR, compared to the hospitalised cohort. Indeed, fewer patients had normal eGFR at the time of the study visit than on admission to hospital. Almost half of the post-discharge cohort was anaemic, similar to the prevalence of anaemia during the hospital admission.

Ischaemic heart disease was the primary aetiology of HF for the majority of the post-discharge cohort, consistent with this being the commonest cause of HF in Western countries. However, almost one-third of patients had an ‘unknown’ primary aetiology of heart failure.

When the clinical data of the post-discharge cohort were analysed according to whether the patients had HF-REF or HF-PEF, the majority of clinical characteristics were similar between the two groups. This is consistent with previous reports that patients with HF-PEF cannot be distinguished from those with HF-REF on the basis of symptoms and signs, CXR or ECG findings (19). However, there were some notable differences between the two groups. Patients with HF-PEF were older, more likely to be female, more likely to have hypertension and less likely to have had a MI, in comparison to those with HF-REF. These findings are consistent with previous studies of HF-PEF (22;24;155). Prescribing of recommended pharmacological treatments for HF was greater amongst patients with HF-REF, an unsurprising result given the

evidence-base for the use of these medications exists only for patients with HF-REF and no treatment is of proven benefit in HF-PEF. Prescribing of calcium channel blockers was more common amongst those with HF-PEF, perhaps reflecting the use of these agents as antihypertensive treatment. Apart from SBP and pulse pressure, there were no differences in clinical examination findings between the two groups. There were also no differences in the proportions in sinus rhythm or AF between the two groups. QRS duration and QTc interval were longer amongst patients with HF-REF. The majority of biochemical and haematological tests performed did not differ according to LVEF. However, the differences in BNP concentrations between the two groups, on admission to hospital and at the study visit, were striking. Patients with HF-REF had median BNP concentrations almost twice that of those with HF-PEF. Previous studies in patients with decompensated HF have demonstrated similar findings (156). Anaemia was more common amongst those with HF-PEF, consistent with previous reports (23).

In summary, many of the symptoms, signs and blood tests of the post-discharge cohort showed an expected improvement compared to data recorded during hospitalisation with decompensated HF. The post-discharge cohort still exhibited many abnormal clinical characteristics, many of which are consistent with prior findings published in chronic HF cohorts, and the majority of patients had HF-REF.

CHAPTER SIX

MICROVOLT T-WAVE ALTERNANS

6.1 Introduction

This chapter will describe the results of MTWA testing in the post-discharge cohort. The eligibility for MTWA testing will be described and the reasons for ineligibility outlined. The potential eligibility in the entire hospitalised cohort will also be outlined. This will demonstrate whether or not the post-discharge cohort was similar, in terms of eligibility for MTWA testing, to that of an unselected cohort of patients with HF. The clinical characteristics of the post-discharge cohort, described in chapter 5, will be stratified by eligibility for MTWA testing. This will determine if there were any significant differences in the clinical characteristics of the patients eligible for MTWA testing compared to those ineligible. The results of MTWA testing and the prevalence of positive, negative and indeterminate results will be described, including an outline of the reasons for an indeterminate test. The functional capacity of the patients will also be displayed including the reasons for terminating exercise, average duration of exercise and metabolic equivalent values (METs). This will allow an evaluation of the practicality of this test in HF patients. For patients unable to exercise, MTWA testing at rest will be described.

6.2 Results

6.2.1 Eligibility

The spectral analysis method of MTWA testing is not suitable for all patients. It is mandatory that patients are in sinus rhythm, and able to perform sub maximal treadmill exercise in order to raise their heart rates to 110 beats per minute. Patients are ineligible for MTWA testing if they are in AF, continuously ventricular pacing (and therefore unable to produce a chronotropic response), or unable to perform sub maximal exercise on a treadmill. The reasons for the latter may be multifactorial and include physical incapabilities as well as medical contraindications, for example severe symptomatic aortic stenosis. Figure 6.1 illustrates the potential eligibility for MTWA testing in the hospitalised cohort. This includes the non-attendees, as well as the post-discharge cohort. For the former, eligibility is based on clinical

data collected during hospitalisation and therefore may not be truly accurate. For example, a patient in AF whilst hospitalised with decompensated HF could have cardioverted to sinus rhythm before the study visit. Furthermore it is impossible to estimate the rhythm for non-attendees with paroxysmal AF. Therefore, the rhythm during the index hospitalisation was used for determining potential eligibility for non-attendees. An accurate assessment of a patient's ability to exercise is also difficult to establish during hospitalisation and is likely to be underrepresented in Figure 1. Thus, Figure 6.1 provides an approximate assessment of eligibility for MTWA testing for the hospitalised cohort. Of 1003 patients enrolled, 549 patients (54.7%) were potentially eligible for MTWA testing. A large proportion was therefore ineligible. The most common reason for this was AF, affecting 364 patients (36.3%). Only 35 patients (3.5%) were in a paced ventricular rhythm and 56 patients (5.6%) were unable to attempt exercise. An inability to attempt exercise included patients who were physically incapable as well as those with medical contraindications, for example severe aortic stenosis.

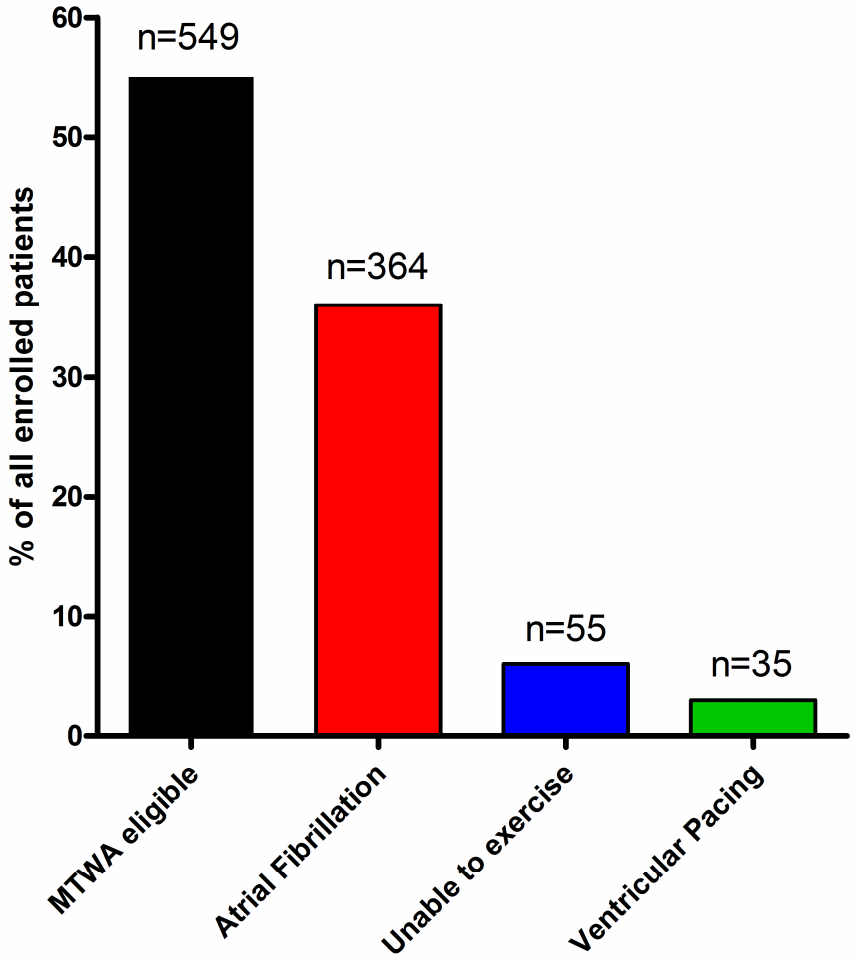


Figure 6.1: Potential eligibility for MTWA testing in the hospitalised cohort

Eligibility for MTWA exercise testing at the study visit is displayed in Figure 6.2. Just over half of the attendees were eligible for MTWA exercise testing (50.9%). The proportion of patients eligible for MTWA testing was similar to the potential eligibility in the hospitalised cohort (50.9% versus 54.7%, respectively). The most common reason for ineligibility was AF, accounting for 242 patients (37.3%) attending the study visit. The remaining patients were ineligible for MTWA testing because of continuous ventricular pacing (5.1%) and inability to exercise (6.6%). The latter included patients who could not satisfactorily exercise on the treadmill as well as patients with a contra-indication to performing exercise, such as severe aortic stenosis. Satisfactory exercise was defined as an ability to walk on the treadmill for at least two minutes. Of all patients taking the MTWA test, 43 patients (6.6%) were unable to exercise, the majority of whom attempted exercise (n=26). Figure 6.3 displays the breakdown of reasons for being unable to exercise for two minutes. The reasons why exercise was not attempted in the remaining 17 patients are displayed in Figure 6.4. MTWA testing was performed at rest in all patients unable to exercise to assess if alternans activity was present at rest. In these cases, only a positive MTWA result could be included in the subsequent analyses – a negative result would not be possible without raising the heart rate to 110 beats per minute and these results could not be classified as indeterminate.

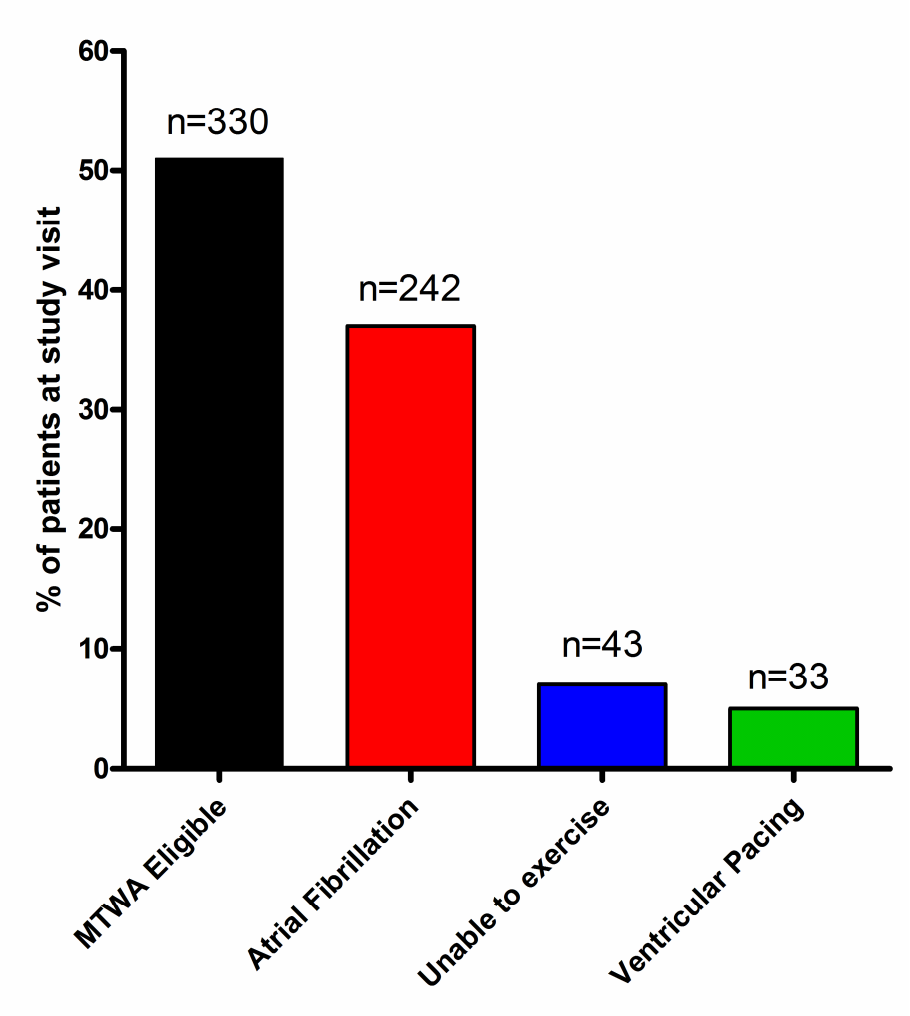


Figure 6.2: Eligibility for MTWA testing in 648 patients attending the study visit

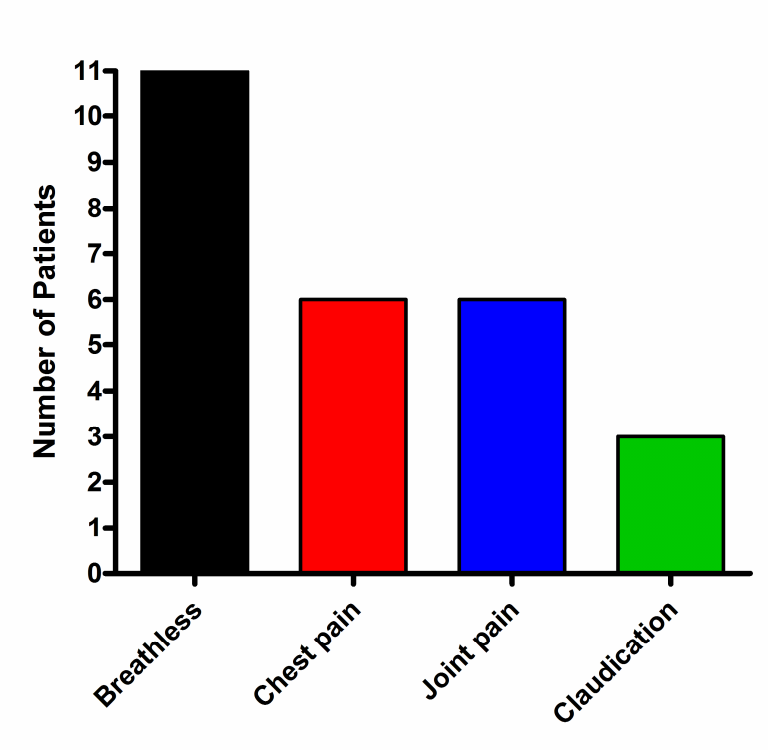


Figure 6.3: Reasons for discontinuing exercise for 26 patients who attempted exercise but were unable to exercise for 2 minutes

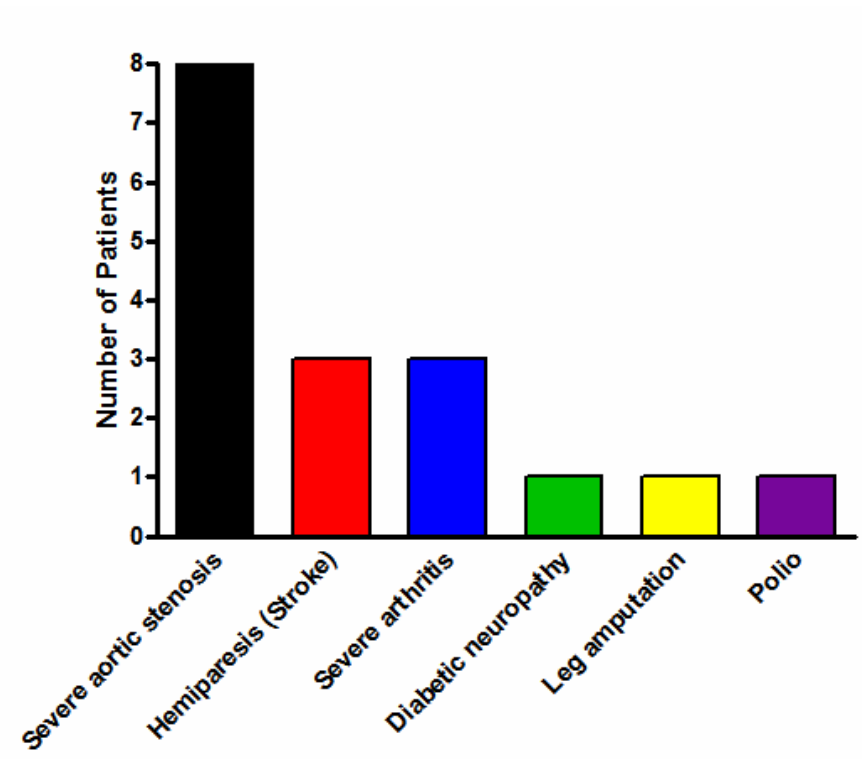


Figure 6.4: Reasons for not attempting exercise in 17 patients

6.2.2 Clinical characteristics stratified by MTWA eligibility

All of the clinical characteristics of the post-discharge cohort, as described in the results section of chapter 5, were analysed according to eligibility for MTWA testing. Details of a previous history of HF, as outlined in section 4.2.3 of chapter 4, and medical history, as outlined in section 4.2.5 of chapter 4, were also included. Only statistically significant differences in clinical characteristics, between those eligible for the MTWA test and those ineligible for MTWA testing, are presented in Tables 6-1 to 6-3. A probability value of $p<0.05$ was considered significant for statistical analyses.

Table 6-1 displays the parameters that differed according to MTWA eligibility for the following characteristics; demographics, history of HF and current HF symptoms. Patients ineligible for MTWA testing were older ($p<0.0001$), by an average of approximately 4 years, and therefore a greater proportion were 75 years of age or older ($p=0.046$). There was no difference in gender between the two groups. A diagnosis of HF prior to the index admission to hospital was more common amongst patients ineligible for MTWA testing ($p=0.00013$). Duration of hospitalisation and readmission to hospital since recruitment were similar in both groups. Patients ineligible for MTWA testing were more symptomatic, in terms of NYHA functional class, with more patients in classes III and IV than those eligible for MTWA testing (0.015). Of the other symptoms of HF described in Section 5.2.3 of Chapter 5, ankle swelling differed between the two groups, a greater proportion of ineligible patients having this symptom at the study visit ($p=0.00022$).

Table 6-1: Demographics, history of heart failure and current heart failure symptoms for the post-discharge cohort, stratified by MTWA eligibility (significant results only). Data are expressed as number (%) or mean (SD).

Parameter	Ineligible (n=318)	Eligible (n=330)	Overall (n=648)	p value*
Demographics				
Male	179 (56.3)	198 (60.0)	377 (58.2)	0.34
Age, years	72.7 (9.5)	68.8 (11.3)	70.8 (10.6)	<0.0001
Age ≥ 75	126 (39.6)	106 (32.1)	232 (35.8)	0.046
History of HF				
Diagnosis of HF pre-hospitalisation	163 (51.3)	120 (36.4)	283 (43.7)	0.00013
Diagnosis HF > 2 yrs	124 / 163 (76.1)	79 / 120 (65.8)	203 / 283 (71.7)	0.059
Current HF symptoms				
NYHA I-II	197 (61.9)	237 (71.8)	434 (67.0)	0.015
III-IV	121 (38.1)	93 (28.2)	214 (33.0)	
Current ankle swelling	112 (35.2)	73 (22.1)	185 (28.5)	0.00022

* Inter-group comparisons using Student's t-test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the groups.

Table 6-2 displays the medical comorbidities and medications that differed according to MTWA eligibility. The prevalence of many cardiovascular conditions differed between the two groups of patients. More patients eligible for MTWA testing had a history of a previously reported MI, compared to ineligible patients (p=0.033). Similarly, more eligible patients had a history of angina (p=0.02). For those who had previously undergone coronary angiography, a greater proportion of eligible patients had evidence of significant coronary artery disease (defined as > 50% stenosis in at least 1 major epicardial vessel) (p=0.012). PCI was also more common amongst eligible patients (p=0.0031).

Predictably, the proportion of patients with either past or present AF differed between the two groups of patients (p<0.0001). Over 90% of those ineligible for MTWA testing had a history of AF. The high prevalence of this arrhythmia is expected as it was the commonest reason for ineligibility in the post-discharge cohort. Almost one fifth of eligible patients had a history of past or paroxysmal AF – none were in AF at the time of the study visit, as this would have rendered them ineligible for MTWA testing. Previous or current valvular heart disease was more common amongst ineligible patients (p<0.0001). Furthermore the prevalence of a valve replacement was also greater amongst those ineligible for MTWA testing, although of borderline statistical significance (p=0.057).

The number of patients with a pacemaker differed between the two groups, 34 (10.7%) of those ineligible compared with 7 eligible patients (2.1%) [p<0.0001]. This is unsurprising as the majority of patients with a pacemaker were continuously ventricular pacing, unable to produce a chronotropic response and thus ineligible for MTWA testing.

The prescribing of HF disease-modifying medications was similar in the two groups. However there were many differences in the prescribing of other cardiovascular medications between the two groups of patients (Table 6-2). Unsurprisingly, there was greater prescribing of both digoxin (p<0.0001) and warfarin (p<0.0001) in the ineligible group, reflective of the higher proportions of AF amongst these patients. There was greater prescribing of both aspirin (p<0.0001) and clopidogrel (p=0.0057) amongst eligible patients, consistent with the higher proportions of MI and PCI amongst this group. The prescribing of anti-arrhythmic therapy was highest amongst eligible patients, possibly reflecting the ability of these medications to maintain sinus rhythm and thus eligibility for MTWA (p=0.0045).

Table 6-2: Medical comorbidity and medications for the post-discharge cohort, stratified by MTWA eligibility (significant results only). Data are number (%).

Parameter	Ineligible (n=318)	Eligible (n=330)	Overall (n=648)	p value*
Medical comorbidity				
MI	123 (38.7)	155 (47.0)	278 (42.9)	0.033
History of angina	160 (50.3)	196 (59.4)	356 (54.9)	0.02
Angiographic CAD	90 / 137 (65.7)	134 / 169 (79.3)	224 / 306 (73.2)	0.012
PCI	32 (10.1)	60 (18.2)	92 (14.2)	0.0031
AF (past or present)	288 (90.6)	84 (25.5)	372 (57.4)	<0.0001
Valvular heart disease	169 (53.1)	117 (35.5)	286 (44.1)	<0.0001
Valve replacement	31 (9.7)	19 (5.8)	50 (7.7)	0.057
Pacemaker	34 (10.7)	7 (2.1)	41 (6.3)	<0.0001
Medications				
Digoxin	140 (44.0)	23 (7.0)	163 (25.2)	<0.0001
Warfarin	192 (60.4)	61 (18.5)	253 (39.0)	<0.0001
Aspirin	129 (40.6)	233 (70.6)	362 (55.9)	<0.0001
Clopidogrel	43 (13.5)	72 (21.8)	115 (17.7)	0.0057
Anti-arrhythmic	9 (2.8)	26 (7.9)	35 (5.4)	0.0045

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the groups.

CAD = coronary artery disease (defined as >50% stenosis in ≥ 1 major epicardial vessel, denominator is number of patients who have undergone angiography)

There was no difference in LVEF according to MTWA eligibility, mean LVEF 39% versus 41% for eligible versus ineligible, respectively (p=0.11). There was also no difference in the proportions of patients with HF-REF compared to HF-PEF according to eligibility for MTWA testing (50.4% and 51.1% eligibility for HF-PEF and HF-REF, respectively [p=0.89]).

There were no differences in routine physiological findings or BMI measurements between the two groups. Table 6-3 displays the clinical examination, ECG and blood parameters that differed according to MTWA eligibility. Peripheral oedema was the only clinical examination sign that differed between the two groups. The presence of ankle (p<0.0001) and knee oedema (p=0.029) was more common amongst patients ineligible for MTWA testing.

ECG parameters that differed between the two groups were sinus rhythm, AF, a paced rhythm and Q waves (p<0.0001 for all four parameters). The greater proportion of eligible patients in sinus rhythm is unsurprising given that this rhythm is mandatory for the spectral method of MTWA testing. AF and paced rhythms were more common amongst ineligible patients, unsurprising as MTWA testing is not possible in either of these conditions. Proportionately more eligible patients had Q waves present on their ECG, consistent with the greater prevalence of a previous MI amongst this group.

There were biochemical and haematological parameters that differed between the two groups of patients (Table 6-3). Log B-type natriuretic peptide (BNP) concentration was higher amongst patients ineligible for MTWA testing (p=0.0045). Eligible patients had a greater decline in median BNP, from hospitalisation to study visit, than ineligible patients (p=0.046). Renal function differed between the two groups of patients. Those ineligible for MTWA testing had proportionately more patients with renal impairment and fewer patients with normal renal function, than eligible patients (p=0.0039). Bilirubin (p<0.0001), alkaline phosphatase (p=0.0098) and GGT (p<0.0001) concentrations were higher amongst patients ineligible for MTWA testing. Higher urate levels were also present amongst ineligible patients (p<0.0001). Haemoglobin concentration was slightly lower amongst those eligible for MTWA (p=0.034), although there was no difference in the prevalence of anaemia between the two groups. Lymphocyte concentration was lower amongst ineligible patients (p=0.02).

Table 6-3: Clinical examination, ECG and blood parameters stratified by MTWA eligibility (significant results). Data are number (%), mean (SD) or median [IQR].

Parameter	Ineligible (n=318)	Eligible (n=330)	Overall (n=648)	p value*
Clinical examination				
Peripheral oedema – ankle	146 (45.9)	92 (27.9)	238 (36.7)	<0.0001
Peripheral oedema – knee	28 (8.8)	15 (4.5)	43 (6.6)	0.029
ECG				
Sinus rhythm	43 (13.5)	328 (99.4)	371 (57.3)	<0.0001
AF	242 (76.1)	0 (0.0)	242 (37.3)	<0.0001
Paced rhythm	33 (10.4)	2 (0.6)	35 (5.4)	<0.0001
Q waves	14 (4.4)	47 (14.2)	61 (9.4)	<0.0001
Blood tests				
Log (BNP)	6.1 (1.0)	5.9 (1.1)	6.0 (1.1)	0.0045
Δ BNP (hosp – study visit) (pg/ml)	208 [12.0-704.0]	301 [32.5-858.5]	240.5 [17.8-771.3]	0.046
eGFR (ml/min/1.73m^2)	54.6 (18.6)	58.7 (19.8)	56.7 (19.3)	0.007
eGFR <30	27 (8.5)	24 (7.3)	51 (7.9)	0.0039
30-60	183 (57.6)	149 (45.1)	332 (51.2)	
60-90	100 (31.4)	140 (42.4)	240 (37.0)	
≥90	8 (2.5)	17 (5.2)	25 (3.9)	
Bilirubin (µmol/l)	13.1 (8.7)	10.1 (6.8)	11.6 (7.9)	<0.0001
GGT (U/l)	57 [32-110]	39 [25-66]	45 [28-88]	<0.0001
Alk Phos (U/l)	94 [75-121]	91 [73-112]	92 [74-118]	0.0098
Urate (mmol/l)	0.49 (0.1)	0.44 (0.1)	0.47 (0.1)	<0.0001
Haemoglobin (g/dl)	12.7 (2.1)	12.4 (1.9)	12.5 (2.0)	0.034
Lymphocytes (x10^9/l)	1.8 (0.8)	2.0 (1.6)	1.9 (1.3)	0.02

* Inter-group comparisons using Student's t-test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the groups.

6.2.3 Automated computer-generated report

A computer generated report is automatically produced following the completion of each MTWA test. An example is shown in Figure 6.5. Each report contains the following; a graph of heart rate trend, artefacts that may be potentially obscuring true alternans (for example ectopic activity or noise), measurement of alternans activity in individual vector and praecordial leads, artefacts that may be potentially creating false alternans and the alternans classification (positive, negative or indeterminate). Each report contains two pages, the first displaying data for the four vector leads (VM, X, Y and Z) and the second displaying data for praecordial leads V1-6.

The heart rate trend contains two lines; an uneven line that corresponds to the instantaneous heart rate, or 'real time' heart rate, and a smooth line that corresponds to the 'epic' heart rate present over time. The instantaneous heart rate provides information about sudden variations in heart rate or the occurrence of ectopic beats. The 'epic' heart rate is the average heart rate in each of the epics and is produced by using an enhanced ECG noise reduction algorithm. Each epic consists of 128 consecutive beats selected for analysis. The beats are aligned and each T wave in the epic is analysed at the same relative point in time. All alternans parameters are measured against the epic, or smoothed, heart rate.

Ectopic beats and noise are the two main artefacts that can obscure the presence of true physiological alternans. If the number of ectopic beats, displayed in the report as 'bad beats', in each epic exceeds the threshold of 15% then the detection of true alternans cannot be performed and the trend will be shaded grey in the corresponding areas. Figure 6.5 shows almost undetectable levels of ectopic beats. The noise trend represents the noise level in the VM vector lead, a measure of overall noise in the system. Like ectopic beats, the presence of excessive noise can prevent the detection of true physiological alternans. If the noise level exceeds the threshold of 1.8 microvolts then the detection of true alternans cannot be performed and the trend will be shaded grey in the corresponding areas. The noise level in Figure 6.5 is <1 microvolt and within acceptable limits.

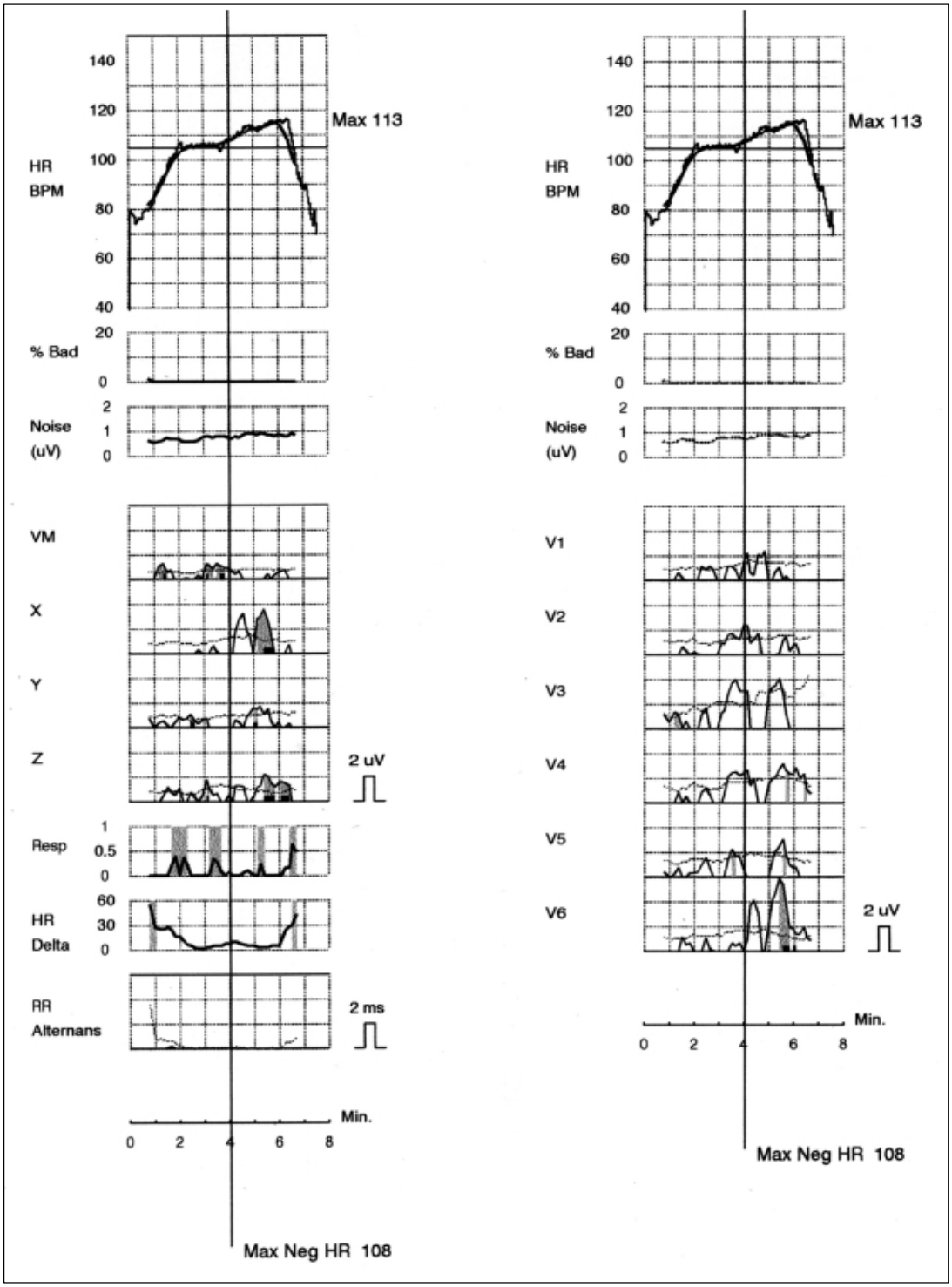


Figure 6.5: Example of a MTWA test report (a negative MTWA test)

Each alternans trend on the report displays alternans voltage, alternans noise and alternans ratio. This information is illustrated in Figure 6.5. For each of the ten leads, the timing of alternans activity is charted along the bottom of the report. Each square on the Y axis represents 2 microvolts of alternans. The solid line outlining the grey shaded areas signifies the alternans voltage and the dotted line represents the alternans noise. The shaded grey area indicates the presence of statistically significant alternans, present for brief periods in leads X, Z and V6 in Figure 6.5. The thicker black horizontal line below the shaded grey areas represents artefact-free periods and signifies intervals where no artefacts are present that could potentially cause alternans.

The main artefacts that can potentially create false alternans are displayed in three rows along the bottom of the first page of the report, below the vector leads. These artefacts are; respiration, heart rate delta and RR alternans. Trends of these artefacts are shaded in grey, highlighting if acceptable levels have been exceeded. Premature ventricular beats can also cause false alternans but these are usually short-lived and would not meet criteria for sustained alternans.

Finally, at the bottom of both pages of the MTWA report is the automated interpretation of whether or not sustained alternans is present and a clinical classification of the alternans result (positive, negative or indeterminate). The report also suggests how a determinate test may be achieved on retesting, if the result is indeterminate. Previous clinical studies have suggested that immediately repeating indeterminate MTWA tests due to noise reduces the rate of indeterminate tests by at least 50% (123).

6.2.4 MTWA Classification

Significant alternans is present when the following criteria are met; the voltage of alternans is equal to or exceeds 1.9 microvolts, alternans activity is present in any of the vector leads or a praecordial lead and an adjacent lead, and the alternans is sustained. The latter occurs when alternans is consistently present above a patient-specific onset heart rate, the duration of alternans is at least one minute and there is a period of artefact-free data. A positive test occurs when sustained alternans occurs at rest or at an onset heart rate $\leq$ 110 bpm. Criteria for a negative test are met when there is no sustained alternans and the maximum negative

heart rate is ≥ 105 bpm. Sustained alternans at an onset heart rate of > 110 bpm but with a maximum negative heart rate > 105 bpm is also classified as a negative result. An indeterminate test is one where the test does not fulfil either positive or negative test criteria, due to physiological (for example insufficient heart rate, ectopic activity or noise) or user reasons (for example poor skin preparation prior to application of the proprietary electrodes). Nonsustained alternans activity would also be classified as an indeterminate result.

An example of a positive MTWA test for a patient in this study is shown in Figure 6.6. This test fulfils the criteria for a positive result. Alternans activity is present at the start of exercise with an onset heart rate of 96 bpm and the voltage of alternans often exceeds the required 1.9 microvolts. When the heart rate drops below 96 bpm, alternans activity is not always present but does always occur above the onset heart rate of 96 bpm. Alternans activity is always present in at least one vector or praecordial lead and adjacent praecordial lead. There are many periods of artefact-free data, represented by the solid black horizontal line below each shaded grey area, and the duration of alternans is greater than one minute. Thus, this MTWA test is positive. Of note, there are few ectopic beats present in this test. Noise levels are often high but do not exceed levels that prevent interpretation of this test.

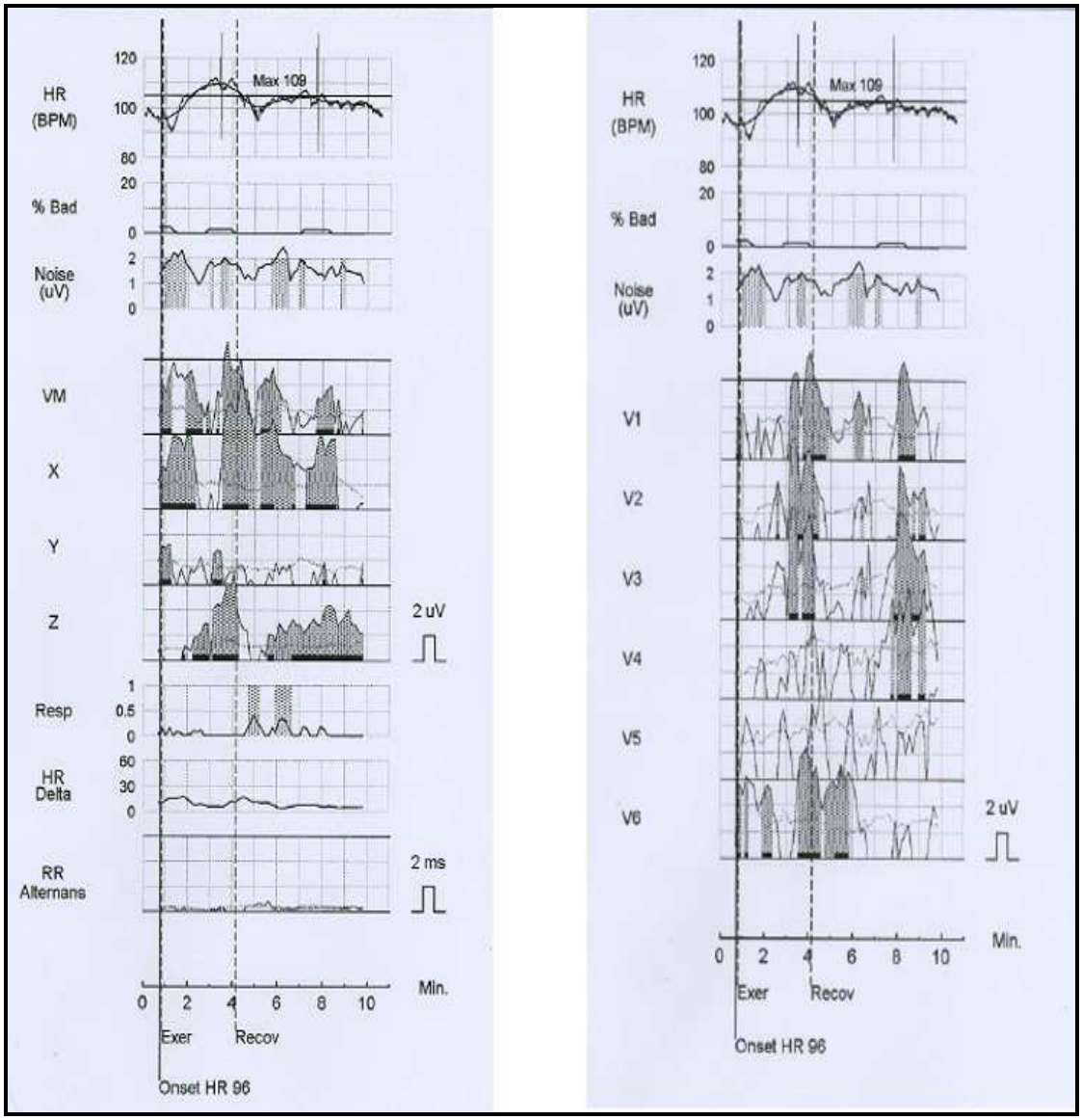


Figure 6.6: The automated MTWA test report for a study patient with a positive MTWA result

An example of a negative MTWA test for a patient in this study is shown in Figure 6.7. There is brief evidence of alternans activity in vector lead X at the start of the test, prior to commencing exercise, but this is not sustained. There is also alternans activity in praecordial lead V6 but not in an adjacent praecordial lead. Furthermore, the alternans activity in lead V6 is not sustained. There is evidence of alternans activity in the vector leads towards the end of the test but this is not significant as alternans is not consistently present above this heart rate. The maximum negative heart rate attained is 112 bpm.

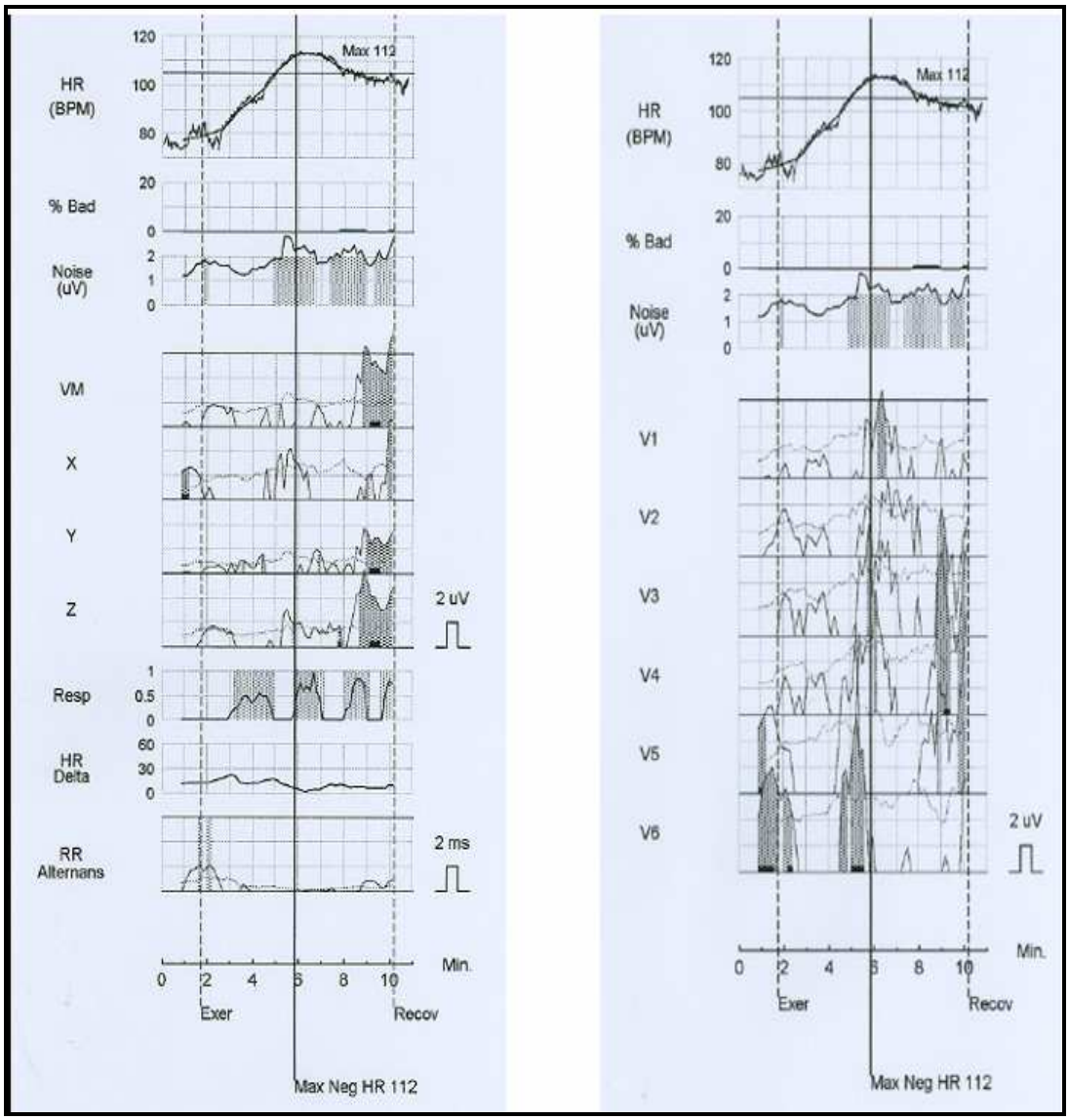


Figure 6.7: The automated MTWA test report for a study patient with a negative MTWA result

6.2.5 Prevalence Study

Of 648 patients attending the post-discharge study visit, 330 (50.9%) had MTWA exercise tests performed. The results are displayed in Figure 6.8. As outlined earlier in this chapter (section 6.2.1), 43 patients were unable to exercise for at least two minutes.

A positive MTWA result occurred in 100 patients (30.3%). Of these patients, 93 had no evidence of alternans activity at rest and sustained alternans occurred during exercise at an onset heart rate <110 bpm. The remaining 7 patients with positive MTWA tests had evidence of sustained alternans present at rest. Only 1 positive result occurred in a patient unable to perform exercise due to physical frailty. The remaining 6 patients with sustained alternans at rest were able to exercise satisfactorily and had sustained alternans present throughout the period of exercise.

A negative MTWA result occurred in 78 patients (23.6%). Of these patients, 75 had no evidence of sustained alternans activity and had a maximum negative heart rate >105 bpm. Only 3 patients had sustained alternans with an onset heart rate >110 bpm but with a maximum negative heart rate >105 bpm.

An indeterminate MTWA result occurred in 152 patients (46.1%). The reasons for an indeterminate result are described later in this section.

When analysed in the contemporary way as non-negative versus negative; 252 (76.4%) of all MTWA exercise tests were non-negative (Figure 6.9).

Of the 43 MTWA tests performed in patients unable to exercise (either unsatisfactory exercise or no exercise at all), only 1 patient had sustained MTWA alternans at rest. The remaining 42 patients had no evidence of sustained alternans at rest, the results of which are not included in the subsequent figures or analyses.

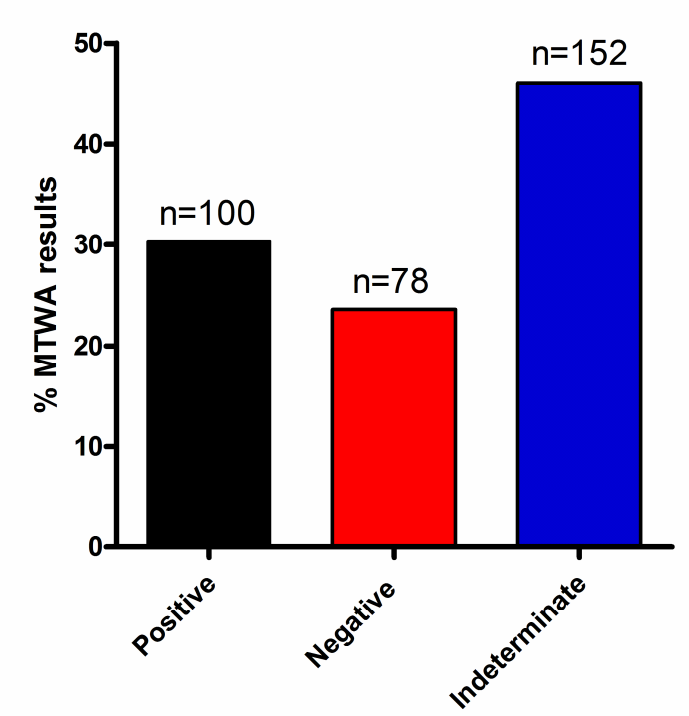


Figure 6.8: MTWA test results for 330 patients of the post-discharge cohort

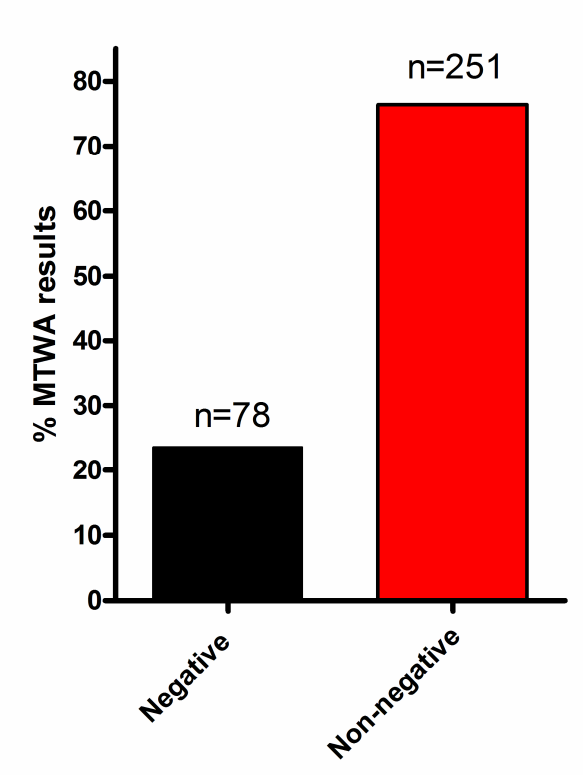


Figure 6.9: MTWA tests for the post-discharge cohort; non-negative versus negative

Almost half of all MTWA exercise test results were indeterminate. The reasons for an indeterminate MTWA test are displayed in Figure 6.10. The majority of these tests were indeterminate because of a failure to achieve the required heart rate of 110bpm (75% of all indeterminate tests). There were two principal reasons patients had an insufficient heart rate. Firstly, some patients had a low resting heart rate, due to being on maximal dose of beta-blocker therapy. These patients were often physically able to exercise for a sufficient period of time, exceeding 10 minutes in many cases, but unable to elevate their heart rate and it was clear that prolonging exercise would not achieve the desired heart rate of 110 bpm (represented as 'chronotropic incompetence' in Figure 6.11). The other reason for an insufficient heart rate was exercise intolerance preventing attainment of a heart rate of 110bpm (represented as 'physical limitations' in Figure 6.11). The remaining MTWA tests were indeterminate due to the presence of one of the following; ectopic activity (16.4%), noise (5.9%), non-sustained alternans (2%) or a rapid rise in heart rate (0.7%).

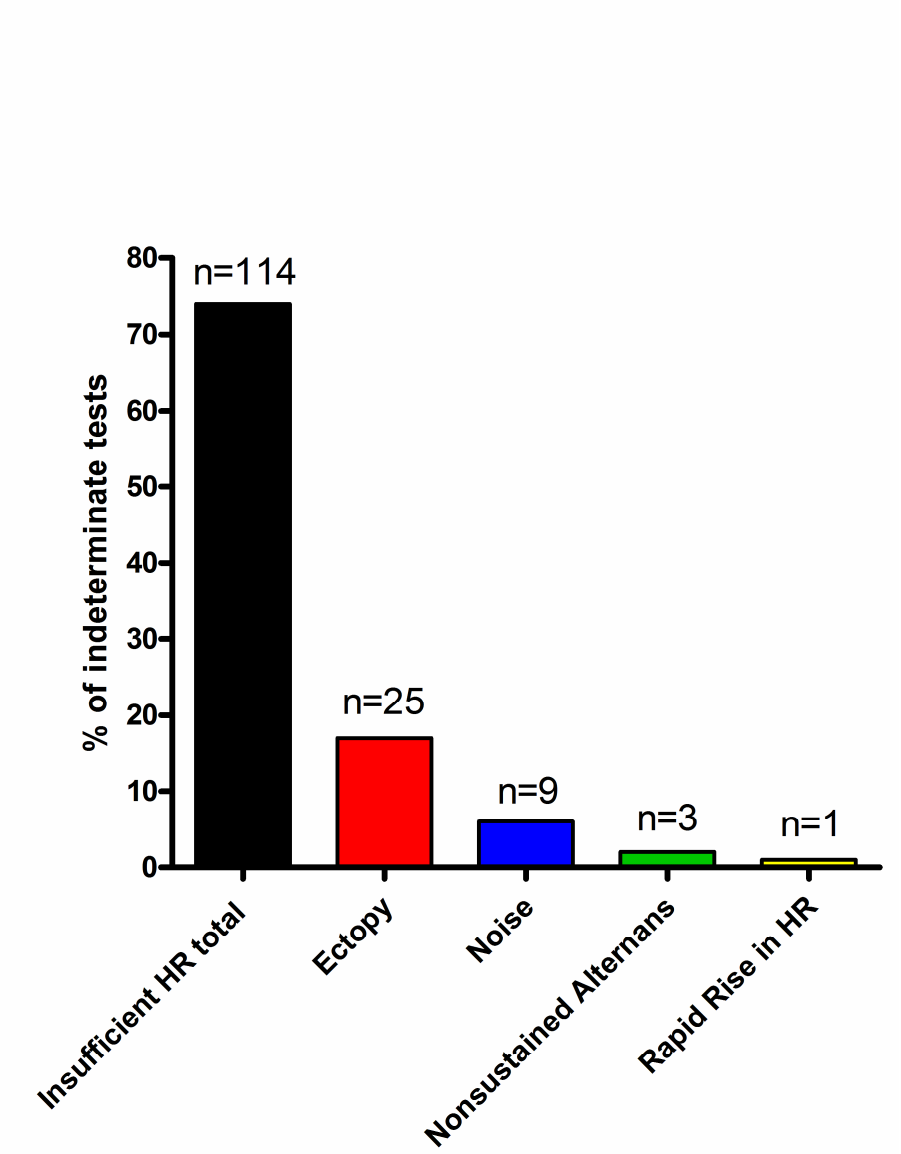


Figure 6.10: Classification of reasons for an indeterminate MTWA test result in the post-discharge cohort.

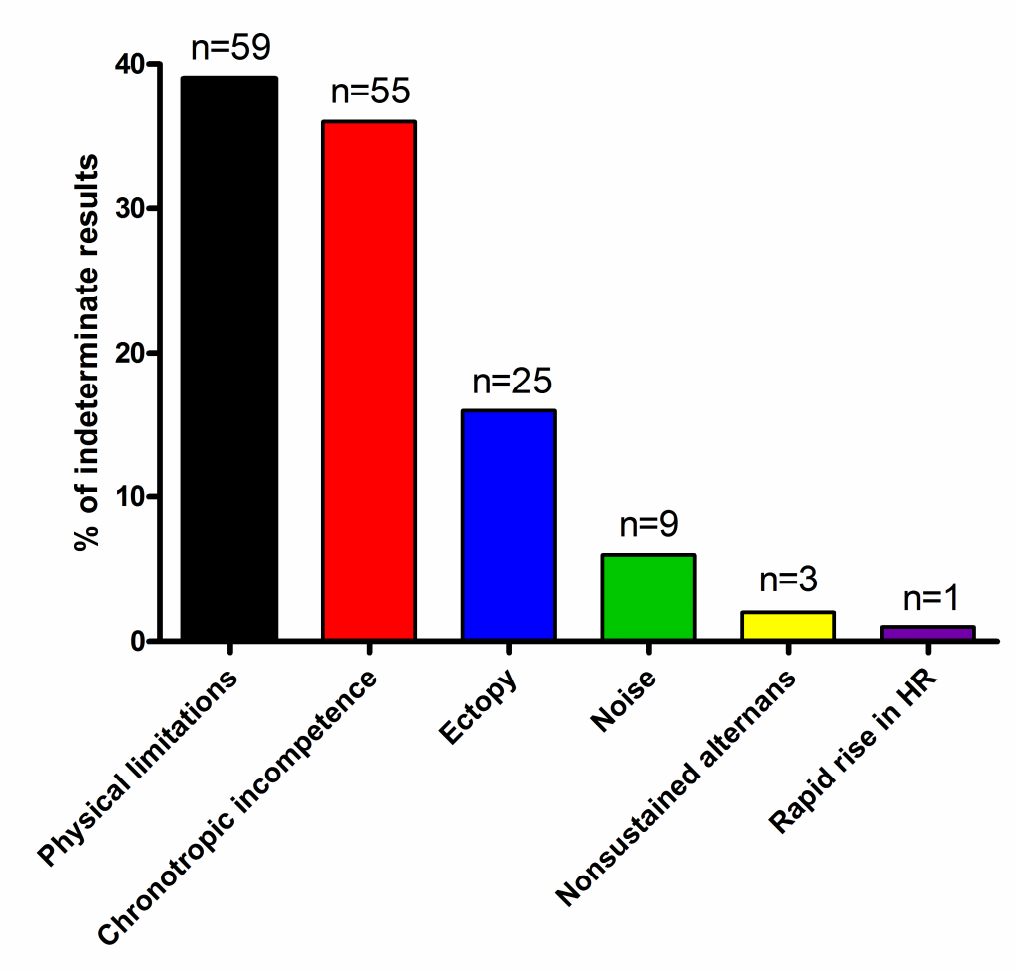


Figure 6.11: Classification of reasons for an indeterminate MTWA test result in the post-discharge cohort; highlighting the two reasons for an insufficient heart rate.

6.2.6 Functional capacity of study cohort

Assessing the cohort's ability to complete the MTWA treadmill test was important for the evaluation of the suitability of this test for a cohort of patients with HF.

Table 6-4 displays details of the exercise performed by those who managed MTWA exercise testing for at least 2 minutes. The mean duration of exercise was 6.7 minutes and patients achieved, on average, almost 70% of their predicted heart rate. The expenditure of energy for each patient was calculated in metabolic equivalents of task (METs). Exercise capacity is often reported in METs. MET capacity is the body's ability to expend energy compared to what it expends at rest. One MET is equivalent to the body's metabolism at rest. MET capacity is used as a prognostic indicator in patients with coronary artery disease, an exercise capacity of at least 10 METs being associated with a good prognosis. The mean METs for the patients who performed MTWA exercise testing in this study was 2.5.

There were several reasons why patients discontinued exercise (Table 6-4). The most common reason was achievement of a peak heart rate. This encompassed patients who reached the target heart rate for completing the MTWA test (110 bpm) and also those who attained a maximum heart rate (below 110 bpm) that failed to rise with further exercise. The latter consisted largely of patients on maximal dose beta-blockers who were unable to elevate their heart rate to 110 bpm despite prolonged exercise with increases in both the speed and gradient of the treadmill machine. However, the majority of patients discontinued exercise because of various physical limitations (Table 6-4).

Table 6-4: Exercise parameters and reasons for terminating exercise for 330 patients

Exercise parameter	Mean (SD) or n (%)
Duration of exercise (mins)	6.7 (3.9)
% predicted heart rate	69.5 (10.8)
Max exercise (METS)	2.5 (1.2)
Reason exercise stopped	
Peak HR achieved	138 (41.8)
Fatigue	85 (25.8)
Breathless	55 (16.7)
Joint / muscle pain	34 (10.3)
Claudication	13 (3.9)
Pre-syncope	3 (0.9)
Chest pain	2 (0.6)

6.2.7 Optimal heart failure therapy

An assessment of whether or not patients were prescribed optimal HF therapy was made for all patients undergoing a MTWA test (Figure 6.12). Optimal therapy for patients with reduced left ventricular systolic function was defined as being prescribed the target dose of at least two HF disease modifying agents, including a beta-blocker. The target dose was the dosage used in the pivotal HF clinical trials. A past history of intolerance to specific HF medications or being prescribed a sub-optimal dose, because of intolerance to higher doses, was also classed as optimal medical therapy. In many cases it was unclear whether patients were not prescribed optimal HF therapy because of previous intolerance or because of failure to prescribe – these cases were recorded as 'unknown'. Overall, 138 patients (41.8%) completing MTWA exercise testing were prescribed optimal HF therapy. The prescribing was sub-optimal in 93 patients (28.2%), and in 99 patients (30.8%) it was unknown whether or not they were being optimally managed. Patients with indeterminate MTWA test results were more likely to be on optimal medical therapy, than the other two groups ($p<0.0001$). The corollary of this was also true; those with indeterminate MTWA tests were less likely to be prescribed sub-optimal HF therapies than the other two groups. The difference between the three groups in the proportions of patients with unknown optimal HF therapy regimes was less striking.

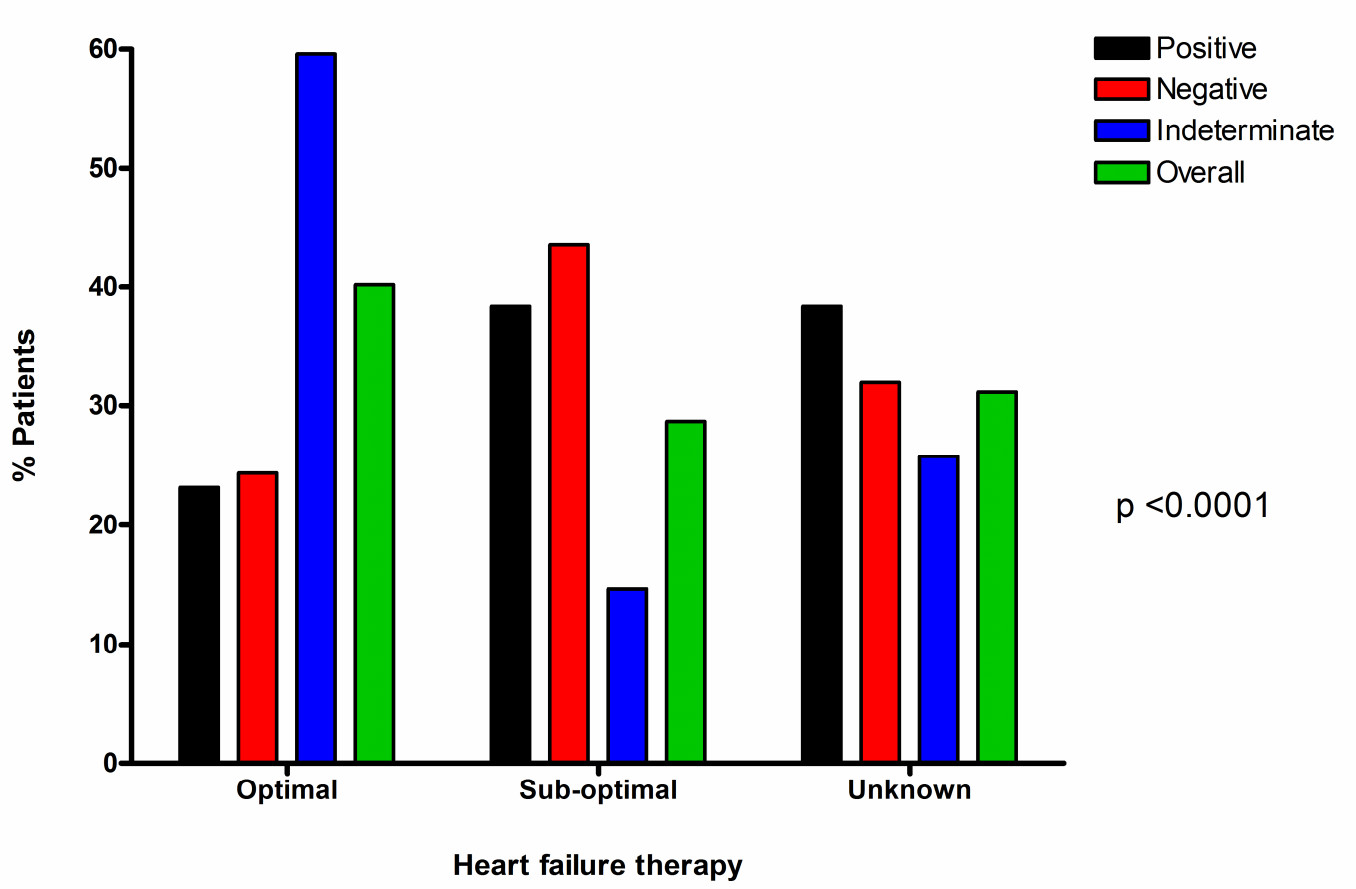


Figure 6.12: Rate of prescribing of optimal heart rate therapy for patients undergoing MTWA exercise tests*

* Inter-group comparisons using χ^2 test, p value < 0.0001 indicates a significant difference between the groups.

6.2.8 Adjudication of MTWA test results

All automated computer-generated MTWA test results were interpreted by a single clinician (Dr Rachel Myles) experienced in reviewing MTWA reports. The clinician was blinded to both the patient details and the automated computer-generated result. Of 373 MTWA tests (330 on exercise and 43 at rest), 358 automated results matched the interpreted results (96%). For the 15 cases where a discrepancy existed between the clinician's interpretation and the computer-generated result, the clinician's analysis was used for the results. All 15 discrepancies were from exercise MTWA tests. Of the 43 MTWA tests at rest, one test was reported positive by both the clinician and the computer. The remaining 42 tests at rest were reported as 'MTWA not present at rest' by both reporting modes.

6.2.9 Comparison with other MTWA clinical studies

The results of MTWA exercise testing for this study were compared to the major LVSD and HF MTWA clinical studies that have been performed to date. Two comparisons were performed; firstly the proportions of positive, negative and indeterminate results, (Figure 6.13), and then the proportion of non-negative to negative results (Figure 6.14). In both figures, my study is referred to as 'Glasgow MTWA'.

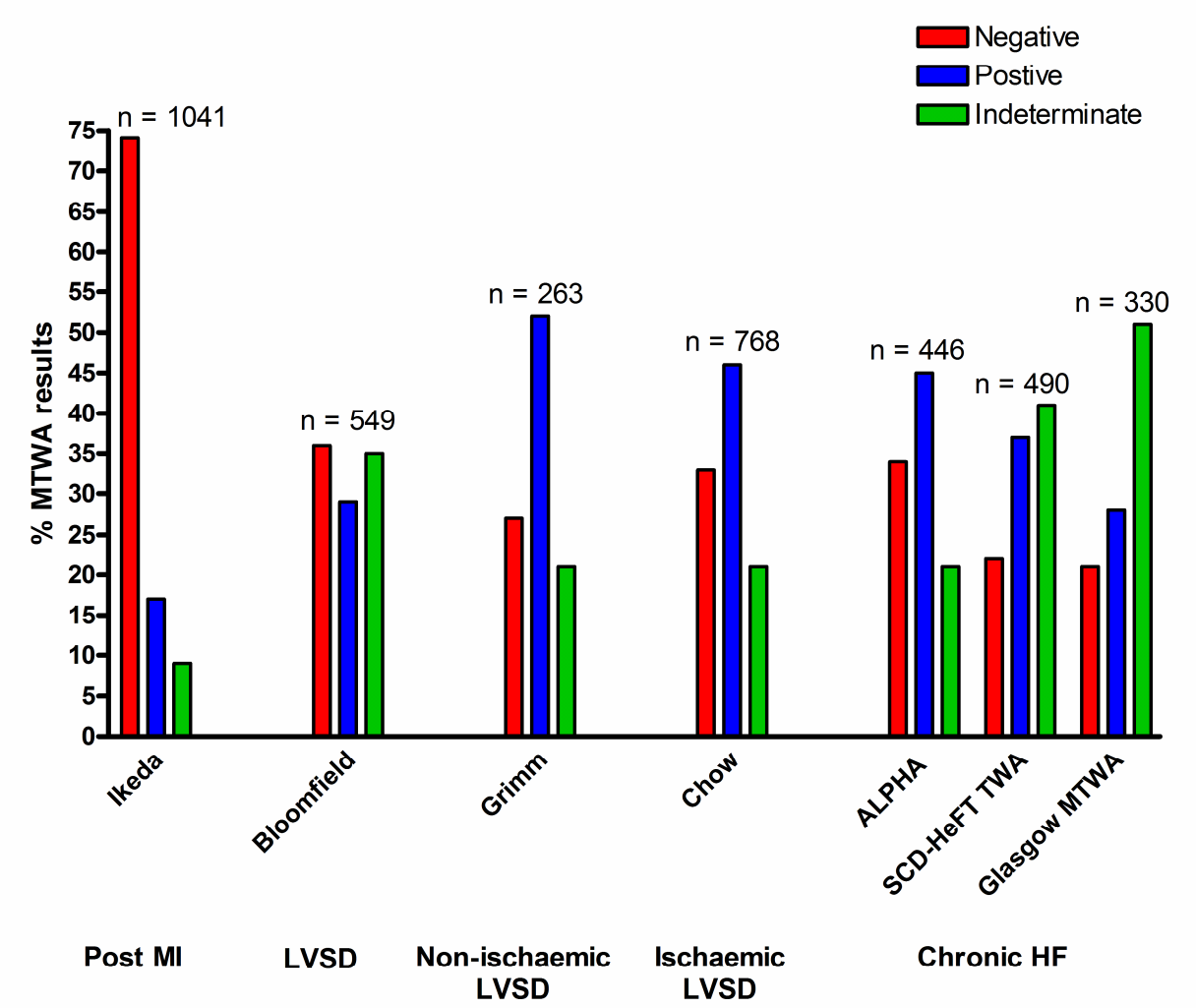


Figure 6.13: Comparison of Glasgow MTWA study to other major clinical MTWA studies to date (102;107;109;113;118;119) – positive, negative and indeterminate results

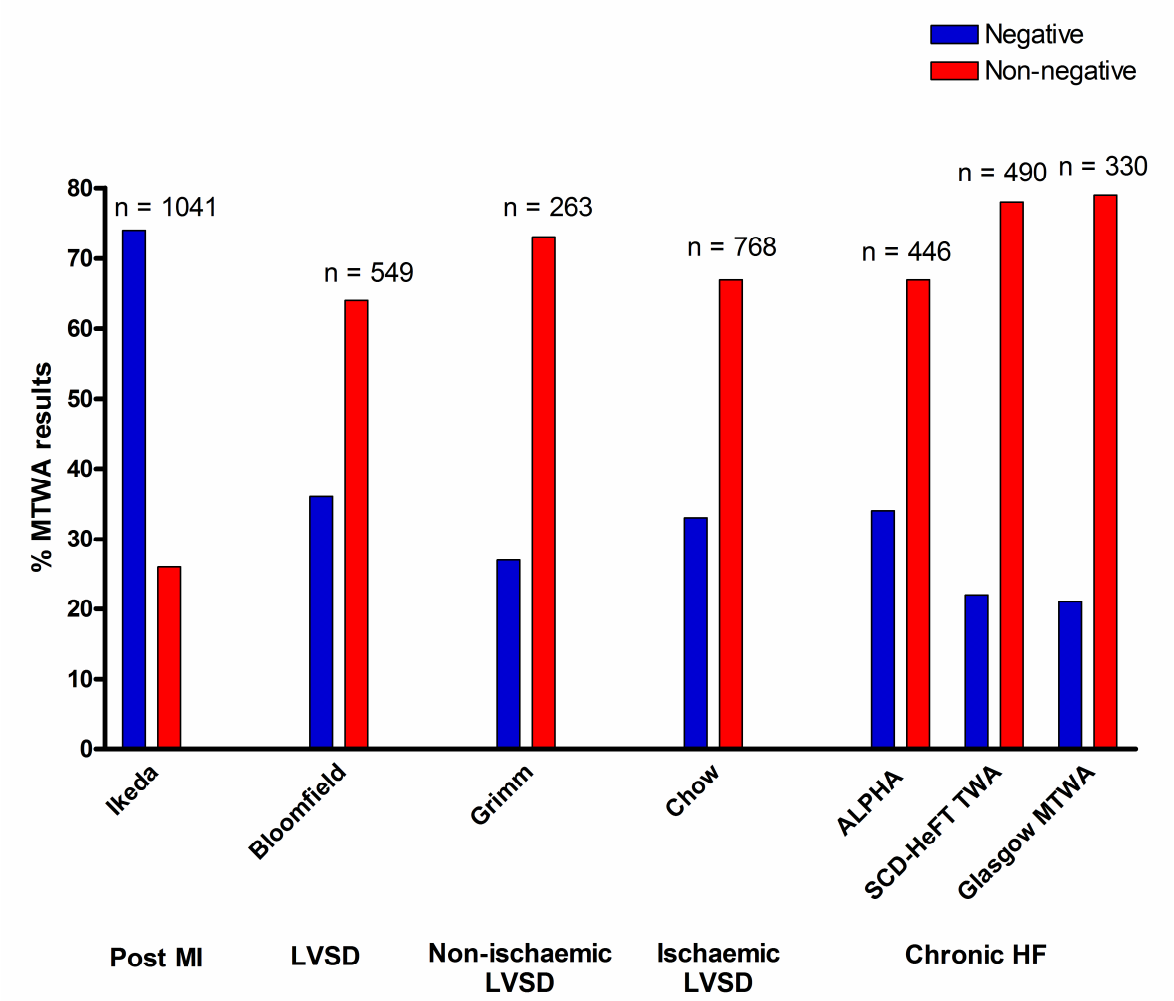


Figure 6.14: Comparison of Glasgow MTWA study to other major clinical MTWA studies to date (102;107;109;113;118;119) – non-negative and negative results

6.3 Discussion

Chapter 6 has described the practical application of the MTWA exercise test in an unselected cohort of patients with HF. Eligibility of the post-discharge cohort was similar to the potential eligibility of the hospitalised cohort.

A significant number of patients were ineligible for MTWA testing. This is the first observational prospective study to describe the reasons for ineligibility in a 'real-life' HF population. The majority of patients were ineligible due to permanent AF. A small proportion

were ineligible due to pacemaker dependency, this may be greater in a well treated cohort with a higher percentage of CRT implantation. A significant number of patients were physically unable to perform this sub maximal treadmill test. The clinical value of any test is limited if nearly half of the patients are ineligible for the test.

Many of the characteristics of the ineligible patients in my study suggested they had a poor prognosis, including the highest log (BNP) concentration. BNP is also an independent predictor of sudden cardiac death (53), suggesting that the patients at the highest arrhythmic risk may in fact not be eligible for MTWA testing. These findings suggest the utility of the MTWA test as a means of detecting those at highest risk of sudden death is likely to be limited as many such patients are ineligible for the test. Patients ineligible for MTWA testing were older than patients eligible for testing and a higher proportion had a history of pre-admission HF. Ineligible patients also had more evidence of persisting or advanced HF, with a higher proportion having NYHA functional class III or IV symptoms and a greater frequency of peripheral oedema. Those ineligible for MTWA testing also had a greater prevalence of renal dysfunction, liver enzyme abnormalities, hyperuricaemia and lymphopenia. There was, however, no difference in LVEF according to MTWA eligibility and the use of HF medication was similar between the groups.

An indeterminate MTWA test was the most common result in this study with a positive MTWA test was found in only 30% and a negative test in 24%. The majority of indeterminate tests were because of failure to elevate the heart rate to 110 bpm. This was due to chronotropic incompetence or physical limitations, with similar proportions of each. The majority of chronotropic incompetence was secondary to beta-blocker therapy. Many other clinical MTWA studies have discontinued beta-blockers prior to MTWA testing in order to achieve determinate results. However a primary aim of this study was to evaluate the use of MTWA on optimal HF therapy, including beta-blockers. This was to determine both the prevalence of an abnormal MTWA result on beta-blocker therapy and assess the prognostic value of this test for patients on optimal HF therapy. Other reasons for an indeterminate MTWA test were outlined. This is the first prospective study to characterise the types of indeterminate result, particularly detailing the two types of insufficient heart rate, and highlight how common a result this is in an unselected HF population on optimal HF therapy.

The functional capacity of the cohort was poor. There was no significant difference in the duration of exercise or energy expended during exercise (measured in METS), between the three groups. The majority of patients discontinued the MTWA test because of physical limitations, with only 42% achieving the target heart rate of 110bpm required for completion of the MTWA test. This is perhaps unsurprising as many of the patients were elderly with multiple comorbidities. However this does question the general usefulness of this test in 'real-life' HF patients.

The automated computer-generated results were highly accurate when adjudicated against the blinded clinician interpretation. The automated result matched the clinician's interpretations in over 95% of cases. This is the first study to present results of the accuracy of the automated report.

The prevalences of positive, negative and indeterminate results in my study were different to other clinical MTWA studies. One of the major differences was the number of indeterminate results (Figure 6.13). The other studies had proportionately fewer indeterminate results than my study. The reasons for this are likely multifactorial and may be explained by many of the limitations of the current studies to date, addressed in section 1.3 of chapter 1. One of these is patient selection. My study was performed in an unselected cohort of patients with recent decompensated HF. This cohort had a higher mean age with extensive medical comorbidity and a significant proportion of physically frail patients, compared to the other MTWA studies.

My study shared some similar and contrasting results to the other MTWA HF studies. The ALPHA study (118) had proportionately more negative and positive results and fewer indeterminate results than my study. These differences may be explained by the types of cohorts studied. The ALPHA study was performed exclusively in non-ischaemic heart failure patients with reduced left ventricular systolic function, defined as ejection fraction $\leq 40\%$, and the mean age was only 59 years. On the other hand, the SCD-HeFT MTWA study (119) exhibited a similar pattern of the three test results to the Glasgow MTWA study, an indeterminate result being most common followed by positive then negative. The proportions

of negative results in the two studies were similar whereas the SCD-HeFT MTWA study had proportionately more positive results and fewer indeterminate results than the Glasgow MTWA study. One possible explanation for the similarities between these two studies may be inclusion of both ischaemic and non-ischaemic aetiologies of heart failure. Moreover, both studies contained similar proportions of beta-blocker prescribing (74% in the SCD-HeFT MTWA study and 64% in the Glasgow MTWA study), although the SCD-HeFT MTWA study withheld these medications for at least 24 hours prior to MTWA testing.

Analysis of the Glasgow MTWA study results in the contemporary way of non-negative and negative yielded similar proportions to the majority of other clinical studies (Figure 6.14). In most studies a non-negative MTWA result was prevalent in at least two-thirds of the cohort. The exception to this was the study performed by Ikeda *et al* (102) in which over two-thirds of the cohort had a negative MTWA result. This study was performed in a cohort of post myocardial infarction patients. The high proportion of negative MTWA results may be explained by all patients having preserved left ventricular systolic function, as well as few patients being prescribed beta-blocker therapy.

In summary, almost half of all patients in the post-discharge cohort were ineligible for MTWA testing. Of the original 1003 patients enrolled in this study, only 330 underwent MTWA exercise testing. Of the 330 patients who were eligible, many were unable to complete the test due to chronotropic incompetence, secondary to beta blocker therapy, or physical limitations. These issues show that MTWA treadmill testing is not widely applicable to an unselected, real-life HF population. Finally, the most common result was an indeterminate one, the clinical associates of which will be explored in the Chapter 7.

CHAPTER SEVEN

CLINICAL ASSOCIATES OF MICROVOLT T-WAVE ALTERNANS

7.1 Introduction

This chapter will describe the clinical characteristics of the post-discharge cohort stratified by MTWA result. The clinical characteristics discussed in chapter 5 will be analysed to determine if any of these characteristics differ between the three groups of patients according to their MTWA results (positive, negative and indeterminate). Analyses will also be performed to determine if any differences exist when the MTWA groups are classified as negative and non-negative. A probability value of $p<0.05$ will be considered significant for statistical analyses. The characteristics that differ between the three groups of MTWA results will then be analysed separately, in three pairs, using logistic regression analyses. These pairs will comprise; positive versus negative, positive versus indeterminate and negative versus indeterminate. A probability value of $p<0.1$ in the former analyses will be used for selecting variables for inclusion in the logistic regression. These analyses will reveal the main associates of each MTWA result.

7.2 Results 1: Differences in clinical characteristics according to MTWA result

7.2.1 Demographics

Table 7-1 displays the demographics of the post-discharge cohort, stratified by MTWA result. The overall results for all patients completing the MTWA test are also displayed. Patients with a negative MTWA result were younger than those with a positive or indeterminate result ($p=0.00013$). Patients with an indeterminate result were older than those with a positive result. There was no difference between the three groups in the proportion of patients with a history of chronic HF prior to enrolment into the MTWA study. Few patients who underwent MTWA exercise testing were readmitted to hospital with decompensated HF following recruitment. Readmission rates were similar in all three groups.

Table 7-1: Demographics stratified by MTWA result. Data are expressed as number (%) or mean (SD).

Parameter	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Male sex	65	44	89	198	0.45
	(65)	(56.4)	(58.6)	(60)	
Mean age, years	68.1	64.9	71.4	68.8	0.00013
	(12.5)	(12.0)	(9.3)	(11.3)	
Age ≥ 75 years	36	17	53	106	0.081
	(36)	(21.8)	(34.9)	(32.1)	
Diagnosed HF before enrolment into study	31	25	64	120	0.13
	(31)	(32.1)	(42.1)	(36.4)	
Re-admission since recruitment	3	4	14	21	0.12
	(3)	(5.1)	(9.2)	(6.4)	

* Inter-group comparisons using ANOVA F-test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the groups.

7.2.2 Symptoms of heart failure

Table 7-2 shows the HF symptoms stratified by MTWA result. The majority of patients who underwent MTWA exercise testing experienced an overall improvement in their HF symptoms since discharge from hospital. There was no difference between the three groups in the number of patients who experienced deterioration in their overall symptom status. This was also reflected in the proportions of patients in each of the four NYHA classes. There were no differences between the three groups in the proportions of patients in each NYHA category. Of the five principal symptoms recorded at the study visit (Table 7-2), only palpitations differed between the groups ($p=0.021$). Fewer patients with an indeterminate MTWA result experienced palpitations compared with those with positive and negative results.

Table 7-2: Current heart failure symptoms stratified by MTWA result. Data are expressed as number (%).

Symptom	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Deterioration in HF symptoms since discharge	10 (10)	5 (6.4)	17 (11.2)	32 (9.7)	0.51
NYHA Class I	3 (3)	7 (9.0)	6 (3.9)	16 (4.9)	
II	66 (66)	56 (71.8)	99 (65.1)	221 (66.9)	0.24
III	31 (31)	15 (19.2)	46 (30.3)	92 (27.9)	
IV	0 (0)	0 (0)	1 (0.7)	1 (0.3)	
Paroxysmal nocturnal dyspnoea	13 (13)	13 (16.7)	16 (10.5)	42 (12.7)	0.41
Orthopnoea	27 (27)	12 (15.4)	38 (25)	77 (23.3)	0.15
Ankle swelling	23 (23)	13 (16.7)	37 (24.3)	73 (22.1)	0.4
Palpitations	29 (29)	22 (28.2)	24 (15.8)	75 (22.7)	0.021
Wheeze	18 (18)	21 (26.9)	33 (21.7)	72 (21.8)	0.36

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the groups.

7.2.3 Common medical comorbidity

The common medical comorbidities, stratified by MTWA result, are shown in Table 7-3. The prevalences of most comorbidities were similar in all three groups. The exceptions to this were MI and AF.

Patients with an indeterminate or positive MTWA result were more likely to have had a previous MI than those with a negative test, those in the indeterminate group having the highest prevalence of this condition (p=0.016). The prevalences of angina, PCI and CABG were also lowest amongst those with a negative result, although these were not statistically significant.

Sinus rhythm is mandatory for the spectral method of MTWA exercise testing used in this study. Thus all patients who underwent MTWA testing were in sinus rhythm at the time of the study visit. A history of AF for these patients meant either past AF, paroxysmal AF or permanent AF at the time of enrolment into the study. All patients with permanent AF during hospitalisation, and subsequently eligible for MTWA testing, would have spontaneously cardioverted to sinus rhythm by the study visit. A history of AF was more common amongst those with an indeterminate result than the other two groups (p=0.015).

Anaemia was more common amongst patients with an indeterminate result than the other two groups, although this difference only showed a trend towards being statistically significant (p=0.08).

The prevalences of hypertension, cerebrovascular disease, diabetes mellitus, cancer, peripheral arterial disease and osteoarthritis were all greatest amongst patients with an indeterminate MTWA result, although the differences were not statistically significant. COPD was more common amongst patients with a negative result, although the difference between the three groups was not statistically significant.

Table 7-3: Common medical comorbidities stratified by MTWA result. Data are expressed as number (%).

Condition	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
MI	50 (50)	29 (37.2)	87 (57.2)	166 (50.3)	0.016
History of angina	62 (62)	39 (50)	95 (62.5)	196 (59.4)	0.15
PCI	18 (18)	11 (14.1)	31 (20.4)	60 (18.2)	0.5
CABG	19 (19)	10 (12.8)	25 (16.4)	54 (16.4)	0.53
Hypertension	62 (62)	44 (56.4)	102 (67.1)	208 (63.0)	0.27
TIA/CVA	15 (15)	14 (17.9)	39 (25.7)	68 (20.6)	0.099
History of AF	14 (14)	16 (20.5)	54 (35.5)	84 (25.5)	0.015
Prosthetic heart valve	7 (7)	4 (5.1)	8 (5.3)	19 (5.8)	0.81
Pacemaker	4 (4)	1 (1.3)	2 (1.3)	7 (2.1)	0.48
Prior arrhythmia	4 (4)	7 (9.0)	11 (7.2)	22 (6.7)	0.39
Diabetes mellitus	26 (26)	21 (26.9)	56 (36.8)	103 (31.2)	0.12
Anaemia	39 (39)	30 (38.5)	78 (51.3)	147 (44.5)	0.08

Condition	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Depression	19 (19)	21 (26.9)	33 (21.7)	73 (22.1)	0.44
History of cancer	9 (9)	10 (12.8)	23 (15.1)	42 (12.7)	0.31
COPD	24 (24)	27 (34.6)	44 (28.9)	95 (28.8)	0.3
PAD	16 (16)	11 (14.1)	32 (21.1)	59 (17.9)	0.36
Osteoarthritis	18 (18)	15 (19.2)	38 (25)	71 (21.5)	0.36

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the groups.

PAD = peripheral arterial disease

7.2.4 Medications

The prescribing of HF medications, stratified by MTWA result, is shown in Table 7-4. Optimal therapy for patients with HF-REF was as previously defined in Chapter 6 (section 6.2.7). Patients with an indeterminate MTWA test were most likely to be prescribed optimal therapy, with more than double the proportion of patients on optimal therapy than either the positive or negative groups ($p<0.0001$).

Consequently there were significant differences between the three groups in the proportions of patients prescribed beta-blocker therapy ($p<0.0001$). As expected, the pattern was similar to optimal therapy prescribing, those with an indeterminate MTWA test having the highest prescribing of beta-blocker therapy - almost 80%. Significantly fewer patients with a positive MTWA test were prescribed beta-blockers with the lowest prescribing amongst those with a negative test. The proportion of patients prescribed diuretics showed a trend towards greater prevalence amongst those with a positive or indeterminate MTWA result, although the difference was not statistically significant ($p=0.059$). The proportion of patients prescribed ACE inhibitors showed a trend towards greater prevalence amongst those with a positive MTWA result ($p=0.066$). The prescribing of ARBs, aldosterone antagonists and digoxin was similar in all three groups.

The frequencies of prescribing of common cardiovascular medications, stratified by MTWA result, are shown in Table 7-5. The only significant difference between the three groups was the prescribing of statin therapy ($p=0.029$). Three-quarters of all patients who underwent MTWA exercise testing were taking statins. Statins were used most commonly in patients with an indeterminate MTWA result; over 80% were prescribed this therapy. This finding is consistent with a greater prevalence of coronary heart disease amongst this group of patients. Statin prescribing was similar in the positive and negative groups. The frequencies of prescribing of common non-cardiovascular medications, stratified by MTWA result, are shown in Table 7-6. The prescribing of bronchial inhalers was highest amongst the negative group, consistent with a greater prevalence of COPD in this group, although not a statistically significant difference. The proportions of patients prescribed other non-cardiovascular medications were similar in all three groups.

Table 7-4: Frequency of heart failure medication prescribing stratified by MTWA result. Data are expressed as number (%).

Heart failure medication	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Optimal therapy	23 (23)	19 (24.4)	89 (58.6)	131 (39.7)	<0.0001
Diuretics	97 (97)	71 (91.0)	148 (97.4)	316 (95.8)	0.059
ACE inhibitor	80 (80)	52 (66.7)	103 (67.8)	235 (71.2)	0.066
Beta-blocker	56 (56)	39 (50)	118 (77.6)	213 (64.5)	<0.0001
ARB	7 (7)	13 (16.7)	21 (13.8)	41 (12.4)	0.12
Aldosterone blocker	16 (16)	10 (12.8)	19 (12.5)	45 (13.6)	0.71
Digoxin	7 (7)	3 (3.8)	13 (8.6)	23 (7.0)	0.41

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the groups.

Table 7-5: Frequency of cardiovascular medication prescribing stratified by MTWA result. Data are expressed as number (%).

Cardiovascular medication	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Statin	69 (69)	55 (70.5)	125 (82.2)	249 (75.5)	0.029
Aspirin	70 (70)	55 (70.5)	108 (71.1)	233 (70.6)	0.98
Clopidogrel	24 (24)	13 (16.7)	35 (23.0)	72 (21.8)	0.44
Aspirin or clopidogrel	75 (75)	56 (71.8)	120 (78.9)	251 (76.1)	0.4
Warfarin	16 (16)	17 (21.8)	28 (18.4)	61 (18.5)	0.61
Calcium channel blocker	15 (15)	15 (19.2)	30 (19.7)	60 (18.2)	0.61
Anti-arrhythmic	5 (5)	4 (5.1)	17 (11.2)	26 (7.9)	0.12
Long-acting nitrates	14 (14)	10 (12.8)	30 (19.7)	54 (16.4)	0.3
Nicorandil	17 (17)	9 (11.5)	27 (17.8)	53 (16.1)	0.45
Oral hypoglycaemic agents	19 (19)	14 (17.9)	35 (23.0)	68 (20.6)	0.45
Insulin	10 (10)	5 (6.4)	18 (11.8)	33 (10.0)	0.43

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the groups.

Table 7-6: Frequency of prescribing of common non-cardiovascular medications stratified by MTWA result. Data are expressed as number (%).

Non-cardiovascular medication	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Bronchial inhalers	22 (22)	27 (34.6)	40 (26.3)	89 (27)	0.17
Antidepressants	11 (11)	9 (11.5)	23 (15.1)	43 (13)	0.57
Vitamins (B1 & B complex)	11 (11)	10 (12.8)	16 (10.5)	37 (11.2)	0.87
NSAIDs	0 (0)	5 (6.4)	0 (0)	5 (1.5)	NA
Antihistamines	3 (3)	3 (3.8)	8 (5.3)	14 (4.2)	0.67
Incontinence meds	0 (0)	0 (0)	6 (3.9)	6 (1.8)	NA

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the groups.

7.2.5 Clinical examination

7.2.5.1 Routine physiological measurements

Table 7-7 displays the routine physiological findings stratified by MTWA result. Patients with an indeterminate result were more likely to have a lower resting heart rate, consistent with the higher rate of beta-blocker prescribing ($p<0.0001$). Those with a negative result had the highest resting heart rates. Patients with an indeterminate result were also more likely to have lower diastolic blood pressure than patients in the other two groups ($p<0.0001$). Those with a negative result had highest diastolic blood pressure. Although there was no difference in systolic blood pressure between the three groups, there was a difference in pulse pressure. Patients with a negative MTWA result were more likely to have a normal pulse pressure whilst those with a positive or indeterminate MTWA result were more likely to have an elevated pulse pressure (defined as greater than 60mmHg) [$p=0.016$]. Temperature and respiratory rate at rest were similar in all three groups.

7.2.5.2 Body mass index measurements

The BMI measurements stratified by MTWA result are shown in Table 7-8. These measurements were similar in all three MTWA groups.

7.2.5.3 Cardiovascular examination signs

Table 7-9 shows the frequencies of cardiovascular examination signs, focusing on signs of HF, stratified by MTWA result. The number of patients with clinical signs of HF was much less than during hospitalisation. There were no differences between the three groups in the prevalences of any of these signs.

Table 7-7: Physiological findings stratified by MTWA result. Data are expressed as mean (SD) or number (%).

Variable	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Heart rate (bpm)	80 (13.2)	84 (11.8)	72 (13.5)	77 (14)	<0.0001
SBP (mmHg)	133 (25.3)	129 (21.5)	131 (23.2)	131 (23.5)	0.56
DBP (mmHg)	68 (12.6)	72 (10.9)	64 (12.5)	67 (12.5)	<0.0001
Pulse pressure (mmHg)	65 (25.1)	57 (19.3)	67 (21.8)	64 (22.5)	0.016
Temperature (°C)	36.2 (0.6)	36.2 (0.5)	36.2 (0.6)	36.2 (0.6)	0.64
Respiratory rate (breaths per minute)	19 (3.8)	19 (3.6)	19 (3.4)	19 (3.6)	0.2

* Inter-group comparisons using ANOVA F-test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the groups.

Table 7-8: BMI measurements stratified by MTWA result. Data are expressed as mean (SD) or number (%).

Measurement	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Mean height (cm)	165 (9.4)	163 (10.3)	163 (10.3)	164 (10.0)	0.31
Mean weight (kg)	76.3 (19)	76.1 (19.4)	77.1 (19.6)	76.6 (19.3)	0.92
Mean BMI (kg/m^2)	27.9 (6.0)	28.3 (6.1)	28.9 (6.8)	28.5 (6.4)	0.46
Mean BMI class					
< 18.5 (underweight)	4 (4)	1 (1.3)	4 (2.6)	9 (2.7)	0.79
18.5 – 24.9 (normal weight)	27 (27)	25 (32.1)	44 (28.9)	96 (29.1)	
25 – 30 (overweight)	37 (37)	26 (33.3)	46 (30.3)	109 (33.0)	
> 30 (obese)	32 (32)	26 (33.3)	58 (38.2)	116 (35.2)	

* Inter-group comparisons using ANOVA F-test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the groups.

Table 7-9: Cardiovascular examination findings stratified by MTWA result. Data are expressed as number (%).

Clinical sign	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Third heart sound	2 (2)	1 (1.3)	1 (0.7)	4 (1.2)	0.63
Pulmonary crackles					
None	72 (72)	59 (75.6)	116 (76.3)	247 (74.9)	0.79
Basal	27 (27)	19 (24.4)	34 (22.4)	80 (24.2)	
Mid-zones	1 (1)	0 (0)	2 (1.3)	3 (0.9)	
Pleural effusion (s)	1 (1)	0 (0)	4 (2.6)	5 (1.5)	NA
Peripheral oedema – ankle	28 (28)	21 (26.9)	43 (28.3)	92 (27.9)	0.98
Peripheral oedema – knee	4 (4)	4 (5.1)	7 (4.6)	15 (4.5)	0.94
Peripheral oedema – thigh	0 (0)	0 (0)	2 (1.3)	2 (0.6)	0.31
Ascites	0 (0)	1 (1.3)	1 (0.7)	2 (0.6)	0.55

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the groups.

7.2.6 Electrocardiography

The frequencies of resting electrocardiograph (ECG) findings, stratified by MTWA result, are shown in Table 7-10. The proportion of patients with LVH showed a trend towards greater prevalence amongst those with a positive result (p=0.07). Patients with an indeterminate result were more likely to have a longer QTc interval than patients in the other two groups (p=0.0035). Patients with a negative result were more likely to have shorter QTc intervals than patients with a positive result. There were no differences between the three MTWA groups in the prevalence of other recorded ECG parameters.

7.2.7 Exercise parameters

The frequencies of exercise parameters recorded during the MTWA test, stratified by MTWA result, are shown in Table 7-11. Patients with positive and negative MTWA results were more likely to achieve higher predicted heart rates than those with indeterminate results (p<0.0001). Maximum ST depression was recorded during the MTWA test. Those with a positive result were more likely to have deeper ST depression than the other two groups (p=0.02). Those with an indeterminate result had the least ST depression. These findings are consistent with the trend for the percentage predicted heart rate for the three groups.

There was no difference between the three groups in the duration of exercise, although patients with an indeterminate result had the shortest time. Maximum exercise expended was similar in all three groups.

Table 7-10: Electrocardiographic parameters stratified by MTWA result. Data are expressed as number (%), mean (SD) or median [IQR].

ECG	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
RBBB	9 (9)	4 (5.1)	5 (3.3)	18 (5.5)	0.19
LBBB	21 (21)	20 (25.6)	27 (17.8)	68 (20.6)	
Pathological Q waves	15 (15)	9 (11.5)	23 (15.1)	47 (14.2)	0.74
LVH	23 (23)	9 (11.5)	21 (13.8)	53 (16.1)	0.07
Ischaemic ST depression	5 (5)	2 (2.6)	3 (2.0)	10 (3.0)	0.38
Median QRS (ms)	104 [91.5-134.5]	100 [88-129.5]	102 [92-120]	102 [90-125.5]	0.52
QRS duration (ms) <120	68 (68)	52 (66.7)	112 (73.7)	232 (70.3)	
120-150	16 (16)	18 (23.1)	30 (19.7)	64 (19.4)	0.15
≥ 150	16 (16)	8 (10.2)	10 (6.6)	34 (10.3)	
Mean QTc (ms)	437 (27.6)	432 (29.6)	446 (36.3)	440 (32.8)	0.0035
QTc ≥ 440	46 (46)	32 (41)	86 (56.6)	164 (49.7)	0.056

* Inter-group comparisons using ANOVA F-test (continuous variables) and $\chi 2$ test (categorical variables), p value < 0.05 indicates a significant difference between the groups.

Table 7-11: Exercise parameters stratified by MTWA result. Data are expressed as mean (SD) or median [IQR].

Exercise Parameter	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Duration of exercise (mins)	6.0 [3.5-9.9]	7.1 [4.0-9.0]	5.8 [3.8-8.1]	6.0 [3.8-8.7]	0.43
Max ST depression (mm)	0.66 (0.67)	0.63 (0.42)	0.47 (0.41)	0.57 (0.51)	0.02
% predicted HR	74.9 (8.3)	74.8 (6.6)	63.1 (10.7)	69.5 (10.8)	<0.0001
Max exercise (METS)	2.5 (1.3)	2.6 (1.4)	2.4 (1.0)	2.5 (1.2)	0.56

* Inter-group comparisons using ANOVA F-test (continuous variables), p value < 0.05 indicates a significant difference between the groups.

7.2.8 Ejection fraction by echocardiography

The mean left ventricular ejection fractions (LVEF) for the three groups of patients are illustrated in Figure 7.1. Patients with a positive test were more likely to have a lower LVEF than patients in the other two groups (p=0.022). The mean LVEF for patients with a positive result was 36.6%. Those with indeterminate and negative results had similar mean LVEF, 40.8% and 40.4%, respectively.

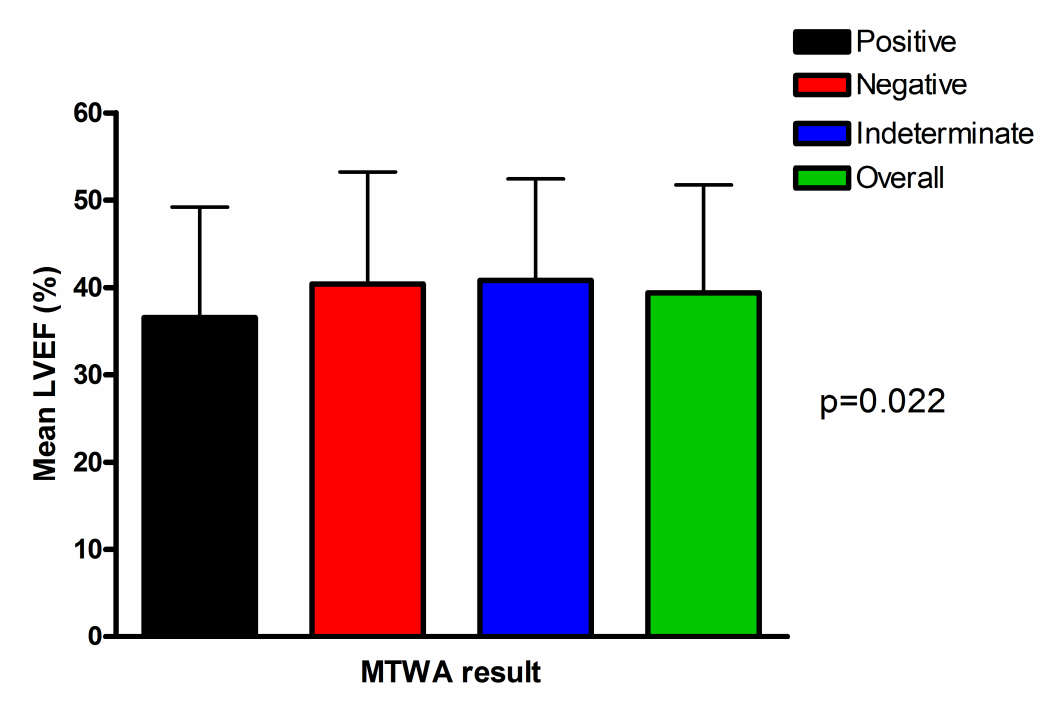


Figure 7.1: LVEF stratified by MTWA result. Data are expressed as mean (SD)*

* Inter-group comparison using ANOVA F test, p value <0.05 indicates a significant difference between the groups.

7.2.9 Heart failure with reduced versus preserved ejection fraction

The proportions of patients with HF-REF and HF-PEF, stratified by MTWA results are shown in Figure 7.3. Patients with HF-REF had proportionately more patients with a positive MTWA result, and similar proportions of patients with negative and indeterminate results, compared to patients with HF-PEF.

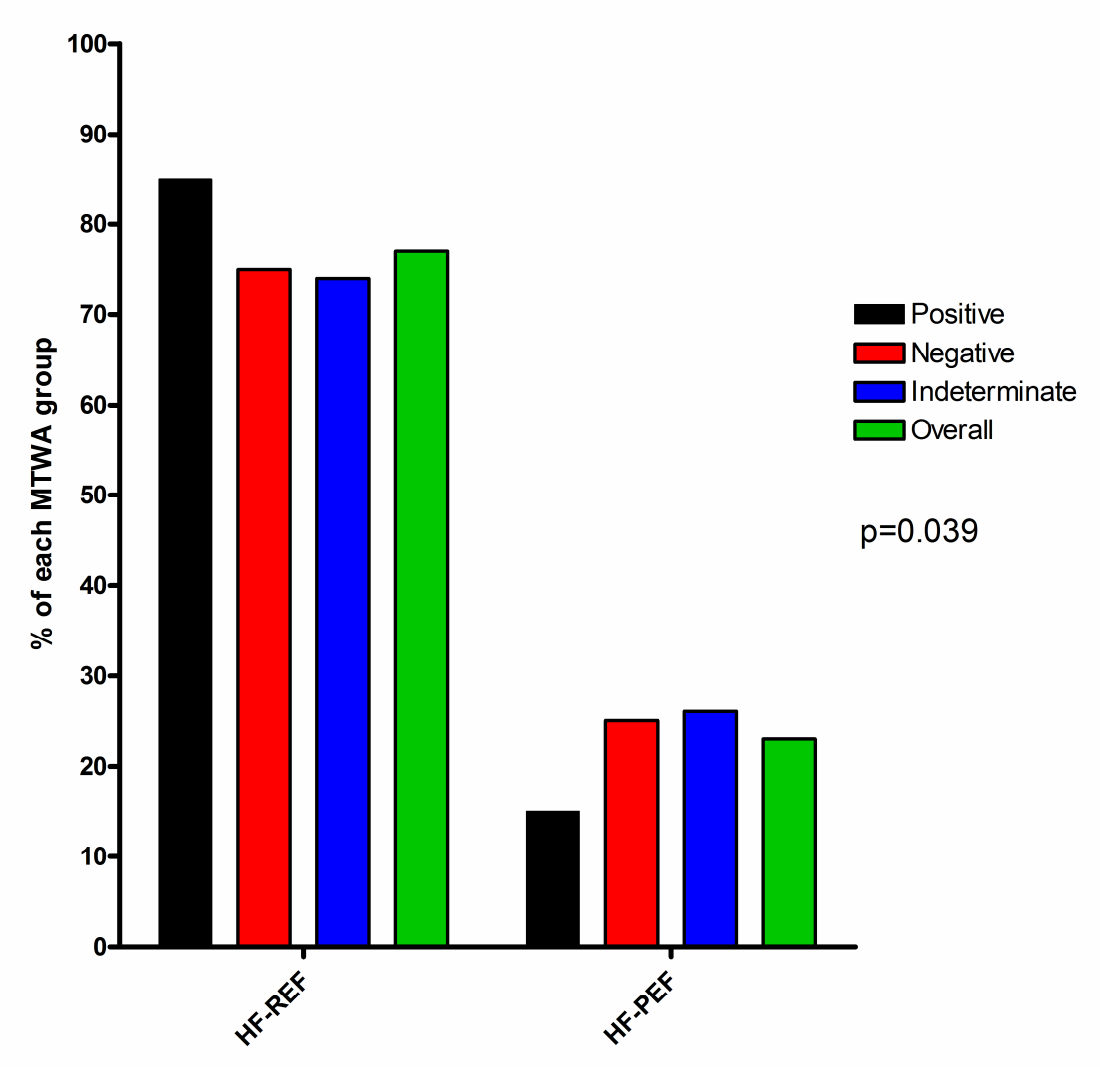


Figure 7.2: Proportions of patients with HF-REF and HF-PEF, stratified by MTWA result

Inter-group comparison using χ^2 test, p value <0.05 indicates a significant difference between the groups.

7.2.10 Haematology

Table 7-12 shows the full blood count parameters stratified by MTWA result.

Haemoglobin concentration was lower in patients with an indeterminate result than those with a positive or negative result (p=0.0053). Furthermore patients with an indeterminate result had the greatest proportion of patients meeting WHO criteria for anaemia (139). Of 152 patients with an indeterminate result, 96 (63.2%) were anaemic, approximately 20% more than those with positive or negative results (p=0.0009).

Total white blood cell count, red cell distribution width and lymphocyte concentration were similar in the three groups. However, the proportion of patients who were lymphopenic (defined as lymphocyte concentration $<1x10^9$/l) showed a trend towards a difference between the three groups (p=0.07). Over 10% of patients with an indeterminate result were lymphopenic, more than double the proportion of patients with a positive result and almost three times the proportion of patients with a negative result.

Table 7-12: Full blood count parameters stratified by MTWA result. Data are expressed as mean (SD), number (%) or median [IQR].

Parameter	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
WBC count ($x10^9$/l)	8.1 (2.1)	7.8 (2.0)	7.9 (2.9)	7.9 (2.5)	0.58
Haemoglobin (g/dl)	12.8 (1.8)	12.5 (2.0)	12.0 (1.8)	12.4 (1.9)	0.0053
Haemoglobin <13 M; <12 F	41 (41)	35 (44.9)	96 (63.2)	172 (52.1)	0.0009
RDW (%)	14.9 [13.9-16.3]	14.8 [13.7-15.9]	14.9 [14-16.2]	14.8 [13.9-16.2]	0.79
RDW ≥15	50 (50)	36 (46.2)	75 (49.3)	161 (48.8)	0.86
Lymphocytes ($x10^9$/l)	1.9 [1.5-2.5]	1.9 [1.4-2.4]	1.8 [1.4-2.3]	1.8 [1.4-2.4]	0.91
Lymphocytes <1	5 (5)	3 (3.8)	17 (11.2)	25 (7.6)	0.07

* Inter-group comparisons using ANOVA F-test (continuous variables) and $\chi 2$ test (categorical variables), p value < 0.05 indicates a significant difference between the groups.

7.2.11 Biochemistry

The biochemical tests results stratified by MTWA result are shown in Tables 7-13 to 7-16. The BNP and troponin I results are displayed in Table 7-13. Log BNP levels were highest in patients with an indeterminate result whilst those with a negative result had the lowest log BNP levels (p=0.035). The proportions of patients with an elevated troponin result (defined as ≥ 0.04 µg/l) were similar in all three groups.

Table 7-14 displays the renal function parameters. Hyponatraemia (defined as a sodium concentration <135mmol/l) was more common in patients with an indeterminate test, double the prevalence of patients with a positive result and four times the prevalence of those with a negative result (p=0.05). Patients with an indeterminate result also had higher urea concentrations than patients in the other two groups (p=0.041), and consequently the greatest proportion of patients with an elevated urea concentration (defined as urea equal to or above 7.5mmol/l) [p=0.013]. Those with a positive result had fewest patients with an elevated urea concentration, yet this was still more than half of this group. Creatinine concentration also differed between the three groups. Creatinine concentration was higher in patients with an indeterminate result, whilst patients with positive or negative results had similar concentrations (p=0.012). There was a significant difference between the three groups in the prevalence of moderate, or worse, renal dysfunction (defined as eGFR <60ml/min/1.73m^2) [p=0.00011]. Patients with indeterminate MTWA results had proportionately more patients with moderate, or worse, renal dysfunction.

The liver function parameters are displayed in Table 7-15. Albumin was the only parameter that differed between the groups. Patients with indeterminate MTWA results had lower albumin concentrations than those with positive or negative results (p=0.016). Other biochemical test parameters stratified by MTWA result are displayed in Table 7-16. Free T4 differed between the three groups, a higher concentration occurring amongst those with indeterminate results (p=0.0084). Patients with an indeterminate result were more likely to have a higher urate concentration than the other two groups (p=0.038). Total cholesterol and HDL concentration differed between the groups (p=0.00059 and p=0.0064, respectively), patients with an indeterminate MTWA result having the lowest concentration of both parameters, whilst those with a positive result had the highest.

Table 7-13: BNP and troponin I results stratified by MTWA result. Data are expressed as median [IQR], mean (SD) or number (%).

Parameter	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
BNP (pg/ml)	316 [186-689]	291 [114-542]	408 [175-945]	356 [160-793]	0.11
Log BNP	5.9 (1.0)	5.6 (1.2)	6.0 (1.2)	5.9 (1.1)	0.035
TnI ≥ 0.04 (µg/l)	19 (19)	12 (15.4)	24 (15.8)	55 (16.7)	0.75

* Inter-group comparisons using ANOVA F-test (continuous variables) and $\chi 2$ test (categorical variables), p value < 0.05 indicates a significant difference between the groups.

Table 7-14: Renal function results stratified by MTWA result. Data are expressed as mean (SD), number (%) or median [IQR].

Parameter	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Sodium (mmol/l)	139.5 (3.0)	139.4 (2.7)	138.7 (3.7)	139.1 (3.3)	0.12
Sodium <135	5 (5)	2 (2.6)	16 (10.5)	23 (7.0)	0.05
Potassium (mmol/l)	4.0 (0.5)	4.1 (0.5)	4.1 (0.5)	4.1 (0.5)	0.14
Urea (mmol/l)	7.6 [5.7-10.3]	8.0 [5.8-11]	9.3 [6.6-12.8]	9.5 [4.8-8.1]	0.041
Log (urea)	2.08 (0.43)	2.09 (0.45)	2.21 (0.49)	2.14 (0.46)	0.052
Urea ≥ 7.5	51 (51)	45 (57.7)	105 (69.1)	201 (60.9)	0.013
Creatinine (µmol/l)	99 [88-120.3]	99 [84.3-118.8]	109.5 [89-142.5]	102.5 [87-131.8]	0.012
Log (creatinine)	4.7 (0.3)	4.6 (0.3)	4.7 (0.4)	4.7 (0.3)	0.011
eGFR (ml/min/1.73m^2)	61.8 [49.1-73.5]	63.5 [46.5-76.3]	52.9 [40.8-67.0]	58.3 [43.4-72.0]	0.002
eGFR < 60ml/min/1.73m^2	41 (41)	33 (42.3)	99 (65.1)	173 (52.4)	0.00011

* Inter-group comparisons using ANOVA F-test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the groups.

Table 7-15: Liver function test results stratified by MTWA result. Data are expressed as median [IQR], number (%) or mean (SD).

Parameter	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Bilirubin (µmol/l)	8 [6-13]	7 [5-10]	8 [6-12]	8 [6-12]	0.46
Bilirubin > 22	7 (7)	5 (6.4)	8 (5.3)	20 (6.1)	0.84
AST (U/l)	22 [18-26]	19 [16-26]	21 [16-25]	21 [16-26]	0.69
ALT (U/l)	17 [12-25]	17 [13-24]	18 [13-25]	17 [13-25]	0.54
GGT (U/l)	36 [25-61]	38 [25-60]	43 [24-75]	39 [25-66]	0.64
Alk Phos (U/l)	90 [72-106]	93 [76-119]	91 [75-110]	91 [73-112]	0.8
Albumin (g/l)	39.7 (3.9)	39.4 (4.0)	38.4 (3.6)	39.0 (3.8)	0.016
Albumin < 35	7 (7)	8 (10.3)	21 (13.8)	36 (10.9)	0.23

* Inter-group comparisons using ANOVA F-test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the groups.

Table 7-16: Other biochemical test results stratified by MTWA result. Data are expressed as median [IQR] or mean (SD).

Parameter	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
TSH (mU/l)	1.3 [0.8-2.2]	1.6 [1.0-2.2]	1.5 [0.9-2.4]	1.5 [0.9-2.2]	0.63
T4 (pmol/l)	13.6 (2.1)	14.0 (2.6)	14.8 (4.1)	14.3 (3.3)	0.0084
HBA1c (%)	6.4 (1.3)	6.2 (1.4)	6.5 (1.4)	6.4 (1.4)	0.35
Urate (mmol/l)	0.43 (0.1)	0.42 (0.2)	0.46 (0.1)	0.44 (0.1)	0.038
Chol (mmol/l)	4.6 (1.3)	4.2 (1.0)	4.1 (1.1)	4.3 (1.1)	0.00059
Chol : HDL	4.0 (1.5)	3.9 (1.3)	3.9 (1.3)	3.9 (1.4)	0.73
HDL (mmol/l)	1.25 (0.46)	1.18 (0.39)	1.1 (0.31)	1.16 (0.38)	0.0064
Triglycerides (mmol//l)	1.8 [1.2-2.4]	1.4 [1.0-2.0]	1.6 [1.1-2.2]	1.6 [1.1-2.3]	0.48
Phosphate (mmol/l)	1.16 (0.21)	1.21 (0.22)	1.19 (0.21)	1.19 (0.21)	0.34

* Inter-group comparisons using ANOVA F-test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the groups.

7.2.12 Aetiology of heart failure

The primary aetiologies of HF (Figure 7.4) differed according to MTWA result (p=0.034). Patients with an indeterminate or positive MTWA result were more likely to have an established ischaemic cause of HF than those with a negative result. Patients without a prior MI or a coronary angiogram performed by the time of the study visit were classed as 'unknown' primary aetiology of HF. This applied to approximately one-quarter of all patients who completed a MTWA exercise test. There were only small proportions of patients with non-ischaemic causes of HF.

There were no significant differences between the three MTWA groups in contributing causes of HF, although those with an indeterminate MTWA test had the highest proportions of hypertension, paroxysmal AF and diabetes mellitus (Table 7-17). Patients with a positive MTWA test had the highest proportions of both valvular heart disease and alcohol as contributing causes of HF.

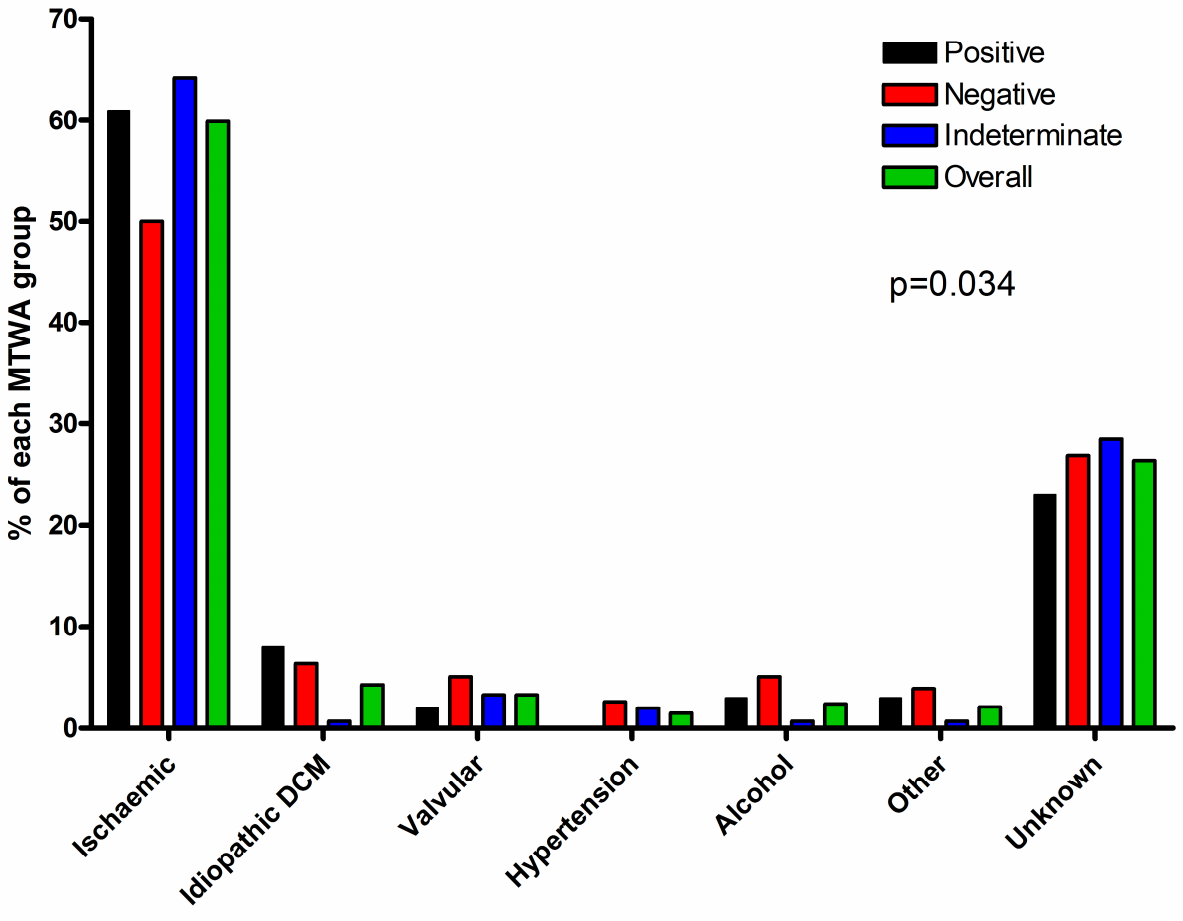


Figure 7.3: Primary aetiologies of heart failure stratified by MTWA result (inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference in proportions of positive, negative or indeterminate MTWA results between the seven groups)

Table 7-17: Contributing aetiologies of heart failure stratified by MTWA result. Data are expressed as number (%).

Contributing aetiology	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
Hypertension	62 (62)	43 (55.1)	104 (68.4)	209 (63.3)	0.13
Valvular heart disease	37 (37)	21 (26.9)	44 (28.9)	102 (30.9)	0.27
Paroxysmal atrial fibrillation	6 (6)	5 (6.4)	19 (12.5)	30 (9.1)	0.14
Diabetes mellitus	26 (26)	21 (26.9)	55 (36.2)	102 (30.9)	0.16
Alcohol	24 (24)	17 (21.8)	30 (19.7)	71 (21.5)	0.72

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the groups.

7.3 Results 2: Differences in clinical characteristics - negative and non-negative MTWA results

Every clinical parameter examined in Section 7.2 was analysed to determine if there were any differences between the MTWA groups when classified as negative and non-negative. Only the parameters where a significant difference ($p<0.05$) existed are displayed in Table 7-18. Patients with a negative result were approximately 5 years younger than those with a non-negative result. Consequently, there was a notable difference in the proportion of patients aged 75 years or older, over 35% of those with a non-negative result compared to 21% with a negative result. More patients with a non-negative MTWA result had a prior MI. No other medical comorbidities were differed between the two groups.

As mentioned in the previous section, only a quarter of patients with a negative test were on optimal HF therapy, nearly half the proportion of patients with a non-negative result. This is likely explained by the significant difference in proportions prescribed beta-blockers, only half of patients with a negative test compared to almost 70% of patients with a non-negative test. The difference in beta-blocker prescribing is also a likely explanation for the significant difference in resting heart rate between the two groups. Patients with a negative test had a higher resting heart rate than those with a non-negative result. Patients with a non-negative test had a lower mean DBP and an elevated pulse pressure, compared to patients with a negative result.

QTc was the only ECG parameter that differed between the two groups, patients with a non-negative result being more likely to have a longer QTc. There was no difference between the two groups in the proportion of patients with HF-REF and HF-PEF. Patients with a negative test achieved a higher percentage of their predicted heart rate during MTWA exercise testing. Finally, log BNP and moderate, or worse, renal dysfunction (defined as eGFR $<60ml/min/1.73m^2$) were the only blood parameters that differed significantly between the two groups. Patients with a non-negative result were more likely to have a higher log BNP and more patients with moderate, or worse, renal dysfunction.

Table 7-18: Clinical variables stratified by negative and non-negative MTWA classification (significant results only). Data are mean (SD) or number (%).

Variable	Negative (n=78)	Non-negative (n=252)	Overall (n=330)	p value*
Age (years)	65 (12.1)	70 (10.8)	69 (11.3)	0.00041
MI	29 (37.2)	137 (54.4)	166 (50.3)	0.008
Optimal therapy	19 (24.4)	112 (44.4)	131 (39.7)	0.0012
Diuretics	71 (91.0)	245 (97.2)	316 (95.8)	0.018
Beta-blockers	39 (50)	174 (69.0)	213 (64.5)	0.0021
Heart rate (bpm)	84 (11.8)	75 (14.0)	77 (14.0)	<0.0001
Diastolic BP (mmHg)	71.6 (10.9)	65.9 (12.7)	67.3 (12.5)	0.0004
Pulse pressure (mmHg)	57.8 (19.3)	65.9 (23.1)	64.0 (22.5)	0.0053
QTc (ms)	432 (29.6)	442 (33.4)	440 (32.8)	0.012
% predicted HR	74.8 (6.6)	67.8 (11.4)	69.5 (10.9)	<0.0001
Log (BNP)	5.6 (1.2)	6.0 (1.1)	5.9 (1.1)	0.015
eGFR < 60ml/min/1.73m^2	33 (42.3)	139 (55.2)	172 (52.1)	0.04

* Inter-group comparisons using Student's t-test (continuous variables) and χ^2 test (categorical variables), p value < 0.05 indicates a significant difference between the groups.

7.4 Results 3: Differences in clinical characteristics for the three MTWA pairings

7.4.1 Negative versus positive MTWA

All clinical characteristics where a statistically significant difference existed between the three MTWA groups were evaluated by logistic regression analysis to determine if certain variables were associated with a specific MTWA result.

The results for the comparison of negative versus positive MTWA are displayed in Table 7-19. Overall there were three parameters where a significant difference ($p<0.05$) existed between negative and positive MTWA results. Patients with a negative result were less likely to be treated with an ACE inhibitor and more likely to have a higher LVEF, than patients with a positive result. These differences were of borderline statistical significance. Those with a negative test were also more likely to have a lower cholesterol concentration than patients with a positive result. Fewer patients with a negative result had electrocardiographic evidence of LVH and a lower pulse pressure was more common amongst those with a negative result, these differences only showed a trend towards statistical significance.

Table 7-19: Logistic regression analysis for negative versus positive MTWA results

Parameter	Odds Ratio	95% Confidence Interval	p value*
Age (by 10 years)	0.81	0.64 - 1.04	0.095
Palpitations	0.96	0.5 - 1.85	0.91
MI	0.59	0.32 - 1.08	0.089
TIA / CVA	1.24	0.56 - 2.75	0.6
Previous AF	1.59	0.72 - 3.49	0.25
HR (per 10bpm)	1.27	1 - 1.61	0.054
DBP (per 10mmHg)	1.25	0.97 - 1.61	0.088
Pulse pressure	0.99	0.97 - 1.0	0.051
Optimal HF therapy	0.92	0.43 - 1.98	0.42
Diuretics	0.31	0.08 - 1.26	0.1
ACE inhibitors	0.5	0.25 - 0.99	0.046
β-blockers	0.79	0.43 - 1.42	0.43
Statins	1.07	0.56 - 2.05	0.83
LVH	0.44	0.19 - 1.01	0.052
QTc	0.99	0.98 - 1.0	0.25
Max ST depression	0.86	0.5 - 1.56	0.57
% predicted HR	1.0	0.96 - 1.04	0.88
LVEF (by 5%)	1.13	1.0 - 1.27	0.049
Log (BNP)	0.78	0.59 - 1.04	0.09
Sodium < 135mmol/l	0.5	0.09 - 2.65	0.41
Log (Urea)	1.1	0.56 - 2.17	0.78
Log (Creatinine)	0.81	0.29 - 2.2	0.67
eGFR (per ml/min/1.73m^2)	1.0	0.99 - 1.02	0.73
eGFR <60 ml/min/1.73m^2	1.06	0.58 - 1.92	0.86
Albumin (g/l)	0.98	0.91 - 1.06	0.68
T4 (pmol/l)	1.09	0.96 - 1.24	0.21
Urate (mmol/l)	0.41	0.05 - 3.59	0.42
Cholesterol (total) (mmol/l)	0.71	0.54 - 0.94	0.016
HDL (mmol/l)	0.67	0.33 - 1.37	0.27
Haemoglobin (g/dl)	0.93	0.79 - 1.09	0.36
Lymphocytes <1x10^9/l	0.76	0.18 - 3.28	0.71

* p value < 0.05 indicates a significant difference

7.4.2 Indeterminate versus positive MTWA

The results for the comparison of indeterminate versus positive MTWA are displayed in Table 7-20. Overall there were twenty-two parameters where a significant difference ($p<0.05$) existed between indeterminate and positive MTWA results.

Patients with an indeterminate result were older and more likely to have a history of AF and cerebrovascular disease, than patients with a positive result. Those with an indeterminate result were less likely to experience palpitations than patients with a positive result. Patients with an indeterminate result had a lower resting heart rate and DBP. In terms of HF medications, patients with an indeterminate result were more likely to be on optimal HF therapy, with a higher rate of beta-blocker prescribing but lower rate of ACE inhibitor prescribing than those with a positive result. Patients with an indeterminate result were more likely to be taking statins. Patients with an indeterminate result had a longer QTc interval, than patients with a positive result. During MTWA exercise testing, patients with an indeterminate result achieved a lower percentage of their predicted heart rate than those with a positive result. Patients with an indeterminate test had a higher LVEF than patients with a positive result. There were several significant biochemical differences between the two groups of patients. Those with an indeterminate test had a higher proportion of patients with elevated log (urea) and log (creatinine) concentrations and lower eGFR concentrations. Consequently more patients with indeterminate results had at least moderate chronic kidney disease (defined as eGFR < 60 ml/min/1.73m^2). They also had lower albumin concentrations and higher free T4 levels, than patients with a positive result. Total cholesterol and HDL levels were lower amongst those with an indeterminate result than patients with positive results. Finally, patients with an indeterminate result were more likely to be anaemic.

Table 7-20: Logistic regression analysis for indeterminate versus positive MTWA results

Parameter	Odds Ratio	95% Confidence Interval	p value
Age (by 10 years)	1.34	1.05 - 1.7	0.019
Palpitations	0.46	0.25 - 0.85	0.013
MI	1.34	0.81 - 2.22	0.26
TIA / CVA	1.96	1.01 - 3.78	0.046
Previous AF	3.38	1.76 - 6.52	0.00027
HR (per 10bpm)	0.62	0.5 - 0.75	<0.0001
DBP (per 10mmHg)	0.76	0.62 - 0.93	0.0093
Pulse pressure	1.0	0.99 - 1.02	0.49
Optimal HF therapy	6.13	3.08 - 12.17	<0.0001
Diuretics	1.14	0.25 - 5.23	0.86
ACE inhibitors	0.53	0.29 - 0.95	0.035
β-blockers	2.73	1.57 - 4.72	0.00034
Statins	2.08	1.15 - 3.77	0.016
LVH	0.54	0.28 - 1.03	0.063
QTc	1.01	1.0 - 1.02	0.03
Max ST depression	0.62	0.37 - 1.02	0.062
% predicted HR	0.88	0.85 - 0.91	<0.0001
LVEF (by 5%)	1.16	1.04 - 1.29	0.0088
Log (BNP)	1.11	0.88 - 1.4	0.19
Sodium < 135mmol/l	2.24	0.79 - 6.31	0.13
Log (Urea)	1.86	1.06 - 3.26	0.03
Log (Creatinine)	2.68	1.17 - 6.11	0.019
eGFR (per ml/min/1.73m^2)	0.98	0.97 - 0.99	0.0046
eGFR < 60ml/min/1.73m^2	2.69	1.6 - 4.52	0.00019
Albumin (g/l)	0.91	0.85 - 0.98	0.0085
T4 (pmol/l)	1.19	1.06 - 1.33	0.0026
Urate (mmol/l)	6.22	0.83 - 46.46	0.075
Cholesterol (total) (mmol/l)	0.66	0.53 - 0.83	0.0004
HDL (mmol/l)	0.34	0.17 - 0.68	0.0023
Haemoglobin (g/dl)	0.79	0.69 - 0.92	0.0017
Lymphocytes <1x10^9/l	2.39	0.85 - 6.71	0.097

* p value < 0.05 indicates a significant difference

7.4.3 Indeterminate versus negative MTWA

The results for the comparison of indeterminate versus negative MTWA are displayed in Table 7-21. Overall there were nineteen parameters where a significant difference ($p<0.05$) existed between indeterminate and negative MTWA results.

Patients with an indeterminate result were older and more likely to have had a previous myocardial infarction and a history of AF, than those with a negative result. They were less likely to be symptomatic from palpitations than patients with a negative result. Those with an indeterminate result had a lower resting heart rate and diastolic blood pressure but a higher pulse pressure than patients with a negative result. In terms of heart failure medications, patients with an indeterminate result were more likely to be on optimal heart failure therapy. These patients had significantly more prescribing of both beta-blockers and diuretics than those with a negative result. Patients with an indeterminate result were also more likely to be prescribed statins. Patients with an indeterminate result had longer QTc intervals. During MTWA exercise testing those with an indeterminate result achieved a lower percentage of their predicted heart rate, than patients with a negative result. LVEF was similar in patients with indeterminate and negative results. There were several significant biochemical differences between these two groups. Patients with an indeterminate test had higher log BNP concentration, higher log (creatinine) concentration and lower eGFR concentration. Consequently, they were more likely to have at least moderate chronic kidney disease than patients with a negative result. They were also more likely to be hypoalbuminaemic and have higher urate levels than patients with a negative result.

Table 7-21: Logistic regression analysis for indeterminate versus negative MTWA results

Parameter	Odds Ratio	95% Confidence Interval	p value
Age (by 10 years)	1.81	1.36 - 2.41	<0.0001
Palpitations	0.48	0.25 - 0.92	0.028
MI	2.26	1.29 - 3.96	0.0043
TIA / CVA	1.58	0.8 - 3.12	0.19
Previous AF	2.14	1.12 - 4.06	0.021
HR (per 10bpm)	0.48	0.38 - 0.62	<0.0001
DBP (per 10mmHg)	0.6	0.48 - 0.77	<0.0001
Pulse pressure	1.02	1.01 - 1.03	0.0034
Optimal HF therapy	6.64	3.23 - 13.63	<0.0001
Diuretics	3.65	1.03 - 12.87	0.044
ACE inhibitors	1.05	0.59 - 1.88	0.87
β-blockers	3.47	1.93 - 6.23	<0.0001
Statins	1.94	1.02 - 3.67	0.043
LVH	1.23	0.53 - 2.83	0.63
QTc	1.01	1.0 - 1.02	0.0036
Max ST depression	0.65	0.35 - 1.21	0.18
% predicted HR	0.87	0.84 - 0.91	<0.0001
LVEF (by 5%)	1.01	0.9 - 1.14	0.85
Log (BNP)	1.35	1.06 - 1.71	0.015
Sodium < 135mmol/l	4.47	1.19 - 9.7	0.05
Log (Urea)	1.66	0.93 - 2.98	0.089
Log (Creatinine)	2.85	1.21 - 6.7	0.016
eGFR (per ml/min/1.73m^2)	0.98	0.97 - 0.99	0.0044
eGFR < 60ml/min/1.73m^2	2.55	1.46 - 4.46	0.0011
Albumin (g/l)	0.92	0.86 - 1.0	0.046
T4 (pmol/l)	1.09	0.98 - 1.2	0.1
Urate (mmol/l)	9.81	1.34 - 72.14	0.025
Cholesterol (total) (mmol/l)	0.9	0.69 - 1.16	0.41
HDL (mmol/l)	0.49	0.22 - 1.1	0.082
Haemoglobin (g/dl)	0.87	0.75 - 1.01	0.064
Lymphocytes <1x10^9/l	3.15	0.89 - 11.09	0.074

* p value < 0.05 indicates a significant difference

7.5 Discussion

This chapter has described the clinical characteristics associated with specific MTWA results. When the patients were analysed in three separate groups, according to the MTWA result, there were 27 clinical characteristics that differed significantly ($p<0.05$) between the groups of patients. A large amount of clinical data was included in these analyses and the limitations of multiple testing are recognised. However, 12 of the 27 characteristics that differed between the three groups had p values <0.01. When analysis was performed according to the contemporarily accepted classification of non-negative and negative (85), only 12 clinical characteristics differed significantly between the two groups ($p<0.05$), with 8 having p values <0.01. This novel finding highlights that the patients with non-negative MTWA results are a heterogeneous group of patients, in terms of clinical characteristics, and may explain the observation in other studies that patients with an indeterminate test result had a higher all-cause mortality rate than those with a positive result (84;94;100;102;116). Pair-wise analysis of MTWA results (negative versus positive; indeterminate versus positive; indeterminate versus negative) revealed notable differences also. In particular, this analysis exposed major difference between the indeterminate group and the other two groups of patients (and fewer differences between those with positive and negative tests). There were 22 clinical characteristics that significantly differed ($p<0.05$) between the indeterminate and positive groups, 14 with p values <0.01. There were almost as many significant differences between the indeterminate and negative groups, with 11 differences having a p value <0.01. Interestingly, there were only 3 clinical characteristics with significant differences between the negative and positive groups and none of these had a p value <0.01.

In summary, this chapter has highlighted that patients with indeterminate MTWA results are a distinct group of patients with more abnormal clinical characteristics than patients with positive or negative results. This novel finding argues against the current classification of patients into two groups, as non-negative and negative, and proposes that MTWA results should be considered as three separate groups: positive, negative and indeterminate. Whether or not this translates into a difference prognostically, thereby influencing how MTWA results should be classified for risk stratification purposes will be the focus of Chapter 8.

CHAPTER EIGHT

PROGNOSTIC VALUE
OF MICROVOLT T-WAVE ALTERNANS

8.1 Introduction

This chapter will describe the outcomes of the post-discharge cohort, focusing on the patients who underwent MTWA testing. The unadjusted mortality rates for each MTWA result will be illustrated. The most powerful predictors of prognosis will be determined using a three stage multivariable model. Finally the incremental prognostic value of MTWA will be assessed in the multivariable model.

8.2 Results

8.2.1 Overall survival of post-discharge cohort

The follow-up duration was calculated from the date of the study visit (first appointment 16th January 2007) to the date of death or censoring at 31st July 2009. The mean follow-up was 526 days (SD 243) or 18 months (SD 8.1) with a range 52-973 days. Median follow-up was 494 days. Of the 648 patients in the post-discharge cohort, 131 died during the follow-up period. Median survival was not calculable as 50% had not died by the censor date. Of 131 deaths, 20 were SCD and 63 cardiovascular deaths (excluding SCD). The remaining 48 patients died from non-cardiovascular causes. Table 8-1 shows unadjusted one and two year survival rates for the 648 patients. Almost one quarter of the post-discharge cohort were deceased by 2 years of follow-up. Of the original 1003 patients enrolled in the study, 329 patients (33%) died during the follow-up period.

Table 8-1: Overall survival for 648 patients in the post-discharge cohort

	Survival (%)	95% Confidence Interval
1 year	86.6	83.9 – 89.3
2 year	75.3	71.4 – 79.4

8.2.2 Survival stratified by MTWA eligibility

Of the 648 patients attending the post-discharge study visit, there were proportionately more deaths amongst those ineligible for MTWA exercise testing (Table 8-2). The difference in all cause mortality showed a trend towards statistical significance (p=0.057). There were no significant differences in the rates of SCD or resuscitated cardiac arrest and cardiovascular death (excluding sudden) between the two groups (Table 8-2).

Table 8-2: Mortality outcomes for the post-discharge cohort, stratified by eligibility for MTWA testing. Data are expressed as number (%).

Outcome	Eligible (n=330)	Ineligible (n= 318)	Overall (n=648)	p value*
All cause mortality	57 (17.3)	74 (23.3)	131 (20.2)	0.057
SCD or resuscitated cardiac arrest	9 (2.7)	11 (3.5)	20 (3.1)	0.59
Cardiovascular death (excluding sudden)	27 (8.2)	36 (11.3)	63 (9.7)	0.18

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the groups.

Table 8-3 shows one and two year survival rates for patients stratified by MTWA eligibility at the study visit. The one year unadjusted case survival rates were 88.8% and 79.4% for eligible and ineligible groups, respectively. The two year unadjusted case survival rates were 79.4% and 71.4% for eligible and ineligible groups, respectively. The differences were not statistically significant.

Table 8-3: Overall unadjusted survival for 648 patients in the post-discharge cohort, stratified by MTWA eligibility

	Eligible (n=330)		Ineligible (n=318)	
	Survival (%)	**95% CI**	**Survival (%)**	**95% CI**
1 year	88.8	85.3 – 92.5	84.3	80.3 – 88.5
2 year	79.4	74.4 – 84.6	71.4	65.6 – 77.7

8.2.3 Survival stratified by LVEF

Table 8-4 shows one and two year survival rates for patients stratified by LVEF. The one year unadjusted case survival rates were 86.3% and 86.4% for HF-PEF and HF-REF groups, respectively. The two year unadjusted case survival rates were 83.3% and 72.8% for HF-PEF and HF-REF, respectively. The differences were not statistically significant but the confidence intervals only just overlap by two year survival, suggesting the two groups may have significantly different survival rates with follow-up beyond two years. Unadjusted Kaplan-Meier curves for all-cause mortality graphically demonstrate no significant difference in survival between the two LVEF groups, with the curves crossing early on in follow-up (log rank test p= 0.172) (Figure 8.1).

Table 8-4: Overall unadjusted survival for 648 patients in the post-discharge cohort, stratified by LVEF

	HF-PEF (n=127)		HF-REF (n=521)	
	Survival (%)	**95% CI**	**Survival (%)**	**95% CI**
1 year	86.3	80.4 – 92.6	86.4	83.3 – 89.5
2 year	83.3	76.8 – 90.3	72.8	68.1 – 77.8

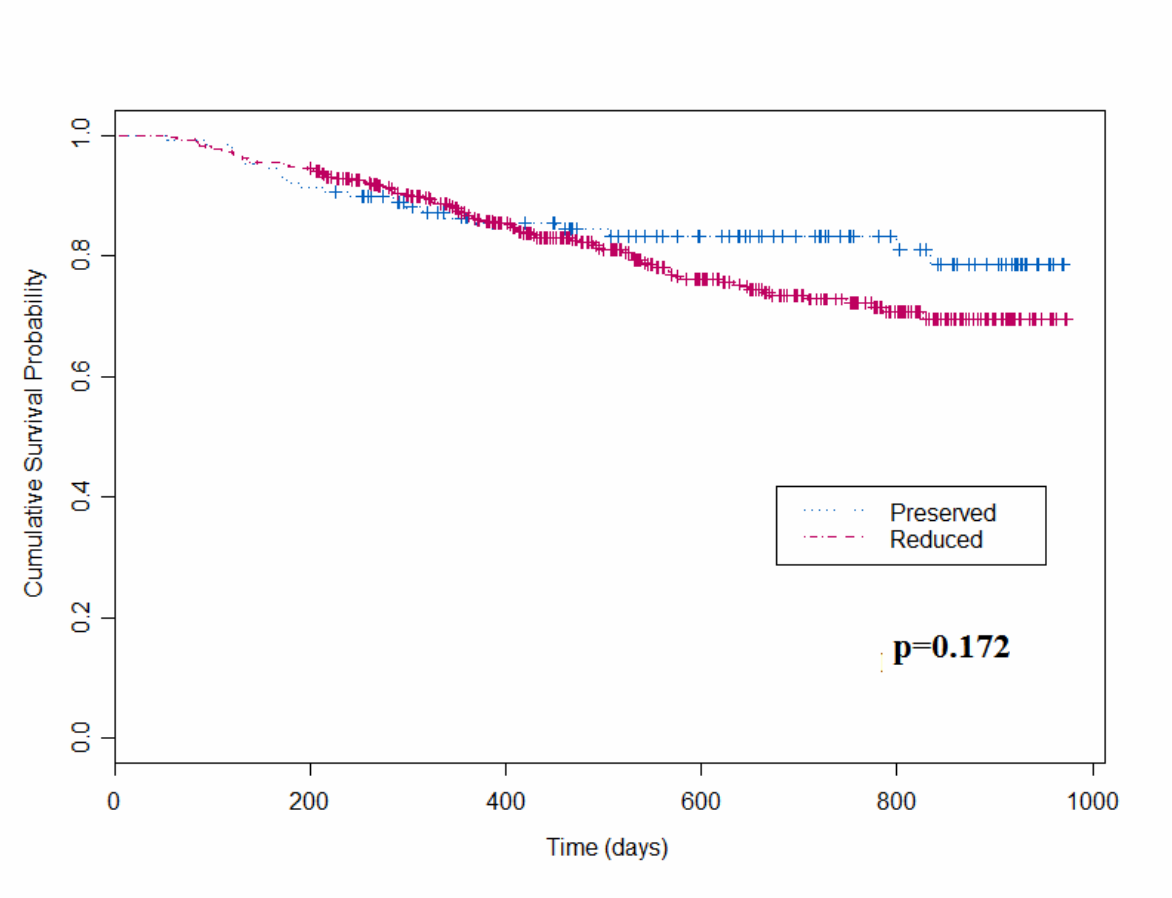


Figure 8.1: Kaplan-Meier survival curves for HF-PEF and HF-REF (curves were compared using the log rank test, where p<0.05 indicates a significant difference between the two groups).

8.2.4 Unadjusted outcomes for MTWA result

The breakdown of causes of death according to MTWA classification is displayed in Table 8-5. Of 100 patients with a positive MTWA result, 12 (12%) died during the follow-up period. Of 78 patients with a negative MTWA result, 16 (20.5%) died during the follow-up period. Of 152 patients with an indeterminate MTWA result, 29 (19.1%) died during the follow-up period. The difference in all cause mortality rates was not statistically significant. Unadjusted Kaplan-Meier curves for all-cause mortality demonstrated no significant difference in survival between the three MTWA groups (log rank test p= 0.1989) (Figure 8.2). The survival curve analyses for the secondary outcome measures are displayed in Figures 8.3 and 8.4. There were

no significant differences in the rates of secondary outcome measures between the three MTWA groups (Table 8-5) [p=0.82 and p=0.077, respectively].

Table 8-6 shows one and two year survival rates for patients stratified by MTWA result. Patients with a positive or indeterminate MTWA result did not have a higher all-cause mortality rate than those with a negative result. The one year unadjusted case survival rates were 85.7%, 94.5% and 86.7% for negative, positive and indeterminate results, respectively. The two year unadjusted case survival rates were 74.7%, 83.6% and 79.2% for negative, positive and indeterminate results, respectively. The differences were not statistically significant.

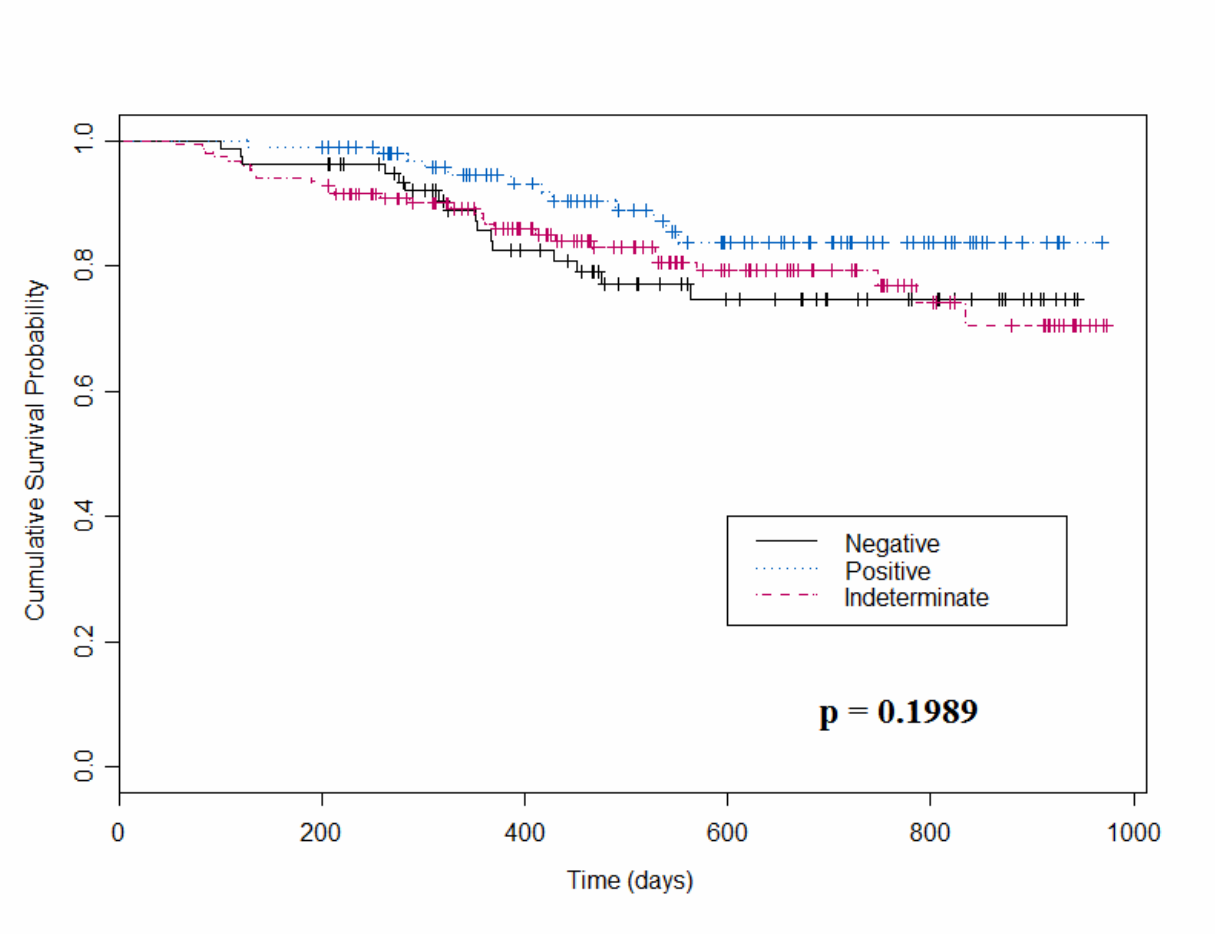


Figure 8.2: Kaplan-Meier survival curves for all-cause mortality for negative, positive and indeterminate MTWA results (curves were compared using the log rank test, where p<0.05 indicates a significant difference between the three groups).

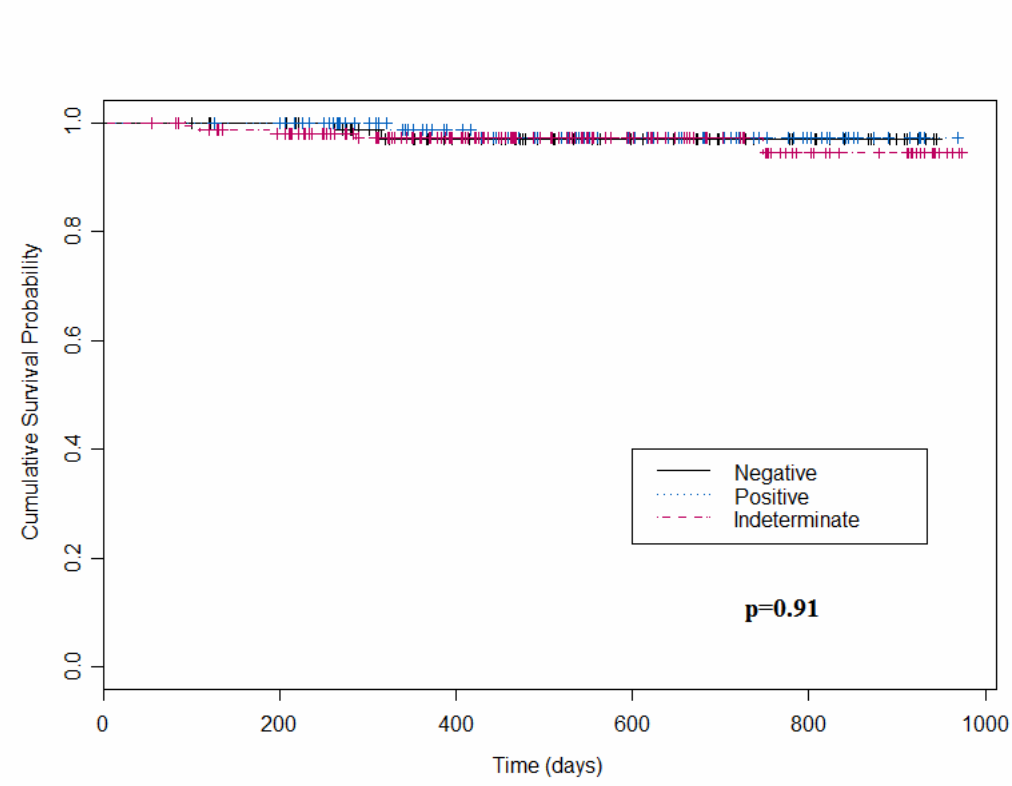


Figure 8.3: Kaplan-Meier survival curves for sudden cardiac death or resuscitated cardiac arrest for negative, positive and indeterminate MTWA results

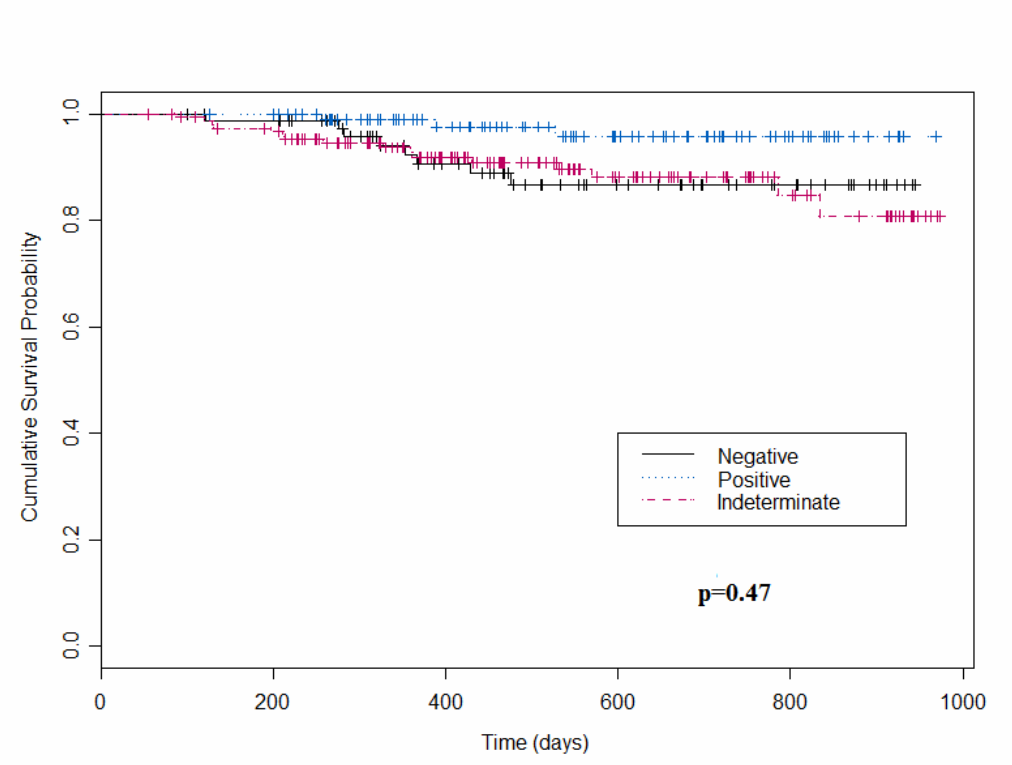


Figure 8.4: Kaplan-Meier survival curves for cardiovascular death (excluding sudden) for negative, positive and indeterminate MTWA results

Table 8-5: Unadjusted mortality outcomes stratified by MTWA result. Data are expressed as number (%)

Outcome	Positive (n=100)	Negative (n=78)	Indeterminate (n=152)	Overall (n=330)	p value*
All-cause mortality	12 (12)	16 (20.5)	29 (19.1)	57 (17.3)	0.24
SCD or resuscitated cardiac arrest	2 (2)	2 (2.6)	5 (3.3)	9 (2.7)	0.82
Cardiovascular death (excluding sudden)	3 (3)	8 (10.3)	16 (10.5)	27 (8.2)	0.077

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the groups.

Table 8-6: Unadjusted survival rates for patients with negative, positive and indeterminate MTWA results

	Negative (n=78)		Positive (n=100)		Indeterminate (n=152)	
	Survival (%)	**95% CI**	**Survival (%)**	**95% CI**	**Survival (%)**	**95% CI**
1 year	85.7	77.8 – 94.4	94.5	89.9 – 99.3	86.7	81.3 – 92.5
2 year	74.7	64.4 – 86.6	83.6	75.4 – 92.8	79.2	72.1 – 87.0

Mortality outcomes were also analysed in accordance with accepted practice as non-negative and negative MTWA results (85). This did not alter the outcome; a non-negative MTWA result was not significantly different to a negative MTWA result in determining all-cause mortality (Figure 8.5 and Table 8-7) or the secondary outcome measures (Table 8-8). Table 8-8 shows one and two year case survival rates for MTWA result dichotomised to negative and non-negative. The one year unadjusted case survival rates were 85.7% and 89.8%, for negative and non-negative results, respectively. The two years unadjusted survival rates were 74.7% and 80.9%, for negative and non-negative, respectively. The differences were not statistically significant.

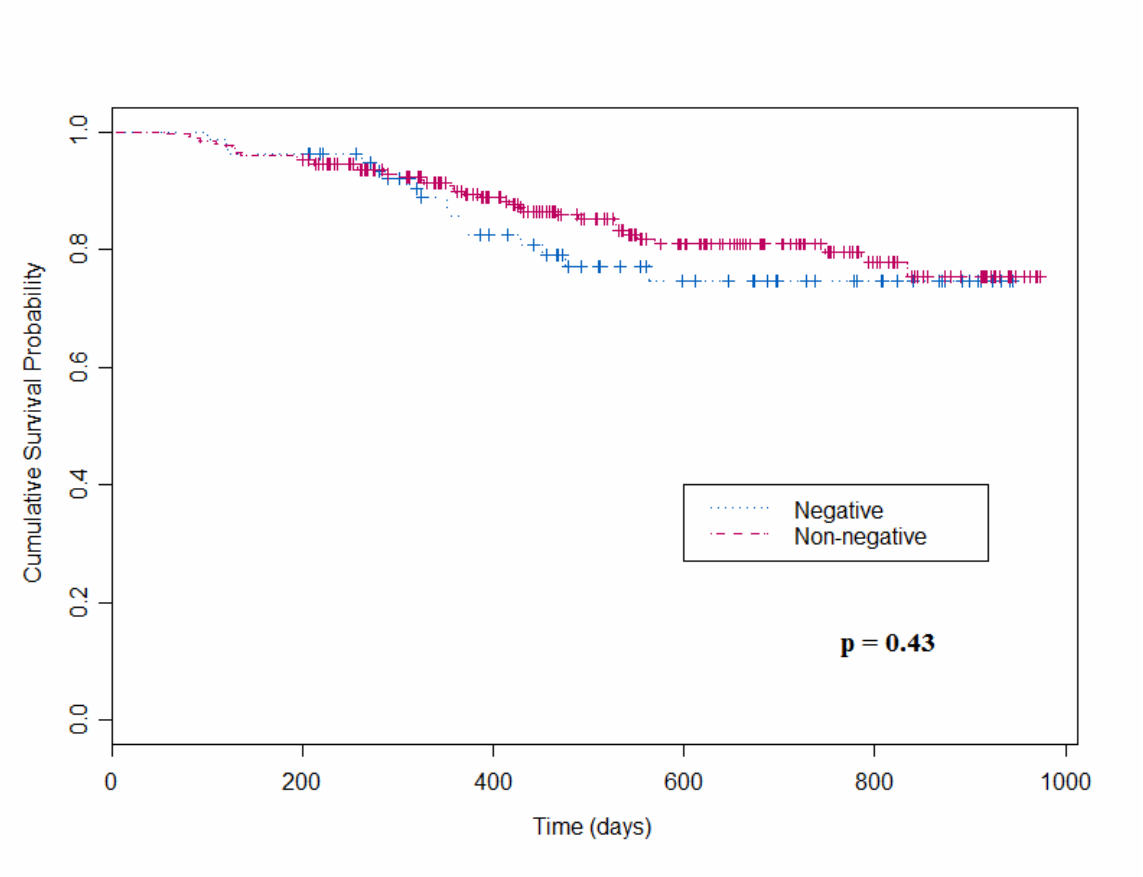


Figure 8.5: Kaplan-Meier survival curves for negative and non-negative MTWA results (curves were compared using the log rank test, where p<0.05 indicates a significant difference between the two groups).

Table 8-7: Unadjusted mortality outcomes stratified by negative and non-negative MTWA result. Data are expressed as number (%)

Outcome	Negative (n=78)	Non-negative (n=252)	Overall (n=330)	p value*
All-cause mortality	16 (20.5)	41 (16.3)	57 (17.3)	0.39
SCD or resuscitated cardiac arrest	2 (2.6)	7 (2.8)	9 (2.7)	0.92
Cardiovascular death (excluding sudden)	8 (10.3)	19 (7.5)	27 (8.2)	0.44

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the groups.

Table 8-8: Survival rates for patients with negative and non-negative MTWA results

	Negative (n=78)		Non-negative (n=252)	
	Survival (%)	95% CI	Survival (%)	95% CI
1 year	85.7	77.8 – 94.4	89.8	86.0 – 93.8
2 year	74.7	64.4 – 86.6	80.9	75.4 – 86.8

The indeterminate MTWA results were further analysed according to the classification illustrated in Figure 6.11 (page 233). This was to determine if the different types of indeterminate result had different outcomes, particularly the two main indeterminate results. As previously described in chapter 6, the majority of indeterminate tests were because of a failure to achieve the required heart rate of 110bpm (75% of all indeterminate tests). There were two principal reasons for this. Firstly, some patients had a low resting heart rate, due to being on maximal dose of beta-blocker therapy. These patients were often physically able to exercise for a long period of time but unable to elevate their heart rate and it was clear that prolonging exercise would not achieve the desired heart rate of 110 bpm (represented as 'insufficient HR – chronotropic incompetence' in Table 8-9). The other reason for an insufficient heart rate was exercise intolerance preventing attainment of a heart rate of 110bpm (represented as 'insufficient HR – physical limitations' in Table 8-9). The remaining MTWA tests were indeterminate due to the presence of ectopic activity (16.4%), noise (5.9%), non-sustained alternans (2%) or a rapid rise in heart rate (0.7%). These are represented as 'Indeterminate – Other' in Table 8-9.

Patients with indeterminate results due to an insufficient heart rate secondary to physical limitations had proportionately more events for all three outcomes, compared to other MTWA results, although these differences were not statistically significant. There was no significant difference in any of the three outcomes according to the type of indeterminate MTWA result. There were too few events to permit survival curve analyses.

Table 8-9: Mortality outcomes stratified by type of indeterminate MTWA result. Data are expressed as number (%)

Outcome	Positive (n=100)	Negative (n=78)	Indeterminate – insufficient HR due to physical limitation (n=59)	Indeterminate – insufficient HR due to chronotropic incompetence (n=55)	Indeterminate Other (n=38)	Overall (n=330)	p value*
All-cause mortality	12 (12)	16 (20.5)	14 (23.7)	9 (16.4)	6 (15.8)	57 (17.3)	0.15
SCD or resuscitated cardiac arrest	2 (2)	2 (2.6)	3 (5.1)	2 (3.6)	0 (0)	9 (2.7)	0.65
Cardiovascular death (excluding sudden)	3 (3)	8 (10.3)	8 (13.6)	5 (9.1)	3 (7.9)	27 (8.2)	0.11

* Inter-group comparisons using χ^2 test, p value < 0.05 indicates a significant difference between the five groups.

8.2.5 Comparison of mortality rates to other LVSD and HF MTWA studies

The mortality rates of LVSD and HF MTWA studies are shown in Table 8-10. All-cause mortality and SCD rates, if available, are presented. My study is displayed in the last row. Only studies with at least 10 deaths during their follow-up period are displayed in this table.

There are several reasons limiting direct comparisons between these studies. Firstly, the wide range of follow-up durations prevents direct comparisons of overall event rates. Thus approximate mortality rates per 100 patient-years of follow-up were calculated (Table 8-11). Secondly, the differences in the patient population included in each study limits comparisons between studies, for example some studies are exclusively ischaemic or non-ischaemic HF patients whilst others include both. Also some studies are post-MI LVSD, likely containing patients asymptomatic of HF. Finally, some studies do not present the numbers for all-cause mortality or sudden cardiac death according to the MTWA result. Several studies only present results for non-negative patients, preventing comparison of positive and indeterminate results separately. Some studies only present actuarial mortality rates according to MTWA result rather than absolute numbers of death according to MTWA result, preventing direct comparison with other studies. Many studies do not present the numbers of patients who succumbed to SCD.

Approximate mortality rates per 100 patient-years of follow-up were calculated to allow a comparison of all-cause mortality between studies (Table 8-11). The higher mortality rate of my study may reflect the unselected nature of my cohort, including more elderly patients with comorbidity.

The proportion of all deaths that were SCD is displayed in the last column of Table 8-10. The range of this proportion is wide, from 17-58%. The limitations in the definition of SCD used in my study, addressed in chapter 2 (section 2.6.3, page 89), likely account for the low proportion of all deaths that were sudden in my study. This prevents meaningful comparisons to the other MTWA studies, all of which used a more robust definition (section 2.6.3, page 89).

Table 8-10: Distribution of all-cause mortality and sudden cardiac death in LVSD and HF MTWA studies*

Study	N	Population	Mean FU (SD)	All Cause Mortality, N (%)					Sudden Cardiac Death, N (%)					
				Pos	Ind	N-N	Neg	Total	Pos	Ind	N-N	Neg	Total	% ACM
Chow (107)	768	Ischaemic LVSD	18 (10)	44/355 (12)	34/159 (21)	78/514 (15)	21/254 (8)	**99 (13)**	17 (5)	16 (10)	33 (6)	9 (4)	**42 (5)**	**42**
Gold (119)	490	HF - LVSD	30 [-]	33/182 (18)	32/173 (19)	65/355 (18)	16/135 (12)	**81 (17)**	12 (7)	6 (4)	18 (5)	8 (5)	**26 (5)**	**32**
Chow (104)	575	Post-MI LVSD	25 (11)	-	-	46/361 (13)	13/214 (6)	**59 (10)**	-	-	7 (2)	3 (1)	**10 (2)**	**17**
Bloomfield (109)	549	LVSD	20 (6)	-	-	38/360 (11)	2/189 (1)	**40 (7)**	-	-	-	1 (<1)	-	-
Huikuri (105)	312	Post-MI LVSD	22 (6)	-	-	-	-	**38 (12)**	-	-	-	-	**8 (3)**	**21**
Grimm (113)	263	HF –DCM	52 (12)	-	-	-	-	**33 (13)**	-	-	-	-	**17 (7)**	**52**
Salerno-Uriarte (118)	446	HF – DCM	19 [18-24]	-	-	25/292 (9)	3/154 (2)	**28 (6)**	-	-	7/282 (2)	0	**7 (2)**	**25**
Hohnloser (103)	129	Post-MI LVSD	17 (8)	-	-	16/94 (17)	4 (11)	**20 (16)**	-	-	8/94 (9)	0	**8 (6)**	**40**
Bloomfield (85)	177	Post-MI LVSD	20 (6)	-	-	-	-	**20 (11)**	-	-	-	-	-	-
Rashba (106)	144	Ischaemic LVSD	17 (13)	-	-	-	-	**14 (10)**	-	-	-	-	-	-
Klingenheben (116)	107	HF – LVSD	15 (-)	-	-	-	-	**12 (11)**	-	-	-	-	**7 (7)**	**58**
Jackson	**330**	**HF**	**18 (8)**	**12/100 (12)**	**29/152 (19)**	**41/252 (16)**	**16/78 (21)**	**57 (17)**	**2 (2)**	**5 (3)**	**7 (3)**	**2 (3)**	**9 (3)**	**16**

* Studies with ≤ 10 deaths during follow-up not included in this table (108;111;112;114;115). Order is according to number of deaths during follow-up. N = number; FU = follow-up (months); pos = positive; ind = indeterminate; N-N = non-negative; neg = negative; DCM = dilated cardiomyopathy (non-ischaemic); - = data not presented

Table 8-11: Approximate mortality rates *per* 100-patient years of follow-up for studies in Table 8-10

Study	N	Population	Mean FU (months)	All-cause mortality, N (%)	Mortality rate per 100-patient years
Chow (107)	768	Ischaemic LVSD	18	99 (13)	8.6
Gold (119)	490	HF - LVSD	30	81 (17)	6.6
Chow (104)	575	Post-MI LVSD	25	59 (10)	4.9
Bloomfield (109)	549	LVSD	20	40 (7)	4.4
Huikuri (105)	312	Post-MI LVSD	22	38 (12)	6.6
Grimm (113)	263	HF -DCM	52	33 (13)	2.9
Salerno-Uriarte (118)	446	HF - DCM	19	28 (6)	4.0
Hohnloser (103)	129	Post-MI LVSD	17	20 (16)	10.9
Bloomfield (85)	177	Post-MI LVSD	20	20 (11)	6.8
Rashba (106)	144	Ischaemic LVSD	17	14 (10)	6.9
Klingenheben (116)	107	HF - LVSD	15	12 (11)	9.0
Jackson	**330**	**HF**	**18**	**57 (17)**	**11.5**

8.2.6 Stepwise multivariable models without MTWA

A detailed description of the variables selection and the statistical analyses employed in the multivariable models is given in chapter 2 (section 2.6, page 86). Multivariable analysis was carried out using a Cox proportional hazards regression three stage model. The multivariable models were created using the significant univariate variables at each stage. These analyses are for all-cause mortality only. There were too few events to allow analyses for the secondary outcome measures.

The univariate and multivariable analysis for stage one is presented in Table 8-12. Increasing age, lower LVEF, lower BMI, NYHA class III or IV, a diagnosis of HF for more than two years and a history of a previous MI were univariate predictors of all-cause mortality. After adjusting for the variables in the Cox regression model, lower BMI, NYHA class III or IV and previous MI were found to be independent predictors of all-cause mortality.

The univariate and multivariable analysis for stage two is presented in Table 8-13. Lower eGFR, higher RDW, higher bilirubin and lower haemoglobin concentrations were univariate predictors of all-cause mortality. After adjusting for the variables in the Cox regression model, lower eGFR, higher bilirubin and lower haemoglobin concentration were found to be independent predictors of all-cause mortality.

The univariate and multivariable analysis for stage three is presented in Table 8-14. This showed elevated levels of both novel biomarkers BNP and troponin I to be independent predictors of all-cause mortality.

Table 8-12: Univariate and multivariable analysis for stage 1 variables

Stage 1 Variable	Univariate			Multivariable[1]			Multivariable[2]		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Age (per year)	1.03	1.01 - 1.04	0.0057	1.01	0.99 - 1.03	0.17	-	-	-
LVEF (per 5% increase)	0.91	0.84 - 0.97	0.0062	0.94	0.87 - 1.02	0.13	-	-	-
DM - No	1.0		0.7749	-	-	-	-	-	-
- Insulin	1.25	0.68 - 2.29							
- Other	1.05	0.7 - 1.57							
BMI (per kg/m^2 increase)	0.95	0.92 - 0.98	0.0008	0.96	0.93 - 0.99	0.0072	0.95	0.92 - 0.98	0.0005
Sex (Female)	1.0	0.71 - 1.42	0.99	-	-	-	-	-	-
NYHA - I / II	1.0		<0.0001						
- III /IV	2.23	1.58 - 3.14		2.07	1.45 - 2.97	<0.0001	2.1	1.48 - 2.96	<0.0001
Bundle branch block	1.36	0.94 - 1.97	0.1	-	-	-	-	-	-
Cardiomegaly	1.1	0.74 - 1.63	0	-	-	-	-	-	-

Stage 1 Variable	Univariate			Multivariable[1]			Multivariable[2]		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
SBP (per 10 mmHg increase)	0.99	0.99 - 1.0	0.21	-	-	-	-	-	
Chronic HF > 2 years	1.51	1.06 - 2.14	0.022	1.27	0.88 - 1.84	0.2	-	-	-
Previous MI	1.99	1.4 - 2.82	0.0001	1.67	1.15 - 2.41	0.0066	1.82	1.28 - 2.59	0.0009
Dependent oedema	1.3	0.92 - 1.83	0.14	-	-	-	-	-	-
HR (per 10bpm)	1.0	0.99 - 1.01	0.57	-	-	-	-	-	-
AF	0.88	0.61 - 1.26	0.49	-	-	-	-	-	-

1 = Multivariable analysis containing significant ($p < 0.05$) univariate variables only

2 = Multivariable analysis after removing non significant ($p \geq 0.05$) variables

HR = hazard ratio; CI = confidence interval

Table 8-13: Univariate and multivariable analysis for stage 2 variables

Stage 2 Variable	Univariate			Multivariable[1]			Multivariable[2]		
	HR*	95% CI	p value	HR*	95% CI	p value	HR*	95% CI	p value
eGFR (ml/min/1.73m^2)	0.99	0.98 - 0.99	0.0071	0.99	0.98 - 0.99	0.027	0.99	0.98 - 0.99	0.026
Log (RDW)	3.33	1.17 - 9.5	0.025	1.84	0.58 - 5.88	0.3	-	-	-
Log (Bilirubin)	1.58	1.16 - 2.14	0.0034	1.6	1.15 - 2.22	0.0052	1.71	1.26 - 2.3	0.0005
Haemoglobin (g/dl)	0.89	0.82 - 0.97	0.0077	0.93	0.85 - 1.03	0.15	0.91	0.84 - 0.99	0.037
Log (Lymphocytes)	0.62	0.43 - 0.9	0.011	0.89	0.58 - 1.37	0.61	-	-	-
Urate (mmol/l)	2.42	0.74 - 7.95	0.14	-	-	-	-	-	-
Phosphate (mmol/l)	1.25	0.56 - 2.75	0.59	-	-	-	-	-	-
HBA1c (%)	0.97	0.38 - 2.51	0.95	-	-	-	-	-	-

1 = Multivariable analysis containing significant ($p < 0.05$) univariate variables only

2 = Multivariable analysis after removing non significant ($p \geq 0.05$) variables

* = Hazard ratio is per unit increase for all variables

Table 8-14: Univariate and multivariable analysis for stage 3 variables

Stage 3 Variable	Univariate			Multivariable		
	HR*	**95% CI**	**p value**	**HR***	**95% CI**	**p value**
Log (BNP)	1.68	1.41 - 2.0	<0.0001	1.54	1.27 - 1.85	<0.0001
Troponin I ≥ 0.04 (μg/l)	2.51	1.73 - 3.65	<0.0001	1.733	1.16 - 2.6	0.0079

* Hazard ratio is per unit increase for log (BNP)

The multivariable analysis for the significant variables from all three stages is shown in Table 8-15. All predictors from the multivariable analysis for stages 1 and 3 remained independent predictors of all-cause mortality. None of the predictors from the stage 2 multivariable analysis were predictive after adjusting for variables from stage 1 and 3. The independent predictors of all-cause mortality were lower BMI, NYHA class III or IV, previous myocardial infarction, elevated log (BNP) concentration and raised troponin I.

Table 8-15: Multivariable analysis for variables from stages 1, 2 and 3

Variable	**Multivariable[1]**			**Multivariable[2]**		
	HR*	**95% CI**	**p value**	**HR***	**95% CI**	**p value**
Stage 1						
BMI (kg/m^2)	0.96	0.93 - 0.99	0.0073	0.96	0.93 - 0.99	0.01
NYHA (III/IV v I/II)	1.71	1.19 - 2.45	0.0038	1.72	1.2 - 2.47	0.0032
Previous MI	1.68	1.18 - 2.4	0.004	1.68	1.18 - 2.4	0.0039
Stage 2						
eGFR ($ml/min/1.73m^2$)	0.99	0.98 - 1.0	0.15	-	-	-
Log (Bilirubin)	1.36	0.97 - 1.89	0.074	-	-	-
Haemoglobin (g/dl)	0.94	0.85 - 1.03	0.15	-	-	-
Stage 3						
Log (BNP)	1.26	1.03 - 1.54	0.026	1.36	1.12 - 1.65	0.0019
Troponin I ($\geq$ 0.04 µg/l)	1.49	0.99 - 2.26	0.058	1.57	1.04 - 2.37	0.033

1 = Multivariable analysis with significant ($p < 0.05$) variables from stages 1-3

2 = Multivariable analysis after removing non significant ($p \geq 0.05$) variables

* Hazard ratio is per unit increase for continuous variables (BMI, eGFR, log [bilirubin], haemoglobin, log [BNP])

8.2.7 Multivariable models with MTWA

The results of the univariate analysis for MTWA are displayed in Table 8-16. As already described in section 8.2.3, the unadjusted MTWA result did not predict all-cause mortality.

Table 8-16: Univariate analysis for MTWA

MTWA result	HR	95% CI	p value*
Negative	1.0		
Positive	0.56	0.27 : 1.18	0.1989
Indeterminate	0.96	0.52 : 1.76	
Non-negative	0.79	0.44 : 1.41	0.43

* p value <0.05 indicates significant difference between the MTWA groups.

The additional prognostic value of MTWA was evaluated by fitting it into each stage of the multivariable models. MTWA result (negative, positive or indeterminate) was not an independent predictor of all-cause mortality at any stage after adjusting for other significant variables, with overall p values of 0.0578, 0.2242 and 0.1496 for stages 1, 2 and 3, respectively (data from individual stages not shown). MTWA was added to the final multivariable model with significant predictors of mortality from all three stages (Table 8-17). Again, at this stage after adjusting for significant variables, MTWA had no additional explanatory value for all-cause mortality.

Table 8-17: Multivariable analysis for final model with MTWA

Variable	Multivariable analysis with MTWA in 3 categories			Multivariable analysis with MTWA in 2 categories		
	HR	**95% CI**	**p value***	**HR**	**95% CI**	**p value***
BMI (per 1kg/m^2 increase)	0.96	0.92 : 1.01	0.11	0.96	0.92 : 1.01	0.14
NYHA (III/IV v I/II)	2.09	1.2 : 3.65	0.0094	2.06	1.19 : 3.59	0.01
Previous MI	1.85	1.05 : 3.26	0.033	1.89	1.07 : 3.33	0.028
Log (BNP) (per unit increase)	1.39	1.05 : 1.85	0.021	1.45	1.09 : 1.91	0.01
Troponin I (≥ 0.04 µg/l)	1.5	0.79 : 2.85	0.22	1.41	0.75 : 2.69	0.29
MTWA 3 Categories						
Negative	1.0		0.0608			
Positive	0.41	0.19 : 0.87		NA		
Indeterminate	0.69	0.36 : 1.3				
MTWA 2 Categories						
Negative	NA			1.0		0.06
Non-negative				0.56	0.31 : 1.03	

* p value <0.05 indicates significant difference between the MTWA groups.

8.3 Discussion

This chapter has described the outcomes for the 648 patients in the post-discharge cohort. Mortality rates were high, almost one quarter of all patients were deceased by two years follow-up. This is an expected finding given all patients had recently been hospitalised with decompensated HF. The overall mortality for the 1003 enrolled patients was 33%, comparable with recently published mortality rates for Scottish patients hospitalised for HF (147).

There were proportionately more deaths amongst the patients ineligible for MTWA testing than those eligible. Many of the reasons for being ineligible for MTWA testing (AF, pacemakers and medical comorbidities preventing exercise) are also risk factors for adverse outcomes in HF. This is the first study to describe outcomes in patients ineligible for MTWA testing and highlights the adverse mortality rates of these patients.

There was no significant difference in mortality rates between patients with HF-REF and HF-PEF in this study. This finding is consistent with recent studies reporting no significant difference in survival between the two groups of patients (19;23). However the number of patients in this study is relatively small, with even fewer deaths and the Kaplan-Meier curves and two year unadjusted survival figures suggest that differences in survival between those with HF-REF and HF-PEF may emerge with longer term follow-up.

MTWA did not predict any of the study's prespecified outcomes. The failure to predict SCD can be partly explained by the small numbers of patients with this outcome. However, it was expected that an abnormal MTWA result (positive or indeterminate) may predict all-cause mortality (99;100;102;104;105;111). In fact patients with a positive result had proportionately fewest events overall with patients with indeterminate and negative results having proportionately similar mortality rates, although there was no significant difference in mortality rates between the three groups. This result was surprising. Indeed, the results from Chapter 7 had demonstrated that patients with positive and negative results were more similar, in terms of clinical characteristics, than those with indeterminate results. However, this did not

translate prognostically. Also patients with indeterminate results because physical limitations prevented elevation of their heart rate had proportionately more events than patients with other indeterminate results, although these differences were not statistically significant. MTWA was also analysed in the accepted way of non-negative (positive and indeterminate) and negative (85), but this did not alter the results. Moreover the very different mortality rates for those patients with positive and indeterminate results challenges the use of this 'non-negative' classification. In the original study that classified patients with positive and indeterminate as 'non-negative', patients with positive and indeterminate MTWA results had two year actuarial mortality rates of 14.5% and 20.1%, respectively. The authors of this small (n=177) study of patients with ischaemic LVSD concluded that these were similar mortality rates and positive and indeterminate tests should be classified as 'non-negative'. Many studies since have only reported 'non-negative' mortality rates, preventing an understanding of the exact risk conferred by a positive or indeterminate test. The findings of my study strongly suggest this approach is incorrect.

The mortality rate (expressed as an approximate event rate per 100 patient-years of follow-up) was higher in my study than in prior LVSD and HF MTWA studies (Table 8-11, page 298). This likely reflects the unselected nature of my cohort, including more elderly patients with comorbidity. One noticeable difference between my study and the other studies presented in Table 8-10 (page 297) is the mortality rates for the patients with negative MTWA results. Of the studies that presented mortality rates according to the MTWA result, all had a lower mortality rate for patients with a negative MTWA result compared with the overall mortality rate for each study. By contrast, my study demonstrated the exact opposite; the mortality rate was 21% for patients with negative MTWA results compared to an overall mortality rate of 17% for all patients undergoing MTWA testing. The exact reason for this unexpected finding is unclear. This may reflect the different population enrolled, compared with previous studies. Perhaps the MTWA test does not identify those at greatest risk when used in unselected cohorts with more elderly patients and patients with more comorbidity. The lower rate of beta-blocker prescribing amongst patients with negative MTWA results, compared to patients with indeterminate results, may be a contributory factor to the unexpected higher mortality amongst patients with negative results. Patients with indeterminate MTWA results were more than three times more likely to be prescribed a beta-blocker than those with negative results (OR 3.47, $p<0.0001$).

However this does not explain the higher mortality of patients with negative MTWA results compared to those with positive results. Although beta-blocker prescribing was less common amongst those with a negative MTWA result, compared to those with a positive result, this difference was not significant (OR 0.79, p 0.43). Higher beta-blocker prescribing amongst patients with an indeterminate result may have been expected to confer a prognostic advantage. The high mortality of the patients with indeterminate results is likely multifactorial and explained by the multiple risk factors for poor prognosis present in this group, including advancing age, diabetes, anaemia and renal dysfunction.

The proportion of all deaths that were SCD was reported by most LVSD and HF MTWA studies and varied from 17-58%. The limitations in the definition of SCD used in my study (section 2.6.3, page 89) likely account for the low proportion of all deaths that were sudden in my study and thus further comparisons to the other studies were not made. The MASTER study (104) had a noticeably lower proportion of SCD compared to the other studies in Table 8-10. All patients in this study fulfilled MADIT-II criteria and underwent ICD implantation following MTWA testing. During the follow-up period 9% of negative patients and 12% of non-negative patients received appropriate ICD therapy, many of which may have resulted in SCD if an ICD had not been implanted. Furthermore, although the proportions of events for positive and indeterminate patients are not reported separately in this study, the proportion of indeterminate results is low in this study (12%). One reason for this may be the use of pharmacological means of stress or pacing for patients who were unable to exercise. The low rate of indeterminate results together with a low proportion of SCD highlights a possible relationship between an indeterminate result and risk of sudden cardiac death. Few studies have reported the numbers of SCD, thus it is difficult to extrapolate a potential link between indeterminate results and SCD. I could not explore a potential relationship between indeterminate results and SCD in my study due to the limitations acknowledged above. However, in the largest study to date of MTWA in patients with LVSD, patients with an indeterminate result had the highest proportion of SCD and SCD accounted for 42% of all-cause mortality in this study (107). Another possible explanation for the MASTER study (104) having a lower proportion of SCD may be the high rate of beta-blocker prescribing (87%). Excluding the MASTER study, there is still a wide range in the proportion of all deaths that were sudden in the other studies presented in Table 8-10 (21-58%), likely reflective of the inherent difficulties in determining SCD.

MTWA had no incremental prognostic value in my study when added to a multivariable model containing the strongest predictors of mortality in this study. The independent predictors of all-cause mortality following stepwise multivariable modelling were; lower BMI, NYHA III/IV, previous MI, elevated log (BNP) concentration and raised troponin (defined as ≥ 0.04 μg/l). The small number of independent predictors may be explained by the relatively small number of events that occurred during the follow-up period for those who underwent MTWA testing.

In summary, MTWA had no prognostic value in my cohort of unselected patients with HF. There was no evidence to suggest that this test is of benefit in the risk stratification of 'real-life' patients with HF. The independent predictors of mortality in this study included BNP and cardiac troponin, a novel biomarker in HF. Both are simple, cheap biochemical tests to perform. The other three independent predictors of mortality were clinical variables that are readily available. This straightforward model containing only five simple variables identified the patients at most risk in my study.

CHAPTER NINE

DISCUSSION

9.1 Major findings of the study

HF is a major health concern internationally and associated with considerable morbidity and mortality. Despite advances in the management of HF in recent decades, the prognosis remains poor for many patients (147). This emphasises the importance of prognostication in HF, particularly when several therapies available for the management of this condition are expensive and require accurate targeting to optimise their use. However the solution to risk stratification in HF remains elusive. There are many established predictors of mortality in HF, as outlined in Chapter 1, but few have been shown to predict cause-specific death. This is particularly important in HF where many deaths may be attributed to SCD caused by VTE, which may be prevented by appropriate selection of patients for primary prevention ICDs. MTWA has recently been proposed as a potential tool for assisting in the selection of patients for primary prevention ICD therapy by identifying those at risk of SCD. As outlined in Chapter 1, there are many unresolved issues regarding the clinical utility of MTWA testing in HF.

This study has provided a comprehensive evaluation of the use of MTWA in a real-life, near-consecutive and well-defined population of patients with HF, accounting for aetiology and LVEF. The proportion of patients eligible for MTWA testing has been demonstrated. The prevalence of positive, negative and indeterminate results and the tolerability of the exercise protocol have been assessed. The clinical characteristics associated with each MTWA result have been determined. The predictive value of MTWA testing for all-cause mortality has been evaluated alongside established predictors of outcome, including BNP, and more novel biomarkers, such as cardiac troponin. This study has achieved its main aim of determining if MTWA testing has a role in the risk stratification of patients with HF.

Of 2361 patients with suspected decompensated HF screened for inclusion in the study, 1003 were recruited. The majority of the cohort was elderly with multiple medical co-morbidities and LVSD. Of those recruited, 648 patients (65%) attended the study visit approximately 4 weeks after discharge from hospital. The most common reason for failing to attend the study visit was refusal to participate (n=167, 17%). A significant proportion of patients died prior to

the study visit appointment (n=115, 11%) and many patients were unable to attend because of deterioration in their health (n=73, 7%). The patient's clinical characteristics recorded during hospitalisation were analysed according to whether or not they subsequently completed the study visit. Patients attending the study visit were similar, in terms of clinical characteristics, to the group of patients who withdrew from participating in the study visit. The groups who failed to complete the study visit due to deteriorating health or death had proportionately more patients with markers of adverse prognosis in HF. The clinical characteristics recorded during hospitalisation were updated at the study visit. Many of the symptoms, signs and laboratory values showed an improvement, as expected, compared with the findings recorded during hospitalisation.

In patients evaluated after discharge, the clinical characteristics of those with HF-REF and HF-PEF were compared. The majority of these characteristics were similar between the two groups, consistent with previous reports that patients with HF-PEF cannot readily be distinguished from those with HF-REF on the basis of symptoms and signs, CXR or ECG findings (19). However, there were some notable differences between the two groups. Patients with HF-PEF were older, more likely to be female, more likely to have hypertension and less likely to have had a MI, in comparison to those with HF-REF. These findings are consistent with previous studies of HF-PEF (22;24;155). Prescribing of recommended pharmacological treatments for HF was greater amongst patients with HF-REF, an unsurprising result given the evidence-base for the use of these medications exists only for patients with HF-REF and no treatment is of proven benefit in HF-PEF. Prescribing of calcium channel blockers was more common amongst those with HF-PEF, perhaps reflecting the use of these agents as antihypertensive treatment. Apart from SBP and pulse pressure, there were no differences in clinical examination findings between the two groups. There were also no differences in the proportions in sinus rhythm or AF between the two groups. QRS duration and QTc interval were longer amongst patients with HF-REF. The majority of biochemical and haematological test findings were similar in the two LVEF groups. The major exception was BNP and here the differences in average concentrations between the two groups were striking, both on admission to hospital and at the post-discharge study visit. Median BNP concentrations in patients with HF-REF were almost twice those of patients with HF-PEF at both time points. Previous studies in patients with decompensated HF have demonstrated similar findings (156).

Anaemia was more common amongst patients with HF-PEF, consistent with previous reports (23).

Of 648 patients who completed the study visit, 330 (51%) were eligible for MTWA testing. Thus, almost half were ineligible for MTWA testing. The clinical value of any test is limited if nearly half of the patients are ineligible for the test. This is the first prospective observational study to describe the reasons for ineligibility in a 'real-life' HF population. Patients were ineligible because of conditions commonly associated with HF, such as AF, ventricular pacing and an inability to exercise. AF accounted for three-quarters of those who were ineligible in my study i.e. 38% of all patients. This is higher than the ~23% reported in two earlier studies, although those studies enrolled only patients with HF of non-ischaemic aetiology (113;118). Although only a small proportion of patients (7% overall) were ineligible because of physical inability to attempt the sub-maximal treadmill test, this is an underestimate of this problem as many patients simply did not attend for the test because of poor health. Furthermore, as discussed later, many of those who did attempt the test could not perform satisfactorily.

Many of the characteristics of the ineligible patients in my study suggested they had a poor prognosis, including the highest log (BNP) concentration. BNP is also an independent predictor of sudden cardiac death (53), suggesting that the patients at the highest arrhythmic risk may in fact not be eligible for MTWA testing. These findings suggest the utility of the MTWA test as a means of detecting those at highest risk of sudden death is likely to be limited as many such patients are ineligible for the test. Patients ineligible for MTWA testing were older than patients eligible for testing and a higher proportion had a history of pre-admission heart failure. Ineligible patients also had more evidence of persisting or advanced heart failure, with a higher proportion having NYHA functional class III or IV symptoms and a greater frequency of peripheral oedema. Those ineligible for MTWA testing also had a greater prevalence of renal dysfunction, liver enzyme abnormalities, hyperuricaemia and lymphopenia. There was, however, no difference in LVEF according to MTWA eligibility and the use of HF medication was similar between the groups.

An indeterminate MTWA test was the most common result in this study (46%), with a positive MTWA test found in only 30% and a negative test in 24%. This is the first prospective study to demonstrate how common an indeterminate result is in an unselected HF population – the majority of which were on optimal medical therapy. This is also the first study to characterise the causes of indeterminate results in detail. The majority of indeterminate test results were due to failure to elevate the heart rate to 110bpm. This was due to chronotropic incompetence or physical limitations, with similar proportions of each. Other reasons for an indeterminate MTWA test included ectopy, noise, nonsustained alternans and a rapid rise in heart rate. Most cases of chronotropic incompetence were due to beta-blocker therapy. Importantly, this is the first study to identify two types of insufficient heart rate response. As discussed in Chapter 1, beta-blocker treatment was discontinued prior to MTWA testing in many previous studies in order to avoid indeterminate tests occurring due to heart rate limitation (98;106;107;113;114;119). There is evidence that acute beta-blockade can reduce the magnitude of MTWA, potentially converting a positive to a negative test (122). Omission of beta-blockers may increase the number of positive tests as well as reducing the number of indeterminate tests. However a primary aim of this study was to evaluate the use of MTWA as a predictor of the residual risk of SCD in patients on optimal therapy, including a beta-blocker (as beta-blockers reduce the risk of SCD). ICDs are only indicated in patients remaining at substantial risk of SCD, despite optimal medical therapy. It is hard to see the value of a test that predicted SCD in patients not optimally treated. Thus the high proportion of indeterminate results in my study, compared with most prior studies (Figure 6.13, page 239), may, in part, reflect the high rate of use of beta-blockers in our patients. This further highlights the potentially limited value of MTWA testing as a generally applicable tool for risk-stratification in HF.

Beta-blocker use may not be the whole explanation for the high proportion of indeterminate results in our study. In one other large study in which patients with ischaemic and non-ischaemic HF were tested off beta-blockers, the prevalence of a positive, negative and indeterminate result was 37%, 22% and 41% (119), respectively, very similar to the distribution observed in my study. This suggests that cessation of beta-blockers may not be an effective means of limiting the number of indeterminate tests in HF patients. This is especially pertinent given that there is also a potential risk to HF patients in the withdrawal of beta-blockers. In addition, the value of a test that is positive off-treatment, but negative or

indeterminate on-treatment, in targeting ICD therapy is unclear; a test that remains positive on optimal therapy should be more useful in clinical decision-making.

The high proportion of indeterminate tests in our study may also reflect the patient population studied and not just discontinuation of beta-blocker therapy, as already discussed. My study was carried out in an unselected cohort of patients who had recently been hospitalised with decompensated HF. Many of these patients were elderly with extensive medical comorbidities and physical frailty. The majority of other MTWA studies have been cohorts of younger patients with less comorbidity (Table 1-4, page 54).

The functional capacity of the cohort was poor. There was no significant difference in the duration of exercise or energy expended during exercise (measured in METS) according to MTWA result. The majority of patients discontinued the MTWA test because of physical limitations, with only 42% achieving the target heart rate of 110bpm required for completion of the MTWA test. This is perhaps unsurprising as many of the patients were elderly with multiple comorbidities. However, this does question the general usefulness of this test in 'real-life' HF patients.

When the patients were analysed according to their MTWA result (positive, negative or indeterminate), there were 27 clinical characteristics that differed ($p<0.05$) between the groups of patients. A large amount of clinical data was included in these analyses and the limitations of multiple testing are recognised. However, 12 of the 27 characteristics that differed between the three groups had p values <0.01. Yet when analysis was performed according to the contemporarily accepted classification of non-negative and negative (85), only 12 clinical characteristics differed significantly between the two groups ($p<0.05$), with 8 having p values <0.01. These results demonstrate that patients with an indeterminate test result are different to those with a positive test. Patients with an indeterminate result were older and more likely to have a history of HF, diabetes, AF, anaemia and renal dysfunction (as well as a higher BNP); characteristics known to be predictive of poor outcome. These findings may explain the observation in other studies that patients with an indeterminate test result had a higher all-cause mortality rate than those with a positive result (85;101;107;109;123). My novel findings

about patients with non-negative MTWA results highlight how heterogeneous this group is, in terms of clinical characteristics, and argues against this binary classification of MTWA test results. Moreover, pair-wise analysis of MTWA results (negative versus positive; indeterminate versus positive; indeterminate versus negative) revealed notable differences in clinical characteristics. In particular, this analysis exposed major difference between the indeterminate group and the other two groups of patients (and, remarkably, fewer differences between those with positive and negative tests). There were 22 clinical characteristics that differed ($p<0.05$) between the indeterminate and positive groups, 14 with p values <0.01. There were almost as many differences between the indeterminate and negative groups, with 11 differences having a p value <0.01. Interestingly, there were only 3 clinical characteristics that differed significantly between the negative and positive groups and none of these had a p value <0.01. Patients with indeterminate MTWA results are a distinct group of patients with more abnormal clinical characteristics than those with positive or negative results. This novel finding suggests that patients should not be classified as non-negative and negative. I propose that MTWA results should only be considered as three separate groups: positive, negative and indeterminate.

The overall mortality rate by two years of follow-up for the 1003 enrolled patients was 33%, comparable with recently published mortality rates for Scottish patients hospitalised for HF (147). The overall mortality for the 648 patients in the post-discharge cohort was also high with almost one-quarter of patients deceased by two years follow-up.

There were proportionately more deaths amongst the patients ineligible for MTWA testing than those eligible. Thus, being ineligible for MTWA testing was a better predictor of an adverse prognosis than the MTWA result itself. Many of the reasons for being ineligible for MTWA testing (AF, pacemakers and medical comorbidities preventing exercise) are also risk factors for adverse outcomes in HF. This is the first study to describe outcomes in patients ineligible for MTWA testing and highlights the adverse mortality rates of these patients.

There was no significant difference in mortality rates between patients with HF-REF and HF-PEF in this study. This finding is consistent with some recent studies reporting no significant

difference in survival between the two groups of patients (19;23). However the number of patients in this study is relatively small, with even fewer deaths and both the Kaplan-Meier curves and two year unadjusted survival figures suggest that differences in survival between those with HF-REF and HF-PEF may emerge with longer term follow-up.

MTWA did not predict any of the study's prespecified outcomes. The failure to predict SCD in this study can be partly explained by the small numbers of patients with this outcome. However, it was expected that an abnormal MTWA result may predict all-cause mortality (106;107;109;111;111;112;118). Patients with a positive result had proportionately fewest events overall with patients with indeterminate and negative results having proportionately similar mortality rates, although there was no statistically significant difference between the three groups. This result was surprising. Indeed, the results from Chapter 7 had demonstrated that patients with positive and negative results were more similar, in terms of clinical characteristics, than those with indeterminate results. However, this did not translate prognostically. Also patients with indeterminate results because physical limitations prevented elevation of their heart rate had proportionately more events than patients with other MTWA results, although this difference was not statistically significant. MTWA was also analysed in the contemporary way of non-negative (positive and indeterminate) and negative, but this did not alter the conclusions. Moreover, the very different mortality for those patients with positive and indeterminate results challenges the use of this 'non-negative' classification. Indeed it is interesting to review the original study that combined positive and indeterminate results into a single 'non-negative' category. Although the authors of that small study (n=177) of patients with ischaemic LVSD concluded that the mortality rates for patients with positive and indeterminate tests were similar, the two year actuarial mortality rates were 14.5% and 20.1%, respectively, a trend similar to that apparent in my study. Many studies have since only reported 'non-negative' mortality rates, preventing, I suggest, a proper understanding of the different risks conferred by positive and indeterminate tests. My findings strongly suggest this approach is incorrect.

The mortality rate (expressed as an approximate event rate per 100 patient-years of follow-up) was higher in my study than in prior LVSD and HF MTWA studies (Table 8-11, page 309). This finding was expected and likely reflects the nature of my patient cohort, consisting of

unselected and recently discharged subjects, including more elderly individuals and patients with comorbidity, compared with prior studies. Unexpectedly, however, I found a higher mortality rate among patients with a negative MTWA result, compared with the mortality rate in the overall cohort. Of the studies that reported mortality rates according to the MTWA result, all described a lower mortality rate in patients with a negative MTWA result, compared with the rate in the overall cohort or in patients with a 'non-negative' MTWA result. By contrast, I found the exact opposite; the mortality rate was 21% for patients with a negative MTWA result compared with the overall rate of 17% in all patients undergoing MTWA testing, although the differences between the groups were not statistically significant. The exact reason for this unexpected finding is unclear. It may reflect the different population enrolled, compared with previous studies. Perhaps the MTWA test does not identify those at greatest risk when used in unselected cohorts with more elderly patients and patients with more comorbidity. The lower rate of beta-blocker prescribing amongst patients with negative MTWA results, compared to patients with indeterminate results, may be a contributory factor to the unexpected higher mortality amongst patients with negative results. Patients with indeterminate MTWA results were more than three times more likely to be prescribed a beta-blocker than those with negative results (OR 3.5, $p<0.0001$). However this does not explain the higher mortality of patients with negative MTWA results compared to those with positive results. Although beta-blocker prescribing was less common amongst those with a negative MTWA result, compared to those with a positive result, this difference was not significant (OR 0.79, $p=0.43$). Higher beta-blocker prescribing amongst patients with an indeterminate result may have been expected to confer a prognostic advantage. The high mortality of the patients with indeterminate results is likely multifactorial and explained by the multiple risk factors for poor prognosis present in this group, including advancing age, diabetes, anaemia and renal dysfunction.

There is wide variation in the proportion of all deaths considered sudden in the LVSD and HF MTWA studies, although only one prior study reported a proportion as low as in my study (I discuss this exception, the MASTER study (104), in more detail below). The low proportion of SCD in my study is likely accounted for by the limitations in the definition I had to use due to the nature of my dataset (section 2.6.3, page 91) and this really precludes further comparison with other studies. However, as noted above, among the other studies, the MASTER study (104) described a notably lower proportion of SCD. All patients in the

MASTER study fulfilled MADIT-II criteria and underwent ICD implantation following MTWA testing. During the follow-up period 9% of negative patients and 12% of non-negative patients received appropriate ICD therapy, some of which may have resulted in SCD if an ICD had not been implanted. Furthermore, although the proportions of events for positive and indeterminate patients are not reported separately in this study, the proportion of indeterminate results is low in this study (12%). One reason for this may be the use of pharmacological means of stress or pacing for patients who were unable to exercise. The low rate of indeterminate results together with a low proportion of SCD highlights a possible relationship between an indeterminate result and risk of SCD. Few studies have reported the numbers of SCD, thus it is difficult to extrapolate a potential link between indeterminate results and SCD. I could not explore a potential relationship between indeterminate results and SCD due to the limitations acknowledged above. However, in the largest study to date in patients with LVSD, patients with an indeterminate result had the highest proportion of SCD and SCD accounted for 42% of all-cause mortality in that study (107). Another possible explanation for the MASTER study (104) having a lower proportion of SCD may be the high rate of beta-blocker prescribing (87%). After excluding the MASTER study and my study, there was still a wide range in the proportion of all deaths that were sudden in the other LVSD and HF studies (21-58%), likely reflective of the inherent difficulties in determining SCD.

MTWA had no incremental prognostic value when added to a multivariable model containing the strongest predictors of mortality in my study. The independent predictors of all-cause mortality following stepwise multivariable modelling were; lower BMI, NYHA III/IV, previous MI, BNP and troponin. The small number of independent predictors may be explained by the relatively small number of events that occurred during the follow-up period for those who underwent MTWA testing.

9.2 Strengths

The major strength of this study is the unselected nature of the patients studied and the consequent high mortality rate compared with other studies (Table 8-11, page 298). This study represented a ‘real-life’ cohort of patients, prospectively studied following hospitalisation with

decompensated HF. The unselected approach to enrolment meant that patients were recruited irrespective of age, gender, LV dysfunction and comorbidities. All patients had a validated diagnosis of HF and all fulfilled ESC criteria for HF. The nature of this cohort allows extrapolation of these results to 'real-life' HF patients and not the minority who may fulfil clinical trial inclusion criteria. Previous MTWA clinical studies have enrolled highly selective cohorts.

The second major strength is the extensive phenotyping of all enrolled patients. The patients enrolled in this cohort are similar in many ways to those included in large epidemiological studies of HF. Moreover, this extensive phenotyping has allowed multiple detailed comparisons of the clinical characteristics of the patients. Firstly, those completing the study visit were compared to those who failed to attend due to death, deteriorating health or withdrawal from the study. The patients attending the study visit were then stratified according to eligibility for MTWA testing and the clinical characteristics of the two groups compared. Finally the characteristics were compared according to MTWA result, identifying the distinct clinical characteristics relating to positive, negative and indeterminate MTWA results.

All enrolled patients consented to be "flagged" with the Information Services Division of the Scottish Health Service. This allowed accurate mortality follow-up data to be obtained by linking the study database to information on deaths, held by the General Register's Office for Scotland. Another strength of this study was the creation of an electronic database, held in the Robertson Centre for Biostatistics at the University of Glasgow. Data were manually entered into the electronic database and verified by two independent database managers. All data were subject to manual and prespecified electronic data validation checks. This robust system ensured quality control of the data processed.

9.3 Limitations

Recruitment at the Royal and Western Infirmaries was not completely consecutive because of staff holidays. Clinical research nurses recruited patients from the Royal Alexandra Hospital but staff shortages prevented daily recruitment from this site.

Many enrolled patients were unable to return for MTWA testing one month after discharge from hospital. This, however, is an inevitable consequence of both the effects of HF and participation in a clinical study. Indeed the rate of follow-up was probably greater than in 'real-life' due to the encouragement I gave patients to attend and the fact that transport was provided for them. MTWA testing during hospitalisation for decompensated HF would have been impractical and possibly dangerous.

The large number of inter-group tests for differences in the clinical characteristics of the various groups may have led to chance findings where the p value is not <0.01.

There were limitations in defining events and outcomes. The mortality data provided by ISD are restricted to information documented on the death certificates. Deaths were not adjudicated and medical records and information from next of kin were not available to improve the accuracy of the attributed cause of death. The definition of SCD used in this study may have been pragmatic but is suboptimal nonetheless. Deaths occurring outside hospital and certified as due to acute MI were included as SCD but may have been deaths due to MI. This approach was taken because the majority of SCD occurs outside hospital and is commonly certified as acute MI and verified acute MI is a relatively uncommon event in patients with HF (121;157;158). Unfortunately there was no way of distinguishing between the two causes with the information available. Classifying SCD using only death certificate information is extremely limited and, one could argue, futile. This secondary analysis was included because the biomarker of interest was MTWA.

Information regarding appropriate ICD discharges for ventricular tachyarrhythmias was not available but probably would not have altered the results given the low rate of implantation of these devices in the cohort I recruited.

9.4 Future research analyses

All of the outcome analyses will be repeated with a minimum follow-up of 1 year for every patient. Extending follow-up will help me determine whether my conclusions about the usefulness of MTWA testing will alter upon reanalysis using a larger number of deaths. I think this is unlikely. Instead, I think alternative and more effective investigations are warranted to identify patients with HF at risk of potentially lethal ventricular arrhythmias.

The multivariable models described in chapter 8 were only created in the 330 patients who underwent MTWA testing, as the prognostic value of MTWA was the focus of this study. My next analysis will be to evaluate these models in all 648 patients in the post-discharge cohort to determine whether or not the same variables are independent predictors of mortality, regardless of eligibility for MTWA testing. Identification of the independent predictors of mortality in the entire post-discharge cohort may help create a simple way of risk stratifying patients recently hospitalised with decompensated HF. Ideally I would then externally validate this model in an independent cohort of patients recently hospitalised with decompensated HF.

My future research plans also include using the data from the 1003 patients enrolled in this study to create a simple, prognostic model to help risk stratify in-patients hospitalised with decompensated HF. Clearly, the use of individual risk markers in isolation has limited prognostic utility, as the absence or presence of a single risk marker does not necessarily convey good or bad prognosis. Multiple individual risk markers may be present in any given patient and combining these to form an accurate, individualised prognosis is the current challenge. Established prognostic models exist and are used in clinical practice for acute coronary syndromes, such as the Global Registry of Acute Coronary Events (GRACE) (159) and the Thrombolysis In Myocardial infarction (TIMI) risk scoring systems (160). These are practical, simple to use in the clinical setting and have also been validated to prospectively demonstrate that they accurately predict mortality and the risk of recurrent ischaemic events. An equivalent risk stratification tool is not currently used in HF clinical practice. Combining the most powerful markers of risk in the form of a prognostic model may be a strategy to improve prognostication in HF. Prognostic models predicting mortality risk and risk of

rehospitalisation have been developed in patients with acute decompensated HF and chronic HF, but these have largely remained research tools (76;126;158;161-165). These models have some common shortfalls. Most have been derived from clinical trial populations, which are necessarily selective and limit extrapolation to 'real-life' HF patients. Some have used complex formulae to calculate an individual's risk, reducing the likelihood of use in clinical practice. Only two models have included patients with HF-PEF (76;126); one was derived from a clinical trial population (126), whilst the other has not yet been externally validated (76). Only two models have incorporated BNP into the risk score (76;158). Only one has included cardiac troponin and this model, derived from patients with chronic HF, has not been externally validated (76). The Heart Failure Survival Score (HFSS) has been used in the management of advanced heart failure, particularly for assisting in the selection of appropriate candidates for cardiac transplantation (166). The shortcomings of the HFSS are, however, increasingly recognised (167). Furthermore NT-pro-BNP alone has been shown to be a stronger predictor of death than the HFSS (168).

The ideal prognostic model for assessing prognosis in HF would comprise simple, readily available variables and involve straightforward calculations. I plan to build a simple prognostic risk scoring tool using the independent predictors identified in this study. This model will be validated internally in the original 1003 enrolled patients. If this is a powerful tool for identifying those at highest risk in my cohort the next step would be to externally validate the model in an independent cohort of patients with decompensated HF.

9.5 Conclusion

Of the 1003 patients enrolled into this study during hospitalisation with decompensated HF, 648 completed the study visit approximately 4-6 weeks following discharge. Only 330 patients were eligible for MTWA testing and almost half of all MTWA tests were indeterminate. Many patients were unable to complete the test due to chronotropic incompetence, secondary to beta-blocker therapy or physical limitations. These results show that MTWA treadmill testing is not widely applicable to an unselected real-life HF population.

MTWA had no prognostic value in our cohort of unselected patients with HF. There was no evidence to suggest that this test is of benefit in the risk stratification of ‘real-life’ patients with HF. The independent predictors of mortality in this study included BNP and cardiac troponin, a novel biomarker in HF. Both are simple, cheap biochemical tests to perform. The other three independent predictors of mortality were clinical variables that are readily available (lower BMI, NYHA class III/IV and previous myocardial infarction). This straightforward model containing only five simple variables identified the patients at most risk in our study. At present MTWA cannot be endorsed as a tool for risk stratification for patients with HF.

Appendix I: Screening Sheet

DATE OF SCREENING	☐☐ / ☐☐ / ☐☐	
Hospital	GRI ☐ WIG ☐ RAH ☐	
Ward		
Name		
Hospital number		
Date of birth	☐☐ / ☐☐ / ☐☐	
SCREENING CRITERIA	Yes	No
Admitted with symptoms of HF		
Admitted with signs of HF		
Radiological evidence of pulmonary oedema		
Response to IV diuretics		
CHECKLIST	Yes	No
Stage 1 consent obtained		
BNP sent		
BNP result	pg/ml	
Recruited into study (if no, complete exclusion criteria		
EXCLUSION CRITERIA	Yes	No
BNP <100pg/ml		
Cognitive impairment		
Serious concurrent systemic disease		
ACS complicated by pulmonary oedema		
Geographical or social factors preventing participation		
Refusal to participate		
Already enrolled in study		
Other (specify)		

Appendix II

NHS Greater Glasgow & Clyde Health Board

Glasgow Royal Infirmary and
Western Infirmary Glasgow
Cardiology Departments

Enquiries to Dr Colette Jackson

Tel: 0141 330 2064
Fax: 0141 330 6955

PATIENT INFORMATION SHEET- STAGE 1

You are being invited to take part in a research study involving a gentle walking test (known as microvolt T-wave alternans). Before you decide whether or not to take part it is important you understand why the research is being done and what it involves. Thank you for reading this.

The first part of this study involves having a blood test done and agreeing to the doctors and nurses involved in the study looking at your medical notes and obtaining information about your future progress. This form explains why we want to do this and how it happens.

When you read this you will be in hospital and may have been admitted with shortness of breath or swollen legs. These are symptoms which sometimes indicate a condition called heart failure. Heart failure is a condition where the heart is not pumping blood around the body as well as it should be. As a result fluid often accumulates in the lungs or the legs. Possible causes include previous heart attacks, high blood pressure or damage to the heart valves.

Patients with heart failure are at risk of dying earlier than those without heart failure. This risk can be reduced in some patients by using a special pacemaker known as a cardiac defibrillator. Doctors are currently trying to work out which patients with heart failure should have these pacemakers implanted. Microvolt T-wave alternans testing is a new investigation that may help identify which patients might benefit from this pacemaker. Our study aims to provide more information about this test by studying a large group of patients, and looking at their progress over the following years.

The way that we follow a patient's progress for a study like this is by entering their details into a national database, which uses hospital notes to record when you come into hospital. This database is run by the Scottish Health Service and is confidential. Any information gathered is only available to the doctors running this study. It does not require any participation from you, and no one will contact you or your family as part of this process. If you agree to take part in the study at this stage, we will enter your details into this database.

If you agree to take part, you will have a blood test for B-type natriuretic peptide (BNP), this tests how well the heart is pumping. Approximately 10 mls (two teaspoons) of blood will be taken. Having blood taken is uncomfortable and some people may feel faint. There is a small

risk of bleeding, bruising or infection at the puncture site following the blood test. This blood test is exactly the same as other blood tests that you will have had taken before.

If the blood test is positive then either a doctor or nurse that is involved in this study will visit you before you are discharged from hospital to discuss whether or not you would like to take part in stage 2 of the research study.

Thank you for taking the time to read this patient information leaflet.

Appendix III

NHS Greater Glasgow & Clyde Health Board

Glasgow Royal Infirmary and
Western Infirmary Glasgow
Cardiology Departments

Enquiries to Dr Colette Jackson

Tel: 0141 330 2064
Fax: 0141 330 6955

PATIENT INFORMATION SHEET- STAGE 2

1. Study title

Microvolt T-Wave Alternans in Chronic Heart Failure

A study investigating a walking test in patients with chronic heart failure: Microvolt T-Wave Alternans (MTWA) test.

2. Invitation to take part

You are being invited to take part in a research study involving a gentle walking test. This is called the Microvolt T-Wave Alternans test. Before you decide whether or not to take part it is important you understand why the research is being done and what it involves. Please read the following information carefully and discuss it with others if you wish. Please ask us if anything is not clear or you would like more information. Take time to decide whether or not you wish to take part. You are not obliged to take part. If you decide to participate in the study you will be given a copy of this information sheet and a signed consent form to keep. Thank you for reading this.

3. What is the purpose of the study?

Heart failure is a condition where the heart is not pumping blood around the body as well as it should be. As a result fluid often accumulates in the lungs or the legs. Possible causes include previous heart attacks, high blood pressure or damage to the heart valves.

Patients with heart failure are at risk of dying earlier than those without heart failure. One of the most common causes of dying is a rapid speeding of the heart rate. These problems with heart rhythm are known as arrhythmias. These arrhythmias can be controlled in some patients by placing a special pacemaker known as a cardiac defibrillator under the skin below the

collarbone. Doctors are currently trying to work out which patients with heart failure should have these pacemakers implanted. Microvolt T-wave alternans testing is a new investigation that may help identify patients that are at risk of developing arrhythmias in the future. Our investigation aims to provide more information about this test by studying a large group of patients.

The study will involve a total of around 600 patients and is expected to last 3 years.

4. Why have I been chosen?

You are being invited to consider taking part in this study as you have been admitted to hospital with heart failure.

5. Do I have to take part?

Taking part in this study is entirely voluntary and your decision. If you take part you will receive this information sheet to keep and be asked to sign a consent form. If you take part you are free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

6. What will happen to me if I take part?

When you read this you will be in hospital and may have been admitted with shortness of breath or swollen legs. You will have been asked in stage 1 of the study whether or not you would be willing to have a special blood test. If this blood test shows your heart is not pumping as well as it should be then you will be invited to attend the new British Heart Foundation Glasgow Cardiovascular Research Centre (next to Western Infirmary Glasgow) once approximately four weeks after you get out of hospital. This visit is in addition to your normal hospital and General Practitioner appointments. Your treatment will continue to be supervised by your own hospital doctors and General Practitioner. We will pay your travelling expenses for the visit.

Your visit to the research centre will last approximately 90 minutes.

This visit will involve :

- **Medical history -** speaking to a doctor about your symptoms and previous illnesses

- **Physical examination -** you will be examined and your height and weight will be measured.

- **Echocardiogram –** this is an ultrasound scan of the heart, it is sometimes just called an ‘echo’. For this test you will be asked to lie on a bed and a probe will be placed gently on to your chest to allow pictures of the heart to be taken.

- **Blood test** - a blood sample will be taken from a vein in your arm. This blood test is exactly the same as other blood tests that you will have had taken before. Approximately 20 mls (4 teaspoons) of blood will be taken. Having blood taken is

uncomfortable and some people may feel faint. There is a small risk of bleeding, bruising or infection at the puncture site following the blood test. We are checking the blood for a substance called b-type natriuretic peptide (BNP), which tells us how well the heart is pumping. We will also use this blood sample to check your kidneys and liver and your blood cell counts.

- **Electrocardiogram (ECG) –** this is a recording of the electrical activity of the heart. You will probably have had this test before. To take the recording, you will be asked to lie on a bed while stickers are placed on to their chest wall. This test does not involve discomfort.

- **Microvolt T-Wave Alternans test (MTWA)** – this involves walking at a slow pace on a treadmill for up to 12 minutes while a computer monitors the heart rhythm. This test will not be carried out if you have an irregular pulse or if you already have a type of pacemaker. If you cannot walk well enough we will not ask you to perform this test.

7. What do I have to do?

You will be asked to attend for one visit to the research centre as outlined above.
Taking part in the study should not interfere with your normal lifestyle. You will continue to take all your regular medications as directed by your doctors.

8. What is the investigation that is being studied/tested?

The investigation being tested is called Microvolt T-wave Alternans (MTWA). This is a test that looks at changes in the heart rhythm whilst you raise your heart rate by walking on a treadmill. This test is new and not routinely used in the United Kingdom. It is currently being used in many countries including the United States of America as a test to decide whether or not patients should have special pacemakers implanted.

9. What are the alternatives for investigation?

At present there is no alternative test for assessing who should and who should not have these special pacemakers put in.

10. What are the possible disadvantages and risks of taking part?

Having your blood taken is occasionally uncomfortable and some people may feel faint. There is a small risk of bleeding, bruising or infection at the puncture site following the blood test.

Exercise testing in general carries an extremely small risk of life-threatening complications (about 1 in 5000). The risks will be even lower for MTWA testing, since only gentle exercise is required for this test. Many patients with heart failure have had these walking tests with no serious problems. An experienced doctor and nurse will be present to ensure that any possible problem is dealt with expertly.

11. What are the possible benefits of taking part?

You may not benefit directly from taking part in the study; however the information we get from this study may help us to give better treatment to patients with heart failure in the future.

If the research doctor discovers during the study that you have another medical condition of which you were previously unaware you will be referred to the appropriate doctor for treatment of this condition.

12. What if new information becomes available?

If any new information becomes available that is relevant to your care we will inform you.

13. What happens when the research study stops?

There will be no further participation required.

14. What if something goes wrong?

There are no special compensation arrangements if taking part in this research project harms you. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. The normal National Health Service complaints mechanisms are available if you wish to complain or have any concerns.

15. Will my taking part in this study be kept confidential?

If you consent to take part in the study, the research doctor may inspect your medical records for purposes of analysing the results. Only government regulatory authorities and the research doctor will have access to your medical notes. Your General Practitioner will be informed of your participation in this study.

All information collected about you during the course of the research will be kept strictly confidential. Any information about you, which leaves the hospital, will have your name and address removed so that you cannot be recognised from it. Reports or publications resulting from the study will not contain any personal details.

16. What will happen to the results of the research study?

The results of the research study will be stored on a computer database and are likely to be published in cardiology journals. Reports or publications resulting from the study will not contain any personal details. The research doctor will provide a copy of the results on request.

17. Who is organising and funding the research?

We are seeking funding from the British Heart Foundation. Glasgow University and the Departments of Cardiology in Glasgow Royal Infirmary and the Western Infirmary of Glasgow are performing the study.

18. Who has reviewed the study?

This study has been reviewed and approved by West Glasgow Research Ethics Committee, which is an independent panel.

19. Contact for further information

You are encouraged to ask questions at any time during the study.

Please contact :-

Study Doctor :	Dr Colette E Jackson	0141 330 2064
Supervisor :	Prof Stuart M Cobbe	0141 211 4722
Independent Doctor :	Dr Adrian JB Brady	0141 211 4727

Thank you for taking the time to read this patient information leaflet.

Please let Dr Jackson know if you are admitted to hospital for any reason.

Appendix IV

CONSENT FORM – Stage 1

Title of Project: Microvolt T-Wave Alternans in Chronic Heart Failure

Name of researcher: Dr C. Jackson

1. I agree to a blood sampling to assess how well my heart is pumping. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that my medical records may be looked at by the research doctor or medical staff coordinating the study and this may also involve linkage to a national database. I give permission for these individuals to have access to my records. ☐

Name of patient:

Signature:

Date:

Name of person taking consent:

Signature:

Date:

1 copy for patient; 1 copy for researcher; 1 copy for hospital notes

CONSENT FORM – Stage 2

Title of Project: Microvolt T-Wave Alternans in Chronic Heart Failure

Name of researcher: Dr C. Jackson

1. I confirm that I have read and understand the information sheet dated 04/01/07 (version 3) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I agree to take part in the above study. ☐

Name of patient:

Signature:

Date:

Name of person taking consent:

Signature:

Date:

1 copy for patient; 1 copy for researcher; 1 copy for hospital notes

Appendix V: Case notes sheet

Cardiology Research Study: Microvolt T-Wave Alternans (MTWA) and Chronic Heart Failure

Patient ID

Name
DOB
Hospital number

This patient has kindly agreed to participate in a cardiology research study. The first stage of this study involves a blood test for B-type natriuretic peptide (BNP).

A blood sample for BNP was sent on:……..

If the BNP is positive (>100pg/ml) then either a research Doctor or Nurse will visit the following day to explain the results and discuss their involvement in the second stage of the study. If the BNP test is negative then there will be no further contact with the patient but their BNP result will be available via the hospital biochemistry database, as for routine samples.

Further information : Dr Colette Jackson 0141 330 2064

Project supervision : Prof S Cobbe, Prof J McMurray, Dr M Petrie

Appendix VI: Appointment card

MTWA Study in Patients

with Heart Failure

BHF Glasgow Cardiovascular Research Centre

126 University Place

University of Glasgow

G12 8TA

Dear

Thank you for agreeing to take part in the Heart Failure study.

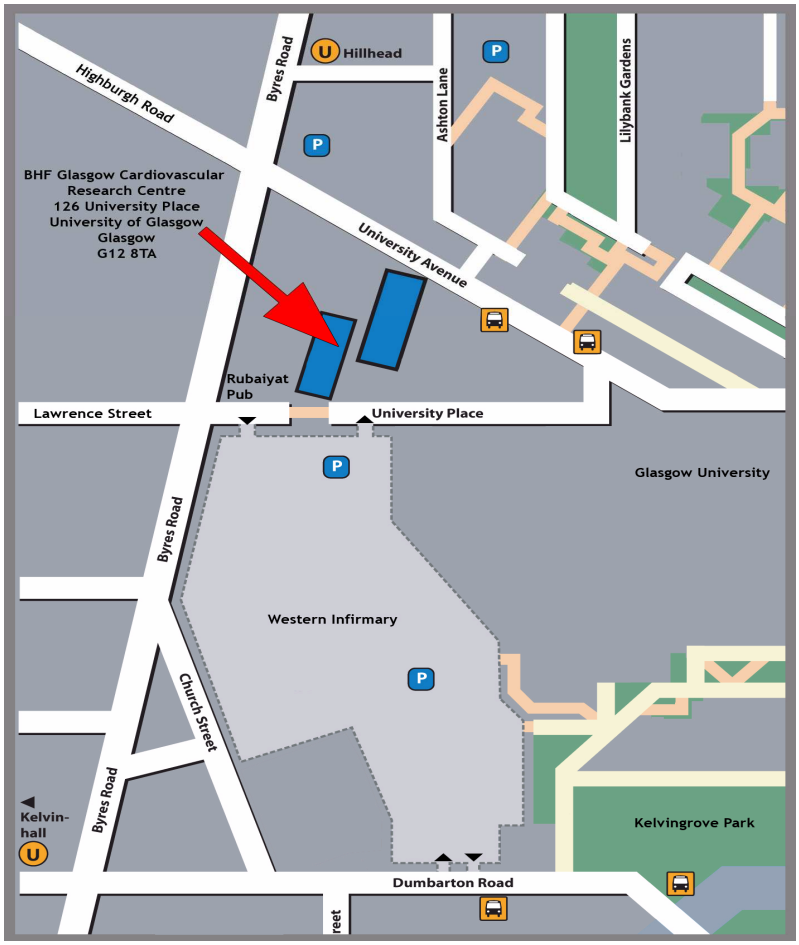
An appointment has been made for you at the BHF Glasgow Cardiovascular Research Centre on

…… at …….

Transport will be organised by us. If you are arriving with your own transport please see the map below for directions. When you arrive please report to reception and someone will take you through to the clinic area. The visit should last no more than 90 minutes. Please bring a list of your medications and comfortable shoes. For appointment queries or to change the date or time please contact the research team on 0141 330 2064

Kind regards

Dr Colette Jackson



Appendix VII

Letter to Patient's GP and Consultant

Dear Dr.

Re : _____

Your patient has been admitted to Glasgow Royal Infirmary / Western Infirmary / Royal Alexandra Hospital with heart failure. This has been confirmed by B-type natriuretic peptide (BNP) testing.

I am currently carrying out a research project in patients admitted to hospital with heart failure. Your patient has kindly agreed to take part in this study.

This will involve one visit to the British Heart Foundation Glasgow Cardiovascular Research Centre, adjacent to the Western Infirmary, approximately 4 weeks after discharge from hospital. Their participation will involve blood sampling, echocardiography and a submaximal exercise treadmill test called microvolt t-wave alternans testing. The exercise test only involves gentle walking to raise the heart rate to 110bpm and they will not participate in this if they have AF, ventricular pacemaker or are physically unable to.

Yours sincerely,

Dr C Jackson
Cardiology Research Fellow
Tel. 0141 330 2064

Project Supervision : Prof S Cobbe, Prof J McMurray and Dr M Petrie

Appendix VIII: Hospital visit case record form

Section 1 : Patient Identification & Contact Information	
Study Patient ID	☐ -- ☐☐☐
Hospital	GRI ☐ WIG ☐ RAH ☐
Date of recruitment	☐☐ / ☐☐ / ☐☐

Name	
Hospital Number	☐☐☐☐☐☐☐☐☐
CHI number	☐☐☐☐☐☐☐☐☐☐
Date of birth (dd/mm/yy)	☐☐ / ☐☐ / ☐☐
Address	
Postcode	
Home phone number	
Mobile phone number	
Work phone number	
Holiday home phone number	
Next of kin (or friend/carer)	
Next of kin phone number	
Next of kin (or friend/carer) address	
GP name	
GP address	
GP number	

Section 2 : Demographics		
Study number	☐ -- ☐☐☐	
Hospital	GRI ☐ WIG ☐ RAH ☐	
Gender	Male ☐ Female ☐	
Date of birth (dd/mm/yy)	☐☐ / ☐☐ / ☐☐	
Race	White ☐	
	Black ☐	
	South Asian ☐	
	Arab/Middle East ☐	
	Oriental ☐	
	Malay ☐	
	Other (specify) ☐ _____	
Date of Admission	☐☐ / ☐☐ / ☐☐	
Date of recruitment	☐☐ / ☐☐ / ☐☐	
Date of Discharge ***OR*** death	☐☐ / ☐☐ / ☐☐	
Symptoms	**YES**	**NO**
Orthopnoea	☐	☐
Paroxysmal nocturnal dyspnoea	☐	☐
Ankle swelling	☐	☐
Palpitations	☐	☐
NYHA class pre-admission		

Section 3 : Medical History		
	YES	**NO**
Myocardial Infarction	☐	☐
History of Angina	☐	☐
If yes, current	☐	☐
If current, stable	☐	☐
Coronary Angiography If yes, year _____	☐	☐
Percutaneous Coronary Intervention (PCI)	☐	☐
Coronary Artery Bypass Graft (CABG)	☐	☐
Treated Hypertension	☐	☐
Cerebrovascular disease (CVA/TIA)	☐	☐
Atrial Fibrillation	☐	☐
If yes, past	☐	☐
paroxysmal	☐	☐
persistent (potential restoration SR)	☐	☐
permanent	☐	☐
Chronic Heart Failure	☐	☐
If yes, previous admission with decompensated heart failure	☐	☐
Diagnosis > 2 years ago	☐	☐
Healthcare professionals involved_____		
Valvular Heart Disease	☐	☐
▪ AS		
▪ AR	☐	----------
▪ MS	☐	----------
▪ MR	☐	----------
Specify severity : Mild / Moderate / Severe	☐	----------
Valve replacement	☐	☐

	YES	NO
Pacemaker ▪ Conventional ▪ CRT-P ▪ CRT-D	☐ ☐ ☐ ☐	☐
Primary Prevention ICD	☐	☐
Syncope (brief loss of consciousness) If yes, how many episodes ☐☐	☐	☐
Prior arrhythmia If yes, ▪ SVT ▪ Ventricular tachycardia 1. Sustained 2. Nonsustained ▪ SSS ▪ AV block 1. 1st degree 2. 2nd degree 3. 3rd degree	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐
Diabetes Mellitus ▪ Diet Controlled ▪ Oral Hypoglycaemic ▪ Insulin	☐ ☐ ☐ ☐	☐
Chronic Renal Failure	☐	☐
Involuntary weight loss (>5% in 6 months)	☐	☐
Depression If yes, current	☐ ☐	☐ ☐
Cancer ▪ Current (specify site on dotted line) ▪ Previous (specify site)	☐ ☐ ☐	☐ --------- ---------
COPD	☐	☐

	YES	NO
Peripheral Vascular Disease	☐	☐
Asthma	☐	☐
Neuropathy	☐	☐
Hypothyroidism	☐	☐
Hyperthyroidism	☐	☐
Rheumatoid Arthritis	☐	☐
Osteoarthritis	☐	☐
Anaemia	☐	☐
Urinary incontinence	☐	☐
Smoker ▪ If yes, current ▪ Ex (<12 months) ▪ Ex (>12 months)	☐ ☐ ☐ ☐	☐
Alcohol ▪ If yes XS ▪ Previous XS	☐ ☐ ☐	☐
Family history heart disease ▪ If yes, coronary heart disease ▪ Cardiomyopathy ▪ Other_____ (specify)	☐ ☐ ☐ ☐	☐
Any other significant medical history (specify) 1. 2. 3. 4. 5. 6.	☐	☐

Section 4 : Medications Pre-Admission		
Cardiovascular Medication	**YES**	**NO**
Diuretics (if yes specify type & total daily dose)	☐	☐
▪ Furosemide	☐	_____mg
▪ Other loop	☐	_____mg
▪ Spironolactone	☐	_____mg
▪ Other K+ sparing	☐	_____mg
▪ Thiazide	☐	_____mg
▪ Other (name)_____	☐	_____mg
ACE-Inhibitor (if yes specify type & total daily dose)	☐	☐
▪ Captopril	☐	_____mg
▪ Enalapril	☐	_____mg
▪ Fosinopril	☐	_____mg
▪ Lisinopril	☐	_____mg
▪ Perindopril	☐	_____mg
▪ Quinapril	☐	_____mg
▪ Ramipril	☐	_____mg
▪ Trandolapril	☐	_____mg
▪ Other (name)_____	☐	_____mg
Beta-blocker (if yes specify type & total daily dose)	☐	☐
▪ Atenolol	☐	_____mg
▪ Bisoprolol	☐	_____mg
▪ Carvedilol	☐	_____mg
▪ Metoprolol	☐	_____mg
▪ Nebivolol	☐	_____mg
▪ Other (name)_____	☐	_____mg
Aldosterone Blocker (if yes specify type & daily dose)	☐	☐
▪ Spironolactone	☐	_____mg
▪ Eplerenone	☐	_____mg

	YES	NO
ARB (if yes specify type & daily dose)	☐	☐
▪ Candesartan	☐	_____mg
▪ Irebesartan	☐	_____mg
▪ Losartan	☐	_____mg
▪ Olmesartan	☐	_____mg
▪ Telmisartan	☐	_____mg
▪ Valsartan	☐	_____mg
▪ Other (name)_____	☐	_____mg
Digoxin (if yes, specify daily dose)	☐	☐ _____mg
Aspirin (if yes, specify daily dose)	☐	☐ _____mg
Clopidogrel (if yes, specify daily dose)	☐	☐ _____mg
Warfarin	☐	☐
Nicorandil (if yes, specify total daily dose)	☐	☐ _____mg
Calcium channel-blocker (if yes specify type & total daily dose)	☐	☐
▪ Amlodipine	☐	_____mg
▪ Diltiazem	☐	_____mg
▪ Nifedipine	☐	_____mg
▪ Verapamil	☐	_____mg
▪ Other (name)_____	☐	_____mg
Anti-arrhythmic (if yes specify type & total daily dose)	☐	☐
▪ Amiodarone	☐	_____mg
▪ Other (name)_____	☐	_____mg

	YES	NO
Long-acting nitrates (not s/c or short acting GTN)	☐	☐
▪ ISDN	☐	☐
▪ ISMN	☐	☐
▪ GTN patch	☐	☐
▪ Other (name)_____	☐	☐
Statin (if yes, specify type & daily dose)	☐	☐
▪ Atorvastatin	☐	_____mg
▪ Pravastatin	☐	_____mg
▪ Rosuvastatin	☐	_____mg
▪ Simvastatin	☐	_____mg
▪ Other_____	☐	_____mg
Other lipid-lowering drug	☐	☐
Diabetic Meds (if yes, specify type & daily dose)	☐	☐
▪ Insulin	☐	_____mg
▪ Sulphonylurea (eg gliclazide)	☐	_____mg
▪ Biguanide (eg metformin)	☐	_____mg
▪ Glitazone	☐	_____mg
▪ Other (specify)_____	☐	_____mg

Non-Cardiovascular Medication		
Bronchodilator (if yes specify type & daily dose)	☐	☐
▪ Beta-agonist tablets	☐	_____mg
▪ Steroid tablets	☐	_____mg
▪ Beta-agonist inhalers	☐	
▪ Anti-cholinergic inhalers	☐	
▪ Steroid inhalers	☐	

Antidepressants (if yes specify type & daily dose) ▪ SSRI ▪ TCA ▪ MAOI ▪ Other (specify)_____	☐ ☐ ☐ ☐ ☐	☐ _____mg _____mg _____mg _____mg
NSAIDs	☐	☐
Vitamins	☐	☐
Incontinence meds	☐	☐
Antihistamines	☐	☐
List any prescribed medications in addition to above prior to admission (state total daily dose) • …… • …… • …… • …… • …… • ……	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ _____mg _____mg _____mg _____mg _____mg _____mg

Section 5 : HF Medications in first 24 hours		
	YES	**NO**
Furosemide ▪ Intravenous once-off ▪ Intravenous regular ▪ Oral once-off ▪ Oral regular	☐ ☐ ☐ ☐ ☐	☐ _____mg _____mg _____mg _____mg
IV nitrate	☐	☐
IV dobutamine	☐	☐
IV dopamine	☐	☐
IV other (name) _____	☐	☐

Section 6 : Examination During Admission		
VITAL SIGNS		
Height	☐☐☐.☐ cm	
Weight	☐☐☐. ☐kg	
SpO2	☐☐ % Air ☐ O2 ☐	
Waist circumference	☐☐☐.☐ cm	
Blood pressure	☐☐☐ / ☐☐☐ mmHg	
Heart rate	☐☐☐ bpm	
Temperature	☐☐ . ☐ ºC	
Respiratory rate	☐☐ bpm	
CARDIOVASCULAR EXAMINATION		
	YES	**NO**
Elevated JVP (>4cm)	☐	☐
Palpable Apex	☐	☐
Displaced Apex	☐	☐
Third Heart Sound	☐	☐
Murmur ▪ AS ▪ AR ▪ MR ▪ MS ▪ TR	☐ ☐ ☐ ☐ ☐ ☐	☐

	YES	NO
Pulmonary crackles If yes ▪ Basal ▪ Middle ▪ Apex	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
Peripheral oedema If yes ▪ Ankle ▪ Knee ▪ Thigh ▪ Sacrum ▪ Abdomen	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐
Ascites	☐	☐
Carotid Bruit ▪ Specify: Right / Left / Bilateral (circle)	☐	☐
Killip Class I ☐ II ☐ III ☐ IV ☐ (I = No clinical signs heart failure, II = lung crackles / gallop rhythm / S3, III = frank pulmonary oedema, IV = cardiogenic shock)		

Section 7 : Investigations during hospital admission
(a) ECG

	YES	NO
Performed	☐	☐
Hard copy obtained for study	☐	☐
If yes, ▪ SR ▪ AF/flutter ▪ BBB (right / left) Specify ▪ Paced ▪ Pathological Q waves ▪ LVH ▪ QRS duration _____ms ▪ QTc duration _____ ms ▪ Other _____	 ☐ ☐ ☐ ☐ ☐ ☐	 ☐ ☐ ☐ ☐ ☐ ☐

(b) CXR

	YES	NO
Performed	☐	☐
If yes, ▪ Cardiomegaly (CTR>0.5) ▪ Upper lobe venous diversion ▪ Interstitial oedema (kerley B lines) ▪ Alveolar oedema (patchy consolidation) ▪ Pleural effusions - Specify: Right / Left / Bilateral (circle)	 ☐ ☐ ☐ ☐ ☐	

(c) ECHO

	YES	NO
Previous echo If yes, year _____	☐	☐
Performed in last year If yes, complete following,	☐	☐
Dilated left ventricle LVEDD _____ (cm)	☐	☐
Left ventricular systolic dysfunction Mild Moderate Severe	☐ ☐ ☐ ☐	☐
Valvular heart disease (if yes, circle severity) AS : Mild / Moderate / Severe AR : Mild / Moderate / Severe MS : Mild / Moderate / Severe MR : Mild / Moderate / Severe TR : Mild / Moderate / Severe Other_____ (specify)	☐ ☐ ☐ ☐ ☐ ☐	☐
Other relevant echo findings		

(d) Admission Blood Results (1st available result during admission)		
▪ **Biochemistry**		
BNP level		pg/ml
TnI		µg/l
Sodium		mmol/l
Potassium		mmol/l
Chloride		mmol/l
Urea		mmol/l
Creatinine		µmol/l
eGFR		ml/min
Bilirubin		mmol/l
AST		mmol/l
ALT		mmol/l
GGT		mmol/l
Alk Phos		mmol/l
Albumin		mmol/l
TSH		mU/l
Free T3		nmol/l
T4		mmol/l
Glucose		mmol/l
Glycosylated haemoglobin		%
Urate		mmol/l
CRP		mg/l
Phosphate		mmol/l

▪ **Lipid Profile** **Fasting** ☐ **Non-fasting** ☐		
Chol (total)		mmol/L
C/HDL		mmol/L
LDL		mmol/L
HDL		mmol/L
Triglycerides		mmol/L

▪ **Haematology**		
WCC		$x10^9$/l
Haemoglobin		g/dl
MCV		fl
RDW		%
Platelets		$x10^9$/l
Lymphocytes		$x10^9$/l

Appendix IX: Study visit case record form

Section 1 : STUDY VISIT		
	YES	**NO**
Attended	☐	☐
If no ▪ Failed/refused to attend ▪ Deteriorating health ▪ Deceased	☐ ☐ ☐	
If deceased, date of death	☐☐/ ☐☐/☐☐☐☐	
Date of study visit	☐☐/ ☐☐/☐☐☐☐	
Section 2 : CHANGES IN MEDICAL CONDITION		
	YES	**NO**
Any changes in health since discharge from hospital Specify_____ Deterioration in HF symptoms post-discharge MI since enrolment Coronary angiography since enrolment New arrhythmia (specify_____)	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐
Symptoms	**YES**	**NO**
Orthopnoea	☐	☐
Paroxysmal nocturnal dyspnoea	☐	☐
Ankle swelling	☐	☐
Palpitations	☐	☐
NYHA class _____		

Section 3 : CURRENT MEDICATIONS		
Cardiovascular Medication	**YES**	**NO**
Diuretics (if yes specify type & total daily dose)	☐	☐
▪ Furosemide	☐	_____mg
▪ Other loop	☐	_____mg
▪ Spironolactone	☐	_____mg
▪ Other K+ sparing	☐	_____mg
▪ Thiazide	☐	_____mg
▪ Other (name)_____	☐	_____mg
ACE-Inhibitor (if yes specify type & total daily dose)	☐	☐
▪ Captopril	☐	_____mg
▪ Enalapril	☐	_____mg
▪ Fosinopril	☐	_____mg
▪ Lisinopril	☐	_____mg
▪ Perindopril	☐	_____mg
▪ Quinapril	☐	_____mg
▪ Ramipril	☐	_____mg
▪ Trandolapril	☐	_____mg
▪ Other (name)_____	☐	_____mg
Beta-blocker (if yes specify type & total daily dose)	☐	☐
▪ Atenolol	☐	_____mg
▪ Bisoprolol	☐	_____mg
▪ Carvedilol	☐	_____mg
▪ Metoprolol	☐	_____mg
▪ Nebivolol	☐	_____mg
▪ Other (name)_____	☐	_____mg
Aldosterone Blocker (if yes specify type & daily dose)	☐	☐
▪ Spironolactone	☐	_____mg
▪ Eplerenone	☐	_____mg

	YES	NO
ARB (if yes specify type & daily dose)	☐	☐
▪ Candesartan	☐	_____mg
▪ Irebesartan	☐	_____mg
▪ Losartan	☐	_____mg
▪ Olmesartan	☐	_____mg
▪ Telmisartan	☐	_____mg
▪ Valsartan	☐	_____mg
▪ Other (name)_____	☐	_____mg
Digoxin (if yes, specify daily dose)	☐	☐ _____mg
Aspirin (if yes, specify daily dose)	☐	☐ _____mg
Clopidogrel (if yes, specify daily dose)	☐	☐ _____mg
Warfarin	☐	☐
Nicorandil (if yes, specify total daily dose)	☐	☐ _____mg

Calcium channel-blocker (if yes specify type & total daily dose)	☐	☐
▪ Amlodipine	☐	_____mg
▪ Diltiazem	☐	_____mg
▪ Felodipine	☐	_____mg
▪ Nifedipine	☐	_____mg
▪ Verapamil	☐	_____mg
▪ Other (name)_____	☐	_____mg
Anti-arrhythmic (if yes specify type & total daily dose)	☐	☐
▪ Amiodarone	☐	_____mg
▪ Other (name)_____	☐	_____mg

Long-acting nitrates (not s/c or short acting GTN)	☐	☐
▪ ISDN	☐	☐
▪ ISMN	☐	☐
▪ GTN patch	☐	☐
▪ Other (name)_____	☐	☐
Statin (if yes, specify type & daily dose)	☐	☐
▪ Atorvastatin	☐	_____mg
▪ Pravastatin	☐	_____mg
▪ Rosuvastatin	☐	_____mg
▪ Simvastatin	☐	_____mg
▪ Other_____	☐	_____mg
Other lipid-lowering drug	☐	☐
Diabetic Meds (if yes, specify type & daily dose)	☐	☐
▪ Insulin	☐	_____mg
▪ Sulphonylurea (eg gliclazide)	☐	_____mg
▪ Biguanide (eg metformin)	☐	_____mg
▪ Glitazone	☐	_____mg
▪ Other (specify)_____	☐	_____mg
Non-Cardiovascular Medication	**YES**	**NO**
Bronchodilator (if yes specify type & daily dose)	☐	☐
▪ Beta-agonist	☐	_____mg
▪ Anti-cholinergic	☐	_____mg
▪ Inhalers	☐	
Antidepressants (if yes specify type & daily dose)	☐	☐
▪ SSRI	☐	_____mg
▪ TCA	☐	_____mg
▪ MAOI	☐	_____mg
▪ Other (specify)_____	☐	_____mg
NSAIDs	☐	☐

Vitamins	☐	☐
Incontinence meds	☐	☐
Antihistamines	☐	☐
List any prescribed medications in addition to above (state total daily dose) • …… • …… • …… • …… • ……	☐ ☐ ☐ ☐ ☐ ☐	☐ _____mg _____mg _____mg _____mg _____mg

Section 4 : PHYSICAL EXAMINATION – STUDY VISIT		
VITAL SIGNS		
Height	☐☐☐.☐ cm	
Weight	☐☐☐. ☐kg	
SpO2	☐☐ % Air ☐ O2 ☐	
Waist circumference	☐☐☐.☐ cm	
Blood pressure	☐☐☐ / ☐☐☐ mmHg	
Heart rate	☐☐☐ bpm	
Temperature	☐☐ . ☐ ºC	
Respiratory rate	☐☐ bpm	
CARDIOVASCULAR EXAMINATION		
	Yes	**No**
Elevated JVP (>4cm)	☐	☐
Palpable Apex	☐	☐
Displaced Apex	☐	☐
Third Heart Sound	☐	☐
Murmur ▪ AS ▪ AR ▪ MR ▪ MS ▪ TR	☐ ☐ ☐ ☐ ☐ ☐	☐

	YES	NO
Pulmonary crackles If yes ▪ Basal ▪ Middle ▪ Apex	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
Peripheral oedema If yes ▪ Ankle ▪ Knee ▪ Thigh ▪ Sacrum ▪ Abdomen	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐
Ascites	☐	☐
Carotid Bruit ▪ Specify: Right / Left / Bilateral (circle)	☐	☐

Section 5 : Investigations at study visit

(a) ECG

	Yes	No
Performed	☐	☐
Hard copy obtained for study	☐	☐
If yes, ▪ SR ▪ AF/flutter ▪ BBB ▪ Paced ▪ Pathological Q waves ▪ LVH ▪ QRS duration _____ms ▪ QTc duration _____ ms ▪ Other _____	 ☐ ☐ ☐ ☐ ☐	

(b) BLOOD RESULTS		
▪ **Biochemistry**		
BNP level		pg/ml
TnI		µg/l
Sodium		mmol/l
Potassium		mmol/l
Chloride		mmol/l
Urea		mmol/l
Creatinine		µmol/l
Egfr		ml/min
Bilirubin		mmol/l
AST		mmol/l
ALT		mmol/l
GGT		mmol/l
Alk Phos		mmol/l
Albumin		mmol/l
TSH		mU/l
Free T3		nmol/l
T4		mmol/l
Glycosylated haemoglobin		%
Urate		mmol/l
Phosphate		mmol/l

▪ **Lipid Profile** **Fasting** ☐ **Non-fasting** ☐		
Chol (total)		mmol/L
LDL		mmol/L
HDL		mmol/L
Triglycerides		mmol/L

▪ **Haematology**		
WCC		$x10^9$/l
Haemoglobin		g/dl
MCV		fl
RDW		
Platelets		$x10^9$/l
Lymphocytes		$x10^9$/l

(c) ECHO – LVEF (Simpson's)		
	YES	**NO**
Preserved (> 50%)	☐	☐
Reduced (≤ 50%)	☐	☐
Value	☐☐ %	
LVEF incalculable If yes, ▪ Estimated preserved ▪ Estimated reduced	☐ ☐	☐ ☐

Section 6 : MTWA TEST

(a) ELIGIBILITY

	YES	NO
Eligible for MTWA treadmill testing (if yes, proceed to test result)	☐	☐
If no, please specify: ▪ AF ▪ Ventricular pacing ▪ Severe AS ▪ Unable to exercise	☐ ☐ ☐ ☐	
If unable to exercise please give reason: ……		
If unable to exercise was MTWA assessed at rest If yes, ▪ Was MTWA present at rest ▪ Resting heart rate ☐☐☐ bpm	☐ ☐	☐ ☐

(b) MTWA TEST - RESULT		
Positive	☐	☐
Indeterminate	☐	☐
Negative	☐	☐
If positive ▪ Sustained alternans at rest ▪ Sustained alternans onset HR <110bpm	☐ (Class I) ☐(Class 2) OHR= ☐☐☐ bpm	
If negative ▪ No sustained alternans and max negative HR >105bpm ▪ Sustained alternans OHR >110bpm and max NHR>105bpm	☐ (Class 5) NHR=☐☐☐ bpm ☐ (Class 3) OHR=☐☐☐ bpm	
If indeterminate ▪ Sustained alternans OHR >110bpm and max NHR <105bpm ▪ Bad beats, noise or nonsustained alternans ▪ Insufficient HR ▪ Other/comments…… ……..	☐ (Class 4) OHR=☐☐☐ bpm NHR= ☐☐☐ bpm ☐ (Class 6) ☐ (Class 4)	

If indeterminate, repeat MTWA test	Yes ☐	No ☐
If positive ▪ Sustained alternans at rest ▪ Sustained alternans onset HR <110bpm	☐ (Class I) ☐(Class 2) OHR=☐☐☐ bpm	
If negative ▪ No sustained alternans and max negative HR >105bpm ▪ Sustained alternans OHR >110bpm and max NHR>105bpm	☐ (Class 5) NHR=☐☐☐ bpm ☐ (Class 3) OHR=☐☐☐ bpm	
If indeterminate ▪ Sustained alternans OHR >110bpm and max NHR <105bpm ▪ Bad beats, noise or nonsustained alternans ▪ Insufficient HR ▪ Other/comments……. ……..	☐ (Class 4) OHR=☐☐☐ bpm NHR=☐☐☐ bpm ☐ (Class 6) ☐ (Class 4)	

Section 7 : AETIOLOGY OF HEART FAILURE

	YES	NO	
Known HF prior to enrolment in this study	☐	☐	
If yes, which healthcare professionals are involved			
▪ GP	☐	☐	
▪ General physician	☐	☐	
▪ Cardiologist	☐	☐	
▪ HF specialist	☐	☐	
▪ HF liaison nurse	☐	☐	
Primary Aetiology			
	Yes	No	Unknown
Ischaemic	☐	☐	☐
If yes, must have			
▪ Definite previous MI	☐	☐	
or			
▪ Angio. CHD (>50% stenosis in ≥ 1 vessel)	☐	☐	
Idiopathic DCM	☐	☐	
Hypertension (if all other causes excluded)	☐	☐	
Alcohol (if all other causes excluded)	☐	☐	
Contributing Aetiologies			
Valvular	☐	☐	
If yes,			
▪ AS	☐		
▪ AR	☐		
▪ MS	☐		
▪ MR	☐		
Diabetes Mellitus	☐	☐	
Atrial Fibrillation	☐	☐	
Hypertension	☐	☐	
Alcohol	☐	☐	
Other (specify) ……			
Unknown	☐	☐	

Publications containing work undertaken in this thesis

1. Profile of Microvolt T-wave Alternans testing in 1003 patients hospitalised with heart failure

Jackson CE, Myles RC, Tsorlalis IK, Dalzell JR, Rocchiccioli JP, Spooner RJ, Rodgers JR, Bezylak V, Greenlaw N, Ford I, Cobbe SM, Petrie MC, McMurray JJV

Submitted to the European Journal of Heart Failure, September 2011

2. Red cell distribution width has incremental prognostic value to B-type natriuretic peptide in acute heart failure

Jackson CE, Dalzell JR, Bezylak V, Tsorlalis IK, Myles RC, Spooner R, Ford I, Petrie MC, Cobbe SM, McMurray JJV.

European Journal of Heart Failure 2009; 11 (12): 1152-54

3. Is Microvolt T-Wave Alternans the Answer to Risk Stratification in Heart Failure?

Myles RC, **Jackson CE**, Tsorlalis I, Petrie MC, McMurray JJV, Cobbe SM.

Circulation 2007; 116: 2984-2991

Presentations to Learned Societies

1. The novel biomarker red cell distribution width (RDW) has prognostic information to B-type natriuretic peptide (BNP) in patients with acute decompensated heart failure.

Jackson CE, Bezylak V, Dalzell JR, Tsorlalis IK, Myles RC, Spooner R, Ford I, Petrie MC, Cobbe SM, McMurray JJV.

Oral presentation – European Society of Cardiology Annual Congress, Barcelona, 2009

European Heart Journal 2009; 30:14

2. Multimarker laboratory testing in acute decompensated heart failure – how much prognostic information do novel biomarkers BNP, troponin and CRP provide in addition to routine laboratory tests?

Jackson CE, Bezylak V, Dalzell JR, Tsorlalis IK, Myles RC, Spooner R, Ford I, Petrie MC, Cobbe SM, McMurray JJV

European Society of Cardiology Annual Congress, Barcelona, September 2009

European Heart Journal 2009; 30: 711

3. The incremental prognostic value of sub-negative troponin I levels in patients hospitalised with decompensated heart failure

Jackson CE, Austin D, Dalzell JR, Tsorlalis IK, Myles RC, Rodgers J, Spooner R, Petrie MC, Cobbe SM, McMurray JJV

British Cardiovascular Society Annual Conference, London, June 2009

Heart 2009; 95 (Supplement I): A53-4

4. Do very low concentrations of troponin I, below the range reported as being negative, improve risk stratification of patients hospitalised with decompensated heart failure?

Jackson CE, Austin D, Dalzell JR, Tsorlalis IK, Myles RC, Rodgers J, Spooner R, Petrie MC, Cobbe SM, McMurray JJV

European Society of Cardiology Annual Congress, Munich, September 2008.

European Heart Journal 2008; 29 (Suppl 51): 521

5. Does troponin I provide additional prognostic information to B-type natriuretic peptide in patients hospitalised with decompensated heart failure?

Jackson CE, Tsorlalis IK, Austin D, Myles RC, Rodgers J, Spooner R, Petrie MC, Cobbe SM, McMurray JJV

European Society of Cardiology - Heart Failure Congress, Milan, June 2008,

European Journal of Heart Failure 2008; 7 (Supplement I): 4

6. Does blood urea concentration predict early mortality in patients hospitalised with decompensated heart failure better than estimated glomerular filtration rate (eGFR)?

Jackson CE, Austin D, Tsorlalis IK, Dalzell JR, Myles RC, Rodgers J, Spooner R, Petrie MC, Cobbe SM, McMurray JJV

European Society of Cardiology - Heart Failure Congress, Milan, June 2008

European Journal of Heart Failure 2008; 7 (Supplement I): 103

7. Blood urea concentration as a predictor of early mortality in patients hospitalised with decompensated heart failure

Jackson CE, Austin D, Tsorlalis IK, Dalzell JR, Myles RC, Rodgers J, Spooner R, Petrie MC, Cobbe SM, McMurray JJV

British Cardiovascular Society Annual Conference, Manchester, June 2008

Heart 2008; 94 (Supplement II): A107

8. Elevated Troponin I and B-type natriuretic peptide in combination is a powerful predictor of outcome in patients hospitalised with decompensated heart failure

Jackson CE, Tsorlalis IK, Gardner RS, Austin D, Myles RC, Rodgers J, Stewart N, Spooner R, Petrie MC, Cobbe SM, McMurray JJV

British Society of Heart Failure, London, November 2007

9. Does Troponin I provide additional prognostic information to B-type natriuretic peptide in patients hospitalised with decompensated heart failure?

Jackson CE, Tsorlalis IK, Austin D, Myles RC, Rodgers J, Stewart N, Spooner R, Petrie MC, Cobbe SM, McMurray JJV

Scottish Society for Experimental Medicine, Glasgow, November 2007

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