MITRAL REGURGITATION and HEART FAILURE (MRAHF)

OTAR LAZARIASHVILI

ROYAL HOLLOWAY, UNIVERSITY OF LONDON

This thesis is submitted in fulfilment of the requirements for the degree of Doctorate of Medicine (Research) from the Royal Holloway, University of London

I declare that this thesis which I submit for a degree “Doctor of Medicine” is my own personal effort.

No part of the work presented in this thesis has been submitted in support of an application for another degree or qualification at this or any other university or other institute of learning.

I am responsible for all the work presented in this thesis.

Dr Otar Lazariashvili, 09/09/2018

ABSTRACT

Background

Acute Heart Failure (AHF) is a well recognised growing healthcare problem with increasing hospitalisation rate, high mortality and severe financial burden on healthcare budget. Mitral regurgitation (MR) is known as a highly prevalent valvular disease with an impact on prognosis in AHF not clearly established.

Aims

The aim of Mitral regurgitation and Heart Failure (MRAHF) program was to assess the prognostic impact of mitral regurgitation (MR) in patients admitted with acute heart failure (HF) or exacerbation of chronic HF in a single center prospective cross-sectional study, to assess the significance of financial burden of admitted HF patients and to look at how many of these patients were managed according to NICE recommendations.

Methods

All patients admitted to a district general hospital with symptoms of AHF over a period of 1 year were included. Patients with raised bedside point-of-care BNP (Brain Natriuretic Peptide) had standard clinical assessment and transthoracic echocardiography within 48 hour of recruitment. Echocardiography included quantitative assessment of MR, assessment of cardiac chambers and other valvular function. MR was categorised as mild, moderate, moderate to severe and severe. MR of moderate severity and above was considered significant. Demographic and comorbidity data including known history of MR, 6 months and 1 year mortality were documented. All MRAHF patients` clinical management pathway has been reviewed with comparison to the NICE guideline, and their outcome were recorded as well.

Results

418 patients were included into the study. All patients (100%) were found to have MR; 165 (39.5%) had significant MR. Those with significant MR had features of left ventricular (LV) remodelling with increase in end-diastolic (LVEDV) (129±58 ml vs 99±49 ml, p<0.0001) and end systolic (LVESV) (82±50ml v s 58±41ml, p<0.0001) volumes and reduction in LV ejection fraction (LVEF) (38±14% vs 45±14%, p<0.0001) in presence of significant volume overload (MR RV 47.8±17.7cm3 vs 17.8±7.0cm3, P<0.0001). Severity of pulmonary hypertension (PHT) and right ventricular (RV) dysfunction were also significantly worse in presence of significant MR: systolic pulmonary artery pressures (SPAP) (57±17.9mmHg vs 49.7±18mmHg, p<0.0001), RV fractional area change (RVFAC) (34.1±12% vs 38.8±12%, p<0.0001). In presence of significant MR there was significant increase in 6-month mortality (34.9% vs 23.8% p<0.05). 232 (55.5%) patients from the whole cohort did not follow the NICE guidelines and most of them had isolated RVSD, significant MR and twice higher mortality. 219 MRAHF patients (52%) had missed diagnosis of HF by coding team. The rest of MRAHF patients had considerably higher expenditure during inpatient stay compared to the average cost of HF admission.

Conclusion

Significant MR is associated with adverse changes in LV geometry, prominent PHT and LV/RV dysfunction and a reduced survival in AHF. Patients with significant MR had a more impaired RV function and prominent PAP then the other group. The majority of HF patients whose management was not based on the NICE guidelines had an adverse outcome. The cost of MRAHF patients with significant RV dysfunction was higher compared to others. The use of bedside BNP test has demonstrated high effectiveness in triaging of HF patients.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank you my supervisors Dr Aigul Baltabaeva, Consultant Cardiologist at the Harefield Hospital, and Prof Pankaj Sharma, Professor of Neurology, the Director of Institute of Cardiovascular Research at the Royal Holloway, University of London. Their support and supervision over the past years has been truly appreciated.

I would also like to extend my gratitude to colleagues from the Research and Development department at Ashford and St Peter`s NHS Trust from making me feel welcome from the day one. Also, I am very grateful to Kate Sergeant, Dr Iona Cotlarciuc and Tracey Jeffreys from the Royal Holloway University for their regular support.

A special thanks to Dr Isaac John, deputy director of the Research and Development department at the Ashford and St Peter`s NHS trust. He was continuously supporting me and was the best advisor in the difficult time.

LIST OF POSTERS at the ESC conference Heart Failure 2018, Viena

1. O. Lazariashvili, J. Stewart, D. Fluck, I. Beeton, P. Sharma, A. Baltabaeva. Cardiac Geometry, Function and Prognosis in Acute Heart Failure in Presence of Significant Mitral Regurgitation.

2. J.Stewart, O.Lazariashvili, D.Fluck, A.Baltabaeva. Right Ventricular Function is a Strong Predictor of Outcome in Acute Heart Failure

3. J. Stewart, O.Lazariashvili, D.Fluck, I.Beeton, P. Sharma, A.Baltabaeva. Arrhythmia Induced Heart Failure in The Emergency Room: Frequency of Avoidable Precipitant of Hospital Admission.

CONTENTS

CHAPTER 1. INTRODUCTION

1.1.1 Background

In recent years, heart failure (HF) has been recognised as a major and increasing public health problem (1-3) on an epidemic scale (4). From 20 million people being affected by HF in 2008(5) ; this figure has grown up to 37.7 million worldwide (3). The incidence of HF hospitalisations has tripled over the last 3 decades (6-8). In Europe, about 5% of all acute hospital admissions are HF related (9,10). It is estimated that HF accounted for 1.2% of National Health Service (NHS) expenditure in the United Kingdom (UK) (11) and similar in other countries (12-15). After discharge, HF patients are at high risk of rehospitalisation or death. 3-month mortality and readmissions are close to 14 and 25% respectively (16). Complex pharmacotherapy, community care, and particularly frequent hospital admissions (17,18) have significant cumulative effect on health economics.

The multifactorial nature of HF makes it difficult to elucidate any single haemodynamic risk factor for recurrent hospital admissions (19). Approximately half of hospitalised HF patients have moderate to severely reduced left ventricular (LV) systolic function, with an ejection fraction (LVEF) of < 40 % (20). It is not clear if changes in LV geometry and mitral valve apparatus could play an additional role in the course of disease. The devastating effect of ischaemic mitral regurgitation (MR) on patient survival (21) might be secondary to the change of myocardial shape. In general, development of significant MR is strongly associated with worsened prognosis in patients with HF, regardless of its aetiology (22).

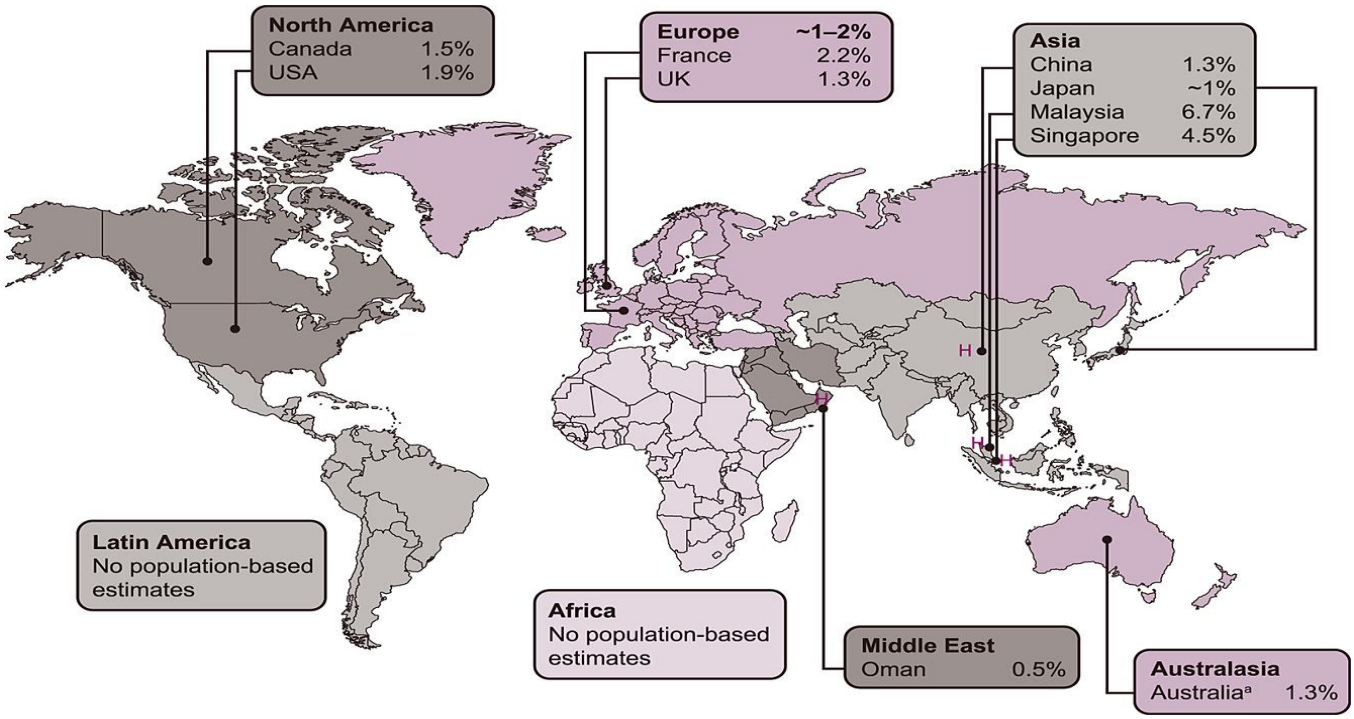
1.1.2 History of Heart failure

Descriptions of heart failure exist from ancient Egypt, Greece, and India, and the Romans were known to use the foxglove as medicine. There was little understanding of the nature of the condition until William Harvey described the circulation in 1628 (23). Röntgen's discovery of X-rays and Einthoven's development of electrocardiography in the 1890s led to improvements in the investigation of heart failure. The advent of echocardiography, cardiac catheterisation, and nuclear medicine have since improved the diagnosis and investigation of patients with heart failure (23).

Blood letting and leeches were used for centuries, and William Withering published his account of the benefits of digitalis in 1785. In the 19th and early 20th centuries, heart failure associated with fluid retention was treated with Southey's tubes, which were inserted into oedematous peripheries, allowing some drainage of fluid (23).

It was not until the 20th century that diuretics were developed. The early, mercurial agents, however, were associated with substantial toxicity, unlike the thiazide diuretics, which were introduced in the 1950s (23). Vasodilators were not widely used until the development of angiotensin converting enzyme inhibitors in the 1970s. The landmark CONSENSUS-I study (first cooperative north Scandinavian enalapril survival study), published in 1987, showed the unequivocal survival benefits of enalapril in patients with severe heart failure (23).

FIGURE 1. **Proportion of the population living with heart failure in individual countries across the globe (24-27). Estimates based on a single centre or hospital are indicated by an H. No population-based studies have reportedly been conducted to estimate the proportion of the population living with heart failure in Africa (28) or Latin America (29).**



1.1.3 The global burden of Heart failure

In many countries, population-based studies have found that about 1–2% of people have heart failure, and similar or higher proportions have been reported in single-centre studies (FIGURE 1)(24-29). Heart failure becomes more common with increasing age. In North America and Europe, few patients with heart failure are 50 years of age or younger (30-32) and more than 80% are 65 years of age or older (33). The number of patients with heart failure is predicted to increase in countries with ageing populations (34). Japan, in particular, has the most rapidly ageing population of all economically developed nations (35). In the USA, there were 5.8 million patients living with heart failure in 2012, and this is expected to rise to 8.5 million by 2030 (36). Another contributing factor to these increasing numbers is the improvement in treating heart attacks and other cardiovascular diseases that damage or place an extra burden on the heart. More patients with these conditions are surviving now than did in the past, but those who survive are at high risk of going on to develop heart failure (37).

In economically developing areas, such as parts of Latin America and Asia, the numbers of patients with heart failure are also increasing (24,38,39). The increase is largely a result of the shift towards a Western-type lifestyle and its associated diseases, for example, conditions such as diabetes increase the risk of developing heart failure.

Infections remain a common cause of heart failure in many parts of the world and can strike at any age. Heart failure is not a disease of the elderly in sub-Saharan Africa, where half of patients

hospitalized with the disease are 55 years of age or younger (40). Patients in the Asia Pacific region also tend to be younger than those in Western regions (41). Rheumatic fever due to preventable bacterial infections is a prominent cause of heart failure in Africa, Asia, Australasia and Latin America (24). HIV infection is also a major contributor to heart-related disease across the world (24). In areas of Latin America where Chagas disease is common, nearly half of all heart failure cases are a direct result of this preventable parasitic infection (39).

1.1.4 Heart failure in different ethnic groups

There is a higher risk of HF incidence among African Americans, which is related to differences in the prevalence of hypertension and diabetes mellitus as well as socioeconomic status (42).The mechanisms of HF differ by ethnicity as well; interim myocardial infarction has the least influence among African Americans, and left ventricular mass increase has the greatest effect among Hispanic and white participants (42).

Although ethnicity has been suggested as an independent risk factor for congestive HF (43,44), the direct effect of ethnicity on incidence of congestive HF has not been demonstrated in a population-based study. Most of the data regarding the incidence of congestive HF are derived from white populations, and, therefore, it is not easy to determine the incidence of congestive HF among other ethnic groups. Previous studies have shown high mortality and hospitalisation rates due to congestive HF among African American compared with white populations (45,46), but did not elucidate the factors that induce the onset of congestive HF in a multi-ethnic population. Discrepancies in the prevalence and consequences of congestive HF between African Americans and whites have been attributed to racial/ethnic differences in the prevalence of coexisting conditions such as hypertension and diabetes mellitus, the quality and availability of medical care, and disparities in socioeconomic factors (46,47).

1.1.5 Acute heart failure and rate of hospitalisation

There are over 67,000 admissions in England with acute heart failure (AHF) each year (48). Most patients admitted to the hospital with AHF have a worsening of chronic HF (CHF), 15- 20% of acute HF hospitalisations represent new diagnoses of HF (49). Patients with a new diagnosis of HF are much more likely to present with pulmonary oedema or cardiogenic shock, while decompensation of chronic HF usually presents with other signs of congestion and fluid retention, such as weight gain, exertional dyspnoea, or orthopnoea. These symptoms can begin days or weeks before presentation (50). Hospitalisations for decompensated HF is a powerful predictor of readmissions and post-discharge death in patients with chronic heart failure (CHF), with mortality as high as 20% after discharge (51,52).

The pattern of hospital admissions has changed dramatically. In the early 1990s only 0.2% of the UK population were hospitalised for HF per annum, but the length of stay (LOS) was significantly long; mean LOS for a HF related admission was 11.4 days on acute medical wards and 28.5 days on geriatric wards. Currently such admissions accounted for more than 5% of adult general medicine and geriatric hospital admissions—outnumbering those associated with acute myocardial infarction (53). Despite significant reduction of LOS many patients require readmission (54). Within the UK

about one third of patients are readmitted within 12 months of discharge, with similar rate reported in the USA (53,55). HF readmission rates are higher than the other major causes of hospitalisation such as stroke, hip fracture, and respiratory disease. Additionally, patients tend to lose their home independence during HF admissions (54).

1.1.6 Precipitants for heart failure hospitalisations

The most common known precipitants for HF hospitalisation are noncompliance with medications or dietary restrictions, uncontrolled hypertension, ischaemia, arrhythmias, and exacerbation of chronic obstructive pulmonary disease with or without pneumonia (56). Other contributors include noncardiac conditions such as renal dysfunction, diabetes mellitus, anaemia, and the side effects of medications (57). Despite this up to 40-50% of acute decompensated HF episodes have no known cause (58). It is imperative that these precipitants, when identified, be defined and treated and that effective interventions be developed to prevent recurrence. Euro HF II survey reported high incidence of valvular heart disease especially MR in 80% of patients, which was reported on echocardiography (59), but no prospective studies are available looking into this matter.

1.2.1 Definition of heart failure

HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood (60). This is a condition in which the heart does not pump enough blood to meet all the needs of the body. Acute heart failure can present as new-onset heart failure in people without known cardiac dysfunction, or as acute decompensation of chronic heart failure.

1.2.2 Asymptomatic heart failure

The current definition of HF restricts itself to stages at which clinical symptoms are apparent. Before clinical symptoms become apparent, patients can present with asymptomatic structural or functional cardiac abnormalities [systolic or diastolic left ventricular (LV) dysfunction], which are precursors of HF. Recognition of these precursors is important because they are related to poor outcomes, and starting treatment at the precursor stage may reduce mortality in patients with asymptomatic systolic LV dysfunction (61,62).

1.2.3 Heart failure as a result of multiple disorders

The clinical syndrome of HF may result from disorders of the pericardium, myocardium, endocardium, heart valves, great vessels or from certain metabolic abnormalities, but most patients with HF have symptoms due to impaired left ventricular (LV) myocardial function. HF may be associated with a wide spectrum of LV functional abnormalities, which may range from patients with normal LV size and preserved ejection fraction (EF) to those with severe dilatation and/or markedly reduced EF. In most patients, abnormalities of systolic and diastolic dysfunction coexist. EF is considered important in classification of patients with HF because of differing patient demographics, comorbid conditions, prognosis, and response to therapies (63) and because most clinical trials select patients based on EF. EF values are dependent on the imaging technique used, method of analysis, and operator.

1.3. Diagnosis

The diagnosis of heart failure was traditionally made at the bedside based on clinical evaluation that combined characteristic symptoms from the history with various signs on physical examination. Other than the obvious need to determine whether a patient has heart failure, it is also important to determine what type of heart failure is present. Patients with heart failure need a comprehensive workup that begins with the history and physical examination (64).

1.3.1 Symptoms and signs

The cardinal manifestations of HF are dyspnoea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral oedema. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of oedema, dyspnoea, or fatigue. Because some patients present without signs or symptoms of volume overload, the term "heart failure" is preferred over "congestive heart failure." (60) There is no single diagnostic test for HF because it is largely a clinical diagnosis based on a careful history and physical examination. **TABLE 1** demonstrates more detailed symptomatic presentation of heart failure with many of them being non-specific.

TABLE 1. Symptoms and signs of heart failure (19,65)

Symptoms	Signs
Typical	**More specific**
Breathlessness Orthopnoea Paroxysmal nocturnal dyspnoea Reduced exercise tolerance Fatigue, tiredness, increased time to recover after exercise Ankle swelling	Elevated jugular venous pressure Hepatojugular reflux Third heart sound (gallop rhythm) Laterally displaced apical impulse
Less typical	**Less specific**
Nocturnal cough Wheezing Bloated feeling Loss of appetite Confusion (especially in the elderly) Depression Palpitations Dizziness Syncope Bendopnea[53]	Weight gain (>2 kg/week) Weight loss (in advanced HF) Tissue wasting (cachexia) Cardiac murmur Peripheral oedema (ankle, sacral, scrotal) Pulmonary crepitations Reduced air entry and dullness to percussion at lung bases (pleural effusion) Tachycardia Irregular pulse Tachypnoea Cheyne Stokes respiration Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure

1.3.2 Clinical classifications

Several classification schemes have been developed for acute HF. Patients are generally divided into those who present with HF for the first time and those whose chronic HF worsens. Of the approximately 80% of acute HF patients with worsening of chronic HF, less than 10% have advanced HF (49). The characteristics of advanced HF include low blood pressure, renal impairment, and signs or symptoms of HF that are refractory to standard therapy.

1.3.2.1 New York Heart Association (NYHA) classification (66)

This symptom-based scale classifies heart failure in four categories. In Class I heart failure, patients do not have any symptoms, there is no limitation of physical activity and they are able to perform ordinary physical activity. In Class II heart failure, there is slight limitation of physical activity. Patients are comfortable at rest, but ordinary physical activity results in symptoms of HF. With Class III, there is marked limitation of physical activity. Patients are comfortable at rest, but less than ordinary activity causes symptoms of HF. Class IV is the most severe, when patients are unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

1.3.2.2 Heart failure classification on clinical and haemodynamic characteristics

The European Society of Cardiology guidelines for the diagnosis and treatment of acute HF classifies patients into 1 of 6 groups on the basis of typical clinical and hemodynamic characteristics (67), based on the work of Cotter (68), Gheorghiade, and colleagues. The first 3 categories of patients (those with acute decompensated heart failure [ADHF], hypertensive acute heart failure [AHF], and AHF with pulmonary oedema) comprise over 90% of AHF presentations. The patient with ADHF typically presents with mild-to-moderate signs and symptoms of congestion and does not meet the criteria for other categories. Hypertensive AHF patients are characterized by their relatively preserved LV systolic function (LVEF > 40%), elevated blood pressure, and pulmonary oedema. The 3rd group, patients who have AHF with pulmonary oedema, has a clinical presentation that is dominated by severe respiratory distress, orthopnoea, signs of pulmonary oedema (verified by rales on physical examination and chest radiography), and hypoxemia (the oxygen saturation is usually <90% on room air).

Patients with low-output syndrome have evidence of tissue hypoperfusion due to HF and display a continuum of severity ranging from a low-output state to cardiogenic shock. High-output failure presents with warm extremities, pulmonary congestion, and at times low blood pressure (that is, sepsis) with high cardiac output and usually an elevated heart rate. Underlying conditions associated with this type of ADHF include anaemia, thyrotoxicosis, and Paget's disease. Right-sided AHF occurs most commonly in patients with underlying lung disease, such as those who have chronic obstructive pulmonary disease and develop cor pulmonale, or those who have pulmonary hypertension for other reasons, including left-heart failure. Right-sided AHF patients generally present with increased jugular venous pressure, hepatomegaly, oedema, low-output syndrome, and hypotension (49).

1.3.2.3 Heart failure with preserved, mid-range and reduced ejection fraction

The main terminology used to describe HF is historical and is based on measurement of the LV ejection fraction (EF). EF is considered important in classification of patients with HF because of differing patient demographics, comorbid conditions, prognosis, and response to therapies (69) and because most clinical trials selected patients based on EF. HF comprises a wide range of patients, from those with normal LVEF [typically considered as ≥50%; also referred to as diastolic HF, HF with preserved EF (HFpEF)] to those with reduced LVEF [typically considered as < 40%; also referred to as systolic HF, HF with reduced EF (HFrEF)] (**TABLE 2).** Patients with an LVEF in the range of 40–49% represent a 'grey area', which we now define as HFmrEF (**TABLE 2**)(19). Differentiation of patients with HF based on LVEF is important due to different underlying aetiologies, demographics, co-morbidities and response to therapies(70).

TABLE 2. Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		**HFrEF**	**HfmrEF**	**HFpEF**
CRITERIA	1	Symptoms ± signs[1]	Symptoms ± signs[1]	Symptoms ± signs[1]
	2	LVEF < 40%	LVEF 40-49%	LVEF ≥ 50%
	3	_____	1. Elevated levels of natriuretic peptides2. 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE). b. diastolic dysfunction.	1. Elevated levels of natriuretic peptides2. 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE). b. diastolic dysfunction.

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF= heart failure with preserved ejection fraction; HFrEF= heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide. [1]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics 2BNP >35 pg/ml and/or NT-proBNP>125 pg/ml. (19)

1.3.2.4 Congestion and hypoperfusion profiles of heart failure

Another clinically relevant and widely used system for classifying ADHF was developed by Stevenson and colleagues (71). In contrast with the European Society of Cardiology system, this system focuses more on the severity of disease at presentation than on the cause of HF. It classifies patients on the basis of the clinical presence or absence of hypoperfusion (cold vs warm) and of congestion at rest (wet vs dry) (**FIGURE 2**). Patients with clinical profile A (warm and dry) had a 6-month mortality rate of 11%, compared with 40% for profile C (cold and wet), which shows that these clinical profiles can have prognostic significance.

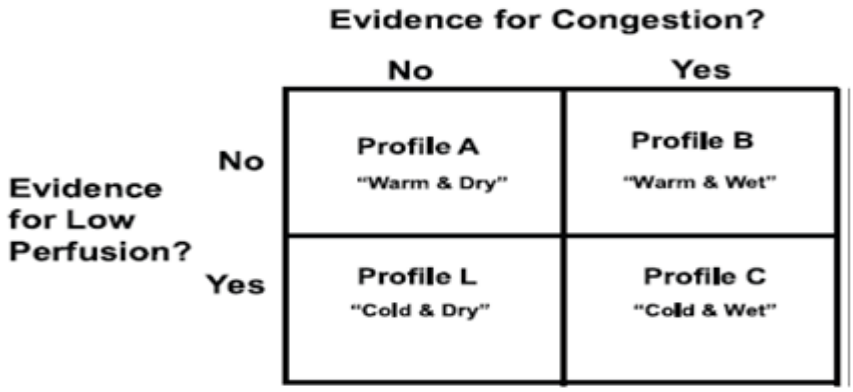


FIGURE 2. Hemodynamic profiles of patients presenting with advanced heart failure.

Modified from: Nohria A, Mielniczuk LM, Stevenson LW. Evaluation and monitoring of patients with acute heart failure syndromes. Am J Cardiol 2005;96(6A):32G-40G.

1.4. Diagnostic tests in patients with suspected heart failure

There are many tests for diagnosis of heart failure (table 3), however echocardiography (ECHO) and electrocardiography (ECG) are the most useful in patients with suspected HF.

1.4.1 Transthoracic echocardiography

Echocardiography provides immediate information on chamber volumes, ventricular systolic and diastolic function, wall thickness, and valve function (72-75). This information is crucial in determining appropriate treatment (e.g. an ACE inhibitor and beta-blocker for systolic dysfunction or surgery for aortic stenosis). Echocardiography is the method of choice in patients with suspected HF, for reasons of accuracy, availability (including portability), safety and cost (76-78).

1.4.1.1 Assessment of left ventricular systolic function

For the assessment of left ventricular systolic function the main characteristic is ejection fraction, which is measured by the modified biplane Simpson`s method. LV end diastolic volume (LVEDV) and LV end systolic volume (LVESV) are obtained from apical four- and two-chamber views. This method relies on accurate tracing of endocardial borders. In case of poor image quality, contrast agents should be used to improve endocardial delineation (78). Tissue Doppler parameters (S wave) and deformation imaging techniques (strain and strain rate) have been shown to detect subtle abnormalities in systolic function in the preclinical stage; however, measurements may vary among vendors and software versions (19,79).

1.4.1.2 Assessment of left ventricular diastolic function

LV diastolic dysfunction is thought to be the underlying pathophysiological abnormality in patients with HFpEF and perhaps HFmrEF, and thus its assessment plays an important role in diagnosis. Although echocardiography is at present the only imaging technique that can allow for the diagnosis of diastolic dysfunction, no single echocardiography variable is sufficiently accurate to be used in isolation to make a diagnosis of LV diastolic dysfunction (19).

1.4.1.3 Assessment of right ventricular function and pulmonary arterial pressure

An obligatory element of echocardiography examination is the assessment of right ventricle (RV) structure and function, including RV and right atrial (RA) dimensions, an estimation of RV systolic function and pulmonary arterial pressure. Among parameters reflecting RV systolic function, the following measures are of particular importance: tricuspid annular plane systolic excursion (TAPSE; abnormal TAPSE < 17 mm indicates RV systolic dysfunction) and tissue Doppler-derived tricuspid lateral annular systolic velocity (s') (s' velocity <9.5 cm/s indicates RV systolic dysfunction) (79,80). Systolic pulmonary artery pressure is derived from an optimal recording of maximal tricuspid regurgitant jet and the tricuspid systolic gradient, together with an estimate of RA pressure on the basis of inferior vena cava (IVC) size and its breathing-related collapse (81). Three-dimensional speckle tracking echocardiography may be an additional quantitative method to assess RV function (82).

1.4.2 Electrocardiography

An abnormal ECG increases the likelihood of the diagnosis of HF, but has low specificity (83-86). Some abnormalities on the ECG provide information on aetiology (e.g. myocardial infarction), and findings on the ECG might provide indications for therapy (e.g. anticoagulation for AF, pacing for bradycardia, CRT if broadened QRS complex). HF is very unlikely (likelihood <2%) in patients presenting acutely and with a completely normal ECG (87-89).

The information provided by these two tests will permit an initial working diagnosis and treatment plan in the majority of patients (90). Routine biochemical and haematological investigations are also important, partly to determine whether renin–angiotensin–aldosterone blockade can be initiated safely (renal function and potassium) and to exclude anaemia (which can mimic or aggravate HF) and because they provide other, useful information.

TABLE 3. Recommendations for the diagnostic investigations for suspected heart failure by European Society of Cardiology (65)

Recommendations	Class[a]	Level[b]
Investigations to consider in all patients		
Transthoracic echocardiography is recommended to evaluate cardiac structure and function, including diastolic function (Section 4.1.2), and to measure LVEF to make the diagnosis of HF, assist in planning and monitoring of treatment, and to obtain prognostic information.	I	C
A 12-lead ECG is recommended to determine heart rhythm, heart rate, QRS morphology, and QRS duration, and to detect other relevant abnormalities (*Table 5*). This information also assists in planning treatment and is of prognostic importance. A completely normal ECG makes systolic HF unlikely.	I	C
Measurement of blood chemistry (including sodium, potassium, calcium, urea/blood urea nitrogen, creatinine/estimated glomerular filtration rate, liver enzymes and bilirubin, ferritin/TIBC) and thyroid function is recommended to: (i) Evaluate patient suitability for diuretic, renin–angiotensin–aldosterone antagonist, and anticoagulant therapy (and monitor treatment) (ii) Detect reversible/treatable causes of HF (e.g. hypocalcaemia, thyroid dysfunction) and co-morbidities (e.g. iron deficiency) (iii) Obtain prognostic information.	I	C
A complete blood count is recommended to: (i) Detect anaemia, which may be an alternative cause of the patient's symptoms and signs and may cause worsening of HF (ii) Obtain prognostic information.	I	C
Measurement of natriuretic peptide (BNP, NT-proBNP, or MR-proANP) should be considered to: (i) Exclude alternative causes of dyspnoea (if the level is below the exclusion cut-point–*see Figure 1*–HF is very unlikely) (ii) Obtain prognostic information.	IIa	C
A chest radiograph (X-ray) should be considered to detect/exclude certain types of lung disease, e.g. cancer (does not exclude asthma/COPD). It may also identify pulmonary congestion/oedema and is more useful in patients with suspected HF in the acute setting.	IIa	C
Investigations to consider in selected patients		
CMR imaging is recommended to evaluate cardiac structure and function, to measure LVEF, and to characterize cardiac tissue, especially in subjects with inadequate echocardiographic images or where the echocardiographic findings are inconclusive or incomplete (but taking account of cautions/contraindications to CMR).	I	C
Coronary angiography is recommended in patients with angina pectoris, who are considered suitable for coronary revascularization, to evaluate the coronary anatomy.	I	C
Myocardial perfusion/ischaemia imaging (echocardiography, CMR, SPECT, or PET) should be considered in patients thought to have CAD, and who are considered suitable for coronary revascularization, to determine whether there is reversible myocardial ischaemia and viable myocardium.	IIa	C
Left and right heart catheterization is recommended in patients being evaluated for heart transplantation or mechanical circulatory support, to evaluate right and left heart function and pulmonary arterial resistance.	I	C
Exercise testing should be considered: (i) To detect reversible myocardial ischaemia (ii) As part of the evaluation of patients for heart transplantation and mechanical circulatory support (iii) To aid in the prescription of exercise training (iv) To obtain prognostic information.	IIa	C

BNP = B-type natriuretic peptide; CAD = coronary artery disease; CMR = cardiac magnetic resonance; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; MR-proANP = mid-regional pro atrial natriuretic peptide; NT-proBNP = N-terminal pro B-type natriuretic peptide; PET = positron emission tomography; SPECT = single photon emission computed tomography; TIBC = total iron-binding capacity.

[a] Class of recommendation.

[b] Level of evidence.

[c] Additional investigations may be indicated in patients with suspected acute HF in the emergency department/hospital, including troponins and D-dimer measurement and right heart catheterization.

1.4.3 Natriuretic peptides

An alternative approach to diagnosis is to measure the blood concentration of a natriuretic peptide, which is increased due to a diseased heart or if the load on any chamber is increased (e.g. by AF, pulmonary embolism, and some non-cardiovascular conditions, including renal failure)(91-94). A normal natriuretic peptide level in an untreated patient virtually excludes significant cardiac disease, making an echocardiogram unnecessary. The upper limit of normal in the non-acute setting for B-type natriuretic peptide (BNP) is 35 pg/mL and for N-terminal pro-BNP (NT-proBNP) it is 125 pg/mL (19). For patients presenting with acute onset or worsening of symptoms, the optimal exclusion cut-off point is 300 pg/mL for NT-proBNP and 100 pg/mL for BNP (95).

1.4.4 Chest X-ray

The chest X-ray (CXR) is mainly used to show pulmonary venous congestion or oedema in a patient with HF, and is more helpful in the acute setting than in the non-acute setting (86,96). It is important to note that significant LV dysfunction may be present without cardiomegaly on the chest X-ray (86,96). Otherwise, CXR is of limited use except to identify some alternative cause of patients symptoms.

1.4.5 Routine blood test

Laboratory testing may reveal the presence of disorders or conditions that can lead to or exacerbate HF. The initial evaluation of patients with HF should include a complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), glycohemoglobin, and blood lipids, as well as tests of both renal and hepatic function. Thyroid function tests (especially thyroid-stimulating hormone) should be measured, because both hyperthyroidism and hypothyroidism can be a primary or contributory cause of HF. A fasting transferrin saturation is useful to screen for hemochromatosis (97).

1.4.6 The role of cardiac imaging in diagnosis of heart failure

Cardiac imaging plays a central role in the diagnosis of HF and in guiding treatment. Apart from echocardiography, which is the one of the main methods for HF diagnosis, there are other modalities which are chosen depending on their ability to answer a specific clinical question or contraindications and risks of specific tests (78,98).

1.4.6.1 Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) is acknowledged as the gold standard for the measurements of volumes, mass and EF of both the left and right ventricles, especially in for patients with nondiagnostic echocardiographic studies (particularly for imaging of the right heart)(99-101).

1.4.6.2 Stress echocardiography

Exercise or pharmacological stress echocardiography may be used for the assessment of inducible ischaemia and/or myocardium viability (102) and in some clinical scenarios of patients with valve disease (e.g. dynamic mitral regurgitation, low-flow–low-gradient aortic stenosis) (102,103).

1.4.6.3 Coronary angiography

Coronary angiography is recommended in patients with HF who suffer from angina pectoris recalcitrant to medical therapy (104), provided the patient is otherwise suitable for coronary revascularization. Coronary angiography is also recommended in patients with a history of symptomatic ventricular arrhythmia or aborted cardiac arrest. Coronary angiography should be considered in patients with HF and intermediate to high pre-test probability of CAD and the presence of ischaemia in non-invasive stress tests in order to establish the ischaemic aetiology and CAD severity (105-107).

1.5. Heart failure with preserved ejection fraction

In developed countries, at least 38–54% of patients with heart failure show preserved left ventricular ejection fraction. The prevalence of heart failure with preserved ejection fraction is steadily increasing and its prognosis is poor (108). It shares a 90-day mortality and readmission rate similar to heart failure with reduced ejection fraction. Whereas hospitalisation for patients with heart failure with reduced ejection fraction (HFrEF) has declined over the past few years, that of patients with HFpEF is on the rise and requires longer lengths of stay (109).

Although patients with HFpEF have a lower 30-day hospital readmission rate compared with patients with HFrEF (25% vs 64%, respectively), no difference is observed in 30-day and 1-year all-cause mortality rates (**Table 4**) (110). Although women have a higher prevalence of HFpEF, the risk of death is much greater in men regardless of whether they have preserved or reduced ejection fraction (111). Thirty percent of patients with HFpEF die of noncardiac causes compared with 17% of patients with systolic heart failure. This comparison emphasizes the role of comorbidities in mortality rates (112).

1.5.1. Pathophysiology of heart failure with preserved ejection fraction

The pathophysiological process of HFpEF is incompletely understood. Although an abnormality in LV relaxation corresponds to diastolic dysfunction, HFpEF is more complex than that, and the pathophysiological mechanisms are the subject of vigorous study. Paulus and Tschope (113) have proposed a new paradigm that suggests that comorbidities such as obesity, diabetes mellitus, and chronic obstructive pulmonary disease lead to a systemic proinflammatory state that induces coronary microvascular endothelial inflammation. This inflammation and resultant oxidative stress cause stiff cardiomyocytes and interstitial fibrosis, which characterize the myocardial dysfunction and ventricular remodelling of HFpEF (112).

Arrows in the TABLE 4 indicate increased or decreased prevalence of comorbidities in the given group of HF

TABLE 4:

Comparison of Patients With HFpEF and HFrEF[a]

Characteristic	HFpEF	HFrEF
Ejection Fraction	≥50	<50
Left Ventricular Remodeling	Concentric	Eccentric
More common in…	Women (62%)	Men (60%)
Age (mean [SD]), y	Older (73.9 [13.2])	Younger (69.8 [14.4])
Prevalence of Hospitalizations	Increasing	Decreasing
Associated Comorbidities		
Chronic hypertension	↑ (77%)	↓ (69%)
Diabetes mellitus	↑ (45%)	↓ (40%)
Obesity	↑ (41.4%)	↓ (35.5%)
Coronary artery disease	↓ (50%)	↑ (59%)
Prior myocardial infarction	↓ (24%)	↑ (36%)
Ventricular arrhythmias	↓ (3%)	↑ (11%)
30-d Hospital Readmission Rate	↓ (25%)	↑ (64%)
Proven Therapies to Decrease Mortality	No	Yes

[a] Arrows indicate increased or decreased prevalence in the given area; parenthetical percentages indicate the rate of the given comorbidity among patients.

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

1.5.2 Diagnosis of heart failure with preserved ejection fraction

The diagnosis of HFpEF remains challenging. LVEF is normal and signs and symptoms for HF (**TABLE 1**) are often non-specific and do not discriminate well between HF and other clinical conditions. The diagnosis of chronic HFpEF, especially in the typical elderly patient with co-morbidities and no obvious signs of central fluid overload, is cumbersome. To improve the specificity of diagnosing HFpEF, the clinical diagnosis needs to be supported by objective measures of cardiac dysfunction at rest or during exercise. The diagnosis of HFpEF requires the following conditions to be fulfilled (see **TABLE 2**) (19):

• The presence of symptoms and/or signs of HF (see **TABLE 1**)

• A 'preserved' EF (defined as LVEF ≥50% or 40–49% for HFmrEF)

• Elevated levels of NPs (BNP > 35 pg/mL and/or NT-proBNP > 125 pg/mL)

• Objective evidence of other cardiac functional and structural alterations underlying HF

• In case of uncertainty, a stress test or invasively measured elevated LV filling pressure may be needed to confirm the diagnosis (19)

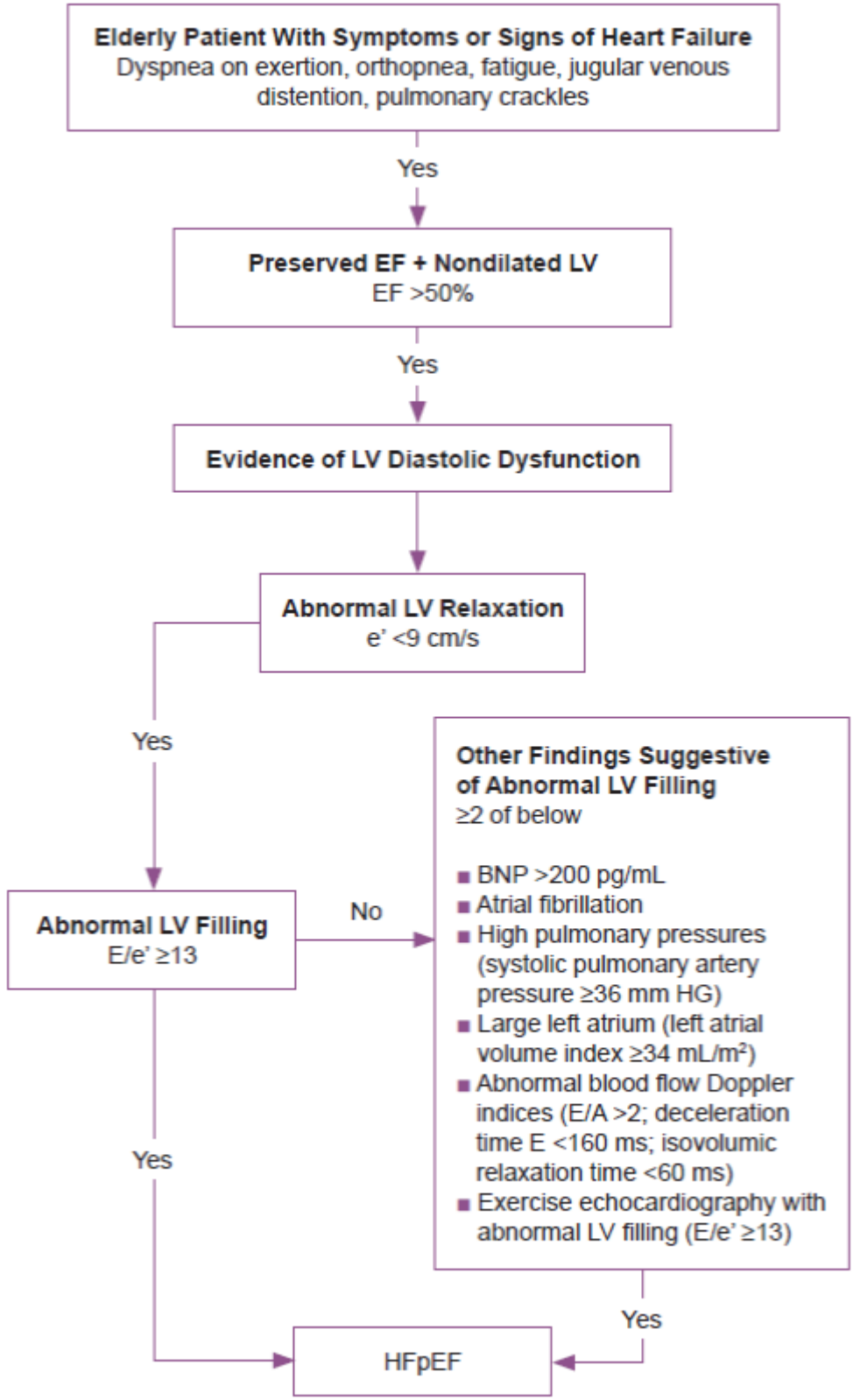


FIGURE 3. Step-by-step diagnosis of heart failure with preserved ejection fraction (HFpEF) (108,113). Shortness of breath without objective signs of pulmonary congestion is a common early symptom of HFpEF. Interpreting this symptom is especially challenging in

elderly patients. Signs or symptoms of heart failure (HF) is the first obligatory criterion in the diagnosis of HFpEF. A nondilated left ventricle (LV) with preserved ejection fraction (EF) is the second required criterion for the diagnosis of HFpEF. Presence of echocardiographic evidence of diastolic dysfunction with both LV relaxation and filling abnormalities is the third required criterion. Abnormal LV relaxation can be a silent echocardiographic finding, whereas abnormal LV filling is associated with symptoms of HF. Abbreviations: A, late mitral valve blood flow Doppler velocity; e', early mitral valve tissue Doppler lengthening velocity; E, early mitral valve blood flow Doppler velocity; BNP, brain natriuretic peptide (112).

The standard approach is to start with the medical history, physical examination, electrocardiography, and chest radiography. If heart failure is suspected, 2-dimensional Doppler echocardiography is the next step. A 2014 article (108) updated the 2007 European Society of Cardiology guideline in terms of evidence for diastolic dysfunction while maintaining the clinical orientation of the original approach. The decision tree starts with a measure of the relaxation velocity of the LV in early diastole (a tissue Doppler recording of the velocity of the LV at the mitral annulus, abbreviated to e') and asks if LV diastolic dysfunction is present. If not, other considerations would be raised, such as primary mitral valve regurgitation, constrictive pericarditis, dyspnoea as an anginal equivalent, and noncardiac dyspnoea.

The stepwise approach then moves to a measure of LV filling pressure (the tissue Doppler index, which is the ratio of the mitral early diastolic blood flow velocity to the mitral annular relaxation velocity, abbreviated to E/e'). If this criterion is fulfilled, the diagnosis is established. A small number of patients will meet these 2 criteria. If these parameters are borderline or the filling pressure is not elevated, the next step is to assess other Doppler/echocardiographic parameters and clinical features, such as response to exercise, pulmonary arterial pressure, left atrial size (expressed as left atrial volume index), brain natriuretic peptide (BNP) levels, and the presence of atrial fibrillation (Figure 3). If 2 or more of these additional findings are met, the diagnosis of HFpEF is established. If none is present, the diagnosis is excluded (112).

1.6. Criteria for hospitalisation

Any patient with ADHF who has hypotension, worsening renal function, or altered mental status should be considered high risk and hospitalised. In addition, ADHF patients who present with dyspnoea, tachypnoea, or hypoxaemia (again, oxygen saturation of <90%) at rest, or with any hemodynamically significant arrhythmia, including atrial fibrillation with rapid ventricular response, warrant hospital admission— as does any patient who presents with evidence of an acute coronary syndrome (114). Hospitalisation should also be considered for HF patients with any of the following: severe weight gain, defined as >5 kg; signs and symptoms of pulmonary or systemic congestion; major electrolyte disturbances; repeated implantable cardioverter-defibrillator firings; or pneumonia. Furthermore, the clinician should be aware that a patient with ADHF has a poor systemic reserve for coping with other medical conditions.

1.7.1 Treatment of heart failure with reduced ejection fraction (HFrEF)

1.7.1.1 Angiotensin-converting enzyme inhibitors (ACEI)

ACEIs have been shown to reduce mortality and morbidity in patients with heart failure with reduced ejection fraction (HFrEF) (62,115-118) and are recommended unless contraindicated or not tolerated in all symptomatic patients. There is evidence that in clinical practice the majority of

patients receive suboptimal doses of ACEI (119). ACEIs are also recommended in patients with asymptomatic LV systolic dysfunction, with a recent or remote history of myocardial infarction (MI) or acute coronary syndrome (ACS), to reduce the risk of HF development, HF hospitalisation and death (60,120).

1.7.1.2 Beta-blockers

Beta blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI (60,121). Beta-blockers reduce mortality and morbidity in symptomatic patients with HFrEF, despite treatment with an ACEI and, in most cases, a diuretic (122-126), but have not been tested in congested or decompensated patients. There is consensus that beta-blockers and ACEIs are complementary, and can be started together as soon as the diagnosis of HFrEF is made. There is no evidence favouring the initiation of treatment with a beta-blocker before an ACEI has been started (127).

An individual patient data meta-analysis of all the major beta-blocker trials in HFrEF has shown no benefit on hospital admissions and mortality in the subgroup of patients with HFrEF who are in AF (128).

1.7.1.3 Aldosterone receptor antagonists (ARA)

ARAs (spironolactone and eplerenone) block receptors that bind aldosterone and, with different degrees of affinity, other steroid hormone (e.g. corticosteroids, androgens) receptors. Spironolactone or eplerenone are recommended in all symptomatic patients (despite treatment with an ACEI and a beta-blocker) with HFrEF and LVEF ≤35%, to reduce mortality and HF hospitalization (129,130).

Caution should be exercised when ARAs are used in patients with impaired renal function and in those with serum potassium levels >5.0 mmol/L.

1.7.1.4 Diuretics

Diuretics are recommended to reduce the signs and symptoms of congestion in patients with HF. A Cochrane meta-analysis has shown that in patients with chronic HF, loop and thiazide diuretics appear to reduce the risk of death and worsening HF compared with placebo, and compared with an active control, diuretics appear to improve exercise capacity (131,132).

Loop diuretics produce a more intense and shorter diuresis than thiazides, although they act synergistically and the combination may be used to treat resistant oedema. However, aggressive diuresis has diverse consequences, including electrolyte disturbances and consequent arrhythmias, intravascular depletion, hypotension, and renal dysfunction. Worsening renal function makes further diuresis more difficult and worsens the prognosis in HF patients (132,133).

1.7.1.5 Angiotensin receptor neprilysin inhibitor

A new therapeutic class of agents acting on the renin–angiotensin–aldosterone system (RAAS) and the neutral endopeptidase system has been developed [angiotensin receptor neprilysin inhibitor

(ARNI)]. The first in this class is a combination of valsartan and sacubitril in a single substance. By inhibiting neprilysin, the degradation of natriuretic peptide (NP), bradykinin and other peptides is slowed. High circulating A-type natriuretic peptide (ANP) and BNP exert physiological effects through binding to NP receptors and the augmented generation of cGMP, thereby enhancing diuresis, natriuresis and myocardial relaxation and anti-remodelling. ANP and BNP also inhibit renin and aldosterone secretion. Selective AT1-receptor blockade reduces vasoconstriction, sodium and water retention and myocardial hypertrophy (134,135). This group is recommended as a replacement for an ACE-I to further reduce hospitalisation and death in HF patients.

1.7.1.6 If-channel inhibitor

Ivabradine slows the heart rate through inhibition of the "If" channel in the sinus node and therefore should only be used for patients in sinus rhythm. Ivabradine reduced the combined endpoint of mortality or hospitalisation for HF in patients with symptomatic HFrEF or LVEF ≤35%, in sinus rhythm and with a heart rate ≥70 beats per minute (bpm) who had been hospitalised for HF within the previous 12 months, receiving treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose), an ACEI (or ARB) and an mineralocorticoid receptor antagonist (MRA) (136).

1.7.1.7 Angiotensin II type I receptor blockers (ARBs)

ARBs are recommended only as an alternative in patients intolerant of an ACEI (137). Candesartan has been shown to reduce cardiovascular mortality (137). Valsartan showed an effect on hospitalisation for HF (but not on all-cause hospitalisations) in patients with HFrEF receiving background ACEIs (138).

1.7.1.8 Digoxin

Digoxin may be considered in patients in sinus rhythm with symptomatic HFrEF to reduce the risk of hospitalisation (both all-cause and HF hospitalisations) (136) although its effect on top of beta-blockers has never been tested. In patients with symptomatic HF and AF, digoxin may be useful to slow a rapid ventricular rate, but it is only recommended for the treatment of patients with HFrEF and AF with rapid ventricular rate when other therapeutic options cannot be pursued (139,140).

1.7.1.9 Implantable cardioverter defibrillator (ICD)

ICDs are effective in preventing bradycardia and correcting potentially lethal ventricular arrhythmias. ICD reduces mortality in survivors of cardiac arrest and in patients who have experienced sustained symptomatic ventricular arrhythmias. The device is recommended in such patients when the intent is to increase survival; the decision to implant should take into account the patient's view and their quality of life, the LVEF (survival benefit is uncertain when the LVEF is > 35%) and the absence of other diseases likely to cause death within the following year (141,142).

1.7.2 Treatment of heart failure with preserved ejection fraction

Unlike systolic heart failure, for which multiple effective medications are available, the pharmacologic treatment of HFpEF is disappointing. No agents have been shown to improve survival

or to enhance quality of life (QOL), exercise tolerance, or diastolic function. The mainstay of medical treatment should be prevention for persons at risk for HFpEF and control of blood pressure, heart rate, and fluid status in patients with established disease (112). For those patients with concomitant medical problems that are associated with HFpEF, management of the underlying condition, such as obstructive sleep apnoea, is reasonable, although there are no outcomes data to support this approach. In patients with type 2 diabetes mellitus, elevated serum triglyceride levels are associated with myocardial steatosis, which in turn causes diastolic dysfunction. Prolonged caloric restriction reduces myocardial triglyceride content and improves diastolic heart function (143).

1.8. Mitral regurgitation (MR)

1.8.1 Mitral regurgitation in heart failure

The exact incidence and prevalence of mitral regurgitation (MR) is unknown, but it probably exceeds five million worldwide (144); MR is the second most common type of heart valve disease requiring surgery in Europe (145). Chronic volume overload by MR plays a large contributing role in the development of heart failure (146,147), but could also develop in response to altered LV geometry (64%) in ischaemic MR detected by echocardiography in post Q-wave MI patients (22) and abnormal afterload (72%) in hypertension (HTN) and aortic valve stenosis (AS) (148). Moderate or severe MR was also an independent predictor of new onset HF in patients with ischaemic LV dysfunction (relative risk: 3.2 [95% CI: 1.9 to 5.2], p = 0.0001) (22).

1.8.2 Primary & Secondary Mitral Regurgitation

MR is classified as primary (also known as organic) when principally due to a structural or degenerative abnormality of the mitral valve (MV), whether of the leaflets, chordae tendineae, papillary muscles, or mitral annulus. Secondary (also known as functional) MR occurs in the absence of organic MV disease, usually from left ventricular (LV) dysfunction. It is more common than primary MR (149), is associated with a worse prognosis (compounded by the underlying cardiomyopathy), and (in contrast to primary MR) the benefits of MV surgery are uncertain (22).

1.8.3 Pathophysiology of MR. Ischaemic & non-ischaemic MR.

The mitral valve consists of 2 leaflets (anterior and posterior) sitting within the annulus (**FIGURE 4**). The posterior mitral leaflet originates from the left atrial (LA) endocardium.

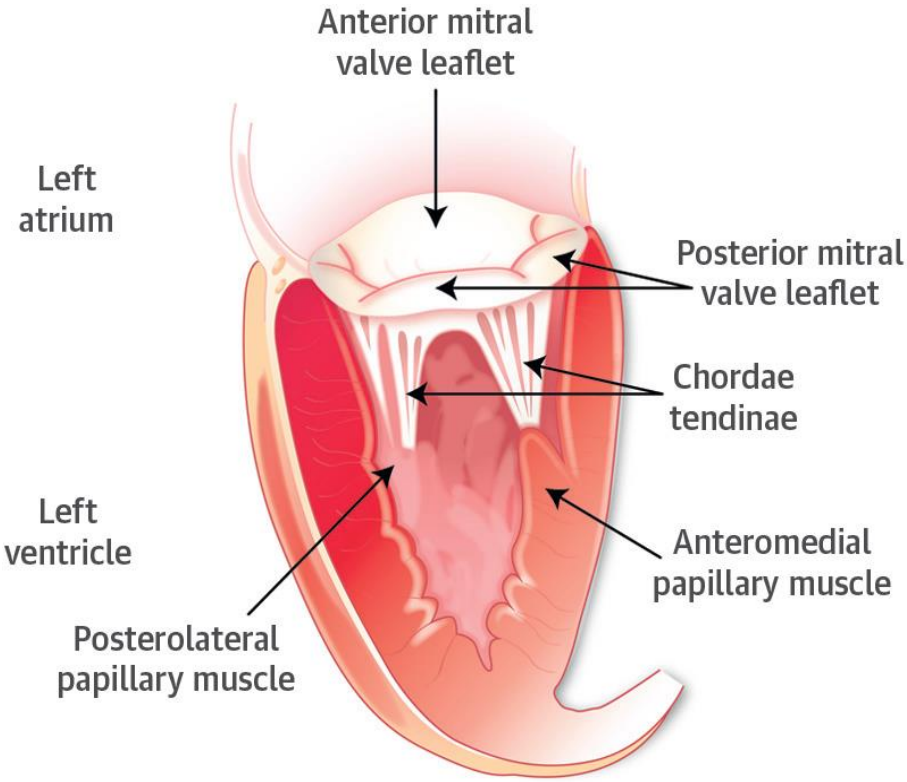


FIGURE 4. Mitral valve anatomy (22).

A subvalvular apparatus, comprising 2 papillary muscles (anterolateral and posteromedial) arising from the LV myocardium and the chordae tendineae, supports the leaflets. LV dilation due to ischaemic or non-ischaemic cardiomyopathy secondarily impairs leaflet coaptation of a structurally normal MV, resulting in secondary MR. Specifically, LV dysfunction and remodelling lead to apical and lateral papillary muscle displacement, resulting in leaflet tethering (150), dilation and flattening of the mitral annulus, and reduced valve closing forces. Because these changes are dependent on loading conditions and the phase of the cardiac cycle, secondary MR is dynamic in nature.

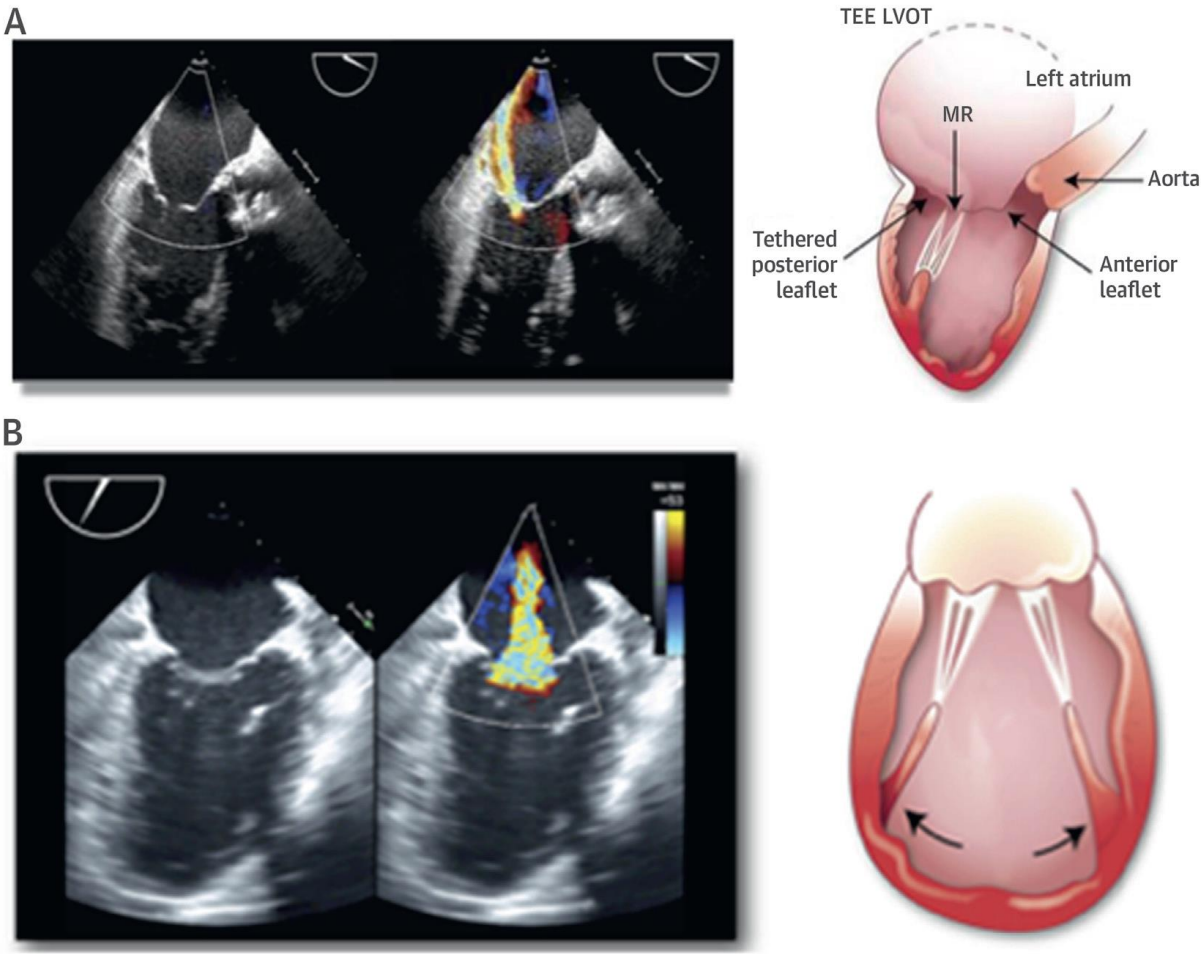


FIGURE 5. Secondary MR due to LV dilatation (22)

(A) A representative echocardiogram and diagram of ischemic MR, with a posteriorly directed jet. (B) A representative echocardiogram and diagram of MR due to idiopathic dilated cardiomyopathy, with a central jet. Note the lateral displacement of the papillary muscles (arrows). Apical displacement is also typically present, although less well demonstrated in these views. LVOT =left ventricular outflow tract; MR = mitral regurgitation; TEE = transoesophageal echocardiography.

Papillary muscle displacement occurs as a result of global LV enlargement or focal myocardial scarring, and can affect 1 or both papillary muscles, causing posteriorly directed or central MR (**Figure 5**) (151). With chronic MR, the mitral leaflet area may increase up to 35% over time, an adaptive response that minimizes the degree of regurgitation; insufficient leaflet remodelling may contribute to severe MR (152,153). However, even in patients with increased mitral leaflet area, papillary muscle displacement with subsequent decreased coaptation length may still result in significant MR (153).

Non-ischaemic MR, most commonly due to longstanding hypertension or idiopathic dilated cardiomyopathy, is characterized by global LV dilation with increased sphericity and (typically) a centrally located regurgitant jet. Symmetric mitral annular dilation is greatest in the septal-lateral direction, and correlates with the severity of LV dysfunction (22,157).

1.8.4 Mortality in heart failure patients

Mortality increases with clinical severity and may be as high as 60% within 1 year for patients with severe (NYHA Class IV) heart failure (158). Five-year mortality in the Framingham Study was 75% in men and 62% in women (158). HF patients experience relatively low in-hospital mortality but are at much higher risk for early post-discharge readmission and mortality. The in-hospital mortality rate for patients hospitalised with this condition is 20-30% (125,126). In general, the mortality rate in patients with CHF is 3 to 5 times that of men and women of a similar age without heart failure (128).

1.8.4.1 Mortality in heart failure patients with mitral regurgitation

A strong association between severity of secondary MR and both all-cause mortality and heart failure hospitalisations has been reported widely (159). Possibly development of myocardial damage after Q-wave MI altered mitral valve apparatus in majority of patients (64%) leading to a development of ischaemic MR (159) which was a powerful, independent predictor of long-term all-cause mortality. In a study from the Duke Cardiovascular Databank, qualitatively assessed 3+ to 4+ MR on left ventriculography was present in 29.8% of 2,057 HF patients with an LVEF <40% and was an independent predictor of 5-year mortality (160). Among 1,256 patients with dilated cardiomyopathy at the Mayo Clinic, quantitatively assessed severe secondary MR was present in 24% of patients, and was an independent predictor of death or HF hospitalisation at median 2.5-year follow-up, independent of LVEF (161). This relationship was present separately for death and HF hospitalisations, and in patients with ischaemic and non-ischaemic MR. Secondary MR is a powerful predictor of death or transplant, even with less severe HF. Thus secondary MR is widely accepted as a predictor of poor prognosis in patients with primary LV dysfunction and HF. Whether reducing MR improves patient prognosis remain unknown.

The recent European based study showed that severe functional MR was a significant predictor of mortality, independent of clinical, and echocardiographic confounders, optimal medical therapy and neurohumoral activation. Subanalysis revealed that severe functional MR was associated with poor outcome in an intermediate-failure phenotype of HFrEF i.e. patients with NYHA class II and III, moderately reduced left ventricular function (162).

1.8.5 Evaluation of secondary MR

Comprehensive evaluation of the patient with HF and secondary MR requires a detailed medical history and physical examination, with laboratory, electrocardiographic, and echocardiographic assessment. Most important is an accurate appraisal of the functional limitations attributable to HF, the MV anatomy and severity of MR, and evaluation of the left and right heart circulation, including measurement of chamber size and cardiac pressures (22). By integrating these findings, secondary MR can be categorized into 4 stages that define prognosis and guide therapy: 1) at risk of secondary MR; 2) progressive secondary MR; 3) asymptomatic severe secondary MR; and 4) symptomatic severe secondary MR (**TABLE 5**) (163).

1.8.6 Treatment of HF patients with MR

The goals of therapy in patients with secondary MR are to improve symptoms and quality of life, reduce HF hospitalisations, and potentially improve survival. To date, the most effective therapies for secondary MR are aimed at the underlying LV dysfunction, including guideline-directed medical therapy (GDMT) for HF and biventricular pacing (CRT) when appropriate. Coronary revascularization may also be considered in patients with extensive ischaemia and preserved myocardial viability, although it rarely markedly reduces or eliminates secondary MR. The role of surgical and transcatheter MV repair or replacement to interrupt the progressive cycle of LV volume overload → LV dilation → secondary MR → increasing LV volume overload and dilation → increasing MR is less well established, although some patients may symptomatically benefit. Finally, in patients with severe HF and secondary MR refractory to standard therapies, consideration should be given to mechanical LV assist devices and heart transplantation (22).

1.8.6.1 Medical therapy for secondary MR

So far medical therapy for HF remains first-line treatment for patients with secondary MR (163). Nevertheless, the outcomes remain poor: among 404 secondary MR patients treated with medical therapy, 4-year cardiac mortality occurred in 43% and 45% with moderate and severe MR, respectively, compared with only 6% with mild MR (p = 0.003)(164). Moderate or severe MR was also an independent predictor of new onset HF in patients with ischaemic LV dysfunction (relative risk: 3.2 [95% CI: 1.9 to 5.2], p = 0.0001). By reversing LV remodelling, maximal GDMT may secondarily reduce severe MR. Surprisingly, however, few studies have examined the effect of medical therapies on secondary MR (22).

1.8.6.2 Surgery for secondary MR

Surgical options for secondary MR include surgical MV repair and replacement, mechanical LV assist devices, and orthotopic heart transplantation. Although MV surgery has never clearly been demonstrated to alter the natural history of the primary myocardial disease (dilated cardiomyopathy) or improve survival and long term outcome (165-167). Isolated MV annuloplasty in severe secondary MR and LVEF ≤ 30% (165) did not present any advantage at 5.5-year follow-up. Lack of success with medical and surgical therapy is certainly secondary to advanced myocardial damage but also might reflect heterogeneity of MR mechanism in this group of patients.

TABLE 5. Stages of Secondary (Functional) MR(163)

Grade	**Valve anathomy**	**Valve Haemodynamics**	**Cardiac Structure and Function**	**Symptoms**
A: At risk of MR	• Normal valve leaflets, chords, and annulus in a patient with coronary disease or	• No MR jet or small central jet area <20% LA on Doppler • Small vena	• Normal or mildly dilated LV size with fixed (infarction) or inducible (ischaemia)	• Symptoms due to coronary ischaemia or HF may be present that respond to revascularization

	cardiomyopathy	contracta <0.30 cm	regional wall motion abnormalities • Primary myocardial disease with LV dilation and systolic dysfunction	and appropriate medical therapy
B: Progressive MR	• Regional wall motion abnormalities with mild tethering of mitral leaflet • Annular dilation with mild loss of central coaptation of the mitral leaflets	• EROA <0.20 cm2 • Regurgitant volume <30 ml • Regurgitant fraction <50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• Symptoms due to coronary ischaemia or HF may be present that respond to revascularization and appropriate medical therapy
C: Asymptomatic severe MR	• Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet • Annular dilation with severe loss of central coaptation of the mitral leaflets	• EROA ≥ 0.20 cm2 • Regurgitant volume ≥ 30 ml • Regurgitant fraction ≥ 50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• Symptoms due to coronary ischaemia or HF may be present that respond to revascularization and appropriate medical therapy
D: Symptomatic severe MR	• Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet	• EROA ≥ 0.20 cm2 • Regurgitant volume ≥ 30 ml • Regurgitant fraction ≥ 50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic	• HF symptoms due to MR persist even after revascularization and optimization of medical therapy

	• Annular dilation with severe loss of central coaptation of the mitral leaflets		dysfunction due to primary myocardial disease	• Decreased exercise tolerance • Exertional dyspnoea

EROA = effective regurgitant orifice area; HF = heart failure; LA = left atrium; LV = left ventricular; MR = mitral regurgitation.

1.8.6.3 Cardiac resynchronization therapy (CRT) for MR

CRT is a well-established treatment for HF in selected patients with LV dyssynchrony. CRT is a Class I recommendation for patients in sinus rhythm with New York Heart Association (NYHA) functional class II to IV symptoms on medical therapy with LVEF ≤ 35%, left bundle branch block (LBBB), and QRS duration ≥ 150 ms. CRT may also be useful in patients with LVEF ≤ 35%, with sinus rhythm and non-LBBB pattern with QRS duration ≥ 150 ms, and in those with LBBB and QRS duration 120 to 149 ms (Class IIa indications) (121). Randomized trials demonstrated improvements in both survival and HF rehospitalisation rates in patients treated with CRT with or without a defibrillator, along with reductions in LV end-diastolic and end-systolic dimensions and improved LVEF (168). In subgroup of HF patients with dyssynchrony resynchronisation therapy showed a reduction in MR severity with restoration of synchronous ventricular contraction and reverse LV remodelling (169). But this effect of CRT on secondary MR was not seen in absence of dyssynchrony (170).

1.8.6.4 The MitraClip

Recent development of transcatheter interventions appears promising. The MitraClip, the first percutaneous mitral valve repair device, provides the next therapeutic option for severe MR patients (171). The MitraClip is a polyester-covered cobalt-chromium clip inserted via the femoral vein and advanced under transoesophageal echocardiographic guidance into the LA following trans-septal puncture (**Figure 6**). The clip is opened, positioned above the regurgitant jet, and advanced into the LV. It is then retracted to grasp the free edges of the mitral leaflets, the grippers are dropped, and the clip is closed and released, emulating a surgical edge-to-edge repair (87). Multiple clips may be safely placed, if necessary (22,172,173).

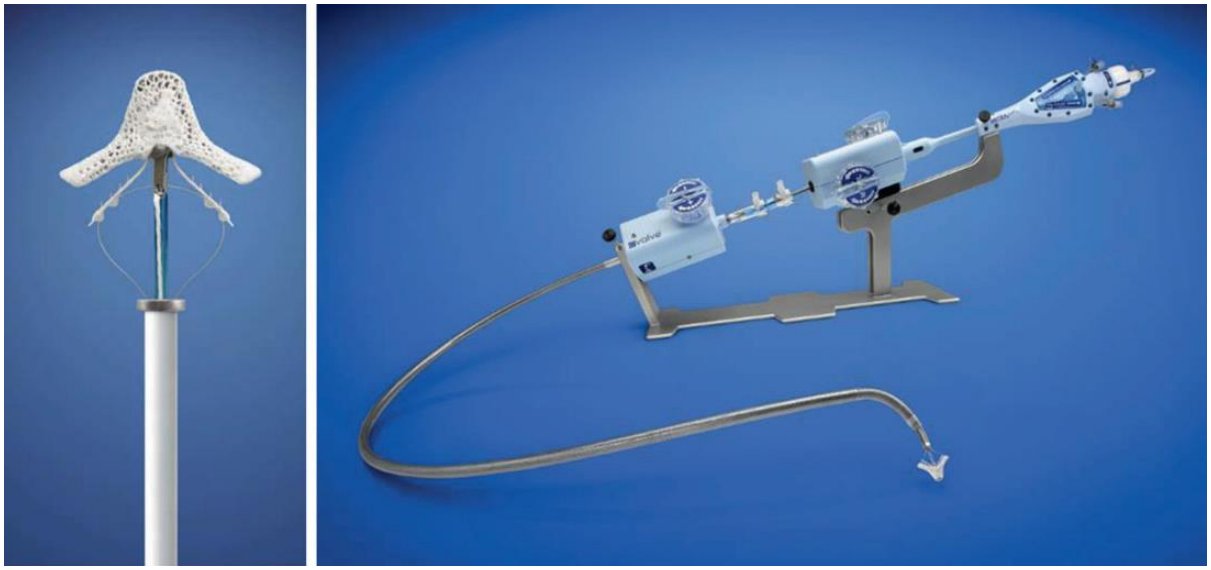


FIGURE 6. Mitral Clip device. Close-up views of the MitraClip device's fabric-covered clip (left) and guiding catheter with clip delivery system (right). Images courtesy of Abbott Vascular, Menlo Park, California (22).

In-hospital (2.9%) and 1-year (15.3%) mortality were similar in patients with secondary and primary MR after procedure, although rehospitalisation for HF was more common in the secondary MR group (25.8% vs. 12.0%, p = 0.009). At 1 year, severe MR was present in only 6% of patients. The MitraClip has also been used successfully in HF patients who are non-responders to CRT (an especially high-risk group), with resultant improvements in MR grade, functional capacity, and LV remodelling (170). In the 25-center, 8-country, 2011 to 2012 European Sentinel Pilot Registry, 72% of 628 MitraClip-treated patients had secondary MR, 86% had NYHA functional class III/IV symptoms, and the mean EuroSCORE was 20.4. Acute procedural success was high (95.4%), with multiple clips used in 39% of patients (174).

Consequently, the 2017 European Society of Cardiology guidelines suggested the use of transcatheter mitral valve treatment in symptomatic patients who are at high surgical risk or are inoperable (175). Percutaneous edge-to-edge repair is generally safe and can improve symptoms and provide reverse LV remodelling despite higher rate of residual mitral regurgitation at 5 years compared to surgical repair (176).

1.9. Cost of Heart Failure to Healthcare Systems, role of mitral regurgitation

1.9.1 Proportion of heart failure expenditure to total healthcare budget

In developed countries, total expenditure on HF ranges between 1-2% of the total healthcare budgets. The healthcare costs increases 8-30 fold with worsening of functional NYHA class (177,178) and driven by hospitalisations due to development of acute or exacerbation of chronic HF. HF accounts up to 5% of American and European hospital admissions. Global per capita spending in 2012 was approximately $24/annum (179). Health expenditure on chronic HF includes both direct and indirect costs.

1.9.2 Cost breakdown for heart failure expenditure

The analytical results showed that from the perspective of the health care provider the direct treatment costs are to be listed as the following sequence (180):

1. **Costs of hospitalisation**: these include the costs of hospitalisation, nursing staff, blood products, medical equipment, anaesthesia, medical examinations, diagnostic tests and the costs of the hospital ward. The weighting of this indicator amounts to a relative frequency of 26.09%. This percentage is the highest value among the identified indicators and is thus ranked first.

2. **Costs of medical services**: these include the costs of diagnosis, general practitioners, medical specialists, pharmacists, home calls, ambulatory care services, therapists, primary care, ambulatory treatment and the costs of the medical care. The weighting of this indicator amounts to a relative frequency of 23.91%.

3. **Costs of medication**: these include the costs of drugs that were prescribed to the chronic HF patients during their treatment. The resulting indicator emphasis is 21.74%.

4. **Costs of intervention**: these include costs of telemonitoring (TM) equipment, TM trained nurses, TM service, TM monitoring, TM support and consulting, TM training as well as the TM based medical supervision. The relative frequency of the indicator thus amounts to 17.39%.

5. **Costs of rehabilitation and emergency services**: these include costs of the emergency ward and the rehabilitation of chronic HF patients. The weighting of the indicator amounts to a value of 10.87%.

The recent data, where 197 countries were included (98.7% of the world`s population), suggests the overall economic cost of HF in 2012 was estimated at $108 billion per annum. Direct costs accounted for 60% ($65 billion) and indirect costs accounted for 40% ($43 billion) of the overall spend (179). Estimated global values of direct, indirect and total costs of HF for the UK (stratified by WDI economic status) in year 2012 direct costs accounted $3223 million, indirect costs - $1461 million and overall HF costs - $4684 million (181).

1.9.3 Medical costs: hospitalisation and investigation

Almost two-thirds of total healthcare expenditure on HF is due to hospitalisation (182,183) and re-admissions (32,35). Inpatient care costs account for 50- 70% of the health costs of patients with HF (184-186). Furthermore, highly prevalent co-morbidities in HF (187) add to frequency of hospital admissions. For example, cardiovascular events, such as stroke and myocardial infarction, and renal failure (188) have a significant impact on hospital admissions.

1.9.3.1 Diagnostic work-up costs

The costs of in-patient investigations represent a substantial proportion of expenditure on hospitalisation. One estimate of investigation costs quantified the total cost of investigation as £57.4 million in the UK per annum (182). This might be grossly underestimated as the cost of echocardiography quoted is significantly less (**TABLE 6**) than an actual cost (189).

TABLE 6: Unit cost of included diagnostic tests/imaging (190)

Diagnostic	Unit cost	Source
BNP or NT-proBNP test	£ 28.13	St George NHS Trust
Departmental simple trans-thoracic echocardiogram	£ 62.60	NHS Reference costs schedule 2012-13

1.9.3.2 Acute care staffing costs

The NICE guideline development group selected the general physician, the cardiologist and the heart failure specialist nurse (HFSN) as the key roles whose time requirement would differ between standard and specialist arrangements of inpatient heart failure care. Other roles and disciplines were considered but excluded on the basis that the level and nature of their input would not differ.

On behalf of the National Clinical Guideline Centre (NCGC), the National Institute for Cardiology Outcomes Research (NICOR) conducted an online survey of 145 NHS Trusts in England and NHS Health Boards in Wales in order to estimate how much time each discipline spent on patient related activities per patient per week in cardiology and general medical wards. The guideline development group formulated the questions. 53 Trusts submitted usable responses. Three submitted unusable responses. Estimates are shown in **TABLE 7**.(190)

TABLE 7. Time spent on patient related activities by discipline

Ward setting	Discipline	Median time on patient related activities (minutes per patient per week)
Cardiology ward	Cardiologist	20
	General physician	23
	HFSN	30
General medical wards (and other non-cardiology wards)	Cardiologist	20
	General physician[a]	15
	HFSN	30

(a) The general physician was assumed to see only 20% of AHF patients on cardiology wards

The cost per hour of a cardiologist and general physician is the same, and consultant grade was selected as a conservative simplification. The HFSN was assumed to be NHS Agenda for Change Band 7. Hourly rates were obtained from the Personal Social Services Research Unit Handbook 2013 and are shown below in **TABLE 8 (191).**

TABLE 8. Unit cost of hospital staff included in the model (191)

Staff role and discipline	Unit cost (per hour)[a]
Consultant Cardiologist	£132
Consultant General physician	£132
Heart failure specialist nurse	£52

(a) Sourced from the Personal Social Services Research Unit Handbook 2013[47]

1.9.3.3 Acute care bed costs

The model included hospital costs other than staff, treatments and diagnostic tests in order to reflect the additional cost of extended length of hospitalisation resultant from incorrect diagnostic work-up. The weighted unit cost for a bed day was calculated from the NHS reference costs EB03H and EB03I (Heart Failure or Shock with and without complications) and was £232.09 (Department of Health. NHS reference costs 2012-13). The median length of stay was 8 days, and the consequence of incorrect diagnosis was an additional 2 days stay, as advised by the guideline development group (192).

For comparison, in the US-based prospective observational study (SUPPORT) of procedures and outcomes in patients hospitalised with an exacerbation of chronic HF, cost-of in-patient care adjusted for disease-severity was $2100 (42.9%) more expensive for treatment by a cardiologist than by a generalist (193). It is not clear whether such differences in treatment alter long-term outcomes.

1.9.4 Medical costs: medications

Medical therapy has been proven to have significant effect on mortality and morbidity in HF (194). It takes up a relatively small proportion in overall costs (21.74%) per patient (180,182,186), but represents a substantial source of healthcare expenditure given the high prevalence of CHF in the community. Treatment with ACE-inhibitors and beta-blockers with the addition of angiotensin receptor blockers and/or aldosterone antagonists in more advanced stages of the disease is still the mainstay of HF therapy aiming at reducing symptoms, improving functional status and survival, and reducing hospitalisation. Diuretics and other drugs remain optional with no firm evidence from randomised trials (131,132). Thus, most HF patients take a large number of pills to treat their chronic HF and the various co-morbidities that are commonly present. Consequently, the costs for drug treatment are high and have been estimated to be $3.2 billion per year in the USA (195) and £128.6 million in the UK (186). Angiotensin converting enzyme inhibitors (ACE-i) (196,197) or Angiotensin II type I receptor blockers (ARBs) (137,138), b-blockers (198-201), Mineralocorticoid/aldosterone receptor antagonists (MRAs**)** (129,130) are an established and cost-effective therapy in heart failure. New drugs such as Sacubitril/Valsartan have entered the list of cost-efficient list of medications (202).

The National Clinical Guideline Centre has estimated the cost of left ventricular systolic dysfunction (LVSD) disease modifying drug therapy and included into its study LVSD patients during the hospitalised periods and the non-hospitalised periods. Three classes of LVSD drug were included because they form the gold standard of care in this group of patients. The weighted average cost per day was calculated using the Prescription Cost Analysis for England 2012 (203). The cost of each drug was weighted by number of prescriptions (although it was not possible to isolate this to prescriptions specifically for heart failure). Unit costs are shown in **TABLE 9** and 90 day treatment costs, by management strategy are given in **TABLE 10.**(190)

TABLE 9. Unit cost of LVSD drugs

Drug class	Drugs	Weighted average cost per day[a]
ACE inhibitor (ACEi)/ Angiotensin receptor antagonist (ARB)	Enalapril maleate, lisinopril, perindopril erbumine, ramipril / candesartan cilexetil, irbesartan, losartan potassium, valsartan	£0.11
Beta blocker (BB)	Bisoprolol fumarate, carvedilol, nebivolol	£0.07
Aldosterone antagonist (AA)	Eplerenone, spironolactone	£0.20

(a) Prescription cost analysis(203)

TABLE 10. LVSD drug treatment cost by care received

Type of care given	90-day LVSD treatment cost[a]
Specialist heart failure team	£24.56
General medical team	£16.18

(a) Based on the probability of being prescribed treatment (National heart failure audit). National Institute for Cardiology Outcomes Research (NICOR). Secondary analysis of the National Heart Failure Audits of England and Wales 2009 - 2013 (unpublished data), 2014

The cost of other standard drugs such as diuretics was not included because the level of their use was assumed to be equivalent in standard and specialist management.

1.9.5 Medical costs: implantable electronic devices and surgical intervention

1.9.5.1 The cost of implantable electronic devices

Some of the cardiovascular implantable electronic devices (cardiac pacemakers, implantable cardioverter-defibrillators and etc) have become an effective treatment option in selected HF patients. In a recent report by Groeneveld et al., time-series regressions between 2003 and 2006 in the USA indicated that a 1% increase in the use of implantable cardioverter-defibrillators (ICD) use in the HF population resulted in $627 higher mean costs ($P < 0.001$). In aggregate, the cost increase attributable to ICDs was $893 million (29% of the total growth)(204).

Based on average selling prices aggregated across all manufacturers of ICDs sold in the UK to the NHS in the financial year of 2011, the cost of a complete ICD system was estimated at £9692, the cost of a complete CRT-P system was estimated to be £3411 and CRT-D system was £12,293. (205)

1.9.5.2 The cost of surgical revascularisation

Surgical intervention in CHF remains of limited use therefore the total cost is insignificant - 2.74% of the total healthcare expenditure on heart failure (189). In the United Kingdom in 1990-91, the costs for surgical revascularisation and cardiac transplantation in CHF patients were estimated at £7.2 and £2.66 million respectively (189). The latest cost of coronary bypass grafting according to the NICE (2011) has not changed significantly and in 2008-2009 was £7.959 (206). LVADs cost £80,569 ($127,887) at 2011 prices, which is cheaper than previous generation device (207).

1.9.5.3 Valvular disease in context of HF

The data on costs of valvular disease in context of HF, especially mitral regurgitation (MR) is also sparse. The French study suggested that presence of HF led to significant differences in cost of care in patients with MR (27). Non-surgical patients with HF and MR had high 12 months mortality and LOS with total cost of care 13,538€ vs 9957€ in patients without HF. Rehabilitation costs were also different. Patients with MR and HF who were managed medically consumed 45% (€ 132.3 million) of the overall annual cost of management of patients with MR (148).

1.9.6 Cost of rehabilitation. Follow up cost

Costs arising during non-hospitalised periods, as a result of an acute admission, include the following on the basis that they would differ between standard and specialist management:

• Heart failure drug therapy (described above)

• Hospital out-patient visits

• Primary care GP visits

• Community HFSN visits

The cost of cardiac rehabilitation was not included because the uptake of this service is low (11%) and cost is uncertain (208).

The occurrence and frequency of health system contacts other than acute admissions are specific to whether or not referral had been made to follow-on services. The national heart failure audit 2013 provides the probability of being referred to cardiology and heart failure nurse services – **TABLE 11** (192,208).

TABLE 11. Probability of being referred to follow-on services (209)

Follow-on service	Specialist heart failure team on a cardiology ward (National Heart Failure Audit 2012-13) (NHFA)	Specialist heart failure team on a general ward (inferred)	General medical team on a general ward (NHFA 2012-13)
Cardiology follow-up	71%	50%	22%
Heart Failure nurse follow-up(a)	68%	71%	23%

(a) HFSN follow-up was costed as a home visiting based service

The unit costs of follow-on services and tests are given in **TABLE 12** (208)

TABLE 12. Unit cost of follow-on services

Follow-on service/type of contact	Unit cost	Source
GP visit	£37	Personal Social Services Research Unit Handbook 2013 (191). 11.7 minute consultation**.**
Community HSFN visit	£42	Personal Social Services Research Unit Handbook 2013 (191). Nurse Specialist (Community), 1 hour.
Hospital outpatient visit	£131	NHS Reference costs schedule 2012-13. (Department of Health. NHS reference costs 2012-13). Cardiology outpatient visit.

1.9.7 Non-medical costs

The non-medical costs of CHF are difficult to estimate. These costs include those of lost earnings, sickness benefits, hospital transportation and social welfare support and the wider effect on patient's families. For example, in one state in America, the transportation costs of hospital out-

patient visits have been estimated to be greater than those spent on drug therapy (210). Socio-demographic inequalities have a certain impact on management and access to therapies (211).

1.10. Conclusion

In summary, during the last decades HF costs have substantially increased and will remain a significant economic burden on healthcare systems worldwide. The total impact of HF on the public is probably not well defined given the sparsity of data on the non-medical impact of HF public service. Although the prognostic impact of secondary MR is well understood, it is not clear if mitral insufficiency is the main driver of hospital admissions and whether correction of secondary MR by less invasive structural intervention will alter the course of disease. Further observational and interventional studies are needed to address this problem.

1.11. The key aims of MRAHF trial.

The MRAHF trial is aimed to study the incidence of significant MR in patients presenting acutely to district general hospital with symptoms of breathlessness and palpitations requiring hospital admission. The previous history of all cause hospital admissions and admissions with heart failure will be collected retrospectively to calculate the economic impact of significant MR. The objectives are:

1. To study the prevalence of MR of any severity in patients admitted acutely with symptoms of HF and its effect on LV function and patients prognosis.
2. To perform analysis of the economic impact of managements of patients with HF driven by significant MR during index acute admission and history of previous inpatient spells.
3. To determine how many acute HF patients are managed according to the National Institute for Health and Care Excellence (NICE) guidelines and to compare with the outcome and results of the group where management of HF is different from the NICE guidelines.

CHAPTER 2: METHODS

2.1. Patients recruitment

2.1.1 Clinical data collection

The suitability of patients for the MRAHF study was established once all heart failure patients had been screened within 24 hours after admission following which they were recruited and consented. The recruitment process took place at St Peter`s Hospital (SPH), which is a part of Ashford and St Peter`s NHS Trust. The following data has been collected from every patient: demographics, number of previous admissions to the SPH and the length of stay in the hospital during the last 12 months, 24 months and 36 months, admissions with primary diagnosis of heart failure for the same period of time, HF symptoms at the moment of presentation, HF stage by NYHA, comorbidities like hypertension, IHD, diabetes mellitus, CKD, CVA, COPD, presence of smoking and a recent blood test results.

2.1.2 Investigations

Echocardiography and cardiology review done within 36 months and at the current admission were registered. ECG results, CXR and the list of HF medications taken by patient were also collected. Every patient had their serum BNP done and thorough transthoracic echocardiography performed for the assessment of mitral regurgitation (MR) severity, left ventricular function and right heart abnormalities.

2.1.3 Ethical approval. Recruitment site and durability

The ethical approval was done by the North of Scotland Research Ethics Committee (REC number 16/NS/0047; 6th of June 2016). Recruitment was started on 4/07/2016 and carried out by two Clinical Research Fellows with occasional help from Research nurses. All staff were based at St Peter`s Hospital. During the 1 year and 2 months that this study has been running, a total of 500 patients have been recruited. 447 patients were included into analysis after all exclusions.

2.2. Recruitment criteria (Inclusion & Exclusion)

2.2.1 Inclusion criteria

Selection for this study had to meet certain inclusion criteria. Patients could be eligible for our study if their age was from 18 years to 100 years, both male or female gender. The main inclusion criteria were clinical signs and symptoms of acute heart failure or decompensated chronic heart failure. After that, they were required to have a bedside B-type natriuretic peptide (BNP) level of > 100 ng/L - according to the European Society of Cardiology the upper limit of normal BNP in the in the acute setting (19). The use of NPs is recommended for ruling out HF, but not to establish the diagnosis (19). Therefore, our choice to have 100 ng/L as the cut off, aimed to reduce the error of missing admitted HF patients.

2.2.2 Exclusion criteria

The main exclusion criteria needed to be met was a bedside serum BNP level <30 ng/L. Also we were aiming to measure BNP level and recruit a suitable patient within the first 2 days of hospital admission. Patients who did not meet these requirements, were excluded from the study along with patients who were not within the specified age range of 18-100 years.

2.3. Data Collection

2.3.1 Screening of patients

Before collecting any data, patients were screened first using the hospital electronic database, which include on-take and clinical handover lists. All patients admitted with symptoms of HF (shortness of breath, peripheral oedema, palpitations and irregular heart beat) were assessed by a Clinical Research Fellow. After individuals with suspected acute heart failure were selected, their clinical notes were then carefully screened and further clinical examinations and assessments to identify the suitability of a patient for our study were carried out.

2.3.2 Consent for the study

Those patients with clear evidence of acute HF were given as much information as they were required to make an informed decision about participation in the study. When the patient decided to participate they were given an information sheet to keep and asked to sign a consent form.

2.3.3 Measurement of Brain Natriuretic Peptide (BNP) plasma level

From those who were consented, a blood sample was taken for bedside i-STAT BNP test (i-STAT 1 Analyser “Immuno-Ready”). The i-STAT BNP monitor was provided by Abbott POCT ltd and calibrated and used according to their instructions. The clinical team remained blind to the results of i-STAT BNP unless it was formally requested via routine hospital requesting system.

The i-STAT BNP test is an in vitro diagnostic test for the quantitative measurement of B-type natriuretic peptide (BNP) in plasma samples using EDTA as the anticoagulant.

The i-STAT BNP test cartridge uses a two-site enzyme-linked immunosorbent assay (ELISA) method. Antibodies specific for BNP are located on an electrochemical sensor fabricated on a silicon chip. The whole blood or plasma sample is brought into contact with the sensors allowing the enzyme conjugate to dissolve into the sample. The BNP within the sample becomes labelled with alkaline phosphatase and is captured onto the surface of the electrochemical sensor during an incubation period of approximately seven minutes. The enzyme bound to the antibody/antigen/antibody sandwich cleaves the substrate releasing an electrochemically detectable product. The electrochemical sensor measures this enzyme product which is proportional to the concentration of BNP within the sample.

2.3.4 Clinical data

Once i-STAT BNP confirmed the diagnosis of HF the following data had been taken from patient`s clinical notes: demographic data (date of birth, gender, ethnicity), clinical data (symptoms, vital signs, ECG, CXR, NYHA class), number of previous admissions in total and with HF for the last 1 year, 2 years and 3 years, previous and current length of hospital stay, cardiology appointments and echocardiography scans for the last 3 years and at the current admission. Also, comorbidities like known mitral regurgitation, ischaemic heart disease, hypertension, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, previous cerebrovascular accident and presence of smoking, mortality in 1, 3, 6 months and 1 year had been recorded.

2.3.5 Pharmacological data

To complete the clinical data collection, the following pharmacological data had been collected: compliance with HF treatment, use of mineralocorticoid receptor antagonists (MRAs), Angiotensin Converting Enzyme inhibitors (ACEi), Angiotensin II Receptor Blockers (ARBs), Angiotensin receptor blockers with Neprilysin inhibitors (ARNIs), beta-blockers, blood vessel dilators, Calcium channel blockers (CCBs), digoxin, diuretics, selective sinus node inhibitors and potassium or magnesium supplementation.

2.4. Echocardiography

2.4.1 Echocardiography protocol and data storage

After the data mentioned above was collected, a transthoracic echocardiography (TTE) was performed on every patient by a Clinical Research Fellow using the GE Vivid S70 ultrasound machine. The Research Fellow was fully accredited by the British Society of Echocardiography (BSE) with reaccreditation having been completed in 2017 during the patient recruitment for our study.

Over 90 % of our patients were scanned by a single echocardiographer (Observer 1) to reduce intra observer variability. All echocardiography studies were screened by another echocardiographer (Observer 2), to minimise inter observer variability in our studies. Analysis was done by Bland – Altman plot (Figure 7, 8).

Figure 7. Bland – Altman plot for regurgitant volume assessment (Observer 1& Observer 2).

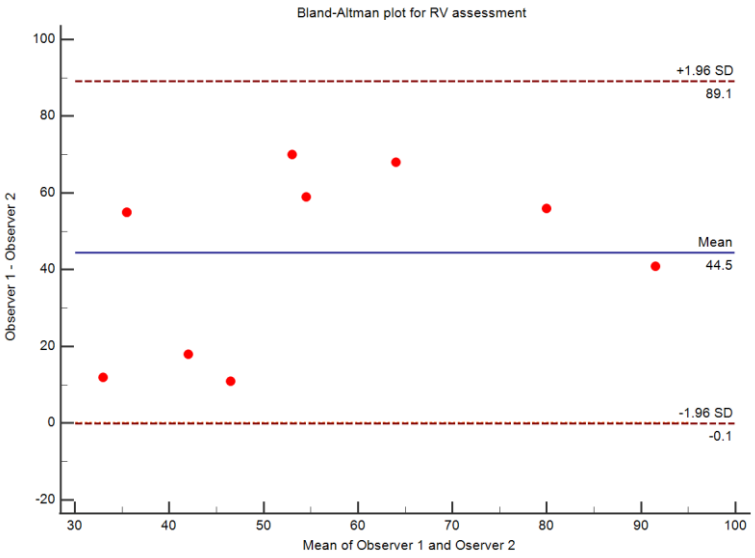
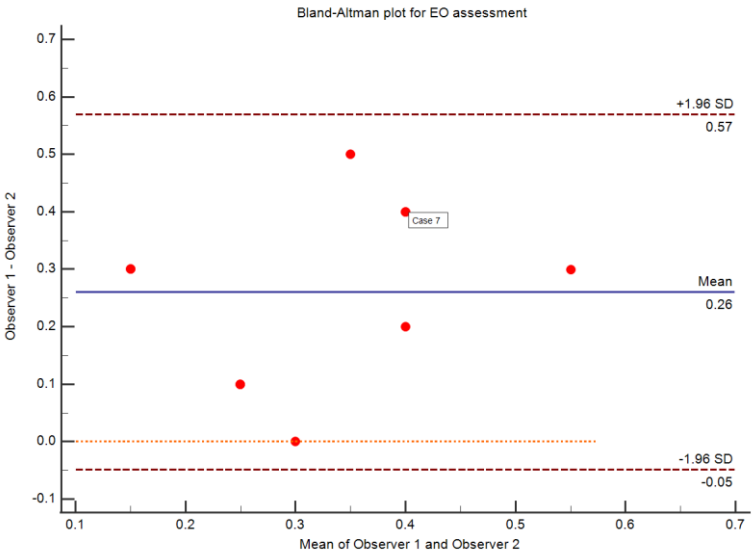


Figure 8. Bland – Altman plot for Effective orifice area assessment (Observer 1 & Observer 2)



Every echocardiography study followed BSE recommendations and included parasternal, apical and subcostal approach for each patient with up to 5 views from every approach assessing the heart anatomy and function by two dimensional echo (2D), M-mode, Colour Doppler, tissue doppler imaging (TDI), pulse wave doppler (PW), continuous wave doppler (CW), Strain and Strain rate. The data from the Echo has been analysed on-line and off-line using ECHOPAC version 201.

The cardiology clinical team, who were working separately from us, also remained blinded to the results of echocardiography unless there had been any severe, life threatening abnormalities identified that required urgent management for the patient`s safety. All studies had been exported to two external hard drives to secure our database.

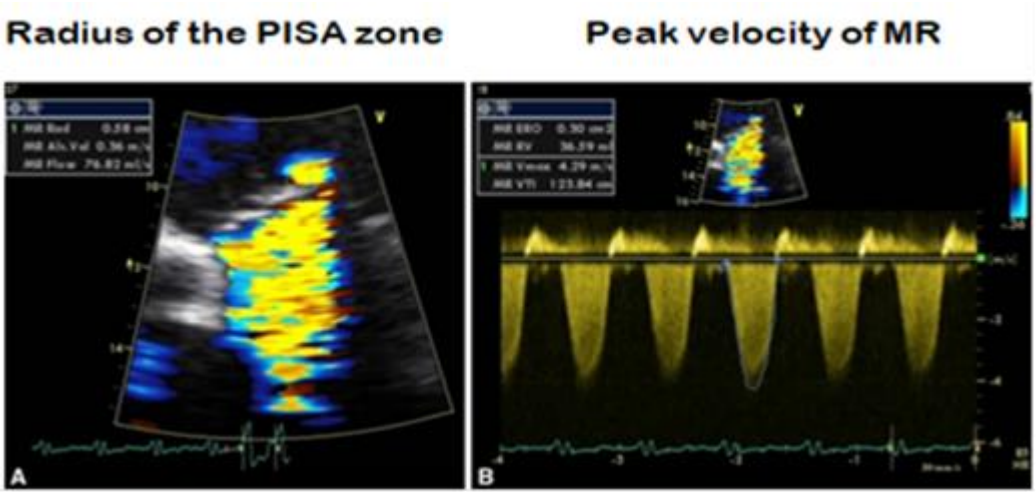


Figure 9. MR quantification – PISA method

2.4.2 Mitral Regurgitation (MR)

The mitral regurgitation was determined by using quantitative, semi-quantitative and qualitative methods. The mitral valve morphology assessment and colour Doppler imaging were part of our qualitative method. Pulmonary venous flow and vena contracta were used for semi quantitative assessment.

For quantitative assessment of MR severity PISA was the method of choice to estimate effective regurgitant orifice area by analysing of flow convergence zone of a regurgitant jet. This was done by measuring the radius of the PISA shell from the left ventricular side, at an aliasing velocity of 40 cm/s, and measuring the peak velocity of MR jet by CW. The **figure 9** demonstrates PISA zone on the left and the measurement of MR peak velocity by CW doppler on the right. Regurgitant volume (RV) we determined using the following formula (212):

RV = EROA x VTI,

Where EROA is effective regurgitant orifice area and VTI is the velocity time integral of the mitral regurgitation jet.

MR was graded as a mild, moderate, moderate to severe and severe valvular insufficiency based on the recommendations by the British Society of Echocardiography. Our focus of interest was a haemodynamically significant MR, where we included moderate, moderate to severe and severe valvular insufficiency. Also a part of assessment was to determine whether MR was a primary or secondary origin based on an aetiology and morphology of the mitral valve and subvalvular apparatus.

In cases with secondary MR, we graded as a severe regurgitation when RV was > 30 ml, and EROA was > 0.2. Primary MR we graded as a mild when RV was < 30 ml and EROA < 0.2. The rest of the patients with values above these figures were graded as having the significant MR.

As part of MR assessment we also measured MV annulus in the late diastole for every patient in parasternal long axis view (PLAX) and apical 2 chamber view (A2C) and determined whether or not our patients with significant MR were suitable for possible Mitral Clip based on the aetiology and morphology of the valvular insufficiency.

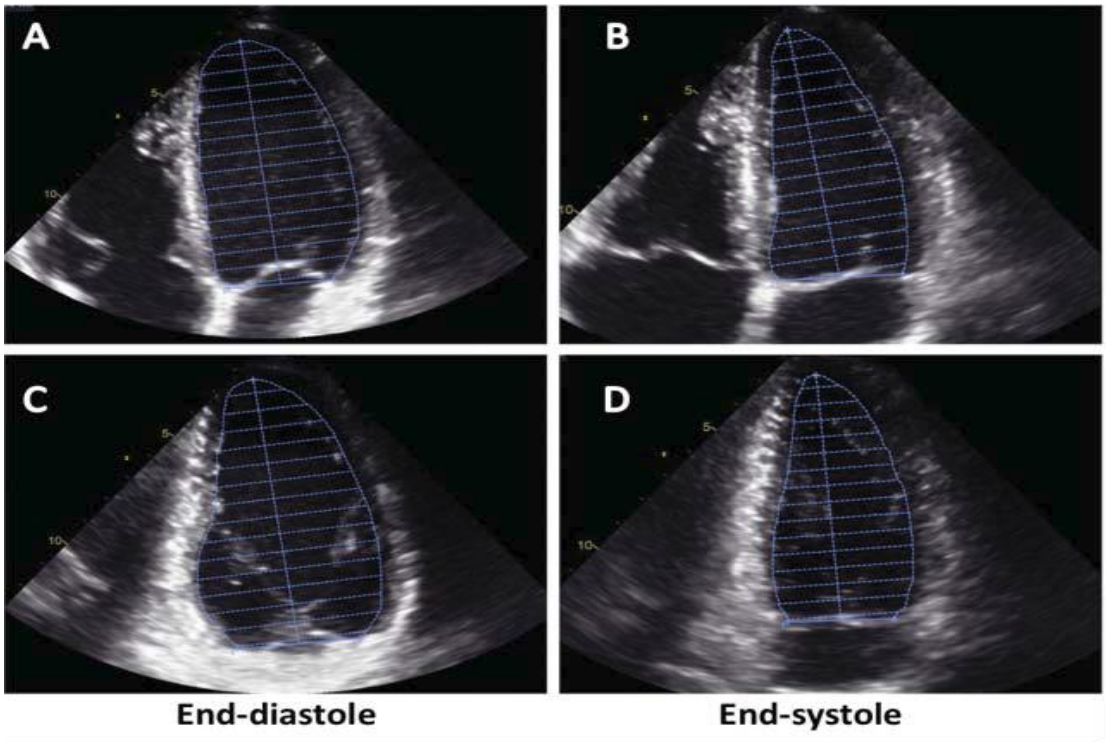


Figure 10. Bi-plane Simpson`s method for LV EF calculation.

2.4.3 Left ventricular (LV) systolic and diastolic function

The left ventricular global systolic function was assessed by biplane Simpson`s method to determine ejection fraction (EF). This was done on-line while acquiring echo images. LV end systolic and end diastolic diameters and volumes had been measured as part of systolic function evaluation (**Figure 10**). The left ventricular pressure rise (LV dP/dt) measurement in early systole was another way of evaluation of LV global systolic function. The regional wall motion abnormalities were identified visually.

To assess LV diastolic function E, A waves and E/A ratio had been measured by pulse wave (PW), E` lateral wave by tissue doppler, pulmonary venous flow by PW.

2.4.4 Right heart function

The right ventricular (RV) function assessment in our patients was more challenging due to poorer visualisation of the right side of the heart compared to the left side and inability to apply quantitative biplane Simpson method. The right ventricular diastolic and systolic areas had been obtained with further calculation of the RV fractional area change (RVAFC), which was one of the main parameter in the assessment of RV systolic function (**Figure 11**). Other methods, which we applied for the right ventricle, were tricuspid annular plane systolic excursion (TAPSE), visual assessment of RV size and systolic function, RV Strain and Strain Rate. Basal RV diameter and TV annulus had been measured in the late diastole as part of right heart function assessment.

RV END-DIASTOLE **RV END-SYSTOLE**

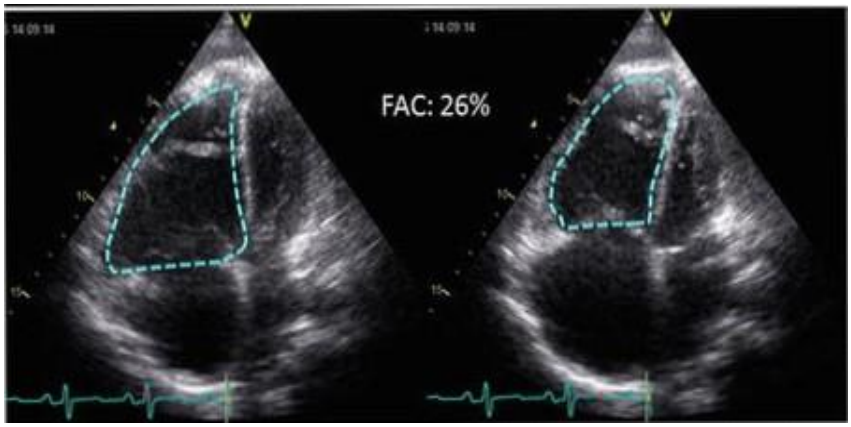


Figure 11. RV fractional area change

The accuracy of RV systole durability was marked by measuring pulmonary valve opening and closing time. Then RV Strain and Strain Rate curves were obtained from basal, mid and apical segments of RV in apical 4 chamber view. Again the analysis has been done offline.

2.4.5 Left and right atriums, other valvular functions

Echocardiography study has been completed with comprehensive assessment of the rest of heart morphology and function. Left and right atrial areas, pulmonary artery pressure, tricuspid, pulmonary and aortic valve functions had been assessed. The tricuspid regurgitation (TR) was graded visually by Colour doppler as a mild, moderate, moderate to severe and severe valvular insufficiency.

2.5. Statistical Analysis

The optimum cut-off for prediction of 6-month mortality was estimated by identifying the sensitivity and specificity associated with the maximum Youden Index. These cut-offs were then used as a binary determinant of significant vs non-significant MR severity.

Socio-demographic and baseline characteristics were summarised by severity group and overall for the complete analysis set. Categorical variables were reported as numbers and percentages and

between-groups comparisons compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were reported as means and standard deviations or as medians and interquartile ranges and compared using Student's t test or the Mann-Whitney U test.

For the primary analysis of 6-month mortality, unstratified Kaplan-Meier curves were constructed. Hazard ratios were estimated using an unadjusted Cox regression model, with statistical significance being assessed using the logrank test. Secondary analyses were carried out using Cox regression analyses adjusted for significant covariates. Selection of covariates to be included was based on initial multiple univariate regression analyses, modified according to clinical opinion from the research team. These were gender, age, body-mass index and pre-existing diagnoses of chronic obstructive pulmonary disorder, hypertension, chronic kidney disease, ischaemic heart disease, diabetes mellitus and cerebrovascular disease. For all comparisons, the threshold of statistical significance was set at a 2-sided α-value of 0.05.

2.6 Data storage

Enrolled patients had objective, echocardiographic and clinical characteristics collected via a standardised collection form which was stored online in a password-protected database specifically devised for study by Metanoic Health Ltd, United Kingdom.

Data was entered by primary operators and double checked by independent specialists. Histograms were performed on all continuous data to screen for statistical outliers using Statistical Package for the Social Sciences (SPSS) version 24 (IBM, USA). Any outlying data points were then rechecked to screen for input errors or errors of measurement. The echocardiography data was retained on two separate hard-drives to allow for off-site analysis and to reduce the risk of data loss in accordance with Good Clinical Practice research protocols.

The study was sponsored by Metanoic Health Ltd. And was registered with ClinicalTrial.gov on 04/04/2016

CHAPTER 3. RESULTS

3.1 Left ventricular (LV) geometry, cardiac function and prognosis in patients with significant mitral regurgitation (MR)

3.1.1 Background

Mitral regurgitation (MR) is one of the most common valvular heart disorders, with an estimated worldwide prevalence more than five million which increases with age (144). MR is classified as primary (also known as organic) when principally due to a structural or degenerative abnormality of the mitral valve (MV) apparatus with deficiencies of function either leaflets, chordae tendineae or papillary muscles. Secondary (also known as functional) MR occurs in the absence of organic MV disease, usually from left ventricular (LV) remodelling and/or dysfunction. Secondary MR is more common than primary MR (22) and associated with a worse prognosis (compounded by the underlying cardiomyopathy). In latter in contrast to primary MR the benefits of MV surgery are uncertain.

A strong association between secondary MR severity and both all-cause mortality and heart failure hospitalisations has been reported (22).

3.1.2 Study results. Total number of recruited patients. Exclusions

616 consecutive patients presenting with symptoms of acute or exacerbation of CHF were assessed for eligibility for the MRAHF study from July 2016 to August 2017. We included 447 (72.6%) patients into the analysis out of 500 patients recruited in total. 53 patients have been excluded due to the variety of reasons such as poor echo windows, incomplete study, terminal stage of disease when echo was not feasible or when they did not meet inclusion criteria into the study, BNP was ≤ 100 pg/ml, the late recruitment, etc.

418 individuals were included in final analysis after excluding the data from rehospitalisation and three individuals lost to follow-up.

3.1.3 Technically difficult cases

Combination of qualitative, semi quantitative and quantitative analysis was used for assessment of MR. We were not able to quantify MR in 97 cases due to lack of CW/colour signal or eccentric nature of MR jet. However, all of them had sufficient echo image quality to allow either semi-quantitative or qualitative assessment of MR severity. So, amongst them visually 94 patients had mild MR, 1 - moderate, 1- moderate to severe and 1 - severe MR.

3.1.4 Mortality data

6 months outcome was available for 445 patients. 2 patients were not UK residents and left the country earlier. 6-months mortality for the whole cohort was 28%.

3.1.5 Group division

All our patients (100%) had some degree of MR. They were divided into 2 groups depending on MR severity. The control group of patients with mild MR included 253 patients (60.5%) and another group with significant MR -165 patients (39.5%) including moderate, moderate to severe and severe MRs.

3.1.6 Primary & secondary MR

The vast majority of patients with significant MR (154 patients, 93.3%) were secondary in origin, when regurgitation was due to LV cavity and/or mitral valve (MV) annular dilatation, papillary muscle displacement leading to poor leaflet tip coaptation. Small minority of patients (11 patients, 6.7%) had MR due to primary abnormality of MV apparatus itself.

3.1.7 Baseline characteristics

The baseline characteristics for the both 2 groups including age, gender, haemodynamics at admission, blood test results, comorbid conditions, ECG rhythm with QRS duration, previous and current cardiology review including previously performed echoes are shown below(**TABLE 13, Appendix 8**).

TABLE 13. Baseline characteristics and observations of patients with mild and significant MR.

	All patients (n = 418)	**Significant MR (n = 165)**	**Mild MR (n = 253)**	**p-value***
Demographics				
Age, mean (SD), y	78·7 (11·7)	79·3 (12·0)	78·3 (11·5)	0·395
Gender (male), n (%)	222 (53·1)	84 (50·9)	138 (54·6)	0·459
Race, n (%)				
White	390 (93·3)	150 (90·9)	240 (94·9)	0·110
BAME	28 (6·7)	15 (9·1)	13 (5·1)	0·110
BMI, mean: kg/m^2 (sd)	28·6 (8·06)	29·5 (8·82)	27·2 (6·52)	0·004
Comorbidities n (%)				
Coronary artery disease	152 (36·4)	65 (39·4)	87 (34·4)	0·300
Hypertension	232 (55·5)	89 (53·9)	143 (56·5)	0·602
Diabetes	130 (31·1)	41 (24·9)	89 (35·2)	0·026
Chronic Kidney Disease	189 (45·2)	73 (44·2)	116 (45·9)	0·733
COPD	61 (14·6)	18 (10·9)	43 (17·0)	0·085
Cerebrovascular disease	64 (15·3)	30 (18·2)	34 (13·4)	0·183
Presentation				
NYHA class, n (%)				
II	37 (8·9)	12 (7·3)	25 (9·9)	0·361
III	161 (38·5)	61 (37·0)	100 (39·5)	0·608
IV	220 (52·6)	92 (55·8)	128 (50·6)	0·299
ECG findings				
Sinus rhythm, n (%)	163 (39·0)	56 (33·9)	107 (42·3)	0·086
AF, n (%)	192 (45·9)	85 (51·5)	107 (42·3)	0·065
Paced, n (%)	39 (9·3)	15 (9·1)	24 (9·5)	0·891
Other rhythm, n (%)	18 (4·3)	5 (3·0)	13 (5·1)	0·300
Observations				
BPs, mmHg mean (sd)	136 (26·4)	133 (25·4)	138 (27·0)	0·040
BPd, mmHg mean (sd)	76 (16·9)	75 (17·7)	76 (16·9)	0·539
HR, bpm mean (sd)	89 (27·2)	89 (27·7)	90 (26·9)	0·663

SpO_2, % mean (sd)	95·0 (3·78)	95·2 (3·82)	94·8 (3·75)	0·209
Biochemistry				
Haemoglobin, g/L mean (sd)	122·5 (21·76)	121·6 (22·39)	123·1 (21·36)	0·486
Creatinine, µmol/L mean (sd)	120·0 (73·44)	126·9 (85·27)	115·6 (64·36)	0·148
eGFR, mL/min/1·73m^2 mean (sd)	48·3 (14·56)	47·1 (15·74)	49·1 (13·72)	0·181
CRP, mg/dL mean (sd)	29·5 (42·74)	31·9 (44·09)	28·0 (41·88)	0·385
BNP, ng/L mean (sd)	1363 (1254·2)	1729 (1315·7)	1124 (1153·9)	<0·0001

BAME = Black, Asian and Minority Ethnic. COPD = Chronic Obstructive Pulmonary Disorder. NYHA = New York Heart Association. AF = Atrial Fibrillation. BPs = Blood Pressure systolic. BPd = Blood Pressure diastolic HR = Heart Rate. SpO_2 = Peripheral Capillary Oxygen Saturation. eGFR = estimated Glomerular Filtration Rate. CRP = C-Reactive Protein. BNP = Brain Natriuretic Peptide.* p-values are estimated using Mann-Whitney U-test for medians, N-1 χ^2 for proportions and independent samples t-test for continuous variables.

There were no significant differences in a number of baseline characteristics for both of our HF patient groups with mild MR and significant MR (**TABLE 13**). There was, however, difference in patients' BMI. Those with significant MR had lower systolic BP on admission, higher level of BNP and less likely to be in sinus rhythm. They also had broader QRS and more likely to be referred for cardiology review.

TABLE 14. Medications on admission

	LVEF <40%	LVEF 40 - 49%	LVEF 50+%	Mild MR	Moderate MR	Moderate-Severe MR	Severe MR	Significant MR	p-value (significant vs non-significant)
ACEi, patients	52 (31.0%)	19 (19.4%)	42 (28.2%)	75 (29.6%)	12 (19.0%)	9 (37.5%)	17 (21.8%)	38 (23.0%)	0.119
ARB, patients	21 (12.5%)	17 (17.3%)	24 (16.1%)	43 (17.0%)	7 (11.1%)	4 (16.7%)	10 (12.8%)	21 (12.7%)	0.218
ARNI, patients	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Beta Blocker, patients	89 (53.0%)	48 (49.0)	93 (62.4%)	140 (55.3%)	30 (47.6%)	14 (58.3%)	47 (60.3%)	91 (55.2%)	0.865
CCB, patients	25 (14.9%)	15 (15.3%)	35 (23.5%)	50 (19.8%)	13 (20.6%)	3 (12.5%)	11 (14.1%)	27 (16.4%)	0.352
Digoxin, patients	23 (13.7%)	7 (7.1%)	19 (12.8%)	28 (11.1%)	7 (11.1%)	2 (8.3%)	12 (15.4%)	21 (12.7%)	0.222
Diuretic, patients	82 (48.8%)	46 (46.9%)	76 (51.0%)	118 (46.6%)	31 (49.2%)	12 (50.0%)	46 (59.0%)	89 (53.9%)	0.180
Ivabradine, patients	1 (0.6%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (1.3%)	2 (1.2%)	0.081
K/Mg supplements, patients	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.6%)	0.218
MRA, patients	20 (11.9)	8 (8.2%)	22 (14.8%)	25 (9.9%)	8 (12.7%)	3 (12.5%)	15 (19.2%)	26 (15.8%)	0.081
Vasodilator, patients	24 (14.3%)	9 (9.2%)	17 (11.4%)	27 (10.7%)	10 (15.9%)	2 (8.3%)	11 (14.1%)	23 (13.9%)	0.922

The **TABLE 16** shows the data on previous admissions taken from the notes or electronic records presented in preceding 12, 24 and 36 months for all cause and HF admissions to the SPH. It demonstrates that there was no difference between all cause admissions between the groups in the preceding 12-36 months, but patients with significant MR had high rate of previous admissions with HF.

TABLE 16. History of previous admissions of patients with mild and significant MR.

	LVEF <40%	LVEF 40 - 49%	LVEF 50+%	Mild MR	Moderate MR	Moderate-Severe MR	Severe MR	Significant MR	P-value
MR severity, number of patients	168 (40.5%)	98 (23.6%)	149 (35.9%)	253 (60.5%)	63 (15.1%)	24 (5.7%)	78 (18.7%)	165 (39.5%)	-
Total previous admissions for 12 months	309	128	240	414	89	46	132	267	<0.00001
Total previous admissions for 24 months	466	191	372	632	138	74	190	402	<0.00001
Total previous admissions for 36 months	610	260	483	848	190	89	234	513	<0.00001
Previous admissions with HF for 12 months	82	22	66	83	20	17	51	88	0.0002
Previous admissions with HF for 24 months	109	32	82	108	29	23	71	123	<0.00001
Previous admissions with HF for 36 months	136	40	118	130	34	28	84	146	<0.00001
First admission for HF in last 12 months, patients	127	82	109	200	49	17	54	120	0.303
Second admission for HF in last 12 months, patients	17	11	25	35	10	1	8	19	0.1738
Third or later admission for HF in last 12 months, patients	24	5	15	18	4	6	16	26	0.0053
First admission for HF in last 36 months, patients	111	72	101	188	44	12	41	97	0.0054
Average length of previous hospital stay, days	6.0	4.6	4.9	4.8	6.9	4.6	5.7	6.0	0.1683
Maximum length of hospital stay, days	90	41	53	53	90	15	46	90	-
Current LOS	8.8	7.8	7.8	7.7	9.4	7.9	9.1	9.0	-

3.1.8 Echocardiography data

Echo data in **TABLE 17** shows haemodynamic parameters obtained during comprehensive bedside study. The full echocardiography study has been performed for every HF patients according to the standardised protocol designed for this study (Appendix 1). Quantitative offline analysis was performed on EchoPAC workstation (version 201, GE Vingmed Ultrasound).

TABLE 17. Echo derived haemodynamic parameters of patients with mild and significant MR.

	LVEF <40% (%/sd)	LVEF 40 - 49% (%/sd)	LVEF 50+% (%/sd)	Mild MR (%/sd)	Moderate MR (%/sd)	Moderate-Severe MR (%/sd)	Severe MR (%/sd)	Significant MR (%/sd)	P-value
Primary MR, number of patients	1 (0.6%)	5 (5.1%)	5 (1.2%)	0(0.0%)	1 (1.6%)	1 (4.2%)	9 (11.5%)	11 (6.7%)	<0.0001
Secondary MR, number of patients	167 (99.4%)	93 (94.9%)	144 (96.6%)	253 (100%)	62 (98.4%)	23 (95.8%)	69 (88.5%)	154 (93.3%)	0.0001
MR Effective regurgitant orifice area (EROA)	0.24 ± 0.140	0.24 ± 0.143	0.202 ± 0.167	0.137 ± 0.063	0.221 ± 0.07	0.299 ± 0.07	0.418 ± 0.163	0.326 ± 0.153	0.0001
MR Regurgitant volume (RV)	34.2 ± 20.7	36.007 ± 19.46	27.28 ± 18.8	17.798 ± 7.097	33.128 ± 8.227	43.261 ± 12.118	60.844 ± 14.8	47.8 ± 17.792	<0.0001
MR Vena contracta	0.40 ± 0.118	0.387 ± 0.13	0.343 ± 0.129	0.302 ± 0.085	0.430 ± 0.087	0.429 ± 0.108	0.509 ± 0.109	0.467 ± 0.108	0.0001
LVEDD, cm	5.75 ± 4.3	4.87 ± 0.765	4.56 ± 0.7	5.03 ± 3.571	5.06 ± 0.9	5.129 ± 0.9	5.34 ± 0.99	5.2 ± 0.955	0.541
LVESD, cm	4.889 ± 4.246	3.754 ± 0.749	3.213 ± 0.6	3.9 ± 3.5	4.086 ± 0.97	4.104 ± 1.175	4.335 ± 1.71	4.2 ± 1.1	0.282
LV EDV, ml	138 ± 56	112 ± 45	81.1 ± 38	99 ± 50	117 ± 50	127 ± 66	140 ± 61	129 ± 59	<0.0001
LV ESV, ml	101 ± 51	62 ± 25	34 ± 17	58 ± 41	72 ± 38	86 ± 56	89 ± 56	82 ± 50	<0.0001
LV EDV index	73.0 (30.7)	58.9 (23.3)	42.3 (18.7)	51.2 (23.4)	62.4 (25.8)	66.9 (34.7)	77.8 (33.5)	70.3 (31.6)	<0.0001
LV ESV index	53.4 (26.4)	32.7 (13.2)	17.9 (8.2)	30.0 (20.6)	38.7 (20.3)	45.1 (29.3)	49.5 (29.8)	44.7 (26.8)	0.0001
LV EF, %	27.8 ± 8	45 ± 3	58 ± 6	45 ± 14	39 ± 13	35 ± 15	40 ± 15	39 ± 15	<0.0001
LV dp/dt	819 ± 359	1040.9 ± 393	1170.9 ± 389	997 ± 415	1019.9 ± 431	927.7 ± 294	932.17 ± 393	964.6 ± 395.9	0.423
E wave	1.01 ± 0.268	1.02 ± 0.325	1.10 ± 0.348	0.98 ± 0.285	1.07 ± 0.351	1.14 ± 0.216	1.23 ± 0.307	1.156 ± 0.320	0.0001
A wave	0.64 ±	0.81 ±	0.82 ±	0.81 ±	0.70 ±	0.65 ±	0.58 ±	0.63 ±	0.0001

	0.325	0.334	0.393	0.373	0.371	0.432	0.232	0.314	
E/A	1.8 ±1.17	1.4 ± 1.02	1.6 ± 1.06	1.4 ± 0.96	1.9 ± 1.13	2.2 ± 0.94	2.3 ± 1.26	2.1 ± 1.18	<0.0001
E prime	0.09 ± 0.037	0.10 ± 0.043	0.10 ± 0.038	0.10 ± 0.039	0.10 ± 0.039	0.10 ± 0.046	0.10 ± 0.035	0.10 ± 0.041	1
LV, TDI S lateral	0.07 ± 0.046	0.077 ± 0.028	0.09 ± 0.029	0.08 ± 0.044	0.08 ± 0.027	0.08 ± 0.025	0.07 ± 0.026	0.07 ± 0.026	0.43
LA, end-systolic area, cm2	29.0 ± 7.9	29.1 ± 7.8	28.2 ± 8.8	26.9 ± 7.5	30.8 ± 8.9	29.9 ± 6.9	32.3 ± 8.5	31.4 ± 8.5	0.0001
MV annulus, cm	3.68 ± 0.6	3.64 ± 0.6	3.63 ± 0.6	3.61 ± 0.6	3.538 ± 0.6	3.762 ± 0.6	3.87 ± 0.5	3.85 ± 0.5	<0.0001
RVAd, mm	22.17 ± 8.99	21.40 ± 9.2	20.36 ± 8.06	20.51 ± 8.48	20.88 ± 7.2	25.0 ± 9.8	23.40 ± 9.70	22.666 ± 8.9	0.013
RVAs, mm	14.76 ± 7.0	13.67 ± 6.5	12.366 ±6.36	12.66 ± 6.24	13.6 ± 5.8	17.43 ± 7.5	15.72 ± 7.8	15.14 ± 7.1	0.0001
RV fractional area change, %	34.4 ± 12.5	36.6 ± 10.5	40.1 ± 12.8	39 ± 12	35.4 ± 13	30.7 ± 10.9	34 ± 11	34 ± 12	<0.0001
Visually enlarged RV (%, patients)	81 (48.2%)	37 (37.8%)	68 (45.6%)	100 (39.5%)	27 (42.9%)	15 (62.5%)	44 (56.4%)	86 (52.1%)	0.011
TAPSE, mm	1.41 ± 0.452	1.61 ± 0.464	1.70 ± 0.549	1.62 ± 0.526	1.49 ± 0.475	1.34 ± 0.308	1.48 ± 0.471	1.47 ± 0.454	0.0008
RV, TDI	0.10 ± 0.035	0.11 ± 0.039	0.12 ± 0.039	0.12 ± 0.040	0.11 ± 0.035	0.11 ± 0.035	0.093 ± 0.036	0.10 ± 0.036	<0.005
RA, systolic area, mm2	24.6 ± 8.6	24.6 ± 8.5	24.1 ± 9.4	23.3 ± 8.4	25.1 ± 8.8	27.3 ± 9.1	26.2 ± 9.8	26.0 ± 9.9	0.004
TV annulus, cm	3.65 ± 0.8	3.59 ± 0.8	3.61 ± 0.8	3.51 ± 0.8	3.78 ± 0.6	3.87 ± 0.8	3.81 ± 0.8	3.73 ± 0.8	0.01
Systolic PAP, mmHg	50.6 ± 17	53 ± 20	55.2 ± 19	50 ± 19	53 ± 16	55 ± 12	61 ± 20	57 ± 18	<0.0001
Significant TR, number of pts (%, pts)	85 (50%)	52 (53%)	78 (52%)	104 (41%)	40 (63%)	17 (71%)	55 (70%)	112 (68%)	<0.0001
Isolated LVSD (%, patients)	168 (100%)	98 (100%)	0 (0.0%)	140 (55.3%)	46 (73%)	19 (79.2%)	62 (79.5%)	127 (77%)	<0.0001
Isolated RVSD (%, patients)	91 (54.2%)	44 (44.9%)	45 (30.2%)	89 (35.2%)	32 (50.8%)	14 (58.3%)	46 (59%)	92 (55.8%)	<0.0001
Bi-ventricular systolic dysfunction (%, patients)	91 (54.2%)	44 (44.9%)	0% (0)	56 (22.1%)	27 (42.9%)	13 (54.2%)	39 (50.0%)	79 (47.9%)	<0.0001

Predominant LVSD (%, patients)	159 (94.6%)	84 (85.7%)	10 (6.7%)	136 (53.8%)	45 (71.4%)	17 (70.8%)	56 (71.8%)	118 (71.5%)	0.0003
Predominant RVSD (%, patients)	160(95.2%)	84 (85.7%)	106 (71.1%)	212 83.8%)	55 (87.3%)	21 (87.5%)	64 (82.1%)	140 (84.8%)	0.773

Those with significant MR had features of left ventricular remodelling with increase in end-diastolic (LVEDV) and end systolic (LVESV) volumes and reduction in LV ejection fraction (LVEF) in presence of significant volume overload (MR regurgitant volume) (**TABLE 3**). LA dilation was significant in group 2. The changes in the right heart geometry and function were even more noticeable between the groups. The study showed that the severity of pulmonary hypertension (PHT) and right ventricular (RV) dysfunction were much worse in the presence of significant MR: there was more prominent rise in systolic pulmonary artery pressures (PAP) and reduced RV fractional area change (RVFAC).

3.1.9 The right ventricular function in acute HF

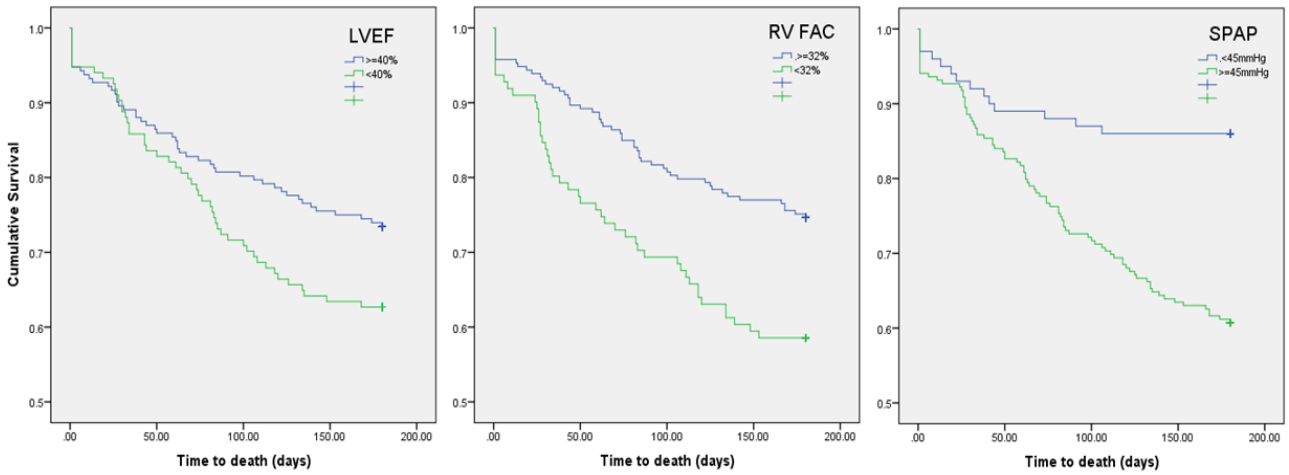
Patients with RV dysfunction as assessed by RVFAC (<32%) showed a significant excess of mortality ($p \leq 0.01$), with a hazard ratio (HR) of 1.9 (95% CI 1.3-2.7, $p<0.01$) (**TABLE 4, FIG 1**). TAPSE – the universal marker of RV function assessment was not a significant predictor of mortality ($p>0.2$) and in fact was reduced in presence of moderate-severe tricuspid regurgitation (TR) ($p<0.05$).

Pulmonary hypertension at rest was a strong predictor of all-cause mortality: SPAP ≥45mmHg was associated with a significant increase in mortality compared to those with <45mmHg ($p= <0.00001$) with a HR of 3.2 (95% CI 1.8-5.5, $p<0.00001$) (**TABLE 18**, **FIG 12**).

TABLE 18. Comparison of hazard ratio for LV failure, moderate to severe pulmonary hypertension and RV failure.

Echocardiographic marker	**Hazard Ratio**	**95% Confidence Interval**	**Significance**
Left Ventricular Failure (LVEF)	1.486	1.006-2.195	P <0.05
Moderate-to-severe pulmonary hypertension	3.151	1.791-5.545	P <0.00001
Right Ventricular Failure (RV FAC)	1.747	1.191-2.564	P <0.01

FIGURE 12. Kaplan-Meier Survival distribution curves for categorised LVEF, RV FAC and SPAP.



3.1.10 Mortality and prognosis

For statistical comparison values were categorised and analysed using Chi-square testing. Kaplan-Meier survival plots were created to demonstrate difference in survival. Independent T-tests were performed to demonstrate statistical difference in continuous data. 6 months mortality in presence of significant MR was 34.9%, in presence of mild MR was 23.8% with P value < 0.05 (**FIGURE 13**).

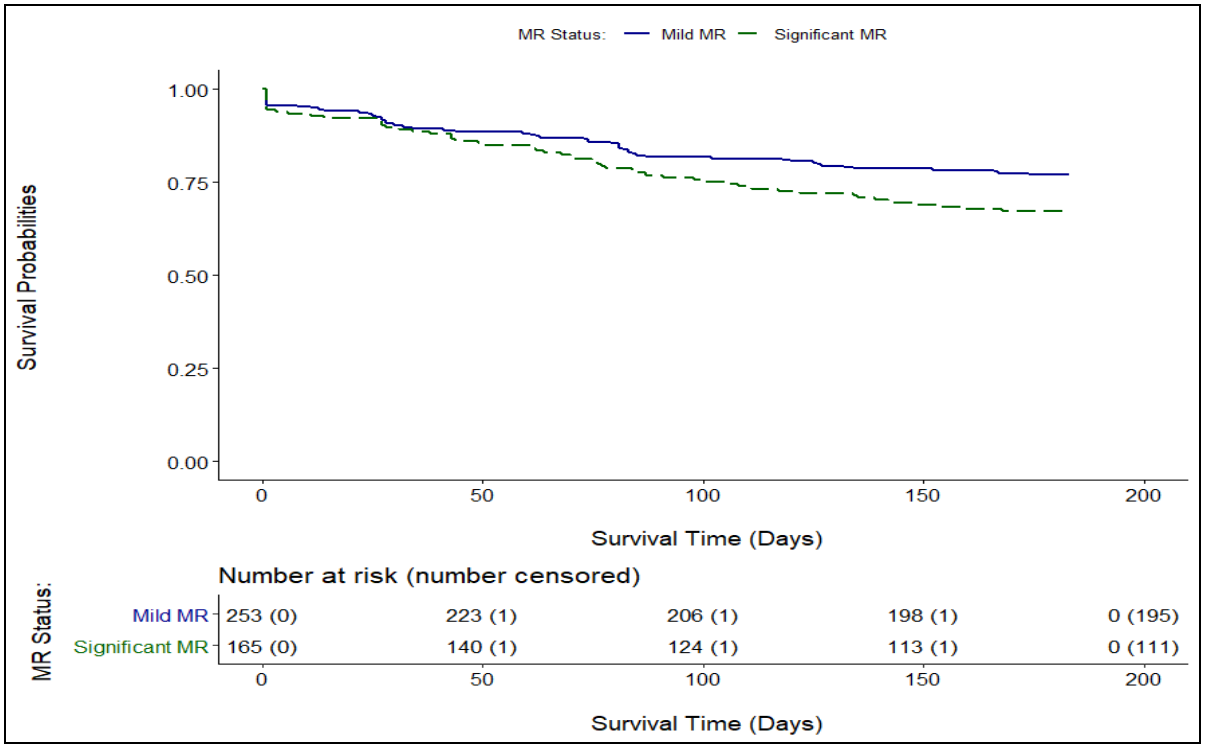


FIGURE 13. 6 months mortality - 34.9% in patients with significant MR & 23.8% in patients with mild MR

Additionally, 198 patients (44.3%) with known history of MR prior to admission demonstrated 6 months mortality to be 34.5% against 23.1% when MR was not known on admission with P value < 0.05 (**FIGURE 14**).

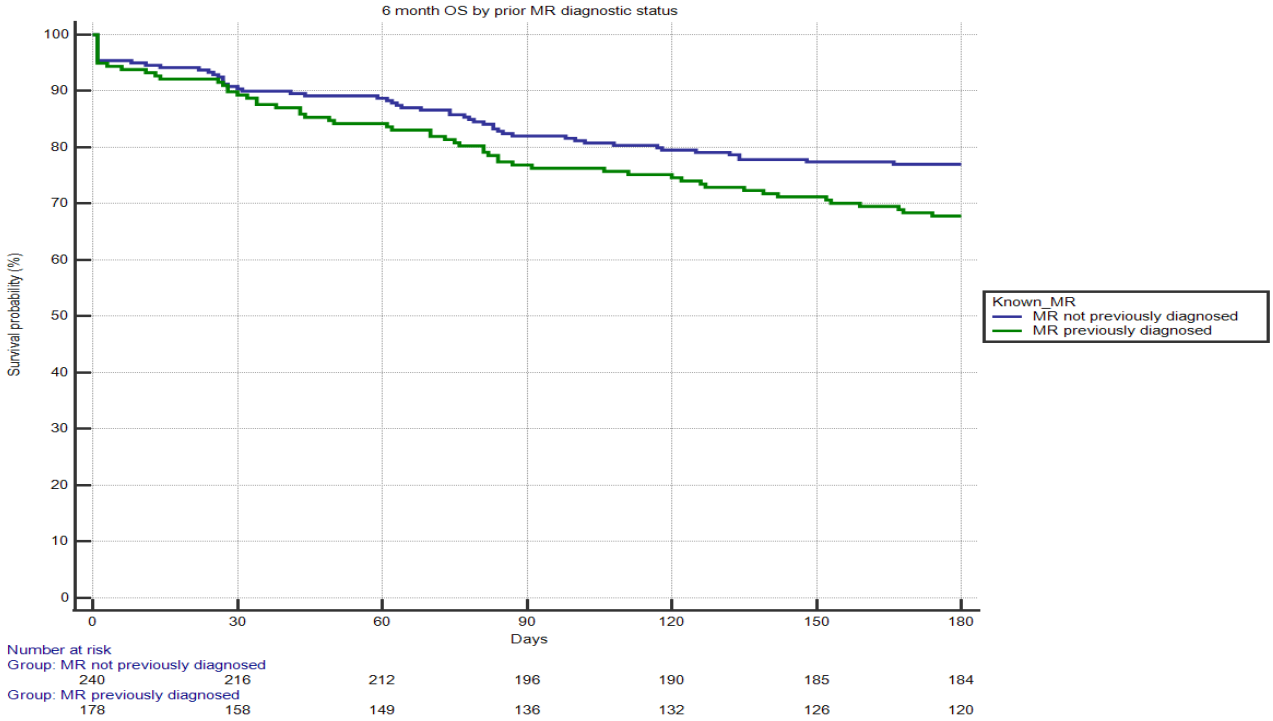


FIGURE 14. 6 months mortality -– 34.5% in patients with known MR & 23.1% when MR was not known

3.1.11 Discussion

In our study we aimed to find out whether severity of MR has an impact on hospital admission rate and prognosis of patients with heart failure. It is not well studied if MR could trigger hospital admission with HF. MRAHF study has demonstrated the prevalence of MR and TR in patients with acute HF and demonstrated importance of right heart dysfunction in short term prognosis.

There was high prevalence of patients with significant MR (39.5%). These patients have number of important characteristics which were different to those who did not have additional effect of volume overload. Amongst important baseline characteristics amongst MRAHF patients there was significant difference in the level of B-type natriuretic peptide (BNP) as an indicator of severity of HF between mild and significant MR patient groups. The patients with significant MR had higher number of BNP level and they were more likely to have previous admissions with HF.

BNP has been proven to be a useful diagnostic marker of severity of HF and a valuable prognostic predictor (213). BNP is secreted by the left ventricular myocardium in response to hemodynamic stimuli such as ventricular volume expansion and pressure overload (214). Initially it is released as a proBNP into the circulatory system and after it is cleaved into the biologically active C-terminal of BNP and the biologically inactive, NT-proBNP. ProBNP is primarily synthesized and released in the ventricle in response to ventricular hemodynamic changes; therefore, it can reflect ventricular

dysfunction better than other natriuretic peptides (NPs) (215). Moreover, it is also known to cause strong vascular relaxation and natriuresis.

Another significant difference between the groups was in patients` BMI. This might be also the results of more advanced HF. Cachexia is a prevalent pathological condition associated with chronic heart failure. Its occurrence predicts increased morbidity and mortality independent of important clinical variables such as age, ventricular function, or heart failure functional class (216). The clinical consequences of cachexia are dependent on both weight loss and systemic inflammation. It is a multifactorial condition where underlying pathophysiological mechanisms are not completely understood making it difficult to develop specific prevention and treatment therapies (216). Our patients with significant MR were not extremely cachectic, however, they were significantly lighter in weight.

ECG findings on admissions demonstrated tendency to broader QRS and arrhythmias in these patients. There is a sinister synergism between atrial fibrillation and heart failure. These common cardiovascular conditions often co-exist and result in significant morbidity and mortality (217). The increased propensity for AF in HF can be explained by structural and electrophysiological atrial remodelling that creates an environment favourable to the development and maintenance of AF (217). Patients with HF and history of atrial arrhythmias exhibit atrial enlargement, loss of functioning atrial myocardium and impaired atrial conduction, which lead to increased inducibility and sustainability of AF (218). Indeed, patients with significant MR had larger LA size (**TABLE 17**). Pressure or volume overload of the atria causes elongation of the cardiomyocytes, i.e. increased stretch. Stretch of the atria is a main contributor to atrial remodelling. These changes occur in atria in patients with heart failure, hypertension, and mitral valve disease prior to clinical presentation with AF (219,220), as such creating a substrate for AF. It is thought that once AF develops the remodelling process deteriorates further (221,222). Thus, atrial remodelling in patients with AF is caused by both the associated diseases and AF itself.

It has also been reported that prolongation of QRS (> or =120 ms) occurs in 14% to 47% of HF patients and predisposes this population to an increased risk of ventricular tachyarrhythmias (223).

The study showed that most of the HF patients have secondary MR rather than primary. It is known that the secondary MR develops as a consequence of LV remodelling, which was clearly evident in patients with significant MR. Interestingly, LV volumes in the group 2 (significant MR group) were within the normal range accepted by current international and national guidelines (76,224,225), but significantly increased when compared with those without significant MR. Beyond LV volumes, the pattern of LV remodelling was recently shown to carry additional predictive value for vascular and heart failure-related events (226). These findings support the hypothesis that the linkage between LV remodelling and outcome occurs not merely through the adverse impact of cardiac pathology per se, but also via the role of LV morphologic change as a measure of concomitant vascular pathology (226).

Both groups had significant pulmonary hypertension, but in patients with significant MR the severity of PHT was more prominent. Pulmonary hypertension in HF is thought to result from congestion and chronic pulmonary venous hypertension. It may initially begin as a passive process resulting from congestion and elevated filling pressures, and pulmonary venous hypertension. With chronic

congestion, pulmonary vascular tone may become irreversibly elevated (227). However, the fundamental mechanisms determining pulmonary vascular responses in response to heart failure and the development of PH remain incompletely understood. There is an evidence that pulmonary hypertension is associated with a negative impact on survival (228).

It is known that RV function is difficult to assess due to its unusual crescent shape, the irregular endocardial surface and complex contraction mechanism; the RV free wall is more difficult for visualisation on echocardiography compared to the rest of the heart (80,229). However, the introduction of new modern ultrasound machines with improvements in image quality and imaging modalities has made it possible to use echocardiography as a first line modality to assess the structure and function of the right heart (230,231). The technique of how we measured RV function (RV FAC) is shown in **FIGURE 15.**

FIGURE 15. RV fractional area change is shown with end-diastolic and end-systolic areas.

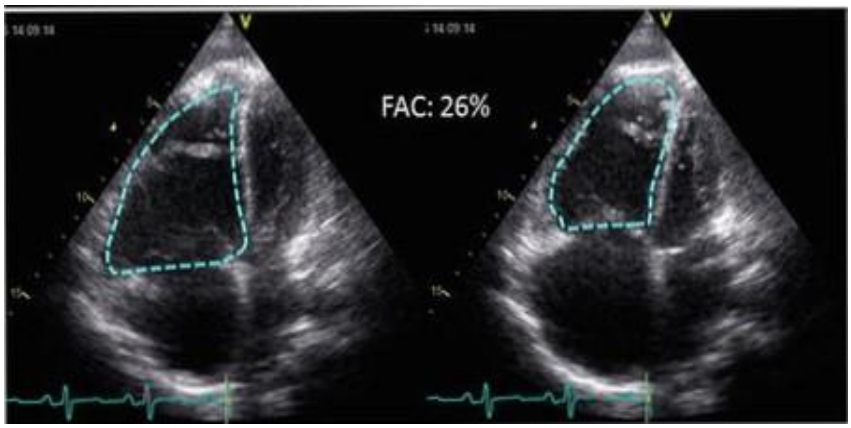
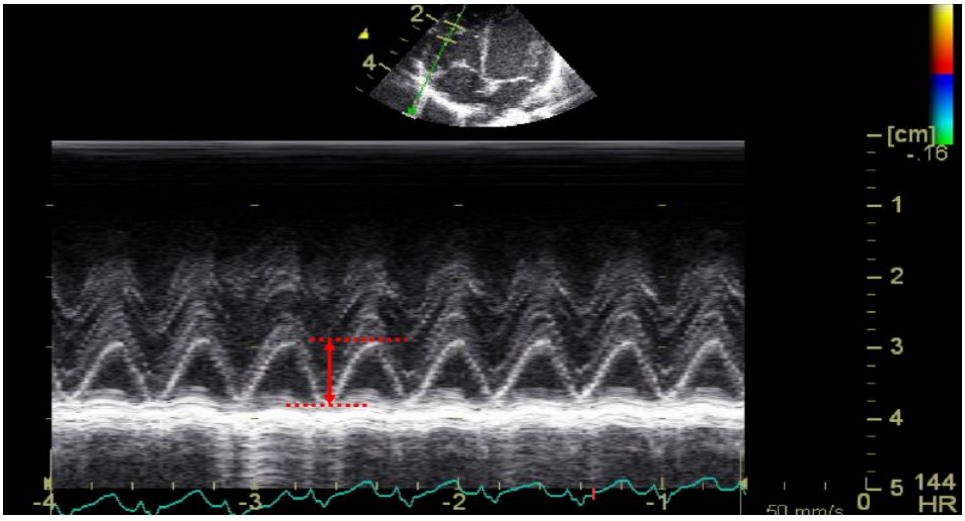


FIGURE 16. TAPSE for an assessment of RV systolic function.



Tricuspid annular plane systolic excursion (TAPSE) is normally widely used for RV systolic function assessment on echocardiography, probably due to the simplicity of the method (**FIGURE 5**). To assess RV function by TAPSE, M-mode is placed on RV free wall across TV annulus level in four chamber view. The level of TV annulus systolic excursion is believed to assess reliably RV longitudinal

systolic function (230-232). Limitations include load and angle dependence, as well as the potential influence of the functional status of the left ventricle. Moreover, this measure does not take into account the contribution of the ventricular septum and/or the right ventricular outflow tract to right ventricular performance. (230,233)

RV systolic function assessment for both radial and longitudinal function in one plane view is called RV fractional area change (RV FAC). It is more time consuming method than TAPSE and calculated by difference between end diastolic area and end systolic area divided by end diastolic area (234) (**FIGURE 15, 16**).

MRAHF study showed that RV FAC as a marker of RV systolic function proved to be more sensitive in predicting outcome rather than TAPSE. Also there is data, which showed that the fractional area change has been found to correlate with magnetic resonance-derived right ventricular ejection fraction, as well as to predict outcome in adult patients with myocardial infarction and pulmonary hypertension (235,236). Similar data does not apply for TAPSE.

RV FAC was lower in presence of significant MR and associated with visually enlarged RV.

Patients with mild and significant MR did not differ in all cause hospital admissions, but significant MR patients had more HF admissions in the last 24-36 months. It is not surprising to find that presence of more advanced HF reflected by higher BNP level and cardiac remodelling led to higher rate of previous admissions with HF. MRAHF is compatible with other studies (22), which proved that the development of significant MR in patients with HF is strongly associated with poor prognosis. In the study from the Duke Cardiovascular databank, which included 2,057 HF patients with an LVEF < 40%, qualitative assessment on left ventriculography showed 29.8% patients had moderate to severe and severe MR and it was an independent predictor of 5 year mortality (237). Another study from Mayo clinic included 1,256 patients with dilated cardiomyopathy and the percentage of severe MR in this cohort of HF patients was 24 %. It was an independent predictor of death or HF hospitalisation during 2.5 years of follow-up (161).

There were a few limitations in our study. One of this is a disadvantage of bedside echocardiography over departmental study. A portable machine, patients` acuity and time limit – all these factors were affecting on the quality and completeness of the study. As part of MRAHF trial protocol echo was done within 48 hours of hospital admission. This was the time when HF patients were more poorly and less able to cooperate due to their haemodynamic instability. For example, some patients found it difficult to remain in left lateral decubitus position for the entire time of echo scan considering that the time required to complete a full echo protocol was between 45 minutes to 1 hour. As a result, some images had respiratory artefacts and did not have fine tuning of scale and ECG traces. In some case the test was foreshortened. This was the reason why we had a few incomplete studies. Performing echoes on the ward was also challenging due to space availability, noise level and bright lighting. The beds did not have ergonomic features of echo couches which made maintaining posture for operators difficult.

Another potential limitation was the fact that MRAHF was a single centre study with data specific to local area. It is difficult to extrapolate with data worldwide without some corrections where demographics and co-morbid conditions could be different.

MRAHF was an observational study, a longitudinal follow up is needed, particularly in mild MR group to see, if MR is a result of progressive LV dilatation or other factors cause simultaneous LV dilatation and MR.

The current literature on MR highlights a strong association between a severity of MR and mortality with HF (22). Few studies have demonstrated that significant MR was an independent predictor of death and HF hospitalisation (161,238,239).

Summary: MRAHF study showed the patients with significant MR presented with higher 6 months mortality in comparison with the group of patients with mild MR. Also, when MR was known on admission, these patients had poorer outcome than HF patients without known MR on admission. These findings of our study proves how much the presence of significant MR, if not treated effectively, can quickly lead to HF progression to higher stage of the disease and poor outcome.

3.2 The effect of use of National Institute for Health and Care Excellence (NICE) guidelines on outcome in MRAHF patients.

3.2.1 Background

The NICE guidelines for HF offers best practice advice on the care of people with acute heart failure and covers important aspects of the diagnosis and evidence based recommendations on management of this condition (NICE 2014) (240).

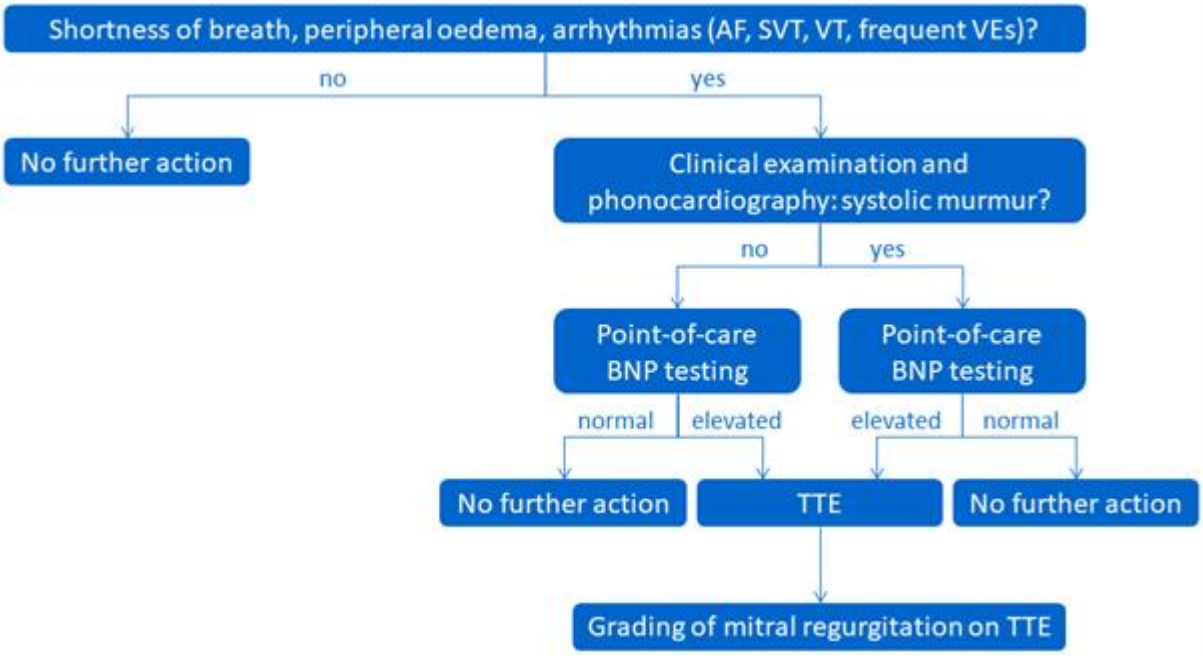
In brief, in patients presenting with new suspected acute heart failure, the NICE guidelines recommends to start with taking detailed history and clinical examination, perform standard investigations – for example, electrocardiography, chest X-ray and blood tests to confirm the presence of heart failure. In people presenting with new suspected acute heart failure, a single measurement of serum natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-B-type natriuretic peptide [NT-proBNP]) is advised using the following thresholds to rule out the diagnosis of heart failure: BNP less than 100 ng/litre or NT-proBNP less than 300 ng/litre. With new suspected acute heart failure and raised natriuretic peptide levels transthoracic Doppler 2D echocardiography should be performed to establish the presence or absence of cardiac abnormalities(240).

Patients with suspected heart failure and previous myocardial infarction (MI) should be referred urgently to have transthoracic Doppler 2D echocardiography and specialist assessment. Transthoracic Doppler 2D echocardiography needs to be performed within 48 hours of admission and review by cardiologist within 24 hours of their admission to a hospital (241).

3.2.2 Study results

The research team of MRAHF study has followed strict international guidelines to identify patients with acute HF (**FIGURE 6**). We have used point of care BNP device in triaging patients (i-STAT 1 Analyzer “Immuno-Ready”), which is in-vitro diagnostic test for bedside measurement of BNP in plasma samples using EDTA as the anticoagulant.

FIGURE 17. Diagnostic algorithm for patients with suspected AHF; AF: atrial fibrillation, SVT: supraventricular tachycardia, VT: ventricular tachycardia, VEs: ventricular extrasystoles, BNP: brain natriuretic peptide, TTE: transthoracic echocardiogram.



The clinical team was blind to the results of research bedside BNP. The inpatient practice at St Peter's hospital does not allow to receive the results of blood test for BNP within 24 hours. We have therefore modified the NICE guidelines and used cardiology review within 24 hours as equivalent of NICE recommended pathway (**FIGURE 18**). It demonstrates the decision tree is based on NICE recommendations. In inpatient clinical practice at St Peter's hospital BNP test is not performed routinely for HF patients before cardiology review. Therefore, referrals to cardiology is based on clinical assessment without prior specific blood tests. The **FIGURE 19** demonstrates the sequence of specialist review and a number of tests received by HF patients after they had been admitted to a hospital.

The patients have been divided into 2 groups (**TABLE 18**). In group 1, which was seen by a cardiologist within 24 hours, there were 204 patients (45.6% from the whole cohort of MRAHF population). Out of 253 patients (57%) with no cardiologist review on admission, 32 patients (Group 2 A) were referred to cardiology review after 24hours (7.6%). The rest of the patients (Group 2B) were not seen by a cardiologist during entire length of admission 221 patients (49.4%).

The main demographic and clinical data is presented in **TABLE 18**. Patients who were not seen by cardiology team were older, of female gender and had higher prevalence of COPD and lower Hb.

TABLE 18. Demographics and haemodynamics.

	Group 1 (Cardiology review in 24 hours)	**Group 2A (Cardiology review later than 24 hours)**	**Group 2B (No cardiology review)**	**P value**
Total number of patients, %	196 (46.9%)	30 (7.1%)	192 (45.9 %)	< 0.0001/0.765
Mean age, years	**75.73 ± 12.5**	**75.3 ± 11.9**	**82.8 ± 9**	**0.856/< 0.0001**
Gender, males	**123 (60.3%)**	**19 (59.4%)**	**92 (43.6%)**	**0.923/0.0007**
BMI	28.7 ± 7.2	30.5 ± 7.2	28.4 ± 8.9	0.189/0.71
BP systolic, mmHg	135.6 ± 26.9	133.2 ± 25.6	136.8 ± 25.8	0.637/0.64
BP diastolic, mmHg	76.7 ± 17.5	75.8 ± 17.8	74.1 ± 16.2	0.788/0.117
HR, bpm	92.7 ± 30.2	92.0 ± 32.9	92.6 ± 28.3	0.904/0.97
BNP, pg/ml	1146 ± 999	1372 ± 980.9	1212 ± 1015	0.234/0.50
Hb, g/L	124.5 ± 22.5	129.2 ± 21.7	118.6 ± 20	0.271/0.005
WBC, $x10^9$/L	10 ± 9.9	8.9 ± 2.8	8.8 ± 5.7	0.534/0.129
CRP mg/dL	33.8 ± 45.6	49.8 ± 61.7	39.0 ± 43.6	0.081/0.267
eGFR, mL/min/1.73m2	38.8 ± 13	43.8 ± 12.2	38.4 ± 13.0	0.043/0.754
CKD, number of patients	88 (43.1%)	13 (40.6%)	107 (50.7%)	0.79/0.121
Known CAD, number of patients	78 (38.2%)	11 (34.4%)	80 (37.9%)	0.681/0.949

HTN, number of patients	106 (52 %)	20 (62.5%)	120 (56.9%)	0.269/0.317
COPD, number of patients	**12 (5.9%)**	**6 (18.8%)**	**46 (21.8%)**	**0.11/<0.0001**
CVA, number of patients	31 (15.2%)	2 (6.3%)	36 (17.1%)	0.178/0.599
DM type 2, number of patients	70 (34.3%)	10 (31.3%)	61 (28.9%)	0.739/0.237
ECG, sinus rhythm	90 (44.1%)	13 (40.6%)	75 (35.5%)	0.711/0.074
ECG, AF	83 (40.7%)	13 (40.6%)	106 (50.2%)	0.992/0.052
ECG, other rhythm	30 (14.8%)	5 (15.6%)	25 (11.9%)	0.906/0.385
ECG, QRS duration, seconds	**113.9 ± 32**	**109.1 ± 34.1**	**106.3 ± 32.7**	**0.435/0.017**

The echo data showed lower LVEF in the group seen by a cardiologist (**TABLE 19**). LVEF in the group 1 was 40.7%, in the group 2A was 40.1% (P = 0.84), in the group 2B – 45.7% (P = 0.0006). There were features of LV remodelling in group 1 and 2A compared to the group 2B (116.6 ml & 146.6 ml vs 99 ml, P 0.005/0.0004). There was higher prevalence of significant MR in patients seen by cardiologist (53.3%), whereas prevalence of RV dysfunction was higher in patients not seen by specialists (67.3%). Also, PAP was higher and the prevalence of significant TR was higher in the group 2B.

TABLE 19. Comparison of ECHO data.

	Group 1	**Group 2A**	**Group 2B**	**P value**
LV EF, %	40.7 %	40.1 %	45.7 %	0.84/0.0006
Mean LV EDV	116.6 ml	146 ml	99 ml	0.005/0.0004
Mean RV FAC	37.6 %	33.3 %	36.8 %	0.08/0.514
Systolic PAP	50.6 mmHg	50.8 mmHg	55.7 mmHg	0.95/0.007
Mild MR	42.7 % (108 pts)	6.7 % (17 pts)	50.6 % (128 pts)	0.043/0.114

Significant MR	53.3 % (88 pts)	7.9 % (13 pts)	38.8 % (64 pts)	0.024/0.15
Mild TR	46.8 % (101 pts)	9.7 % (21 pts)	43.5 % (94 pts)	0.0017/0.645
Significant TR	44.3 % (102 pts)	4.8 % (11 pts)	50.9% (117pts)	0.0116/0.33
Bi-ventricular systolic dysfunction	47.9 % (69 pts)	11.8 % (17 pts)	40.3 % (58 pts)	0.007/0.39
Isolated LVSD	51.3 % (78 pts)	3.3 % (5 pts)	45.4 % (69 pts)	0.039/0.477
Isolated RVSD	26.5 % (13 pts)	6.1 % (3 pts)	67.3 % (33 pts)	0.46/0.013

6 months mortality in the group 1 is 16.7% (34 patients), in the group 2 – 37.4% (91 patients), P value = 0.0001. No 6 months mortality data was available for 3 patients.

19.6% (40 patients) died within 1 year from the group 1, from the group 2 – 41.98% (102 patients) within the same period of time, P value < 0.0001. No mortality data was available for 122 patients.

As shown above patients with significant MR were more likely to be seen by a cardiologist, however a large proportion did not benefit from cardiology input (**TABLE 20**), 41.8% of such patients did not have echo on this admission, while more than 57.6% of them had echo previously within 36 months. Nearly half of the patients had echo within 48 hours (53%) with no significant difference between the groups with mild and significant MR .

TABLE 20. The number of MRAHF patients meeting NICE guidelines requirements for cardiologist review and transthoracic echocardiography on admission.

	Mild MR	Significant MR	Total number of patients
GROUP 1 - Cardiologist review within 24 hours, number of patients (NICE guidelines recommendations)	**108 (42.7%)**	**88 (53.3%)**	**196 (46.9%)**
GROUP 2 A - Cardiologist review later than 24 hours,	17 (6.7%)	13 (7.9%)	30 (7.1%)

number of patients			
GROUP 2 B - Did not have cardiologist review, number of patients	128 (50.6%)	64 (38.8%)	192 (45.9%)
Echocardiography within 48 hours, number of patients (NICE guidelines recommendations)	**145 (57.3%)**	**87 (52.7%)**	**232 (53.2%)**
Echocardiography later than 48 hours, number of patients	12 (4.7%)	9 (5.5%)	21 (5.1%)
Did not have echocardiography, number of patients	95 (37.5%)	69 (41.8%)	164 (41.6%)
Previous echocardiography	144 (56.9%)	95 (57.6%)	239 (57.2%)
No ECHO on current admission, but had ECHO before	75 (29.6%)	57 (34.5%)	132 (82.8%)

FIGURE 18. Decision tree for acute heart failure, initial management (NICE guidelines 2014).

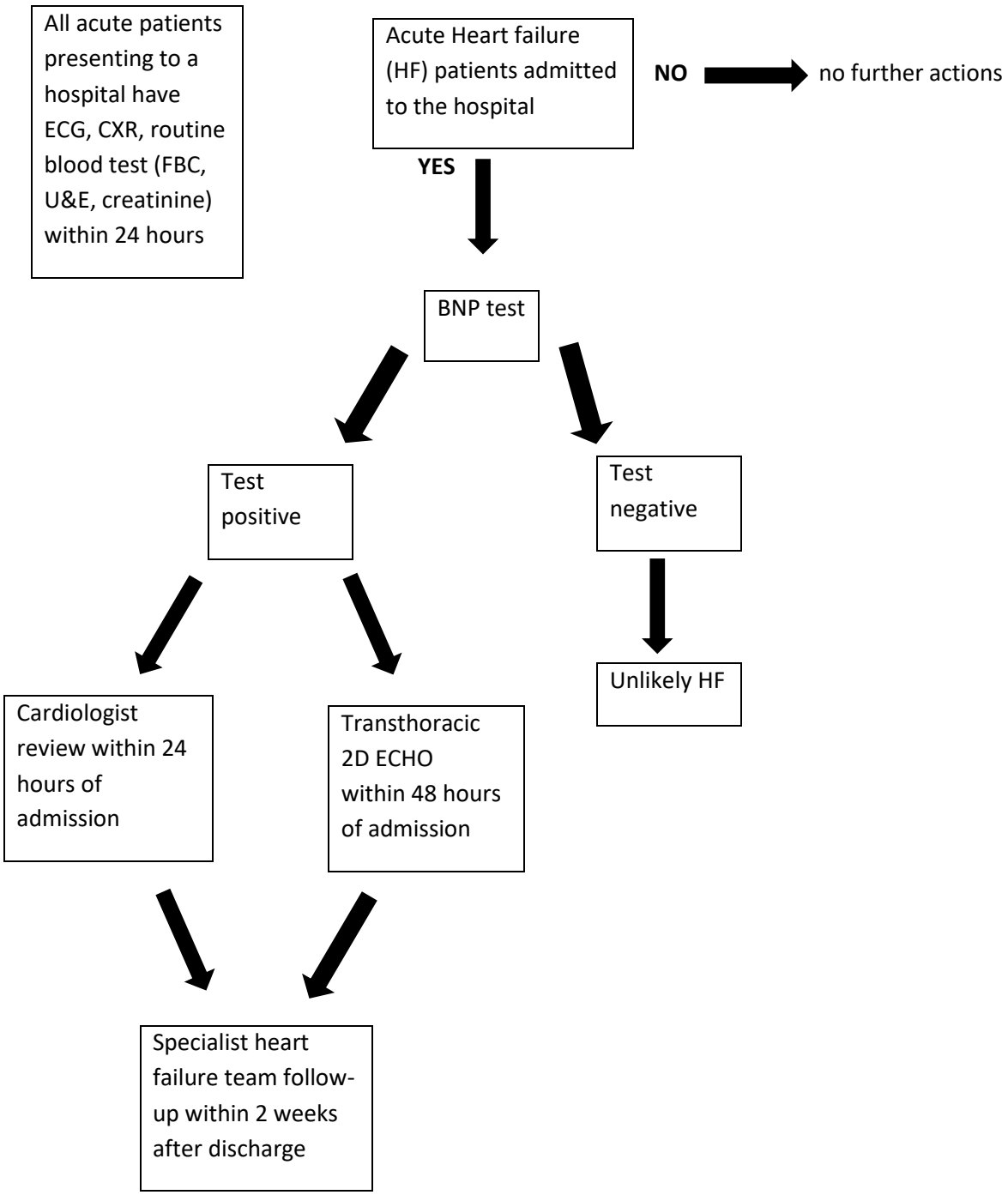
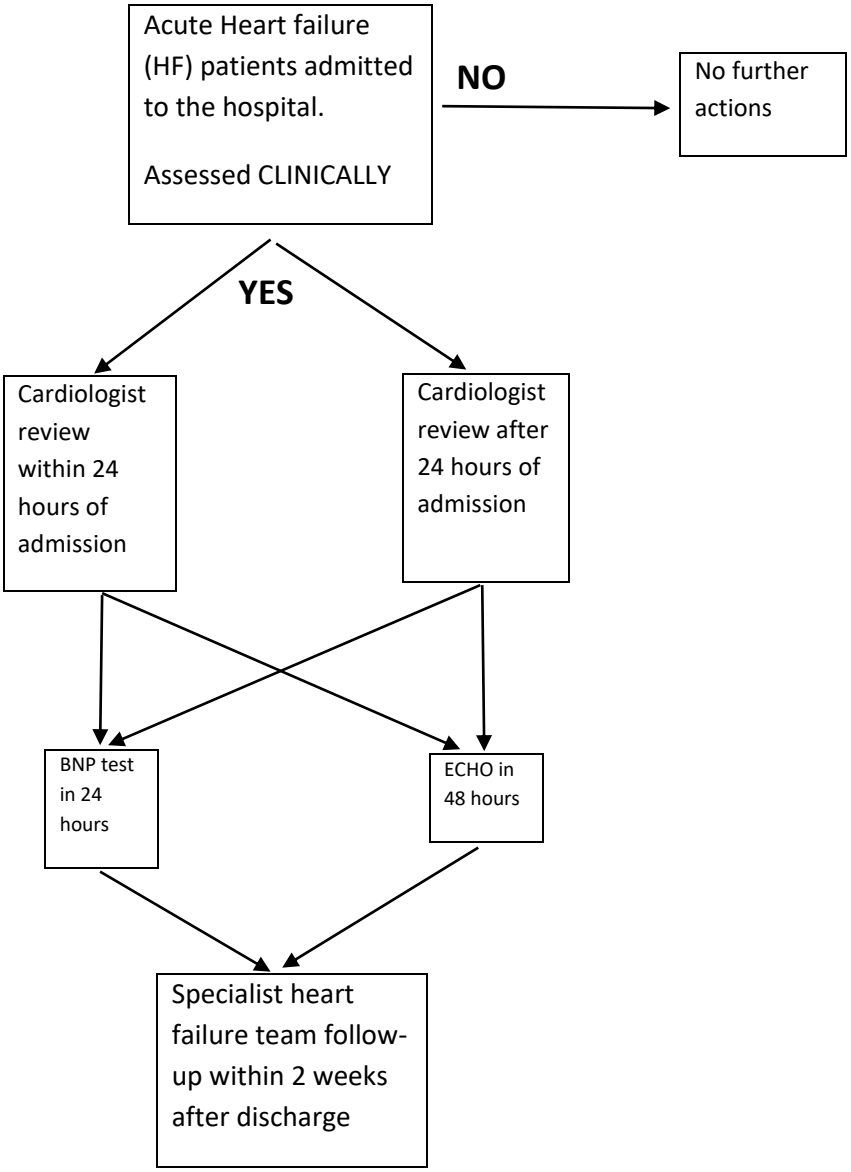


FIGURE 19. Decision tree for acute heart failure at St Peter`s Hospital.



3.2.3 Discussion

It was not possible to use exact NICE guidelines pathway due to local practice. Although all MRAHF patients had BNP test done as part of the recruitment process, clinical team was blind to the results, therefore we used cardiology review as an optimal substitute.

Clinical team have identified a large number of HF patients, however we have found out that slightly more than half of the MRAHF patients did not have cardiology review within 24 hours of admission. This is not surprising given modern complexity of patients with multiple comorbidities when HF was not always the straightforward diagnosis. Taking into consideration all challenges which presented to the clinical team, especially during acute on-call periods with large number of patients attending A&E and acute medical unit, the number of identified HF patients is still impressive.

The main focus of referral to cardiology appears to be on LV function and dilatation, whereas RV geometry and function is overlooked. The majority of patients from the group 2 (73.4%) had an isolated RV dysfunction. This might be driven by the fact that current guidelines are focused on LV function (19). Most of worldwide used HF classifications are based on LV EF, including the latest ESC guidelines with HFpEF, HFmEF and HFrEF. It is historical that grading of HF was focusing on LV contractile function.

The cardiology review had a significant impact on patients` outcome. The patients who did not have cardiology review within 24 hours had significantly poorer outcome and a higher 6 months and 1 year mortality rate in comparison to group reviewed by the specialist team within above mentioned time limit. There are no similar to MRAHF trials have been found to compare with, however, there are number of trials have been done, which investigated the role of specialized multidisciplinary team involvement (either in a clinic or a non-clinic setting) in HF patients` follow up and it showed that this strategy has reduced mortality, HF hospitalisations, all cause hospitalisations and appeared to be cost saving (242).

This data needs to be interpreted with caveat of age difference between the groups. It is not clear if referring team and triaging by cardiologist left elderly patients to be managed by general physicians. There are trials, which demonstrated that elderly patients hospitalised with HF have poor prognosis, particularly if their heart failure symptoms are caused by LV systolic dysfunction. In general, the most of HF patients (up to 80%) are known to be elderly (243). When compared with younger patients, the elderly population has a multiple comorbidities (hypertension, atrial fibrillation, peripheral vascular disease and coronary artery disease, valvular disease and kidney failure or anaemia) and polypharmacy (243).

There is also gender difference in triaging of HF patients for cardiology review, less female patients had cardiology review. It is difficult to explain this kind of phenomenon, but it is obvious that in females it has appeared that diagnosis of HF could be more challenging. It is known that females have better survival in HF (244,245), mainly due to less prevalence of ischaemic cardiomyopathy. They tend to have higher rate of depression (246) and different co-morbid presentation (244,245) which might be reason of referral to other specialist groups. There is reported disparity of care in literature. It has been reported that females receive less invasive treatments and prone to be subscribed less evidence based medical therapy (245,247,248).

In summary, implementation of NICE guidelines in full to complement clinical assessment is likely to improve specialist input in managing AHF patients and therefore short and long term outcomes. The bedside BNP is a feasible replacement option to laboratory defined BNP in acute emergency room. Use of point of care bedside BNP by research team proved it be simple and strait forward procedure which provides instant results.

3.3 Economic impact of HF admissions and length of stay on the hospital budget

3.3.1 Background

The burden of patients with heart failure on health care systems is widely recognised with estimated HF expenditure accounted for 1.2% of National Health Service (NHS) budget in the United Kingdom (UK) (189). Subsequent studies in other countries reached similar results (13-15) with some individual patterns of care and differences in health service related to age, socio-economic factors and the presence of co-morbidities in different countries.

3.3.2 Study results

We asked our Financial department at St Peter`s Hospital to provide us with the list of HF patients admitted to the trust during the period of recruitment process for MRAHF study. Overall, there were 951 patients who had HF as part of clinical diagnosis identified by coding process which is likely to represent all cause admissions with HF (**TABLE 21**). The total expenditure and average cost are given in **TABLE 22**. For the period from 4/07/2016 until 13/09/2017 the total costs for HF patients spent in St Peter`s Hospital was £ 2,144,267 with average cost per patient £2,255.00.

TABLE 21. HF patients admitted to St Peter`s Hospital (SPH) (Finance department data).

Period	Number of Patients	Sum of Total Expenditure	Average Cost per patient
2016/17	570	1,257,919	2,207
2017/18	381	886,348	2,326
Grand Total	951	2,144,267	2,255

219 (49%) patients from our MRAHF dataset had missed diagnosis of HF by the coding team. The distribution of missed diagnosis was slightly prevalent in patients with mild MR (P = 0.099).

TABLE 22. Missed diagnosis of HF by coding team.

	Mild MR	Significant MR	P<
Missed patients for coding, N	142 (52%)	77 (44%)	0.099

The rest of the MRAHF patients registered by the coding team had significantly higher average inpatient cost during this admission when compared to the average cost of HF admission. There was

no significant difference between patients with different severity of MR, probably the fact driven by presence of multiple adverse haemodynamic factors such as LV and/or RV systolic dysfunction (table 23). Similarly to RV FAC, presence of significant TR in isolation could not explain high cost of isolated RVSD which appear to bear highest financial burden in our cohort of patients.

TABLE 23. Cost of index admissions of MRAHF patients.

	Average cost per admission (£)	Max cost per admission (£)	Min cost per admission (£)	P value (comparison made with average cost per patient, Finance dep. Data, Table 21)
Average HF admission cost to SPH	2255 ± 2858	24267	46	_____
Mild MR	3589 ± 3368	17269	199	< 0.0001
Significant MR	3458 ± 3179	13995	342	< 0.0001
Fractional area change > 32%	3596 ± 3529	17269	199	< 0.0001
Fractional area change < 32%	3458 ± 2954	12985	219	< 0.0001
Isolated LVSD	3251 ± 3307	17269	199	0.0001
Isolated RVSD	4355 ± 3648	12985	532	< 0.0001
Bi-ventricular dysfunction	3570 ± 2854	12653	219	< 0.0001
Significant TR	3637 ± 3271	16364	199	< 0.0001

The **TABLE 24** demonstrates the maximum number of recurrent admissions for all cause and heart failure for previous 12, 24 and 36 months with calculated on available cost data from index admission.

Using average cost of HF admission we have calculated the approximate cost of previous hospital admissions for MRAHF population, 350 of them had previous all cause admissions in the preceding 3 years with maximum up to 45 admissions for a single person. 217 patients with mild MR had at least 1 admission, which was 80.1% from this group. 133 patients (75.6%) with significant MR also had repeatedly been admitted during the same period of time.

83 patients (30.6%) with mild MR had been admitted with HF (primary or exacerbation of chronic) whereas 77 patients (43.7%) with significant MR had admissions with HF for the same period.

TABLE 24. Recurrent admissions with cost in patients with HF.

	Mild MR		Significant MR	
	Max number of admissions per person	Calculated cost of admissions based on average cost per admission per patient	Max number of admissions per person	Calculated cost of admissions based on average cost per admission per patient
Previous all cause admissions per person for 12 months	27	£ 96,903	8	£27,664
Previous all cause admissions per person for 24 months	38	£136,382	16	£55,328
Previous all cause admissions per person for 36 months	45	£161,505	18	£62,244
Previous HF admissions per person for 12 months	6	£21,534	5	£17,290
Previous HF admissions per person for 24 months	7	£25,123	6	£20,748
Previous HF admissions per person for 36 months	11	£39,479	7	£24,206

The length of stay of previous admissions in mild MR group was 7.7 days on average with maximum up to 53 days and minimum of 1 day . Patients with significant MR had the average length of hospital stay 9 days with the maximum of 90 days and minimum of 1 day. Unfortunately, we were unable to calculate the effect of prolong hospital stay on the increase of cost due to complicated scheme of financial aspect and absence of pure HF one day hospital stay tariff.

3.3.3 Discussion

MRAHF study has aimed to investigate the financial aspect of hospital admissions with acute heart failure. There are very scarce number of studies, which have investigated financial aspect of HF. Amongst them are ADHERE registry(249) in USA, the EuroHeart Failure Survey(209) in Europe.

The HF population is prone to have recurrent hospital admissions with further increase of cost for patients care. This is why HF patients are heavy burden for a hospital budget and healthcare in

general. According to the NICE data, approximately 67,000 people with acute heart failure were admitted into hospital in England in 2012/13 (190).

The list of HF patients provided by SPH Finance department disclosed difficulties in accurate capturing of the data related to acute HF admissions. There were a number of MRAHF patients, who were missed from the Finance department list. This means that those 219 patients with acute HF did not get appropriate reimbursement for HF to reflect complexity of the ongoing disease. The minimal cost implication based on our calculations is 219 x £2,255.00 (£493,845.00). The average cost of AHF from our cohort suggests that assessment might be grossly underestimating the true costs. We can speculate, that this omission was caused by lack of universal parameter which could be used by coding team to help them navigate in complex discharge letters.

As discussed in the previous chapter, bedside BNP could be used both as clinical and coding triaging marker. The cost of bed-side BNP cartridges is £ 28 per unit at the time of writing this thesis. If used routinely for patients suspected for HF using algorithm suggested by our research project to avoid overuse, bedside BNP, could have led to appropriate coding and reimbursement. Such testing may reduce up-front demand for echocardiography by modifying priority referral pathway for inpatient echocardiography (240).

Patients with mild MR and significant MR did not have any significant difference in average cost at index admission but both had considerably higher in comparison with an average cost of patients without acute HF. Interestingly, MRAHF study showed that patients with isolated RVSD were more expensive in hospital management. Partly, it is explained by the fact that right heart decompensation is the terminal haemodynamic response in failing heart (234-236). Most importantly this might reflect lack of clinical focus on parameters of RV function (250-252). Even in research the focus is mainly on LV function. Routine PubMed search using the key words ‘AHF’, and LV function vs RV function brings 1281 papers on LV dysfunction vs 338 ones for RV dysfunction.

Given the important prognostic implication of RVSD showed in the previous chapter it is of particular importance to improve our knowledge how to detect and address RV dysfunction as early as possible.

The length of hospital stay (LOS) on index admission was considerably shorter when compared to other studies. MRAHF patients had average LOS of 2.3 days compared to the USA (4.3 days in the ADHERE registry (253)) and to Europe (average 11 days in the Euro-Heart Failure Survey (16)). This encouraging data should however be checked against readmission rate as there is a suggestion that the HF patients who are discharged early, tend to have high rate of readmissions (254) and this tendency could make cost even higher that it was expected. The limitation of our study is that previous admissions data is retrospective and does not allow to follow natural history of de novo AHF patients. Nevertheless, it demonstrated that patients with significant MR tend to have higher rate of pure HF admissions with significant price tag attached to such admissions.

In summary, there is large number of AHF patients not identified by coding team. The cause is not entirely clear, but we suspect lack of single markers might be a large contributing factor in complex bouquet of comorbidities presented in discharge letters. Bedside BNP is a feasible and easy to use practical test in hands of clinicians with appropriate screening to avoid overuse. It can be used both

for improving triaging of AHF patients and appropriate capture of such admission by coding team. RVSD is the most expensive haemodynamic decompensation to treat and a low of clinical and research attention is needed for early recognition of RV failure.

We propose to use the combination of BNP and Echo data (SPAP) to be used as indicators of HF admissions for coding.

CHAPTER 4. DISCUSSION

4.1 Background

Heart failure is associated with high frequency of recurrent hospital admissions and high mortality, which leads to a significant economic burden on the UK NHS budget and other western healthcare systems. This is expected to increase further in the future due to the ageing population and increase in complexity of comorbid conditions (255). Cost of hospitalisations is responsible for the largest part of treatment costs and, thus, remains the main target for strategies aiming at cost reduction (255).

Mitral regurgitation is a highly prevalent valvular disease. The development of secondary mitral regurgitation (MR) due to left ventricular dysfunction is strongly associated with a poor prognosis in patients with heart failure (22). The mechanisms underlying secondary MR are multifactorial (22). The prognostic implications of severe organic MR are well known and studied with the prevalence of MR increasing with age in general population (159,161,239). Overall, high cardiac event rates including HF are associated with severity of MR, which is also predictive of mortality (159,160). It is, however, unclear whether severe MR plays major role in acute exacerbation of HF requiring hospitalisation.

According to the European Society of Cardiology the upper limit of normal BNP in the non-acute setting should be 35 pg/mL and in the acute setting, higher values of BNP should be used (> 100 pg/mL) (1). We used BNP test to rule out HF, not for diagnosing it (1). The cut off 100 pg/ml was used for our patients to prevent missing of HF patients.

4.2 Aims

The one of the aims of MRAHF trial was to study prevalence of significant MR in HF patients admitted acutely to the hospital, its effect on the LV and RV geometry and function, and patients` prognosis. It was aimed to assess significance of the financial burden of HF patients with their recurrent admissions in a single district hospital like the SPH. It also was looked, if NICE recommendations for AHF managements were in use in this centre.

4.3.1 Left ventricular geometry, cardiac function, haemodynamics and prognosis in patients with significant mitral regurgitation

The prevalence of significant MR was unexpectedly high in our cohort of patients (39.5%.). The MRAHF study showed that secondary mitral regurgitation was the most prevalent cause in clear majority of patients with significant MR. It has been found a few baseline characteristics were different for HF patients with significant MR compared to another group of patients. Patients with significant MR had higher level of BNP. This might be consequence of additional myocardial stretch exerted by significant MR regurgitant volume leading to relative LV dilatation. It is well known that in chronic severe asymptomatic MR the volume overload leads to significant increase in BNP level, but

magnitude of increase is subtle and remains within the physiologic limits. In our cohort smaller degree of volume overload in already diseased hearts leads to higher intensity of BNP secretion.

The second difference was in patients' body habitus. The presence of more advanced HF might account for lower BMI in patients with significant MR. It is known that cachexia is one of the symptoms of advanced HF and it predicts increased morbidity and mortality independent of important clinical variables such as age, ventricular function, or heart failure functional class (216). This is multifactorial condition with pathophysiology not completely understood (216).

ECG changes in patients with significant MR on admission showed a tendency to a broader QRS and arrhythmias. In broad left bundle brunch block the electrical dyssynchrony alters closing and tethering forces leading to mal-coaptation of MV leaflet tips (256). It is not clear if subtle electrical delay causes worsening of MR in our cohort of patients or merely reflects severity of myocardial disease. The association between the LA enlargement, volume related stretch of atrial wall and increase in LA filling pressures may be the main explanation of high prevalence of AF in this group of patients. At least in acute myocardial infarction this has been the main mechanism (256).

Interestingly, those with significant MR had features of left ventricular remodelling with increase in end-diastolic (LVEDV) and end systolic (LVESV) volumes and reduction in LV ejection fraction (LVEF) in presence of significant volume overload. It is well known that LV dilatation with increased volume and altered chamber configuration play a key role in LV remodelling (226). It is now well established that altered geometry rather than closing forces could exaggerate secondary MR (159). Haemodynamically significant MR leads to LV remodelling through MV annular dilatation, papillary muscle displacement, which eventually changes the size and shape of LV and LA. According to the BSE recommendations the normal cut off for LV diastolic volume is 104 ml for females and 155 ml for males (224). Our data did not demonstrate increase in LV volumes above accepted threshold. All figures were within a normal range. However, LV diastolic and systolic volumes in HF patients with significant MR was considerably larger than in HF patients without volume overload.

When MR EROA was adjusted to LV volumes (i.e. the proportionality index), we observed a rapid separation in survival from index admission for patients with disproportionate MR. Our study indicates that hearts which are disproportionately affected by MR carry a greater risk of mortality, suggesting MR is an active driver of poor outcome. Subject to further confirmation by other outcome studies, our data asserts that functional MR should be assessed and managed completely differently to primary MR - using adjustments including ratio/indexed parameters, rather than absolute volumetric analysis, to define thresholds for intervention in FMR patients.

Patients with significant MR had more advanced pulmonary hypertension. This suggests that additional volume loading from MR to already raised LV filling pressures leads to more significant haemodynamic impact. Pulmonary hypertension develops due to congestion and pulmonary venous hypertension (227). Chronic congestion can lead to irreversibly elevated pulmonary vascular tone and pressure and as a result this process has a negative impact on patients` mortality rate (228).

The right heart geometry and function is also altered in presence of pressure and/or volume overload in setting of acute heart failure (227,235,236). The right ventricular chamber is difficult for imaging and quantification of function due its shape and position in the chest (232). The only

imaging modality considered to provide comprehensive information on volume and function is MRI (235). This is not feasible as a bedside tool. We have therefore employed all the tricks available in the toolbox of echocardiography. Apart from, qualitative method assessing RV by “eyeballing”, we used standard TAPSE method. Tricuspid annular plane systolic excursion (TAPSE) is a widely used technique for assessment of RV systolic function (235,250). The M-mode cursor was placed on the lateral part of TV annulus in the apical four- chamber view and we traced its movement during systole. The level of a TV annulus excursion was used as a surrogate of RV longitudinal systolic function. The limitations of this method were the right ventricular load and angle dependence, and also, the influence of LV function (230,233).

To overcome the limitations of TAPSE RV fractional area change (FAC) has been used to calculate RV longitudinal and radial function in one plane. It was obtained from four- chamber view and was calculated as the difference in end-diastolic area and end-systolic area and divided by end-diastolic area (227,235,236,250). Although this method might not fully represent the RV myocardial performance given the RV outflow tract is not included into the calculation in MRAHF study, the 4 chamber view was consistently well imaged in all patients, which allowed to have reproducible data on RV function.

RV FAC proved to be more sensitive and accurate method rather than TAPSE. MRAHF study showed that RV FAC was a powerful predictor of all-cause mortality in patients with AHF, as was systolic PA pressure. Moreover, RVFAC was a better prognostic marker of patients` survival rather than TAPSE. There is a data showing that RV FAC correlates well with MRI derived RV EF as well as predicts outcome in adult patients (235,236). The accurate assessment of RV function appeared to be very important considering our finding.

The significant role of impaired RV in acute HF and the finding of RVFAC as a more accurate tool for RV contractile function assessment could be considered as a novelty presented by MRAHF study.

It has been seen a considerable increase in 6 months mortality in patients with significant MR. Taking into accounts the above information the further suggestion has been made that significant MR is a likely contributing factor to poor patient outcome. In addition, the history of any degree of MR is also important factor in outcomes.

4.3.2 The effect of use of National Institute for Health and Care Excellence (NICE) guidelines on outcome in MRAHF patients.

The large number of acute HF patients has been identified by clinical team at the SPH. However, slightly more than half of the MRAHF patients did not have cardiology review within 24 hours from admission. This is not surprising, if a whole complexity of modern HF patients with multiple comorbidities would be taken into account, including non-classical presentation of HF and busy on-call periods.

All MRAHF patients had BNP test done as a part of the recruitment process and the test results were not disclosed to a clinical team. The study protocol was not designed to capture the frequency and

time of clinical establishment of BNP level. In general, the cardiology practice at SPH differs from the one suggested by NICE guidelines. BNP test is not part of clinical routine at acute admission and only prescribed by Cardiology team. It is therefore up to admitting team to recognise AHF symptoms and make timely referral to cardiology. We have used Cardiology review as equivalent of NICE BNP triaging.

The cardiology review within 24 hours of admission had significant effect on outcome in patients with AHF. Patients who did not have cardiology review had significantly higher 6 months and 1 year mortality rate compared to the group which had a specialist review. This group was significantly older and had higher prevalence of female patient. This data correlates well with National HF Audit (2017-2018), which stated that the outcome is lower for those admitted to cardiology wards and for those who access specialist care.

The gender gap in frequency of cardiology reviews is difficult to explain. It is known that female patients have different comorbidity profile: they have less prevalence of ischaemic cardiomyopathy as results of previous ischaemic attacks, and overall survival is better (227,244,245). They also present with higher prevalence of depressions (246) and, therefore, might have different complaints leading to referral to other specialities. Nevertheless, it is important to study this issue further as lack of specialist input might delay commencement of appropriate therapy and have significant impact on outcome.

There was also age difference in triaging of acute HF patients. The study showed that more elderly HF patients have not been seen by a specialist compared to the younger population. It is possible the triaging was done towards care of geriatricians.

In summary, poor patient outcome and selection bias towards elderly and females in patients with no cardiology review at index AHF admission suggests that elimination of potential referral/triaging bias by using BNP might lead to better outcome in such patients. It demonstrates that NICE/European Society of Cardiology (ESC) guidelines for acute HF would achieve such objective. Bedside BNP which proved to be easy to use and affordable bedside tool will prevent unnecessary pressure on biochemistry lab if used cautiously based on well-defined protocols similar to MRAHF protocol.

4.3.3 Economic impact of HF admissions and length of stay on the hospital budget

The high expenditure of HF patients is well known fact. We wanted to know, if the significance of MR has any effect on HF cost increase, whether or not any other cardiac structural or functional abnormalities have a negative effect on the expenditure and how much a district general hospital like the SPH spends on HF patients.

The current system of identifying HF without standardised laboratory approach must have contributed to a substantial omission of HF diagnosis amongst MRAHF patients by coding team. Overall, 219 MRAHF patients were not on the HF list presented by financial department. This means

this number of patients did not have an appropriate reimbursement for HF. The minimal cost implication based on our calculations is 219 x £2,255.00 (£493,845.00). The average cost of HF patients was grossly underestimated and the omission of large number of MRAHF patients, apparently, was caused by lack of universal parameter which could be used by coding team to help them navigate in complex discharge letters.

Bedside BNP could be used as a clinical and triaging marker for coding team. Taking into account that the current cost is only £28, this test could be used routinely following the protocol established by our research team. This kind of approach could have led to appropriate coding, reimbursement and may reduce demand for echocardiography by modifying priority referral pathway for HF patients.

Also, the current New York Heart Association (NYHA) classification is suboptimal since people can go up and down the class and HF diagnosis can be missed, whereas American College of Cardiology (ACC) classification could give a definitive structural non-reversible point. The ACC classification is much different than the NYHA functional classification system, in that there is no moving backwards to prior stages. For instance, with development of symptoms of stage C heart failure patients cannot be re-assigned to stage B. Perhaps, the combination of ACC classification and BNP test results done at the earliest stage of HF could provide robust coding point.

MRAHF patients captured in Finance database had the considerably higher average cost compared to the cost of HF patients admitted without acute/exacerbation of chronic HF. The patients with isolated RVSD had higher average cost per admission compared to those with isolated LVSD. This phenomenon could have a few explanations given that decompensated RV is a final haemodynamic response in failing heart (234-236). Also, most of research is focused on LV dysfunction underestimating the role of RV (250,252). The literature review has showed that publication on LV function is nearly four times more than on RV function.

The hospital care comprises of three-quarters of the total treatment costs for HF (195). Average length of hospital stay (LOS) is the main factor affecting on HF expenditure in a hospital. MRAHF patients had a shorter current LOS (2.3 days) compared to the data from USA (4.3 days in the ADHERE registry(253)) and from Europe (average 11 days in the Euro-Heart Failure Survey(16)) and this fact could suggests that the cost of our patients was even relatively lower than in the mentioned countries. However, the shorter duration of inpatient treatment maybe at the cost of a higher risk for early readmission (254). Unfortunately, it was not possible to follow a natural history of new AHF patients, the previous admissions data have been taken retrospectively and therefore not representative of natural history of this cohort of patients. Nevertheless, MRAHF study has demonstrated that patients with significant MR tend to have higher rate of HF admissions and this affected on cost of admissions.

In summary, the large number of HF patients have been missed by coding team. We are not able to explain why this happened, however, the one of the reason could be the lack of a single marker for labelling HF in multiple number of comorbidities. The bedside BNP is easy to perform, not expensive test and could be used for clinical purposes and triaging by coding team at the same time. RV dysfunction has appeared to be the most expensive haemodynamic condition and more research attention is needed to recognise RV failure at early stages of HF.

4.4 Main limitations during MRAHF study

The one of limitations in MRAHF study was a disadvantage of bedside echocardiography over departmental study. Due to the recruitment of acute HF patients in the whole hospital, only a portable machine could be used, and the time limit for a routine research echo study because of acuity of patients played a significant role for the quality and completeness of the study.

Some MRAHF patients presented to the SPH clinically in a very poor condition – severely breathless, sitting in a chair or unable to lie flat for longer than few minutes. These circumstances, sometimes, were making challenging to perform a full echocardiography research study, which normally needed a time of 45 minutes or 1 hour. Also, some of HF patients had a very high BMI and this factor had a negative effect on picture quality.

Also, as a limitation could be considered the fact that the study has been performed in a single district hospital in Surrey with data specific to a local area. There is a probability that if there was an opportunity to cover with a recruitment process a wider region of the UK or at least a bigger hospital, the results of our study could be different.

The limitation of our study was that previous admissions data had been taken retrospectively and this approach did not allow to follow natural history of AHF patients.

MRAHF trial was an observational study. Follow up of our HF patients is needed to find out, if progressive LV dilatation causes worsening of MR.

One of limitation was a lack of financial database, it was impossible to provide exact cost of HF admission due to the system of reimbursement and co-morbid conditions, ambiguity of some of coding criteria.

4.5 Future research

Follow up of AHF patients needs to be done to find out effect of MR on progressive LV dilatation. Although data of elimination of significant secondary MR has been controversial, it is interesting to study, if radical management of significant MR using current structural technologies could delay development of right heart failure.

4.6 Importance of MRAHF study

1) The MRAHF study has found high prevalent of significant MR in AHF patients. The severity of MR and right heart failure determines the outcome in this group of patients.

2) Bedside BNP is easy to use clinical tool which can improve patient triaging and coding.

3) Patients with significant MR has higher costs of hospital admissions and readmission rate for HF.

4.7 Conclusion

MRAHF study showed the role of significant MR on patients with acute HF. The large proportion of HF patients had a significant MR. The significant MR proved to be causing LV remodelling, worsening

of LV systolic function. These HF patients had a poor prognosis with higher mortality. It has appeared that there is a crucial role of the right heart function. Patients with significant MR had a prominent systolic PAP and more impaired RV than the other group. The majority of HF patients who did not follow the NICE guidelines had an isolated RVSD, it was associated predominantly with significant MR and this population had higher mortality. The cost of HF patients with progressive RV dysfunction was also higher than any other category of HF population. The importance of following the NICE guidelines complemented by a clinical assessment has been shown in MRAHF study for improvement of HF patients` management and clinical outcome. The use of the bedside BNP test by the Research team has demonstrated a simplicity and a high effectiveness in triaging of HF patients. The large number of AHF patients has not been identified by the coding team, probably, due to lack of single marker for HF. The data, which would include a combination of bedside BNP test and transthoracic echocardiography results could be indicators of HF for coding team.

References:

(1) Garg R, Packer M, Pitt B, Yusuf S. Heart failure in the 1990s: Evolutions of a major public health problem in cardiovascular medicine. J Am Coll Cardiol 1993;22(4):A5.

(2) Bonneux L, Barendregt JJ, Meeter K, Bonsel GJ, Van der Maas, Paul J. Estimating clinical morbidity due to ischemic heart disease and congestive heart failure: the future rise of heart failure. Am J Public Health 1994;84(1):20-28.

(3) Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nature Reviews Cardiology 2016;13(6):368-378.

(4) McCullough PA, Philbin EF, Spertus JA, Kaatz S, Sandberg KR, Weaver WD. Confirmation of a heart failure epidemic: findings from the Resource Utilization Among Congestive Heart Failure (REACH) study. J Am Coll Cardiol 2002;39(1):60-69.

(5) Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the US, 1979 to 2004. J Am Coll Cardiol 2008;52(6):428-434.

(6) Isis I. Collaborative Group. Randomized trial of intravenous atenolol among 16027 cases of suspect acute myocardial infarction. Lancet 1986;2:57-66.

(7) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349-360.

(8) Julian DG, Moss AJ, Murray GD, Poole-wilson P, Simoons M, Ball S, et al. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Lancet 1993;342(8875):821-828.

(9) Meerding WJ, Bonneux L, Polder JJ, Koopmanschap MA, van der Maas, Paul J. Demographic and epidemiological determinants of healthcare costs in Netherlands: cost of illness study. BMJ 1998;317(7151):111-115.

(10) Rodríguez-Artalejo F, Guallar-Castillón P, Banegas Banegas JR, del Rey Calero J. Trends in hospitalization and mortality for heart failure in Spain, 1980–1993. Eur Heart J 1997;18(11):1771-1779.

(11) McMurray J, Hart W, Rhodes G. An evaluation of the cost of heart failure to the National Health Service in the UK. British Journal of Medical Economics 1993;6:99.

(12) Rodríguez-Artalejo F, Guallar-Castillón P, Banegas Banegas JR, del Rey Calero J. Trends in hospitalization and mortality for heart failure in Spain, 1980–1993. Eur Heart J 1997;18(11):1771-1779.

(13) Ghali JK, Cooper R, Ford E. Trends in hospitalization rates for heart failure in the United States, 1973-1986: evidence for increasing population prevalence. Arch Intern Med 1990;150(4):769-773.

(14) Doughty R, Yee T, Sharpe N, MacMahon S. Hospital admissions and deaths due to congestive heart failure in New Zealand, 1988-91. N Z Med J 1995;108(1012):473-475.

(15) Reitsma JB, Mosterd A, De Craen AJ, Koster RW, Van Capelle FJ, Grobbee DE, et al. Increase in hospital admission rates for heart failure in The Netherlands, 1980-1993. Heart 1996;76(5):388-392.

(16) Cleland J, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe: Part 1: patient characteristics and diagnosis. Eur Heart J 2003;24(5):442-463.

(17) Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. Am Heart J 1999;137(2):352-360.

(18) Stewart S, MacIntyre K, MacLeod M, Bailey A, Capewell S, McMurray J. Trends in hospitalization for heart failure in Scotland, 1990–1996. An epidemic that has reached its peak? Eur Heart J 2001;22(3):209-217.

(19) Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37(27):2129-2200.

(20) Joseph SM, Cedars AM, Ewald GA, Geltman EM, Mann DL. Acute decompensated heart failure: contemporary medical management. Texas Heart Institute Journal 2009;36(6):510.

(21) Bursi F, Enriquez-Sarano M, Nkomo VT, Jacobsen SJ, Weston SA, Meverden RA, et al. Heart failure and death after myocardial infarction in the community. Circulation 2005;111(3):295-301.

(22) Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol 2015;65(12):1231-1248.

(23) Davis RC, Hobbs F, Lip G. ABC of heart failure: history and epidemiology. BMJ: British Medical Journal 2000;320(7226):39.

(24) Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, et al. Heart failure: preventing disease and death worldwide. ESC Heart Failure 2014;1(1):4-25.

(25) Guo Y, Lip GY, Banerjee A. Heart failure in East Asia. Current cardiology reviews 2013;9(2):112-122.

(26) Cowie MR, Anker SD. Cleland J et al. Improving care for patients with acute heart failure: before, during and after hospitalization. 2014.

(27) Galinier M, Bouvet B, Rocchi M, De Groote P, Trochu JN. What is the burden of hospitalizations for Heart Failure in France in 2010? 2012;33:161.

(28) Damasceno A, Cotter G, Dzudie A, Sliwa K, Mayosi BM. No title. Heart failure in sub-Saharan Africa: time for action 2007.

(29) Bocchi EA, Arias A, Verdejo H, Diez M, Gómez E, Castro P. The reality of heart failure in Latin America. J Am Coll Cardiol 2013;62(11):949-958.

(30) TOWNSEND NW. Coronary heart disease statistics. 2012.

(31) Ceia F, Fonseca C, Mota T, Morais H, Matias F, de Sousa A, et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. European journal of heart failure 2002;4(4):531-539.

(32) Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation 2013:01. cir. 0000441139.02102. 80.

(33) Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nature Reviews Cardiology 2011;8(1):30-41.

(34) Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007;93(9):1137-1146.

(35) Shiba N, Shimokawa H. Chronic heart failure in Japan: implications of the CHART studies. Vascular health and risk management 2008;4(1):103.

(36) Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circulation: Heart Failure 2013:HHF. 0b013e318291329a.

(37) Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63(12):1123-1133.

(38) Sakata Y, Shimokawa H. Epidemiology of heart failure in Asia. Circulation Journal 2013;77(9):2209-2217.

(39) Bocchi EA, Braga FG, Ferreira SM, Rohde LE, Oliveira Wd, Almeida Dd, et al. III Brazilian guidelines on chronic heart failure. Arq Bras Cardiol 2009;93(1 Suppl 1):3.

(40) Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, et al. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries: results of the sub-Saharan Africa survey of heart failure. Arch Intern Med 2012;172(18):1386-1394.

(41) Atherton JJ, Hayward CS, Ahmad WAW, Kwok B, Jorge J, Hernandez AF, et al. Patient characteristics from a regional multicenter database of acute decompensated heart failure in Asia Pacific (ADHERE International–Asia Pacific). J Card Fail 2012;18(1):82-88.

(42) Bahrami H, Kronmal R, Bluemke DA, Olson J, Shea S, Liu K, et al. Differences in the incidence of congestive heart failure by ethnicity: the multi-ethnic study of atherosclerosis. Arch Intern Med 2008;168(19):2138-2145.

(43) Kenchaiah S, Narula J, Vasan RS. Risk factors for heart failure. Med Clin North Am 2004;88(5):1145-1172.

(44) He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001;161(7):996-1002.

(45) Alexander M, Grumbach K, Selby J, Brown AF, Washington E. Hospitalization for congestive heart failure: explaining racial differences. JAMA 1995;274(13):1037-1042.

(46) Alexander M, Grumbach K, Remy L, Rowell R, Massie BM. Congestive heart failure hospitalizations and survival in California: patterns according to race/ethnicity. Am Heart J 1999;137(5):919-927.

(47) Dries DL, Exner DV, Gersh BJ, Cooper HA, Carson PE, Domanski MJ. Racial differences in the outcome of left ventricular dysfunction. N Engl J Med 1999;340(8):609-616.

(48) Nicol ED, Fittall B, Roughton M, Cleland JG, Dargie H, Cowie MR. NHS heart failure survey: a survey of acute heart failure admissions in England, Wales and Northern Ireland. Heart 2008;94(2):172-177.

(49) Joseph SM, Cedars AM, Ewald GA, Geltman EM, Mann DL. Acute decompensated heart failure: contemporary medical management. Texas Heart Institute Journal 2009;36(6):510.

(50) O'Connor CM, Stough WG, Gallup DS, Hasselblad V, Gheorghiade M. Demographics, clinical characteristics, and outcomes of patients hospitalized for decompensated heart failure: observations from the IMPACT-HF registry. J Card Fail 2005;11(3):200-205.

(51) Ahmed A, Allman RM, Fonarow GC, Love TE, Zannad F, Dell'Italia LJ, et al. Incident heart failure hospitalization and subsequent mortality in chronic heart failure: a propensity-matched study. J Card Fail 2008;14(3):211-218.

(52) Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. Circulation 2007;116(13):1482-1487.

(53) McMurray J, McDonagh 6T, Morrison CE, Dargie HJ. Trends in hospitalization for heart failure in Scotland 1980–1990. Eur Heart J 1993;14(9):1158-1162.

(54) McMurray JJ, Stewart S. Epidemiology, aetiology, and prognosis of heart failure. Heart 2000;83(5):596-602.

(55) Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. Am Heart J 1999;137(2):352-360.

(56) Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. Arch Intern Med 2008;168(8):847-854.

(57) Adams KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005;149(2):209-216.

(58) Opasich C, Rapezzi C, Lucci D, Gorini M, Pozzar F, Zanelli E, et al. Precipitating factors and decision-making processes of short-term worsening heart failure despite “optimal” treatment (from the IN-CHF Registry). Am J Cardiol 2001;88(4):382-387.

(59) Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola V, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27(22):2725-2736.

(60) Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure. Circulation 2013:CIR. 0b013e31829e8776.

(61) Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation 2003;108(8):977-982.

(62) SOLVD Investigators*. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327(10):685-691.

(63) Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50(8):768-777.

(64) Gopal M, Karnath B. Clinical diagnosis of heart failure. Hosp Physician 2009;45(7):9-15.

(65) McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European journal of heart failure 2012;14(8):803-869.

(66) Dolgin M, Fox AC. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 1994.

(67) Endorsed by the European Society of Intensive Care Medicine, (ESICM), Authors/Task Force Members, Nieminen MS, Böhm M, Cowie MR, Drexler H, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26(4):384-416.

(68) Cotter G, Moshkovitz Y, Milovanov O, Salah A, Blatt A, Krakover R, et al. Acute heart failure: a novel approach to its pathogenesis and treatment. European journal of heart failure 2002;4(3):227-234.

(69) Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50(8):768-777.

(70) Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, et al. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. JACC: Heart Failure 2014;2(2):97-112.

(71) Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol 2003;41(10):1797-1804.

(72) Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J 2010;32(6):670-679.

(73) Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28(20):2539-2550.

(74) Marwick TH, Raman SV, Carrió I, Bax JJ. Recent developments in heart failure imaging. JACC: Cardiovascular Imaging 2010;3(4):429-439.

(75) Paterson DI, OMeara E, Chow BJ, Ukkonen H, Beanlands RS. Recent advances in cardiac imaging for patients with heart failure. Curr Opin Cardiol 2011;26(2):132-143.

(76) Kirkpatrick JN, Vannan MA, Narula J, Lang RM. Echocardiography in heart failure: applications, utility, and new horizons. J Am Coll Cardiol 2007;50(5):381-396.

(77) Nagueh SF, Bhatt R, Vivo RP, Krim SR, Sarvari SI, Russell K, et al. Echocardiographic Evaluation of Hemodynamics in Patients With Decompensated Systolic Heart FailureClinical Perspective. Circulation: Cardiovascular Imaging 2011;4(3):220-227.

(78) Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography 2015;28(1):39. e14.

(79) Voigt J, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. European Heart Journal-Cardiovascular Imaging 2014;16(1):1-11.

(80) Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography: endorsed by the European Association of Echocardiography, a

registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. Journal of the American Society of Echocardiography 2010;23(7):685-713.

(81) Galiè N, Humbert M, Vachiery J, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2015;37(1):67-119.

(82) Smith BC, Dobson G, Dawson D, Charalampopoulos A, Grapsa J, Nihoyannopoulos P. Three-dimensional speckle tracking of the right ventricle: toward optimal quantification of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 2014;64(1):41-51.

(83) van Riet EE, Hoes AW, Limburg A, Landman MA, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. European journal of heart failure 2014;16(7):772-777.

(84) Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, et al. The Diagnostic Value of Physical Examination and Additional Testing in Primary Care Patients With Suspected Heart FailureClinical Perspective. Circulation 2011;124(25):2865-2873.

(85) Davie AP, Francis CM, Love MP, Caruana L, Starkey IR, Shaw T, et al. Value of the electrocardiogram in identifying heart failure due to left ventricular systolic dysfunction. BMJ: British Medical Journal 1996;312(7025):222.

(86) Thomas JT, Kelly RF, Thomas SJ, Stamos TD, Albasha K, Parrillo JE, et al. Utility of history, physical examination, electrocardiogram, and chest radiograph for differentiating normal from decreased systolic function in patients with heart failure. Am J Med 2002;112(6):437-445.

(87) Davie AP, Francis CM, Caruana L, Sutherland GR, McMurray JJ. Assessing diagnosis in heart failure: which features are any use? QJM: monthly journal of the Association of Physicians 1997;90(5):335-339.

(88) Madias JE. Why recording of an electrocardiogram should be required in every inpatient and outpatient encounter of patients with heart failure. Pacing and Clinical Electrophysiology 2011;34(8):963-967.

(89) Khunti K, Squire I, Abrams KR, Sutton AJ. Accuracy of a 12â€•lead electrocardiogram in screening patients with suspected heart failure for open access echocardiography: a systematic review and metaâ€•analysis. European journal of heart failure 2004;6(5):571-576.

(90) McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European journal of heart failure 2012;14(8):803-869.

(91) Ewald B, Ewald D, Thakkinstian A, Attia J. Meta-analysis of B type natriuretic peptide and N-terminal pro B natriuretic peptide in the diagnosis of clinical heart failure and population screening for left ventricular systolic dysfunction. Intern Med J 2008;38(2):101-113.

(92) Doust JA, Glasziou PP, Pietrzak E, Dobson AJ. A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. Arch Intern Med 2004;164(18):1978-1984.

(93) Zaphiriou A, Robb S, Murrayâ€•Thomas T, Mendez G, Fox K, McDonagh T, et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. European journal of heart failure 2005;7(4):537-541.

(94) Maisel A, Mueller C, Adams K, Anker SD, Aspromonte N, Cleland JG, et al. State of the art: using natriuretic peptide levels in clinical practice. European journal of heart failure 2008;10(9):824-839.

(95) Wu AH, Tabas J, Stein J, Potocki M, Mueller C, McCord J, et al. The effect of diabetes on the diagnostic and prognostic performance of mid-region pro-atrial natriuretic peptide and mid-region pro-adrenomedullin in patients with acute dyspnea. Biomarkers 2012;17(6):490-497.

(96) Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. European journal of heart failure 2009;11(2):130-139.

(97) Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119(14):1977-2016.

(98) Garbi M, McDonagh T, Cosyns B, Bucciarelli-Ducci C, Edvardsen T, Kitsiou A, et al. Appropriateness criteria for cardiovascular imaging use in heart failure: report of literature review. European Heart Journal-Cardiovascular Imaging 2014;16(2):147-153.

(99) Gonzalez JA, Kramer CM. Role of imaging techniques for diagnosis, prognosis and management of heart failure patients: cardiac magnetic resonance. Current heart failure reports 2015;12(4):276-283.

(100) Hundley WG, Bluemke DA, Finn JP, Flamm SD, Fogel MA, Friedrich MG, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance. Circulation 2010;121(22):2462-2508.

(101) Kilner PJ, Geva T, Kaemmerer H, Trindade PT, Schwitter J, Webb GD. Recommendations for cardiovascular magnetic resonance in adults with congenital heart disease from the respective working groups of the European Society of Cardiology. Eur Heart J 2010;31(7):794-805.

(102) Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, et al. Stress echocardiography expert consensus statement-executive summary: european association of echocardiography (a registrated branch of the ESC). Eur Heart J 2009;30(3):278-289.

(103) Garnier F, Eicher J, Jazayeri S, Bertaux G, Bouchot O, Aho L, et al. Usefulness and limitations of contractile reserve evaluation in patients with low-flow, low-gradient aortic stenosis eligible for cardiac resynchronization therapy. European journal of heart failure 2014;16(6):648-654.

(104) JolicÅ“ur EM, Dunning A, Castelvecchio S, Dabrowski R, Waclawiw MA, Petrie MC, et al. Importance of angina in patients with coronary disease, heart failure, and left ventricular systolic dysfunction: insights from STICH. J Am Coll Cardiol 2015;66(19):2092-2100.

(105) Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet J, Cremer J, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35(37):2541-2619.

(106) Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34(38):2949-3003.

(107) Roffi M, Patrono C, Collet J, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37(3):267-315.

(108) Penicka M, Vanderheyden M, Bartunek J. Diagnosis of heart failure with preserved ejection fraction: role of clinical Doppler echocardiography. Heart 2013:301321.

(109) Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, et al. Trends in Patients Hospitalized with Heart Failure and Preserved Left Ventricular Ejection Fraction-Prevalence, Therapies, and Outcomes. Circulation 2012:CIRCULATIONAHA. 111.080770.

(110) Quiroz R, Doros G, Shaw P, Liang C, Gauthier DF, Sam F. Comparison of characteristics and outcomes of patients with heart failure preserved ejection fraction versus reduced left ventricular ejection fraction in an urban cohort. Am J Cardiol 2014;113(4):691-696.

(111) Martínez-Sellés M, Doughty RN, Poppe K, Whalley GA, Earle N, Tribouilloy C, et al. Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. European Journal of Heart Failure 2012;14(5):473-479.

(112) Rogers FJ, Gundala T, Ramos JE, Serajian A. Heart failure with preserved ejection fraction. J Am Osteopath Assoc 2015;115(7):432-442.

(113) Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62(4):263-271.

(114) Heart Failure Society of America. Section 12: Evaluation and management of patients with acute decompensated heart failure. J Card Fail 2006;12(1):e103.

(115) CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). New Engl J Med 1987;316:1429.

(116) Solvd Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;1991(325):293-302.

(117) Garg R, Yusuf S, Bussmann WD, Sleight P, Uprichard A, Massie B, et al. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995;273(18):1450-1456.

(118) Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation 1999;100(23):2312-2318.

(119) Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12 440 patients of the ESC Heart Failure Long-Term Registry. European journal of heart failure 2013;15(10):1173-1184.

(120) Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown Jr EJ, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. N Engl J Med 1992;327(10):669-677.

(121) Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure. Circulation 2013:CIR. 0b013e31829e8776.

(122) Hjalmarson ⍰, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). JAMA 2000;283(10):1295-1302.

(123) Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344(22):1651-1658.

(124) Merit-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in-congestive heart failure (MERIT-HF). The Lancet 1999;353(9169):2001-2007.

(125) Poole-Wilson PA. The cardiac insufficiency bisoprolol study II. The Lancet 1999;353(9161):1360.

(126) Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26(3):215-225.

(127) Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 2015.

(128) Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, et al. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. The Lancet 2014;384(9961):2235-2243.

(129) Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341(10):709-717.

(130) Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364(1):11-21.

(131) Faris R, Flather MD, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. Cochrane Database Syst Rev 2006;1.

(132) Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. Int J Cardiol 2002;82(2):149-158.

(133) Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, et al. The prognostic importance of different definitions of worsening renal function in congestive heart failure. J Card Fail 2002;8(3):136-141.

(134) King JB, Bress AP, Reese AD, Munger MA. Neprilysin inhibition in heart failure with reduced ejection fraction: a clinical review. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2015;35(9):823-837.

(135) Mangiafico S, Costello-Boerrigter LC, Andersen IA, Cataliotti A, Burnett Jr JC. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. Eur Heart J 2012;34(12):886-893.

(136) Swedberg K, Komajda M, Bhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. The Lancet 2010;376(9744):875-885.

(137) Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. The Lancet 2003;362(9386):772-776.

(138) Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345(23):1667-1675.

(139) Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. Eur Heart J 2015;36(28):1831-1838.

(140) Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010;362(15):1363-1373.

(141) Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337(22):1576-1584.

(142) Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck K, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. Eur Heart J 2000;21(24):2071-2078.

(143) Hammer S, Snel M, Lamb HJ, Jazet IM, van der Meer, Rutger W, Pijl H, et al. Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases myocardial triglyceride content and improves myocardial function. J Am Coll Cardiol 2008;52(12):1006-1012.

(144) Bonow R, Carabello B, de Leon A, Edmunds LH, Fedderly B, Freed M, et al. ACC/AHA guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on management of patients with valvular heart disease) 11When citing this document, the American College of Cardiology and the American Heart Association recommend that the following format be used: Bonow RO, Carabello B, de Leon AC Jr, Edmunds LH Jr, Fedderly BJ, Freed MD, Gaasch WH, McKay CR, Nishimura RA, O'Gara PT, O'Rourke RA, Rahimtoola SH. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). J Am Coll Cardiol. 1998; 32: 1486–588.22 Address for reprints: A single reprint of this document (the complete Guidelines) is available by calling 800-253-4636 (US only) or writing the American College of Cardiology, Educational Services, 9111 Old Georgetown Road, Bethesda, MD 20814-1699. Ask for reprint No. 71-0153. To obtain a reprint of the shorter version (Executive Summary and Summary of Recommendations) published in the November 3 issue of Circulation, ask for reprint No. 71-0154. To purchase additional reprints, specify version and reprint number: up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 214-706-1466, fax 214-691-6342, or E-mail pubauth@ heart. org. J Am Coll Cardiol 1998;32(5):1486-1582.

(145) Iung B, Baron G, Tornos P, Gohlke-Brwolf C, Butchart EG, Vahanian A. Valvular heart disease in the community: a European experience. Curr Probl Cardiol 2007;32(11):609-661.

(146) Robbins JD, Maniar PB, Cotts W, Parker MA, Bonow RO, Gheorghiade M. Prevalence and severity of mitral regurgitation in chronic systolic heart failure. Am J Cardiol 2003;91(3):360-362.

(147) Varadarajan P, Sharma S, Heywood JT, Pai RG. High prevalence of clinically silent severe mitral regurgitation in patients with heart failure: role for echocardiography. Journal of the American Society of Echocardiography 2006;19(12):1458-1461.

(148) Trochu J, Le Tourneau T, Obadia J, Caranhac G, Beresniak A. Economic burden of functional and organic mitral valve regurgitation. Archives of cardiovascular diseases 2015;108(2):88-96.

(149) De Marchena E, Badiye A, Robalino G, Junttila J, Atapattu S, Nakamura M, et al. Respective prevalence of the different carpentier classes of mitral regurgitation: a stepping stone for future therapeutic research and development. J Card Surg 2011;26(4):385-392.

(150) Hung J, Papakostas L, Tahta SA, Hardy BG, Bollen BA, Duran CM, et al. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty: continued LV remodeling as a moving target. Circulation 2004;110(11 suppl 1):90.

(151) Ray S. The echocardiographic assessment of functional mitral regurgitation. European Journal of Echocardiography 2010;11(10):i17.

(152) Chaput M, Handschumacher MD, Tournoux F, Hua L, Guerrero JL, Vlahakes GJ, et al. Mitral leaflet adaptation to ventricular remodeling: occurrence and adequacy in patients with functional mitral regurgitation. Circulation 2008;118(8):845-852.

(153) Saito K, Okura H, Watanabe N, Obase K, Tamada T, Koyama T, et al. Influence of chronic tethering of the mitral valve on mitral leaflet size and coaptation in functional mitral regurgitation. JACC: Cardiovascular Imaging 2012;5(4):337-345.

(154) Kumanohoso T, Otsuji Y, Yoshifuku S, Matsukida K, Koriyama C, Kisanuki A, et al. Mechanism of higher incidence of ischemic mitral regurgitation in patients with inferior myocardial infarction: quantitative analysis of left ventricular and mitral valve geometry in 103 patients with prior myocardial infarction. J Thorac Cardiovasc Surg 2003;125(1):135-143.

(155) Agricola E, Oppizzi M, Maisano F, De Bonis M, Schinkel AF, Torracca L, et al. Echocardiographic classification of chronic ischemic mitral regurgitation caused by restricted motion according to tethering pattern. European Journal of Echocardiography 2004;5(5):326-334.

(156) Daimon M, Saracino G, Gillinov AM, Koyama Y, Fukuda S, Kwan J, et al. Local dysfunction and asymmetrical deformation of mitral annular geometry in ischemic mitral regurgitation: a novel computerized 3D echocardiographic analysis. Echocardiography 2008;25(4):414-423.

(157) Nagasaki M, Nishimura S, Ohtaki E, Kasegawa H, Matsumura T, Nagayama M, et al. The echocardiographic determinants of functional mitral regurgitation differ in ischemic and non-ischemic cardiomyopathy. Int J Cardiol 2006;108(2):171-176.

(158) Cowie MR, Wood DA, Coats A, Thompson SG, Poole-Wilson PA, Suresh V, et al. Incidence and aetiology of heart failure; a population-based study. Eur Heart J 1999;20(6):421-428.

(159) Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation. Circulation 2001;103(13):1759-1764.

(160) Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003;91(5):538-543.

(161) Rossi A, Dini FL, Faggiano P, Cicoira M, Frattini S, Simioniuc A, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. Heart 2011:hrt. 2011.225789.

(162) Goliasch G, Bartko PE, Pavo N, Neuhold S, Wurm R, Mascherbauer J, et al. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. Eur Heart J 2017;39(1):39-46.

(163) Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135(25):e1195.

(164) Agricola E, Ielasi A, Oppizzi M, Faggiano P, Ferri L, Calabrese A, et al. Long-term prognosis of medically treated patients with functional mitral regurgitation and left ventricular dysfunction. European journal of heart failure 2009;11(6):581-587.

(165) Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol 2005;45(3):381-387.

(166) Silberman S, Oren A, Klutstein MW, Deeb M, Asher E, Merin O, et al. Does mitral valve intervention have an impact on late survival in ischemic cardiomyopathy. Isr Med Assoc J 2006;8(1):17-20.

(167) Milano CA, Daneshmand MA, Rankin JS, Honeycutt E, Williams ML, Swaminathan M, et al. Survival prognosis and surgical management of ischemic mitral regurgitation. Ann Thorac Surg 2008;86(3):735-744.

(168) Cleland JG, Daubert J, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352(15):1539-1549.

(169) Sutton, Martin G St John, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation 2003;107(15):1985-1990.

(170) Auricchio A, Schillinger W, Meyer S, Maisano F, Hoffmann R, Ussia GP, et al. Correction of mitral regurgitation in nonresponders to cardiac resynchronization therapy by MitraClip improves symptoms and promotes reverse remodeling. J Am Coll Cardiol 2011;58(21):2183-2189.

(171) Fedak PW, McCarthy PM, Bonow RO. Evolving concepts and technologies in mitral valve repair. Circulation 2008;117(7):963-974.

(172) Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, et al. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364(15):1395-1406.

(173) Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, et al. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364(15):1395-1406.

(174) Nickenig G, Estevez-Loureiro R, Franzen O, Tamburino C, Vanderheyden M, Lüscher TF, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011–2012 Pilot European Sentinel Registry. J Am Coll Cardiol 2014;64(9):875-884.

(175) Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38(36):2739-2791.

(176) Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, et al. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. J Am Coll Cardiol 2015;66(25):2844-2854.

(177) Davey PG, Clarkson PB, McMahon A, MacDonald TM. Costs associated with symptomatic systolic heart failure. Pharmacoeconomics 1999;16(4):399-407.

(178) Kleber FX, Niemller L, Rohrbacher R. Sozio-konomische Bedeutung der ACE-Hemmer bei Frhformen der Herzinsuffizienz. Mnch Med Wochenschr 1992;134:749-752.

(179) Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol 2014;171(3):368-376.

(180) HAMEED AS, MODRE-OSPRIAN R, SCHREIER G. Identification of Cost Indicators with Significant Economic Impact on the Total Treatment Costs of Chronic Heart Vailure Patients–A Meta-Analysis. 2017;236:161.

(181) Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol 2014;171(3):368-376.

(182) Murrey J, Hart W, Phodes G. An evaluation of the economic cost of heart failure to the National Health Service in the United Kingdom. Br.J Med.Econ. 1993;6:99.

(183) Szucs TD. The growing healthcare burden of CHF. Journal of the Renin-Angiotensin-Aldosterone System 2000;1(1_suppl):2-6.

(184) Szucs T. Gesundheitskonomische aspekte der chronischen herzinsuffizienz. Schweizeriche rztezeitung 2003;84(46):2431-2435.

(185) Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics—2008 update. Circulation 2008;117(4):e146.

(186) Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. European journal of heart failure 2002;4(3):361-371.

(187) Fryback DG, Dasbach EJ, Klein R, Klein BE, Dorn N, Peterson K, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. Medical Decision Making 1993;13(2):89-102.

(188) Krumholz HM, Chen Y, Vaccarino V, Wang Y, Radford MJ, Bradford WD, et al. Correlates and impact on outcomes of worsening renal function in patients≥ 65 years of age with heart failure. Am J Cardiol 2000;85(9):1110-1113.

(189) McMurray J, Hart W, Rhodes G. An evaluation of the cost of heart failure to the National Health Service in the UK. British Journal of Medical Economics 1993;6:99.

(190) National, Clinical Guideline Centre UK. Acute Heart Failure: Diagnosing and Managing Acute Heart Failure in Adults. 2014.

(191) Curtis L. No title. Unit costs of health and social care.Canterbury: Personal Social Services Reseach Unit, University of Kent; 2010 2013.

(192) Cleland J, Dargie H, Hardman S, McDonagh T, Mitchell P. National Heart Failure Audit, April 2012-March 2013. NICOR (National Institute for Cardiovascular Outcomes Research) and The British Society for Heart Failure (BSH) 2013.

(193) Tepper D. Resource Use and Survival of Patients Hospitalized With Congestive Heart Failure: Differences in Care by Specialty of the Attending Physician. Congestive Heart Failure 2000;6(2):118-119.

(194) Berry C, Murdoch DR, McMurray JJ. Economics of chronic heart failure. European journal of heart failure 2001;3(3):283-291.

(195) Braunschweig F, Cowie MR, Auricchio A. What are the costs of heart failure? Europace 2011;13(suppl_2):ii17.

(196) McMurray J, Davie A. The pharmacoeconomics of ACE inhibitors in chronic heart failure. Pharmacoeconomics 1996;9(3):188-197.

(197) Paul SD, Kuntz KM, Eagle KA, Weinstein MC. Costs and effectiveness of angiotensin converting enzyme inhibition in patients with congestive heart failure. Arch Intern Med 1994;154(10):1143-1149.

(198) Levy P, Lechat P, Leizorovicz A, Levy E. A cost-minimization of heart failure therapy with bisoprolol in the French setting: An analysis from CIBIS trial data. Cardiovascular drugs and therapy 1998;12(3):301-305.

(199) Schdlich PK, Paschen B, Brecht JG. Economic evaluation of the cardiac insufficiency bisoprolol study for the Federal Republic of Germany. Pharmacoeconomics 1998;13(1):147-155.

(200) Malek M, Cunningham-Davis J, Malek L, Paschen B, Tavakoli M, Zabihollah M, et al. A cost minimisation analysis of cardiac failure treatment in the UK using CIBIS trial data. Cardiac Insufficiency Bisoprolol Study. Int J Clin Pract 1998;53(1):19-23.

(201) Bacquet P, Levy E, McGuire A, McMurray J, Merot JL, Paschen B, et al. Reduced costs with bisoprolol treatment for heart failure-An economic analysis of the second Cardiac Insufficiency Bisoprolol Study (CIBIS-II). Eur Heart J 2001;22(12):1021-1031.

(202) McMurray JJ, Trueman D, Hancock E, Cowie MR, Briggs A, Taylor M, et al. Cost-effectiveness of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction. Heart 2017:310661.

(203) Care P. No title. Health & Social Care Information Centre.Prescriptions dispensed in the community: statistics for England: 2002 to 2012 2013.

(204) Epstein AJ, Polsky D, Yang F, Yang L, Groeneveld PW. Geographic variation in implantable cardioverter-defibrillator use and heart failure survival. Med Care 2012;50(1):10.

(205) National Institute for Clinical Excellence. Implantable cardioverter defibrillators for arrhythmias. Accessed 1st February 2012.

(206) Henderson RA, O'flynn N. Management of stable angina: summary of NICE guidance. Heart 2012;98(6):500-507.

(207) Clarke A, Pulikottil-Jacob R, Connock M, Suri G, Kandala N, Maheswaran H, et al. Cost-effectiveness of left ventricular assist devices (LVADs) for patients with advanced heart failure: analysis of the British NHS bridge to transplant (BTT) program. Int J Cardiol 2014;171(3):338-345.

(208) McDonagh T, Cleland J, Dargie HJ, Whittaker T, Standing M, Mitchell M, et al. National Heart Failure Audit April 2010â€“March 2011. National Institute For Cardiovascular Outcomes Research (NICOR) 2012.

(209) Cleland J, Dargie H, Hardman S, McDonagh T, Mitchell P. National Heart Failure Audit, April 2012-March 2013. NICOR (National Institute for Cardiovascular Outcomes Research) and The British Society for Heart Failure (BSH) 2013.

(210) Mackowiak J. Cost of heart failure to the healthcare system. Am J Manag Care 1998;4(6 Suppl):338.

(211) Auerbach AD, Hamel MB, Davis RB, Connors AF, Regueiro C, Desbiens N, et al. Resource use and survival of patients hospitalized with congestive heart failure: differences in care by specialty of the attending physician. Ann Intern Med 2000;132(3):191-200.

(212) Steadman C. Assessment and management of mitral regurgitation. Challenging Concepts in Cardiovascular Medicine: A Case-Based Approach with Expert Commentary 2011:71.

(213) Yoo B. Clinical significance of B-type Natriuretic peptide in heart failure. Journal of lifestyle medicine 2014;4(1):34.

(214) Baxter GF. The natriuretic peptides. Basic Res Cardiol 2004;99(2):71-75.

(215) Lee CY, Burnett JC. Natriuretic peptides and therapeutic applications. Heart Fail Rev 2007;12(2):131.

(216) Okoshi MP, Capalbo RV, Romeiro FG, Okoshi K. Cardiac cachexia: perspectives for prevention and treatment. Arq Bras Cardiol 2017;108(1):74-80.

(217) Efremidis M, Pappas L, Sideris A, Filippatos G. Management of atrial fibrillation in patients with heart failure. J Card Fail 2008;14(3):232-237.

(218) Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK, Sparks PB, et al. Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. Circulation 2003;108(12):1461-1468.

(219) De Jong AM, Maass AH, Oberdorf-Maass SU, Van Veldhuisen DJ, Van Gilst WH, Van Gelder IC. Mechanisms of atrial structural changes caused by stretch occurring before and during early atrial fibrillation. Cardiovasc Res 2010;89(4):754-765.

(220) Vaziri SM, Larson MG, Lauer MS, Benjamin EJ, Levy D. Influence of blood pressure on left atrial size: the Framingham Heart Study. Hypertension 1995;25(6):1155-1160.

(221) Cosio FG, Aliot E, Botto GL, Heidbüchel H, Geller CJ, Kirchhof P, et al. Delayed rhythm control of atrial fibrillation may be a cause of failure to prevent recurrences: reasons for change to active antiarrhythmic treatment at the time of the first detected episode. Europace 2007;10(1):21-27.

(222) Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. Circulation 1995;92(7):1954-1968.

(223) Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. J Am Coll Cardiol 2005;46(12):2183-2192.

(224) Wharton G, Steeds R, Allen J, Phillips H, Jones R, Kanagala P, et al. A minimum dataset for a standard adult transthoracic echocardiogram: a guideline protocol from the British Society of Echocardiography. Echo research and practice 2015;2(1):G24.

(225) Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography 2015;28(1):39. e14.

(226) Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. JACC: Cardiovascular Imaging 2011;4(1):98-108.

(227) Shin JT, Semigran MJ. Heart failure and pulmonary hypertension. Heart failure clinics 2010;6(2):215-222.

(228) Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 2001;37(1):183-188.

(229) Napp LC, Luesebrink U, Vogel-Claussen J, Bauersachs J, Roentgen P. Two's Company: Double-Chambered Right Ventricle. Circulation 2013;127(9):e470.

(230) Jurcut R, Giusca S, La Gerche A, Vasile S, Ginghina C, Voigt J. The echocardiographic assessment of the right ventricle: what to do in 2010? European Journal of Echocardiography 2010;11(2):81-96.

(231) Horton KD, Meece RW, Hill JC. Assessment of the right ventricle by echocardiography: a primer for cardiac sonographers. Journal of the American society of echocardiography 2009;22(7):776-792.

(232) Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography: endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. Journal of the American Society of Echocardiography 2010;23(7):685-713.

(233) López-Candales A, Rajagopalan N, Saxena N, Gulyasy B, Edelman K, Bazaz R. Right ventricular systolic function is not the sole determinant of tricuspid annular motion. Am J Cardiol 2006;98(7):973-977.

(234) Markley RR, Ali A, Potfay J, Paulsen W, Jovin IS. Echocardiographic evaluation of the right heart. Journal of cardiovascular ultrasound 2016;24(3):183-190.

(235) Anavekar NS, Gerson D, Skali H, Kwong RY, Kent Yucel E, Solomon SD. Two-Dimensional Assessment of Right Ventricular Function: An Echocardiographic–MRI Correlative Study. Echocardiography 2007;24(5):452-456.

(236) Anavekar NS, Skali H, Bourgoun M, Ghali JK, Kober L, Maggioni AP, et al. Usefulness of right ventricular fractional area change to predict death, heart failure, and stroke following myocardial infarction (from the VALIANT ECHO Study). Am J Cardiol 2008;101(5):607-612.

(237) Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003;91(5):538-543.

(238) Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003;91(5):538-543.

(239) Bursi F, Barbieri A, Grigioni F, Reggianini L, Zanasi V, Leuzzi C, et al. Prognostic implications of functional mitral regurgitation according to the severity of the underlying chronic heart failure: a long-term outcome study. European journal of heart failure 2010;12(4):382-388.

(240) Dworzynski K, Roberts E, Ludman A, Mant J. Diagnosing and managing acute heart failure in adults: summary of NICE guidance. BMJ: British Medical Journal (Online) 2014;349.

(241) Mant J, Al-Mohammad A, Swain S, Laramée P. Management of chronic heart failure in adults: synopsis of the National Institute for Health and Clinical Excellence guideline. Ann Intern Med 2011;155(4):252-259.

(242) McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. J Am Coll Cardiol 2004;44(4):810-819.

(243) Díez-Villanueva P, Alfonso F. Heart failure in the elderly. Journal of geriatric cardiology: JGC 2016;13(2):115.

(244) Hsich EM, Piña IL. Heart failure in women: a need for prospective data. J Am Coll Cardiol 2009;54(6):491-498.

(245) Shin JJ, Hamad E, Murthy S, Pina IL. Heart failure in women. Clin Cardiol 2012;35(3):172-177.

(246) Gottlieb SS, Khatta M, Friedmann E, Einbinder L, Katzen S, Baker B, et al. The influence of age, gender, and race on the prevalence of depression in heart failure patients. J Am Coll Cardiol 2004;43(9):1542-1549.

(247) Klein L, Grau-Sepulveda MV, Bonow RO, Hernandez AF, Williams MV, Bhatt DL, et al. Quality of care and outcomes in women hospitalized for heart failure. Circulation: Heart Failure 2011;4(5):589-598.

(248) Alaeddini J, Wood MA, Amin MS, Ellenbogen KA. Gender disparity in the use of cardiac resynchronization therapy in the United States. Pacing and clinical electrophysiology 2008;31(4):468-472.

(249) Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Reviews in cardiovascular medicine 2003;4:21.

(250) Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography: endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. Journal of the American Society of Echocardiography 2010;23(7):685-713.

(251) Foale R, Nihoyannopoulos P, McKenna W, Kleinebenne A, Nadazdin A, Rowland E, et al. Echocardiographic measurement of the normal adult right ventricle. Heart 1986;56(1):33-44.

(252) Bleeker GB, Steendijk P, Holman ER, Yu CM, Breithardt OA, Kaandorp T, et al. Assessing right ventricular function: the role of echocardiography and complementary technologies. Heart 2006;92(suppl 1):i26.

(253) Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Reviews in cardiovascular medicine 2003;4:21.

(254) O'Connor CM, Fiuzat M. No title. Is rehospitalization after heart failure admission a marker of poor quality?: time for re-evaluation 2010.

(255) Braunschweig F, Cowie MR, Auricchio A. What are the costs of heart failure? Europace 2011;13(suppl_2):ii17.

(256) Bahouth F, Mutlak D, Furman M, Musallam A, Hammerman H, Lessick J, et al. Relationship of functional mitral regurgitation to new-onset atrial fibrillation in acute myocardial infarction. Heart 2010;96(9):683-688.

APPENDIX 1.

RESTING TRANSTHORACIC STUDY. Views and acquisition requirements for MRAHF study.

1. Parasternal Long Axis view:

- 2D loop at moderate (50-70/sec) frame rate
- 2D loop with colour Doppler
- 2D loop with colour tissue Doppler at high (>120/sec) frame rate
- M-mode of aortic root/left atrium
- M-mode of left ventricle
- 2D loop (zoomed) of aortic root for LVOT dimension
- 2D loop RV inflow view (optional)
- 2D loop RV inflow view with CW Doppler for TR (optional)

2. Parasternal short axis view

- 2D loop at aortic valve level
- PW Doppler of RVOT
- 2D loop of MV in short axis
- 2D loop with colour Doppler at MV level at high frame rate
- 2D loop at papillary muscle level at moderate frame rate
- 2D loop with colour tissue Doppler at high (>120/sec) frame rate
- 2D loop at mid left ventricular level
- 2D loop at apical left ventricular level

3. Apical Four Chamber View

- 2D loop at moderate frame rate focusing on all 4 chambers
- 2D loop with colour flow Doppler on all 4 chambers
- 2D loop zoom at moderate frame rate focusing on left and right ventricles

- 2D loop zoom with colour tissue Doppler at high frame rate focusing on left and right ventricles
- Pulsed tissue Doppler of the lateral mitral annulus
- Pulsed tissue Doppler of the septal mitral annulus
- Pulsed tissue Doppler of the right ventricular free wall annulus
- 2D loop with colour flow Doppler focusing on MR (PISA, VC, jet in LA)
- Zoomed 2D loop with colour flow Doppler focusing on MR (PISA, VC, jet in LA)
- 2D loop with colour flow Doppler focusing on TR
- 2D loop at high frame rate to include both atria and pulmonary veins
- Pulsed Doppler of the mitral inflow
- Pulsed wave Doppler of the right upper pulmonary vein
- Continuous wave Doppler of the MR jet
- Pulsed Doppler of the left ventricular outflow
- Continuous wave Doppler of aortic outflow
- Pulsed Doppler of the tricuspid inflow
- Continuous wave Doppler of the TR jet

4. Apical Two Chamber view

- 2D loop at moderate frame rate (LA/LV)
- 2D loop with colour flow Doppler
- 2D loop at moderate frame rate focusing on left ventricle
- 2D loop with colour tissue doppler at high frame rate focusing on left ventricle
- 2D loop zoom at high frame rate on left atrium and pulmonary veins
- 2D loop with colour flow Doppler focusing on MR (PISA, VC and jet in LA)
- Zoomed 2D loop with colour flow Doppler focusing on MR (PISA, VC and jet in LA)

5. Apical Long Axis view

- 2D loop at moderate frame rate
- 2D loop at moderate frame rate focusing on left ventricle
- 2D loop with colour Doppler
- 2D loop with colour flow Doppler focusing on MR (PISA, VC and jet in LA)
- Zoomed 2D loop with colour flow Doppler focusing on MR (PISA, VC and jet in LA)

6. Subcostal view

- IVC dimension and sniff test – 2D + M-mode
- 2D loop of Subcostal long axis view
- 2D loop of Subcostal short axis view at papillary muscle level (optional)
- 2D loop of Subcostal short axis view at A level (optional)

APPENDIX 2.

Patient Informed Consent

Patient Identification Number for this study:

Consent Form

Study Title: Incidence of significant mitral regurgitation in patients presenting with acute heart failure. Journey to Tertiary Centre (MRAHF).

Name of Researcher: Please initial each box

1. I confirm that I have read and understood the Patient Information Sheet dated 25th April 2016, UK version 1.1. I have had the opportunity to consider the information given concerning the MRAHF study and to ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason. My legal rights and medical care will not be affected by my decision.

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I agree that my data collected for the study will be recorded anonymously.

4. I declare my agreement to archiving/storage of my data over a period of at least 5 years after termination of the clinical investigation. After the archiving period my data will be deleted if not otherwise claimed by legal, statutory or contractual regulations for record retention.

5. I agree to take part in the MRAHF study.

1 copy for patient; Original for researcher; 1 copy to be kept with hospital notes

Name of Patient, Date, Signature _____ _____
Name of Person taking Consent (if different from Researcher), Date, Signature _____
_____ _____ _____

Researcher Date Signature _____

APPENDIX 3

Study Title: **Incidence of significant mitral regurgitation in patients presenting with acute heart failure. Journey to Tertiary Centre (MRAHF).**

Patient Information Sheet

Dear Patient,

We would like to ask you to take part in our clinical investigation study. Before you decide whether you would like to take part it is important that you understand why this research is being done and what it will involve. One of our team will go through this information sheet with you and answer any questions or concerns you may have. Please ask us if there is anything that is not clear or if you would like more information and talk to others if you wish. You will have to decide on the first day of your admission to the hospital whether you would like to take part in this study. This information sheet will explain the purpose of the study and what will happen to you if you take part.

Thank you for taking the time to read this.

Part 1

What is the purpose of the study?

The purpose of this study is to assess the prevalence of moderate-to-severe Mitral Regurgitation (MR), also known as leaky valves in patients presenting to hospital in acute Heart Failure (HF). Patients requiring hospital admission.

Why have I been invited?

You have been asked to participate in this study because you have been admitted to hospital with symptoms of heart failure.

Do I have to take part?

Your participation in this study is completely voluntary. You do not have to take part. Please take the time to read this information sheet carefully and discuss it with relatives, friends.

It is up to you to decide whether or not to take part in this clinical study. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You will be 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.

If you have any questions or concerns about this study, or if you do not fully understand any part of it, please ask your research doctor.

What will happen to me if I take part?

If you agree to take part in this clinical study you will be asked to have a recording of heart sounds with a special stethoscope, have a heart scan and a bedside B-type Natriuretic Peptide Blood Test (BNP). The level of BNP will be checked using a small device (i-STAT BNP) at the bedside. The BNP test results will determine your eligibility for inclusion into this study. If your test results indicate elevated BNP level of (>30 pg/ml) you will undergo special procedure called Transthoracic Echocardiography (TTE) for grading of MR severity within 1-7 days of your hospitalisation. A transthoracic echocardiogram (TTE) is the most common type of echocardiogram, which is a still or moving image of the internal parts of the heart using ultrasound. In this case, the probe (or ultrasonic transducer) is placed on the chest or abdomen of the patient to get various views of the heart.

Will expenses be paid?

We are not anticipating expenses to incur as all the investigations will be completed within current hospital admission.

What do I have to do?

Your participation in the study will last for the time you are in hospital.

You will not be eligible to participate in the study if you have other causes of breathlessness or palpitations.

What are the possible disadvantages and risks of taking part?

Participation involves having a heart scan whilst in hospital and additional skin prick to take blood for BNP test.

What are the possible benefits of taking part?

Your participation will be important as it will help us establish whether hospital admissions with heart failure are caused with leaky valves. We will also be in a position to find out if assessment of heart sounds on auscultation is good enough to detect valvular problems as well as value of bedside assessment of BNP. These tests are not routinely available in current clinical settings.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed.

What will happen if I don't want to continue in the study?

You are free to withdraw your participation at any time with no prejudice to your standard of care. We will need to use the data collected on you up until the time of your withdrawal.

What if there is a problem? If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this by contacting Patient Advice and Liaison Service (PALS) within the hospital: Telephone: 01932 723553 Email: pals@asph.nhs.uk

Will my taking part in the study be kept confidential?

Yes. If you consent to take part in the clinical study, any of your medical records may be inspected by the company sponsoring the research for purposes of analysing the results. They may also be looked at by people from the company and from regulatory authorities to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital. The Trust Information Governance Policy and Data Protection Act 1998 will be strictly followed.

We will follow ethical and legal practice and all information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

After the end of this clinical study the results will be analyzed and published in medical scientific journals. As all information that is available from you is collected anonymously you will of course not be identified in any report or publication. The study outcome will be posted on the Trust research and development website, which is located at: http://www.ashfordstpeters.nhs.uk/quality/research . Participants will be provided with the web link to access the information.

Who is organising and funding the study?

This study has been funded by Abbott Vascular Company, and sponsored by Metanoic Health Ltd.

Who has reviewed the study?

The formal review by R&D committee took place on 15.10.2015. Similar detailed review took place at ABBOTT Laboratories Abbott Vascular. Both panels have come to a conclusion that this is an innovative and interesting research project. This study will also be reviewed and approved by Research Ethics Committee (REC) [REC Name: North of Scotland 2]. Contact for Further Information Please feel free to ask any question you have about this study. If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions.

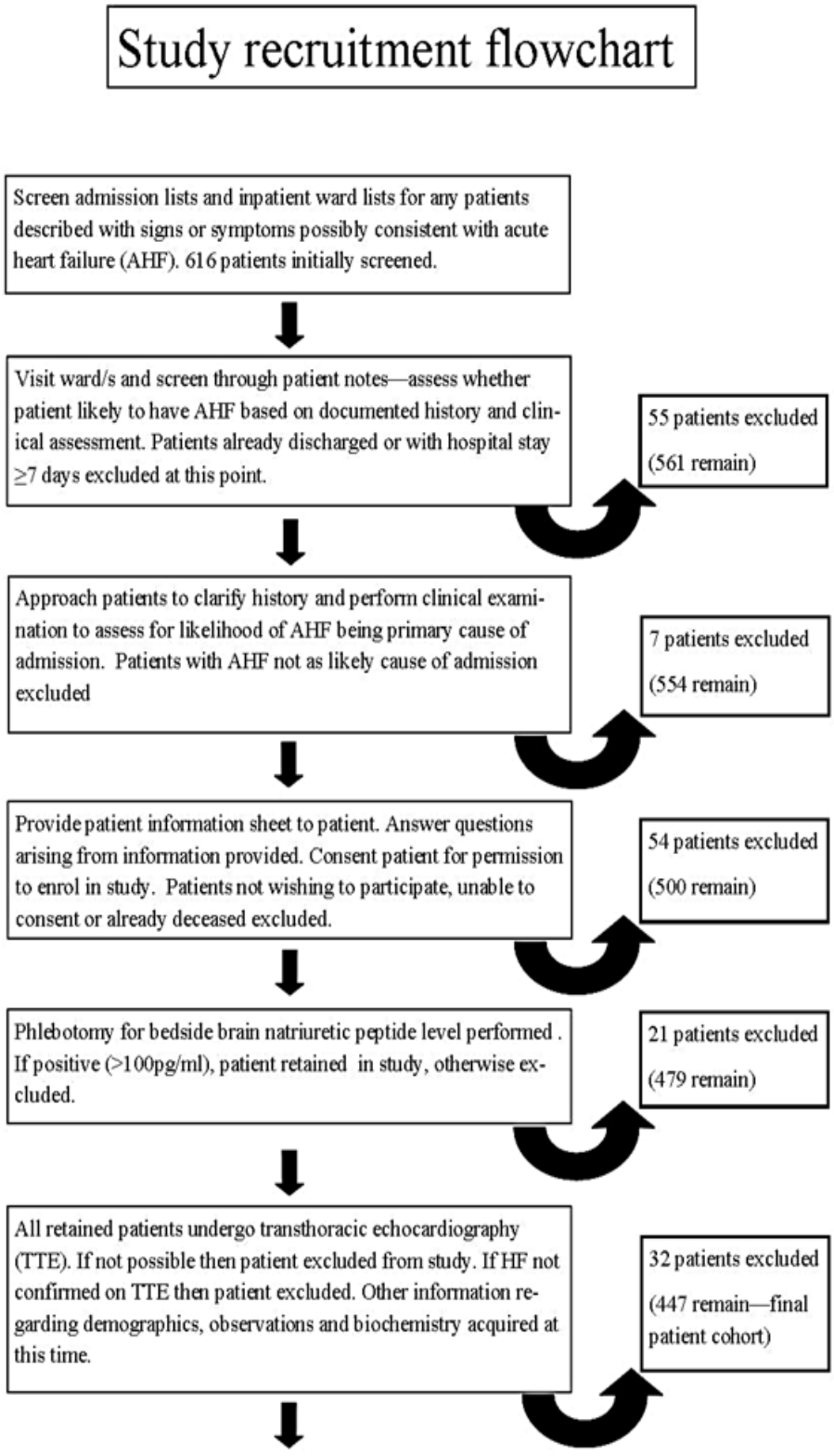
Contact Details:

Name: Dr A. Baltabaeva

Email: Aigul.Baltabaeva@asph.nhs.uk

Tel No.: 01932723534

APPENDIX 4.


Study recruitment flowchart
Screen admission lists and inpatient ward lists for any patients described with signs or symptoms possibly consistent with acute heart failure (AHF). 616 patients initially screened.
Visit ward/s and screen through patient notes—assess whether patient likely to have AHF based on documented history and clinical assessment. Patients already discharged or with hospital stay ≥7 days excluded at this point.
55 patients excluded (561 remain)
Approach patients to clarify history and perform clinical examination to assess for likelihood of AHF being primary cause of admission. Patients with AHF not as likely cause of admission excluded
7 patients excluded (554 remain)
Provide patient information sheet to patient. Answer questions arising from information provided. Consent patient for permission to enrol in study. Patients not wishing to participate, unable to consent or already deceased excluded.
54 patients excluded (500 remain)
Phlebotomy for bedside brain natriuretic peptide level performed . If positive (>100pg/ml), patient retained in study, otherwise excluded.
21 patients excluded (479 remain)
All retained patients undergo transthoracic echocardiography (TTE). If not possible then patient excluded from study. If HF not confirmed on TTE then patient excluded. Other information regarding demographics, observations and biochemistry acquired at this time.
32 patients excluded (447 remain—final patient cohort)

APPENDIX 5. Baseline characteristics and observations

	LVEF <40%	LVEF 40 - 49%	LVEF 50+%	Mild MR	Moderate MR	Moderate-Severe MR	Severe MR	Significant MR	P-value
Total number of patients	168 (40.5%)	98 (23.6%)	149 (35.9%)	253 (60.5%)	63 (15.1%)	24 (5.7%)	78 (18.7%)	165 (39.5%)	<0.0001
Mean age, years	77	80.1	79.6	78.3	81	78.2	78.3	79.3	0.393
Gender, males	104 (61.9%)	54 (55.1%)	63 (42.3%)	138 (54.5%)	36 (57.1%)	14 (58.3%)	34 (43.6%)	84 (50.9%)	0.467
BMI	27.6	28.4	28.7	29.5	27.9	28.1	25.9	27.2	0.004
BP systolic, mmHg	131	141.7	138.3	138.4	135.9	131.9	131	133	0.040
BP diastolic, mmHg	74.8	79	74.7	76	77.2	73	73.8	75	0.555
HR, bpm	92.1	88.8	87.3	89.9	90.5	96.4	85	88.7	0.660
BNP, pg/ml	1902.8	1161.4	910	1124.7	1658.4	1719.9	1789	1729.1	0.0001
Hb, g/L	125.8	118.7	121.7	123.1	122	124.5	120.4	121.6	0.492
WBC, x10^9/l	9.66	9.72	9.03	9.79	9.49	8.21	8.61	8.3	0.062
CRP mg/dL	29.9	23.8	33.1	28	29.6	32.8	33.3	31.9	0.363
eGFR, mL/min/1.73m2	47.6	49.1	48.8	49.1	48.2	48.8	45.7	47.1	0.183
CKD, number of patients	79 (47.0%)	47 (48.0%)	61 (40.9%)	116 (45.8%)	27 (42.9%)	8 (33.3%)	38 (48.7%)	73 (44.2%)	0.747
Known CAD, number of patients	75 (44.6%)	30 (30.6%)	46 (30.9%)	87 (34.4%)	28 (44.4%)	9 (37.5%)	28 (35.9%)	65 (39.4%)	0.299
HTN, number of patients	94 (56.0%)	49 (50.0%)	87 (58.4%)	143 (56.5%)	37 (58.7%)	14 (58.3%)	38 (48.7%)	89 (53.9%)	0.604
COPD, number of patients	19 (11.3%)	14 (14.3%)	27 (18.1%)	43 (17.0%)	5 (7.9%)	5 (20.8%)	8 (10.3%)	18 (10.9%)	0.085
CVA, number of patients	26 (15.5%)	11 (11.2%)	26 (17.4%)	34 (13.4%)	14 (22.2%)	7 (29.2%)	9 (11.5%)	30 (18.2%)	0.189
DM type 2, number of patients	50 (29.8%)	25 (25.5%)	52 (34.9%)	89 (35.2%)	19 (30.2%)	8 (33.3%)	14 (17.9%)	41 (24.8%)	0.026
ECG, sinus rhythm	67 (40.6%)	40 (41.7%)	55 (37.2%)	107 (42.6%)	24 (38.7%)	4 (16.7%)	28 (37.3%)	56 (34.8%)	0.112
ECG, AF	70 (42.4%)	45 (46.9%)	76 (51.4%)	107 (42.6%)	35 (56.5%)	16 (66.7%)	34 (45.3%)	85 (52.8%)	0.044
ECG, other rhythm	28 (17.0%)	11 (11.5%)	17 (11.5%)	37 (14.7%)	3 (4.8%)	4 (16.7%)	13 (17.3%)	20 (12.4%)	0.507
ECG, QRS duration, seconds	0.121	0.108	0.101	0.108	0.113	0.112	0.117	0.115	0.033

ECHO, previously performed, patients	**92 (54.8%)**	**64 (62.1%)**	**96 (59.6%)**	**161 (59.4%)**	**34 (50.7%)**	**17 (68.0%)**	**55 (65.5%)**	**106 (60.23%)**	**0.861**
Previous Cardiology review, patients	**102 (56.7%)**	**63 (61.2%)**	**89 (55.3%)**	**155 (57.2%)**	**34 (50.7%)**	**16 (64.0%)**	**50 (59.5%)**	**100 (56.8%)**	**0.934**
Cardiology review on current admission, within 24 hours/later than 24 hours, patients	**61.7% (108 in total) (94/14)**	**51.5% (50 in total) (44/6)**	**44.1% (67 in total) (57/10)**	**48.3% (131 in total) (108/17)**	**62.7% (40 in total) (35/5)**	**64.0% (15 in total) (14/1)**	**56.0% (46 in total) (39/7)**	**59.7% (102 in total) (88/13)**	**0.018**
Pulmonary oedema, patients	**1 (0.6%)**	**0 (0.0%)**	**1 (0.7%)**	**1 (0.4%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (1.3%)**	**1 (0.6%)**	**0.660**
Peripheral oedema, patients	**110 (65.5%)**	**56 (57.1%)**	**95 (63.8%)**	**166 (65.6%)**	**35 (55.6%)**	**14 (58.3%)**	**49 (62.8%)**	**98 (59.4%)**	**0.105**

APPENDIX 6. Symptoms at hospital presentation

	LVEF <40%		LVEF 40-49%		LVEF 50+ %		Mild MR		Moderate MR		Moderate-Severe MR		Severe MR		Significant MR	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Peripheral oedema, patients	110	65.5%	56	57.1%	95	63.8%	166	65.6%	35	55.6%	14	58.3%	49	62.8%	98	59.4%
Shortness of breath, patients	161	95.8%	90	91.8%	147	98.7%	243	96.0%	58	92.1%	24	100.0%	75	96.2%	157	95.2%
Palpitation, patients	15	8.9%	13	13.3%	23	15.4%	32	12.6%	5	7.9%	5	20.8%	9	11.5%	19	11.5%
Collapse, patients	3	1.8%	0	0.0%	0	0.0%	0	0.0%	1	1.6%	1	4.2%	1	1.3%	3	1.8%
Dizzy, patients	2	1.2%	1	1.0%	6	4.0%	7	2.8%	0	0.0%	1	4.2%	1	1.3%	2	1.2%
Chest Pain, patients	5	3.0%	2	2.0%	9	6.0%	13	5.1%	0	0.0%	1	4.2%	2	2.6%	3	1.8%
Orthopnea, patients	14	8.3%	10	10.2%	10	6.7%	21	8.3%	4	6.3%	2	8.3%	7	9.0%	13	7.9%
Oedema, patients	1	0.6%	0	0.0%	1	0.7%	1	0.4%	0	0.0%	0	0.0%	1	1.3%	1	0.6%
Ascites, patients	1	0.6%	0	0.0%	1	0.7%	2	0.8%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Paroxysmal nocturnal dyspnea, patients	9	5.4%	1	1.0%	5	3.4%	7	2.8%	5	7.9%	1	4.2%	2	2.6%	8	4.8%
Syncope, patients	1	0.6%	0	0.0%	1	0.7%	1	0.4%	1	1.6%	0	0.0%	0	0.0%	1	0.6%
Cough, patients	7	4.2%	5	5.1%	4	2.7%	9	3.6%	6	9.5%	1	4.2%	0	0.0%	7	4.2%
Lethargy, patients	1	0.6%	0	0.0%	0	0.0%	1	0.4%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Fatigue, patients	0	0.0%	0	0.0%	1	0.7%	0	0.0%	0	0.0%	0	0.0%	1	1.3%	1	0.6%
Claudication, patients	0	0.0%	0	0.0%	1	0.7%	0	0.0%	1	1.6%	0	0.0%	0	0.0%	1	0.6%
Decreased ET, patients	0	0.0%	0	0.0%	1	0.7%	0	0.0%	1	1.6%	0	0.0%	0	0.0%	1	0.6%
Central chest pain, patients	0	0.0%	1	1.0%	0	0.0%	1	0.4%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Confusion, patients	1	0.6%	0	0.0%	1	0.7%	1	0.4%	0	0.0%	0	0.0%	1	1.3%	1	0.6%
Reduced mobility, patients	1	0.6%	3	3.1%	1	0.7%	1	0.4%	1	1.6%	0	0.0%	3	3.8%	4	2.4%
RUQ pain, patients	1	0.6%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.3%	1	0.6%

APPENDIX 7. Cause of precipitation.

	LVEF <40%	LVEF 40 - 49%	LVEF 50+%	Mild MR	Moderate MR	Moderate-Severe MR	Severe MR	Significant MR
Acute Cardiomyopathy	0	1	0	1	0	0	0	0
Acute Ischaemia	27	11	16	33	12	1	8	22
Anaemia	1	1	1	2	0	1	0	1
Aortic and Mitral Regurgitation	0	1	0	0	0	0	1	1
Aortic Regurgitation	0	1	0	0	0	0	1	1
Aortic Stenosis	1	1	1	1	2	0	0	2
Arrhythmia	22	6	17	31	4	5	6	15
Bradyarrhythmia	1	3	6	8	0	1	1	2
Bradycardia	1	0	0	1	0	0	0	0
Cardiac Inflammation	0	0	1	1	0	0	0	0
Cardiac Tamponade	0	0	2	2	0	0	0	0
Chronic Ischaemia	9	0	7	11	3	1	1	5
Cor Pulmonale	0	1	4	5	0	0	0	0
Dilated Cardiomyopathy	1	0	0	0	0	0	1	1
Drug Reaction	0	1	0	1	0	0	0	0
Hypertension	1	1	1	2	1	0	0	1
Hypertrophic Cardiomyopathy	0	0	2	0	1	0	1	2
Infection	1	0	1	1	0	1	0	1
Lung Disease	0	0	2	2	0	0	0	0
Mechanical	5	4	0	3	1	0	5	6
Medication withdrawal	6	3	7	11	1	1	3	5
Mitral Regurgitation	1	3	3	1	0	0	6	6
Pericarditis	1	0	1	2	0	0	0	0
Pulmonary oedema	0	1	0	1	0	0	0	0
Restrictive Cardiomyopathy	0	0	1	1	0	0	0	0
Tachyarrhythmia	20	12	14	24	11	4	7	22
Tachybradyarrhythmia	2	0	1	2	0	0	1	1

Takotsubo Cardiomyopathy	**1**	**0**	**1**	**2**	**0**	**0**	**0**	**0**
Unclear	**63**	**41**	**51**	**99**	**22**	**6**	**30**	**63**
Valvular	**4**	**6**	**9**	**5**	**5**	**3**	**6**	**19**

APPENDIX 8. Cardiology review and echocardiography timing as per NICE guidelines.

	LVEF <40%		LVEF 40 - 49%		LVEF 50+%		Mild MR		Moderate MR		Moderate-Severe MR		Severe MR		Significant MR	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Group 1 - Cardiologist review within 24 hours, number of patients	94	56.0%	44	44.9%	57	38.3%	108	42.7%	35	55.6%	14	58.3%	39	50.0%	88	53.3%
Group 2A - Cardiologist review later than 24 hours, number of patients	14	8.3%	6	6.1%	10	6.7%	17	6.7%	5	7.9%	1	4.2%	7	9.0%	13	7.9%
Group 2B - Did not have cardiologist review, number of patients	60	35.7%	48	49.0%	82	55.0%	128	50.6%	23	36.5%	9	37.5%	32	41.0%	64	38.8%
Echocardiography within 48 hours, number of patients	97	57.7%	52	53.1%	82	55.0%	145	57.3%	41	65.1%	11	45.8%	35	44.9%	87	52.7%
Echocardiography later than 48 hours, number of patients	9	5.4%	5	5.1%	7	4.7%	12	4.7%	1	1.6%	4	16.7%	4	5.1%	9	5.5%
Did not have echocardiography, number of patients	62	36.9%	41	41.8%	60	40.3%	95	37.5%	21	33.3%	9	37.5%	39	50.0%	69	41.8%
Previous echocardiography	92	54.8%	59	60.2%	85	57.0%	144	56.9%	30	47.6%	16	66.7%	49	62.8%	95	57.6%
No ECHO on current admission, but had ECHO before	47	28.0%	35	35.7%	48	32.2%	75	29.6%	14	22.2%	8	33.3%	35	44.9%	57	34.5%

APPENDIX 9. Multivariable Cox-regression analysis results

Table I.1: Multivariable Cox-regression analysis (Demographics and comorbidities variables – OS at 6 months)

Predictive Variables	HR for OS	95% CI	p-value
Significant MR	1.48	[1.01, 2.16]	0.044
Gender – Male	1.05	[0.72, 1.54]	0.8
Age - Continuous	1.06	[1.04, 1.09]	<0.001
BMI - Continuous	0.97	[0.94, 1,00]	0.094
Known COPD - Yes	2.01	[1.23, 3.27]	<0.001
Known hypertension - Yes	1.24	[0.83, 1.84]	0.3
Known CKD - Yes	2.16	[1.44, 3.24]	<0.001
Known IHD - Yes	1.08	[0.73, 1.59]	0.7
Known diabetes - Yes	1.27	[0.84, 1.93]	0.3
Known Cerebrovascular disease – Yes	1.13	[0.69, 1.85]	0.6

Table I.2: Multivariable Cox-regression analysis result (Comorbidities variables – OS at 6 months)

Predictive variables	HR for OS	95% CI	p-value
Significant MR	1.58	[1.09, 2.30]	0.017
Known COPD - Yes	1.85	[1.15, 2.96]	0.011
Known Hypertension - Yes	1.28	[0.87, 1.90]	0.2
Known CKD - Yes	2.50	[1.67, 3.74]	<0.001
Known IHD - Yes	1.04	[0.71, 1.53]	0.8
Known Diabetes - Yes	1.00	[0.67, 1.49]	>0.9
Known Cerebrovascular disease – Yes	1.13	[0.70, 1.85]	0.6

Table I.3: Multivariable Cox-regression analysis result (MR, Age, COPD and CKD – OS at 6 months)

Predictive Variables	HR for OS	95% CI	p-value
Significant MR	1.49	1.03, 2.16	0.036
Age - Continuous	1.07	1.04, 1.09	<0.001
Known COPD - Yes	1.88	1.17, 3.01	0.009
Known CKD - Yes	2.28	1.54, 3.37	<0.001

Table I.4 Multivariable Cox-regression analysis of MR defined by ERO/LVEDV > 0·14 cm^2/ml

Predictive Variables	HR for OS	95% CI	p-value
ERO to LVEDV Ratio (Ratio > 0·14cm^2/ml)	1·54	[1·02, 2·34]	0·042
Gender - Male	1·04	[0·96, 0·72]	0·824
Age - Continuous	1·06	[1·03, 1·09]	<0·001
BMI - Continuous	0·99	[0·96, 1·02]	0·62
Known COPD - Yes	1·72	[1·07, 2·75]	0·024
Known hypertension -Yes	1·21	[0·83, 1·75]	0·326
Known CKD - Yes	1·81	[1·24, 2·63]	0·002
Known IHD - Yes	1·20	[0·83, 1·74]	0·329
Known diabetes - Yes	1·08	[0·71, 1·63]	0·723
Known Cerebrovascular disease - Yes	0·74	[0·43, 1·27]	0·275

APPENDIX 10. Adjusted survival curves at 6 months – 3 scenarios

Figure 1: Adjusted Survival curves at 6 months for Mild MR vs Significant MR.

Scenario 1. Multivariable Cox-regression with MR as main risk factor and adjusted for all the demographics and comorbidities variables.

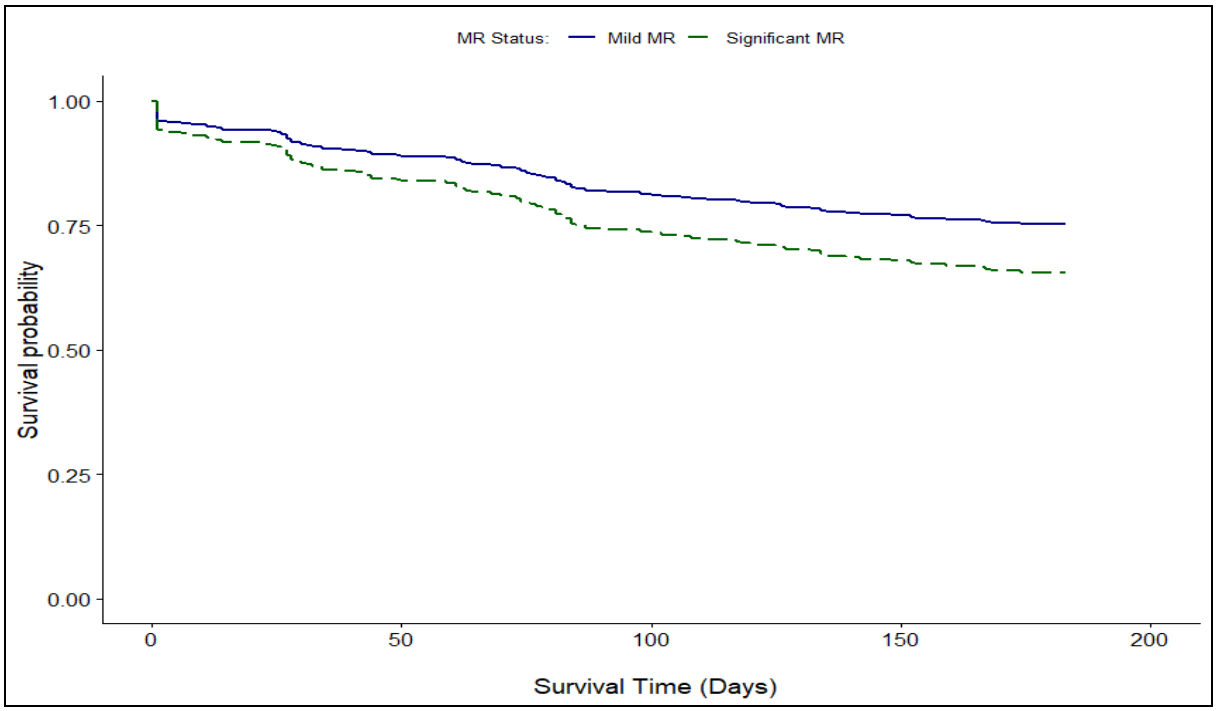


Figure 2: Adjusted Survival curves at 6 months for Mild MR vs Significant MR.

Scenario 2. Multivariable Cox-regression with MR as main risk factor and adjusted for comorbidities variables only.

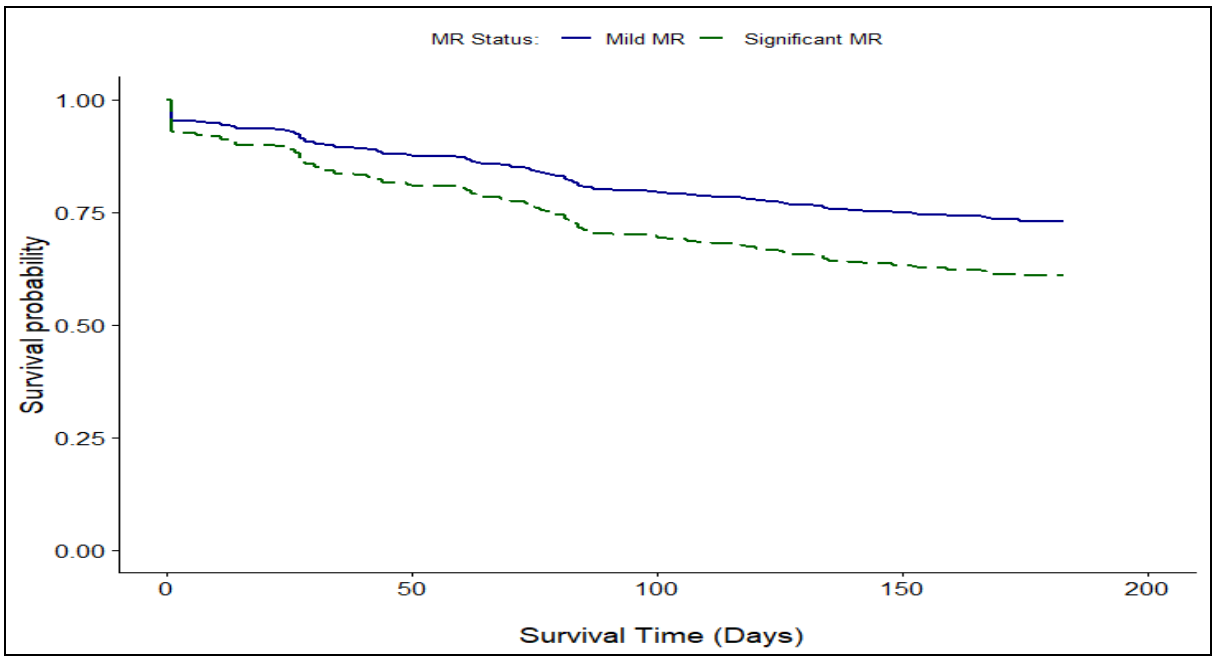
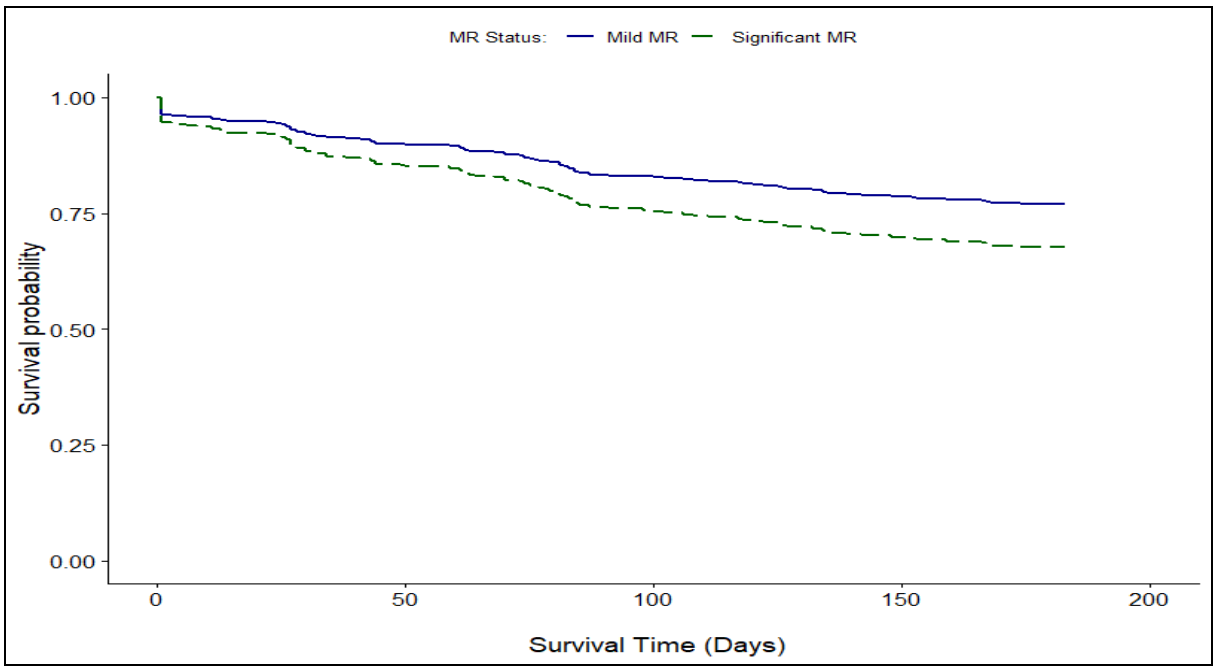


Figure 3: Adjusted Survival curves at 6 months for Mild MR vs Significant MR

Scenario 3. Multivariable Cox-regression with MR as main risk factor and adjusted for all the variables that show a statistical significance at 0.05 in scenarios 1 and/or 2.



APPENDIX 11.

Kaplan-Meier survival analysis

Survival time	Survival_6_12
Endpoint	Censor_6_months
Factor codes	Known_MR

Cases summary

Factor	Number of events [a]		Number censored [b]		Total sample size
	N	%	N	%	
MR not previously diagnosed	55	22.92	185	77.08	240
MR previously diagnosed	57	32.02	121	67.98	178
Overall	112	26.79	306	73.21	418

[a] Censor_6_months = 0
[b] Censor_6_months = 1

Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
MR not previously diagnosed	154.056	3.705	146.794 to 161.317	-	
MR previously diagnosed	145.251	4.690	136.058 to 154.444	-	
Overall	150.308	2.926	144.574 to 156.042	-	

Survival table [Show]

Comparison of survival curves (Logrank test)

Chi-squared	4.0332
DF	1
Significance	P = 0.0446

Hazard ratios[a] with 95% Confidence Interval

Factor	MR not previously diagnosed	MR previously diagnosed
MR not previously diagnosed	-	1.4725 1.0093 to 2.1481
MR previously diagnosed	0.6791 0.4655 to 0.9907	-

[a] Column/Row