# Mitral Regurgitation in Heart Failure:

# Burden, Treatment Options and Outcomes

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# Mitral Regurgitation in Heart Failure:

# Burden, Treatment Options and Outcomes

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# KEY WORDS

Mitral valve, mitral insufficiency, mitral regurgitation, heart failure, acute heart failure, transcatheter mitral valve repair, percutaneous mitral valve intervention, edge to edge repair, transthoracic echocardiography, echo, echocardiogram, transoesophageal echocardiography, primary mitral regurgitation, secondary mitral regurgitation, degenerative mitral regurgitation, functional mitral regurgitation, left ventricular systolic dysfunction, ejection fraction, heart failure with reduced ejection fraction, breathlessness, oedema, functional testing, six minute walk test, stress echocardiography.

# THESIS ABSTRACT

Heart failure (HF) affects an estimated 900 000 people within the United Kingdom (UK), resulting in approximately 60 000 hospital admissions each year (1). Mortality at one year is estimated at as high as 40%, with the risk of death rising with age (1). A common consequence of HF is mitral regurgitation (MR).

MR is one of the most common valvular lesions worldwide. The prevalence within Europe is estimated at 4 million making MR the second most common valve lesion requiring surgery (2, 3). By nature of the disease, severity also worsens with advancing age, and as such by 2030, prevalence is expected to more than double (4).

MR in HF can occur as a consequence of organic leaflet disruption (primary MR) or secondary to annular dilation (secondary MR), with both mechanisms ultimately resulting in geometric changes to the left atrium (LA) and left ventricle (LV), and concomitant symptoms. HF is commonly seen in patients with chronic long standing MR and also those who present in the acute setting. Patients with symptomatic primary MR typically undergo surgery which offers a survival benefit. Recommended treatment options for patients with secondary MR and symptoms focus on the optimisation of medical therapy, cardiac resynchronisation therapy and conventional open heart surgery. However more recently, transcatheter mitral valve repair (TMVR) has been recognised as a novel technique for MR patients with a high surgical risk and multiple

comorbidities, LV systolic dysfunction, and persistent symptoms despite optimal medical therapy (OMT). Currently, there remains a dearth of information regarding the number of HF patients with MR, and the proportion of these patients who despite OMT remain symptomatic with MR and an LV ejection fraction (EF) <50%. Additionally whether or not these individuals meet suitability criteria for TMVR, and the effectiveness of TMVR in reducing the degree of MR, improving symptoms and quality of life is largely unknown.

This thesis therefore aimed to identify the prevalence of MR within the HF population as well as assess the degree of change as a result of OMT. It also investigated the population considered eligible for TMVR based on risk and echocardiography criteria. The thesis then focussed on using current literature and a systematic review to identify predictors of outcomes for patients who have undergone TMVR. Employing these findings, the project then prospectively assessed the usefulness of predictors in relation to quality of life and symptoms.

The thesis concludes that one fifth of all patients presenting with HF have moderate or more MR and that patients with moderate or more MR have a greater risk of mortality. Patients who received OMT do see an element of relief from symptoms and a proportion also experience a reduction in the severity of MR. However, one half of patients with LV systolic dysfunction and MR still remain symptomatic despite OMT. When further evaluating the risk status for these patients, the thesis determines that a significant number of these patients are eligible for TMVR based on echocardiographic and risk criteria.

From a functional assessment perspective, the results of a systematic review demonstrated that six minute walk test (6MWT) may be predictive of outcome for patients who undergo TMVR. Exercise stress echocardiography may also play a role in determining patients with early stage exercise induced severe MR.

The prospective study, although limited, demonstrated variation in quality of life and echocardiography outcomes across the recruited population of eight patients. Further recruitment is needed prior to the provision of more solid conclusions.

More broadly, these findings suggest the burden of MR within the HF population is significant and although medical optimisation can assist in reducing the degree of MR and symptoms, a portion of high risk patients with LV systolic dysfunction remain symptomatic and should be considered for TMVR eligibility assessment. The thesis findings suggest that when identifying patients who have the potential for improvement with MV intervention, the value of 6MWT distance, exercise stress echo, LV volume, the LV/MR ratio, and the degree of LA dilation should be assessed and examined. Further studies should also focus on clarifying recommendations for TMVR in a variety of clinical settings.

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LVESD: left ventricular end systolic dimension; GLS: global longitudinal strain; TDI: tissue Doppler imaging; VTI: velocity time integral; AV: aortic valve; SV: stroke volume; CO: cardiac output; PW: pulsed wave; LA: left atrium; RA: right atrium; RWMAs: regional wall motion abnormalities; RV: right ventricle; PASP: pulmonary artery systolic pressure; NYHA: New York heart association, EPR: electronic patient record; HR: heart rate; LVH: left ventricular hypertrophy; MI: myocardial infarction; BP: blood pressure; $O_2$: oxygen; BMI: body mass index; BSA: body surface area; NT-pro BNP: N-terminal pro B-type natriuretic peptide; CRP: C-reactive protein: eGFR: estimated glomerular filtration rate.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| 2D | Two dimensional |
| 3D | Three dimensional |
| 6MWT | Six minute walk test |
| ACEI | Angiotensin-converting-enzyme inhibitors |
| ACS | Acute coronary syndrome |
| AF | Atrial fibrillation |
| AHF | Acute heart failure |
| ARB | Angiotensin receptor blocker |
| BSA | Body surface area |
| BMI | Body mass index |
| BP | Blood pressure |
| CAD | Coronary artery disease |
| CFI | Colour flow imaging |
| CMR | Cardiac magnetic resonance |
| CI | Chief investigator |
| COAPT | Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation |
| COPD | Chronic obstructive pulmonary disease |
| CPET | Cardiopulmonary exercise test |
| CRP | C-reactive protein |

| | |
|---|---|
| CRT | Cardiac resynchronisation therapy |
| CT | Computed tomography |
| CVIS | Cardiovascular information systems |
| DM | Diabetes mellitus |
| D | Diameter |
| ECG | Electrocardiogram |
| ECHO | Echocardiography |
| EF | Ejection fraction |
| EF1 | First phase ejection fraction |
| eGFR | estimated glomerular filtration rate |
| EPR | Electronic patient record |
| EROA | Effective regurgitant orifice area |
| ESE | Exercise stress echocardiogram |
| FAC | Fractional area change |
| F/U | Follow up |
| GDMT | Guideline directed medical therapy |
| GLS | Global longitudinal strain |
| GSTT | Guy's and St Thomas' NHS Foundation Trust |
| HCM | Hypertrophic cardiomyopathy |
| 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 |
| HSST | Higher specialist scientist training |

| | |
|---|---|
| ICF | Informed consent form |
| ICD | Implantable cardioverter-defibrillator |
| IHD | Ischaemic heart disease |
| IT | Information technology |
| JVP | Jugular venous pressure |
| KCH | King's College NHS Foundation Trust |
| LA | Left atrium |
| LAE | Left atrial enlargement |
| LAD | Left atrial dimension |
| LAV | Left atrial volume |
| LAVi | Left atrial volume indexed |
| LBBB | Left bundle branch block |
| LOS | Length of stay |
| LV | Left ventricle |
| LVOT | Left ventricular outflow tract |
| LVEDD | Left ventricular end diastolic dimension |
| LVEDV | Left ventricular end diastolic volume |
| LVEDVi | Left ventricular end diastolic volume indexed |
| LVEF | Left ventricular ejection fraction |
| LVESD | Left ventricular end systolic dimension |
| LVESV | Left ventricular end systolic volume |
| LVESVi | Left ventricular end systolic volume indexed |
| LVH | Left ventricular hypertrophy |
| LVSD | Left ventricular systolic dysfunction |

| | |
|---|---|
| MMU | Manchester Metropolitan University |
| MI | Myocardial infarction |
| MITRA-FR | Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation |
| MR | Mitral regurgitation |
| MRA | Mineralocorticoid receptor antagonists |
| MS | Mitral stenosis |
| MV | Mitral valve |
| MVA | Mitral valve area |
| MVR | Mitral valve replacement |
| N/A | Not applicable |
| NT-pro BNP | N-terminal pro B-type natriuretic peptide |
| NYHA | New York Heart association |
| $O_2$ | Oxygen |
| OMT | Optimal medical therapy |
| PASP | Pulmonary artery systolic pressure |
| PI | Principal investigator |
| PISA | Proximal isovelocity surface area |
| PM | Pacemaker |
| PMVI | Percutaneous mitral valve intervention |
| PND | Paroxysmal nocturnal dyspnoea |
| QoL | Quality of life |
| RCM | Restrictive cardiomyopathy |
| RCT | Randomised controlled trial |

| | |
|---|---|
| REC | Research ethics committee |
| RV | Right ventricle |
| RVol | Regurgitant volume |
| RV TDI S’ | Right ventricular tissue Doppler imaging S’ wave |
| SV | Stroke volume |
| TAPSE | Tricuspid annular plane systolic excursion |
| TAVI | Transcatheter aortic valve implantation |
| TDI | Tissue Doppler imaging |
| TR | Tricuspid regurgitation |
| TMVR | Transcatheter mitral valve repair |
| TOE | Transoesophageal echocardiography |
| TTE | Transthoracic echocardiography |
| VC | Vena contracta |
| UK | United Kingdom |
| USA | United States of America |

# DECLARATION BY THE CANDIDATE

I declare that this thesis is all my own work and has not been copied from any other sources, or accepted for any other degree in any University. To the best of my knowledge, this thesis contains no material written or distributed previously by any other parties, apart from where I have otherwise stated.

# ABSTRACTS AND PUBLICATIONS ARISING FROM THIS THESIS

## Abstracts

**EuroPCR 2020**

Victor K., Stylianidis V., Bangash F., Hancock J., Monaghan M., Byrne J., Redwood S., McDonagh T., Carr-White G., Prendergast B. (2020). Mitral regurgitation in acute heart failure: under-appreciated, under-treated and under-resourced.

**EuroCongress 2020**

Victor K., Bangash F., Stylianidis V., Hancock J., Monaghan M., Piper S., Byrne J., McDowell G., Redwood S., McDonagh T., Prendergast B., Carr-White G. (2020). Acute heart failure: what is the burden of mitral regurgitation?

**British Cardiovascular Society 2020**

Victor K., Bangash F., Stylianidis V., Hancock J., Monaghan M., Piper S., Byrne J., McDowell G., Redwood S., McDonagh T., Prendergast B., Carr-White G. (2020). Mitral regurgitation in acute heart failure: prevalence and response to treatment.

**British Society of Echocardiography 2020**

Victor K., Hammond-Haley M., Cirillo C., Georgiopoulos G., Hancock J., McDowell G., Monaghan M., Prendergast B. (2020) Transcatheter mitral valve repair and the role of functional testing: a systematic review.

**British Society of Echocardiography 2020**

Victor K., Bangash F., Stylianidis V., Hancock J., Monaghan M., Piper S., Byrne J., McDowell G., Redwood S., McDonagh T., Prendergast B., Carr-White G. (2020). A London based study of acute heart failure: what is the burden of mitral regurgitation?

**British Society of Echocardiography 2020**

Victor K., Stylianidis V., Bangash F., Hancock J., Monaghan M., Byrne J., Redwood S., McDonagh T., Carr-White G., Prendergast B. (2020). Mitral regurgitation in acute heart failure: under-appreciated, under-treated and under-resourced.

# Publications

Victor K., Hammond-Haley M., Cirillo C., Georgiopoulos G., Hancock J., McDowell G., Monaghan M., Prendergast B. (2021) Transcatheter mitral valve repair and the role of functional testing: a systematic review (in preparation).

Victor K., Stylianidis, V., Bangash F., Hancock J., Monaghan M., Byrne J., Redwood S., McDonagh T., Carr-White G., Prendergast B. (2021). Mitral regurgitation in acute heart failure: under-appreciated, under-treated and under-resourced (in preparation).

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To my friends and family, all those promises of catching up after it is all over are about to come to fruition..…… and thank you.

# CHAPTER 1

# INTRODUCTION

## 1.1 Subject Overview

Heart failure (HF) is a complex clinical syndrome characterised by inability of the heart to pump adequate blood volume around the body (1). It affects an estimated 26 million worldwide and is considered a serious disease, often associated with multiple and frequent hospital admissions and a poor prognosis. Mortality rates are high with 40% of newly diagnosed patients dying within one year (1).

A recurrent feature of HF is concomitant mitral regurgitation (MR), which is one of the most common valvular heart abnormalities with a European prevalence exceeding 4 million and an annual mortality of 5% in the absence of interventional treatment (2-4). In light of this, and in addition to an ageing population, it is not surprising that HF with MR is now viewed as a growing global health concern.

MR can occur as a result of both degenerative changes to the valve leaflets (primary) or as a consequence of changes in the geometry of the left ventricle (LV) (secondary).

Regardless of the underlying aetiology, left untreated, severe MR ultimately leads to reduced cardiac output, often accompanied by symptoms of breathlessness, arrhythmia, oedema and reduced exercise tolerance. However, international guidance for the medical and surgical management of patients with primary versus secondary MR differs considerably.

Treatment options for HF patients with secondary MR include optimisation of medical therapy (OMT), cardiac resynchronisation therapy (CRT) and conventional mitral valve (MV) surgery (although for those patients who experience no improvement in the severity of MR or symptoms with medicines and CRT, conventional MV surgery is not always feasible due to prohibitive surgical risk). Fortunately, transcatheter mitral valve repair (TMVR) presents a novel and viable therapeutic option for symptomatic patients with multiple comorbidities and left ventricular (LV) systolic dysfunction who are considered a high surgical risk.

To date, there remains uncertainty regarding the prevalence of MR within the HF population. Additionally, the degree to which there is an improvement in MR severity and symptoms in response to treatment is largely unknown. Furthermore, there remains debate regarding the benefit of TMVR in relation to symptoms, quality of life and long term prognosis.

## 1.2 Thesis Overview

This thesis is in the style of a traditional thesis by monograph with eight chapters, divided into sections and subsections.

**Chapter 2** introduces the topics of HF and MR. It provides a background to the subject and discusses the diagnostic benefit of cardiac imaging, functional testing and biomarkers, and outlines the current treatment options. It also presents a comprehensive literature review focusing on the role of TMVR in relation to outcomes and mortality. This literature review provides the background information necessary for the development of the methodological component of the thesis which is designed to answer the research question. Chapter 2 ends with an outline of the thesis aims and objectives, and provides an impact statement.

**Chapter 3** focuses on assessing the prevalence of patients admitted with HF who have moderate or more MR. It investigates variations in LV systolic function, concomitant comorbidities, and mortality across the population. The impact of OMT on MR, ejection fraction (EF) and symptoms is also examined.

**Chapter 4** determines the number of high-risk patients with moderate or more MR, an EF 20-50% and symptoms, despite OMT. This allows for predictions in relation to the exact number of patients potentially eligible for TMVR on a local and population level in accordance with current international guidelines.

**Chapter 5** provides a systematic review and meta-analysis focussed on the usefulness of TMVR for symptomatic patients with HF and MR, and the role of functional testing in relation to predicting outcomes. It presents informed conclusions, suggesting the application of six minute walk tests and exercise stress echo in future research studies.

**Chapter 6** uses a prospective pilot study approach to examine changes in symptoms, quality of life, and echocardiographic parameters following TMVR. This chapter also aims to investigate the usefulness of functional testing and biomarkers in predicting changes in LV performance. Unfortunately this project work was limited by the consequences of the Covid-19 pandemic which affected recruitment and follow up. The chapter discusses the limitations and concludes with important considerations in relation to symptomatic improvement, and parameters useful in the selection of TMVR candidates.

**Chapters 7 and 8** provide a concluding overall discussion with a focus on important questions that arose throughout the research. The chapters discuss breaking theories and concepts in relation to the application of TMVR. Additionally, the chapters promote rethinking our current ways of work, with suggestions for possible future clinical applications and research.

Prof Bernard Prendergast at Guy's and St Thomas' NHS Foundation Trust (GSTT), London, United Kingdom (UK) and Dr Garry McDowell at Manchester Metropolitan University (MMU), Manchester, UK, have overseen all components of the research

project. Prof Mark Monaghan (King's College Hospital, London, UK) and Dr Jane Hancock (GSTT, London, UK) have been additional external onsite associate supervisors. Dr Fiona Wilkinson (MMU, Manchester, UK) provided assistance with the thesis writing process.

# CHAPTER 2

# ACUTE HEART FAILURE AND MITRAL REGURGITATION: A BACKGROUND AND LITERATURE REVIEW

## 2.1 Acute Heart Failure

Acute heart failure (AHF) is a complex yet common syndrome. Patients most frequently present with symptoms of breathlessness, fatigue and reduced exercise tolerance (1). Affiliated signs of heart failure (HF) may include oedema, tachycardia, elevated jugular venous pressure (JVP) and ascites. In addition, patients experience a change in heart anatomy and volume, and the ability of the heart to eject sufficient forward stroke volume (SV) becomes impaired.

A HF diagnosis is formally defined by the presence of signs and symptoms caused by inadequate pump function of the heart which is likely to result in reduced longevity (5).

### 2.1.3 Aetiology and pathophysiology of HF

HF occurs due to a decrease in the number of functional myocardial cells as a consequence of heart injury (6). The cause of the injury can be isolated or multifactorial. Worldwide, the most frequent causes of HF include ischaemic heart disease (IHD), diabetes and hypertension, with the latter condition doubling the risk of HF development compared to the normotensive patient (7). Within the United Kingdom (UK), atrial fibrillation (AF), and valve disease are also considered common triggers. Less often, HF may occur as a consequence of cardiomyopathies, pericardial disease, infections, or toxins.

There are a number of compensatory mechanisms that occur as part of the HF sequalae. This includes activation at a structural, cellular and molecular level. In the first instance, the heart attempts to increase cardiac output via the Frank-Starling mechanism, with ventricular volumes and wall thickness increasing in response to ventricular remodelling (6, 8). This occurs on a macro level, with structural changes in the myocardial architecture resulting in adaptations to the geometry of the elliptical left ventricular (LV) chamber (9). Classifications in relation to remodelling have been defined as concentric, eccentric and combined, with eccentric and combined more associated with dilated cardiomyopathies, mitral regurgitation (MR) and IHD (Figure 2.1). Tissue perfusion is maintained through the activation of neurohormonal systems. Increased vascular tone and autonomic activity assist in delaying decompensation (8). This multifactorial network of adaptations provides an initial benefit in the early stages of HF, successfully maintaining physiological functioning. Yet despite these attempts,

these changes lead to additional signs and symptoms in the long-term and a vicious cycle of worsening and progressive HF.

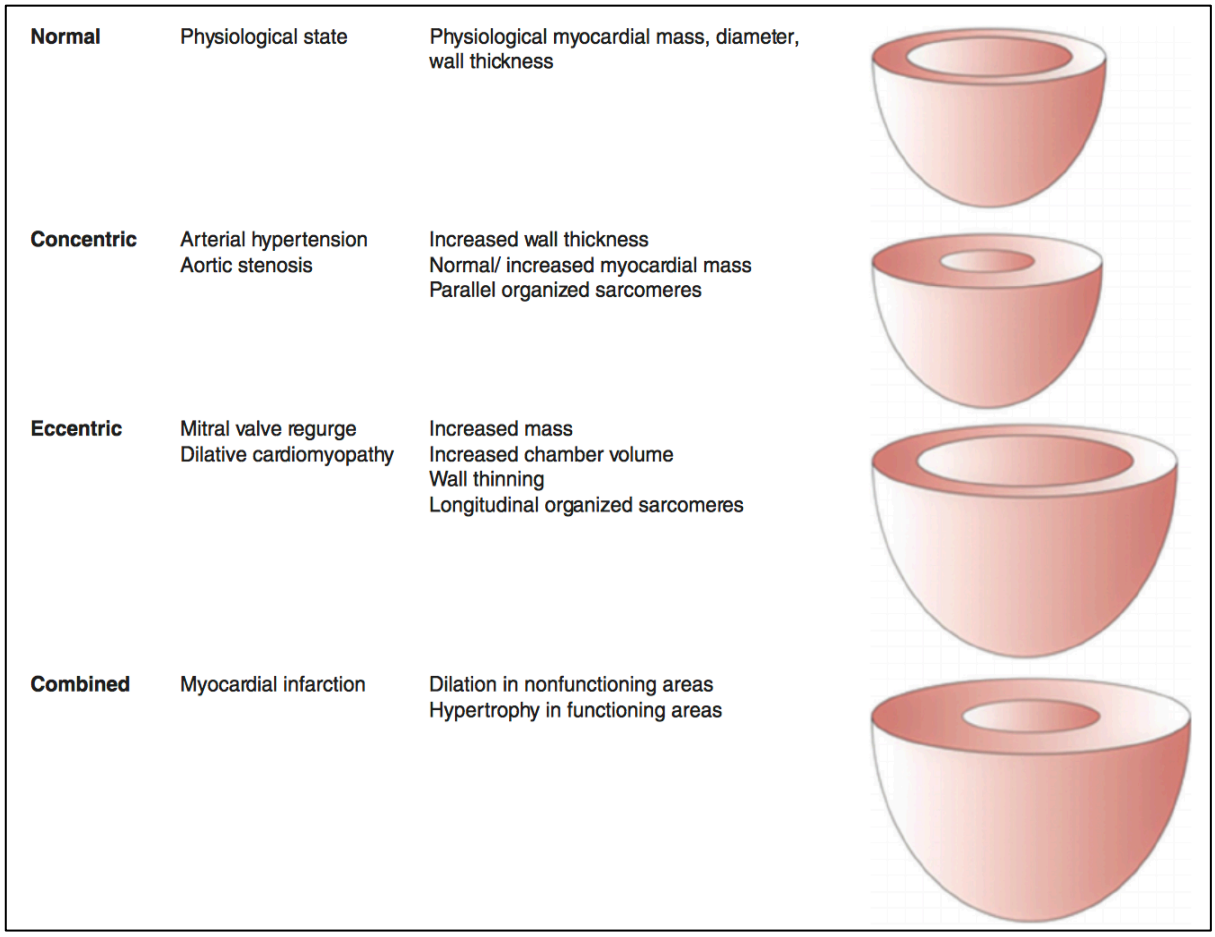


**Figure 2.1.** Pathophysiology of heart failure (HF): structural changes in the geometry of the left ventricle occur as a component of compensatory mechanisms in the setting of HF. This figure outlines a normal response followed by a concentric response as well as an eccentric and combined response (more commonly seen in mitral regurgitation, dilated cardiomyopathies and ischaemic heart disease). Taken from Tanai and Frantz (8).

### 2.1.2 Clinical manifestations of HF

Patients with HF can be broken down into two broad groups: those with preserved ejection fraction (HFpEF) and those with reduced ejection fraction (HFrEF). HFrEF is defined by impaired left ventricular systolic function and a reduced ejection fraction (EF). By contrast, diastolic HF (HFpEF) results as a consequence of impaired ventricular relaxation and filling, increased stiffness of the ventricle, and raised filling pressures, yet systolic function and EF remain preserved. Cut points defining those with impaired versus preserved EF vary between guidelines. According to the 2016 European guideline, HFrEF encompasses patients with an EF <40% (10). Those with an EF >50% are considered amongst the HFpEF category. However, this leaves a grey area for those with an EF >40-49% which has subsequently been defined as heart failure with mid-range ejection fraction (HFmrEF) (10). Despite its prevalence, HF can be complicated, with no one single marker capable of diagnosing HF in isolation. It is important therefore to note that the diagnosis and categorisation of HF are not based on EF alone. The presence of signs and symptoms, raised natriuretic peptides, and manifestations of structural heart disease, such as left ventricular hypertrophy (LVH) and left atrial (LA) enlargement, all play a fundamental role in determining diagnosis (Table 2.1). Ensuring accurate classification and differentiation of the types of HF is essential due to distinctive aetiologies and co-morbidities but most importantly due to their impact in forecasting responses to therapies and predicting prognosis. In the UK, 66% of patients admitted to hospital have HFrEF (1).

**Table 2.1.** Definition of heart failure according to the European 2016 heart failure guideline with criteria for the subclassifications of heart failure (10). Abbreviations: HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; LAE: left atrial enlargement. N/A: not applicable. [b]BNP >35pg/ml and/or NT-pro BNP >125pg/mL.

| Type of HF | | HFrEF | HFmrEF | HFpEF |
|---|---|---|---|---|
| **Criteria** | **1** | Symptoms ± Signs | Symptoms ± Signs | Symptoms ± Signs |
| | **2** | LVEF <40% | LVEF 40-49% | LVEF ≥50% |
| | **3** | N/A | 1. Elevated levels of natriuretic peptides[b]<br>2. At least one additional imaging criterion:<br>a) relevant structural heart disease (LVH and/or LAE)<br>b) diastolic dysfunction | 1. Elevated levels of natriuretic peptides[b]<br>2. At least one additional imaging criterion:<br>a) relevant structural heart disease (LVH and/or LAE)<br>b) diastolic dysfunction |

### 2.1.3 Prevalence, incidence and mortality

Having reached epidemic proportions, HF has now become recognised as a public health concern. Current data suggest that HF affects an estimated 900 000 people within the UK and 26 million people worldwide (11). In the year preceding March 2018 there were approximately 56 000 hospital admissions in England with a primary diagnosis of HF (1, 11). This compares to around 51 000 in 2014. Other UK based

studies estimate new HF diagnoses progressively climbing by 20 000 over the last 12 years (12). However, incidence rates from small studies in 2014 sit at 330 persons per 100 000 suggesting no large incremental increase (12). In light of a proposed reasonably steady rate of incidence, the increased prevalence is likely to be a consequence of an aging population and improved HF survival due to advanced therapies. It may also be related to behavioural changes and prevention programmes focussed on seeking earlier medical attention in acute coronary syndromes (ACS) and reduced rates of smoking. Despite this, projections are worrisome with prevalence expected to rise by 46% by 2030 (11).

The median age for patients admitted with HF in the UK is approximately 80 years, with women slightly higher and men slightly lower (Figure 2.2). It is well recognised that HF is more prevalent in the aging population. On average, there are more men across all age categories other than >85 years (where women are in the majority). In addition, patients with multiple comorbidities including (but not limited to) obesity, diabetes, hypertension, and also those who are considered socio-economically deprived are more likely to develop HF (12). This is the case on a global scale with likely culprits being limited access to healthcare, education in prevention, and dietary habits. There remains, however, a lack of public health data in relation to disease incidence at population level, with some reports documenting an increase in the incidence of HFpEF (13). As such, conclusions regarding total burden and future resource planning can only be based on limited evidence (which may not be representative of the population).

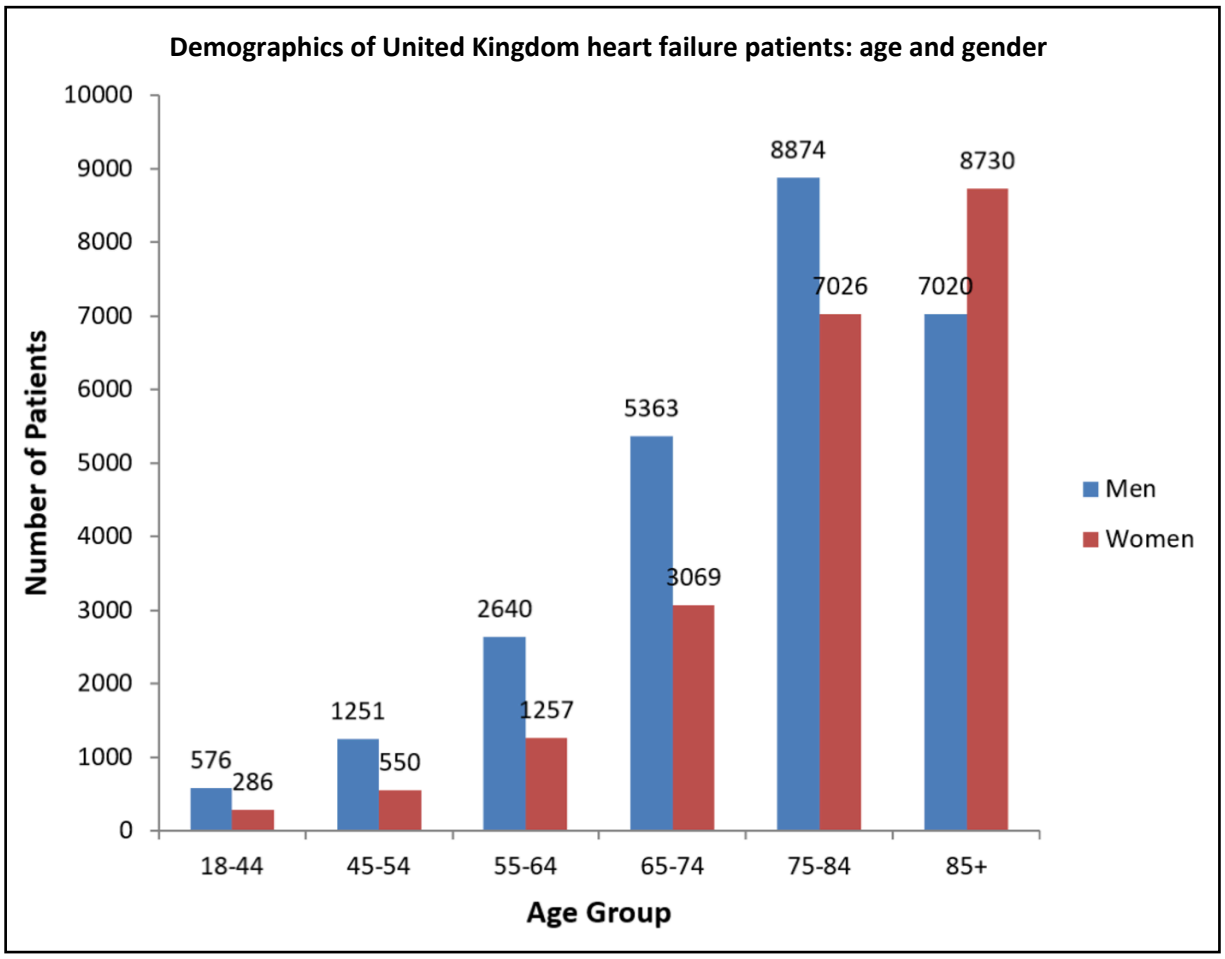


**Figure 2.2.** Characteristics of United Kingdom (UK) heart failure (HF) patients at first HF admission: age and gender demographics. Taken from: NICOR Heart Failure Audit: 2019 Summary Report (1).

Nationally, in-patient mortality for patients with a HF hospital admission is estimated at around 10%. The 1-year mortality for patients after a HF admission remains high at 32% (2017/2018) (1). The quoted 1-year mortality for Europe has been estimated at between 6-24% depending on acute versus chronic HF (14). In the United States of America (US), this was sub-categorised according to the degree of HF and ranged between 35-37% (15). The UK mean length of stay (LOS) for patients with HF ranges depending on the level of care provided, with patients seen within cardiology often staying longer in hospital compared with those cared for within general medicine (9 vs

6 days) (1). This is likely a result of more severe cases within cardiology who may also require initiation and implementation of medical and device therapies. For those patients who survive, their quality of life (QoL) can be poor. Although varying across the HF population, the literature suggests that a diagnosis of HF has a greater impact on QoL compared with many other chronic diseases (including arthritis and chronic lung disease), and a greater influence on mental health than depression (16).

## 2.2 Mitral Regurgitation in Acute Heart Failure

Mitral regurgitation (MR) is a widespread problem affecting approximately 10% of the UK population, increasing with age to approximately 20% in those >65 years (17, 18). It can present in two forms, either 'primary' or 'secondary' (18). Left untreated, both forms may lead to HF as a consequence of ventricular remodelling and changes in chordal and valve anatomy. Unfortunately for patients with HF, concomitant MR contributes to a poor prognosis, frequent hospitalisations, and higher rates of mortality (19).

### 2.2.1 Anatomy of the mitral valve

The mitral valve (MV) comprises two leaflets, the posterior and anterior. Both leaflets are of similar area with noticeable differences in structure. The posterior leaflet is narrower and extends approximately two thirds around the length of the left atrioventricular junction. By contrast, the anterior leaflet is much broader and shorter,

encompassing the remaining one third of the junction. Each leaflet is divided by clefts into three scallops (commonly labelled P1, P2, P3 and A1, A2 and A3) that meet at an anterior or posterior commissure (Figure 2.3). Leaflets and scallops are supported by an annulus, chordae tendineae and papillary muscles. The annulus is located at the junction between the LV and LA and provides attachment for the MV. The fan shaped tendinous chords attach to the leaflets either on the free edge, the ventricular surface or the basal region of the posterior leaflet. At the other end, the chords attach directly to the papillary muscles (typically two papillary muscles in the anterolateral and posteromedial positions) within the mid to apical left ventricular wall. There are anatomical variations in the position and number of papillary muscles (20).

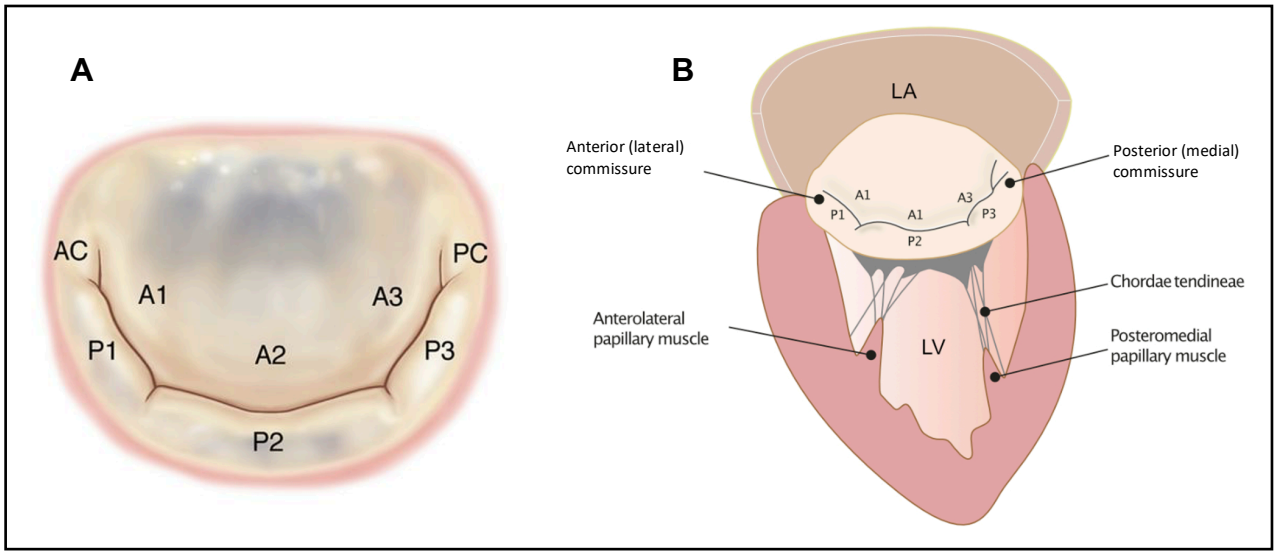


**Figure 2.3.** Anatomy of the mitral valve. A: En face image of the mitral valve which denotes the middle scallop of the posterior leaflet as P2, with P1 lateral and P3 medial. The opposing segments of the anterior leaflet are designated as A1, A2, and A3. AC and PC represent the anterolateral and posteromedial commissures. Taken from: Stone *et al* (21). B: Anatomy of the mitral valve and mitral apparatus including the papillary muscles and chordae tendineae in long axis view. Taken from: Clinical Echocardiography (22). Abbreviations: LA: left atrium; LV: left ventricle.

### 2.2.2 Mechanisms of mitral regurgitation

Mechanisms of MR can be categorised as primary and secondary (also commonly referred to as degenerative and functional respectively). Primary MR occurs where there is a structural or degenerative abnormality with the MV leaflets, chordae tendineae, papillary muscles or MV annulus. Secondary or functional MR occurs in the absence of an organic valve abnormality but in the presence of LV dysfunction. More recent studies also acknowledge the role of LA dilation, annular dilation and AF in the setting of secondary MR (23). Further explanation regarding secondary (functional) MR is outlined below. Categories for MR aetiology are based on the Carpentier classification (Figure 2.4).

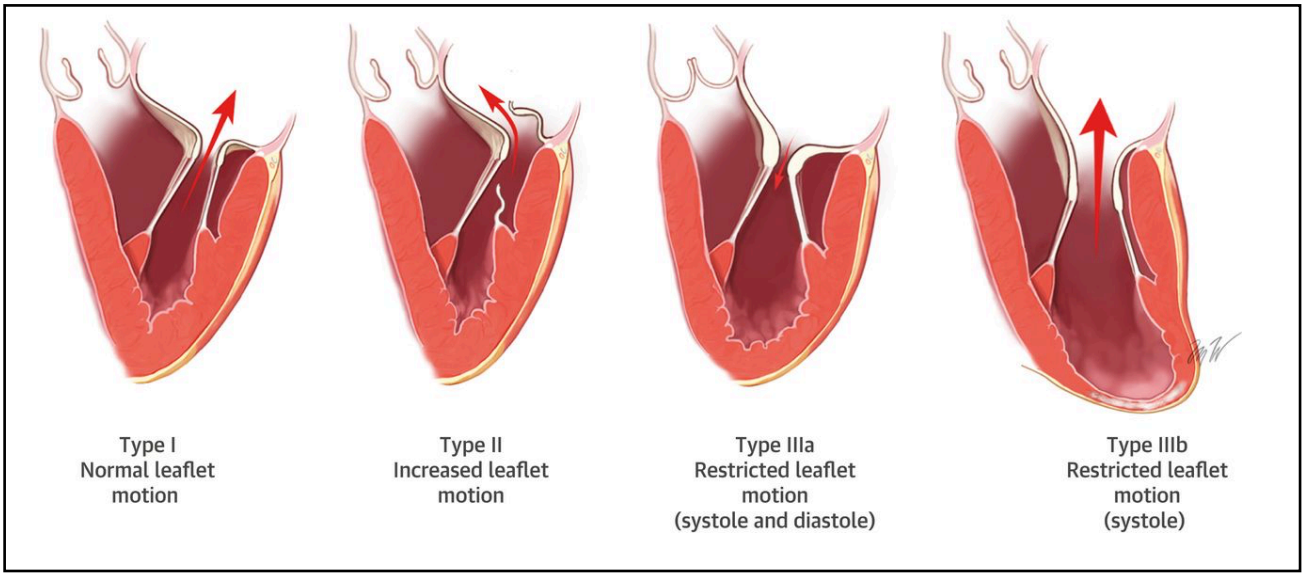


**Figure 2.4.** Mitral valve (MV) anatomy and Carpentier classification of mitral regurgitation (MR). This image depicts the different aetiologies which result in MR. Type I shows normal MV leaflets where annular dilation or perforation of the leaflet is the cause of MR; Type II shows excessive leaflet motion with a flail or prolapsed MV leaflet resulting in MR. Type IIIa shows restricted MV leaflets affecting

opening and closing of the valve as a consequence of thickening or calcification of MV leaflets, commissures or chordae tendineae. Type IIIb demonstrates a problem with closure of the valve leaflets secondary to chordal thickening, shortening or LV dilation. Taken from: Stone *et al* (21).

In the setting of acute HF, primary MR is usually associated with Type II changes characterised by increased leaflet motion as a result of prolapse or chordal rupture. Although Type II primary MR is common, it is less often associated with HF unless volume overload is chronic, prolonged and severe, and myocardial damage has occurred.

For secondary (functional) MR, the most common aetiology is Type IIIb, defined by restricted leaflet motion and closure in systole which is frequently the result of ischaemia (18). Put simply, ischaemia leads to myocardial infarction which causes local remodelling and geometric changes in the LV, resulting in papillary muscle displacement. Dysfunction also offer leads to LV enlargement which causes MV annulus dilation and a simultaneous loss in the saddle shape of the MV annulus (24). From here we see increased tethering forces on the MV leaflet, tenting of the leaflets with reduced leaflet closure forces, and thus MR (24). Although in most instances this will be in the setting of HFrEF, there will be occasions where even in the presence of a regional wall motion abnormality and MR, overall EF remains preserved. LV dyssynchrony may be an additional mechanism by which MR occurs secondary to ischaemia, leaflet dysfunction and retraction. MR is typically posteriorly directed as localised remodelling tends to impact the posteromedial papillary muscle and posterior MV leaflet. Non-ischaemic secondary (functional) MR is characterised by global

dilation and increased LV sphericity, and largely results from long standing hypertension or idiopathic cardiomyopathy (18). The MV tenting height increases symmetrically, reducing coaptation with MR generally central in origin. Occasionally, secondary MR can be the result of isolated mitral annular dilation in the absence of tethering or prolapse (Type I). This is mainly the result of chronic AF but can also be seen in patients with HFpEF (25). Secondary (functional) MR leads to increased preload, LV wall stress and LV workload, and a vicious spiral towards HF.

Prognosis for patients with acute HF and primary MR is very good with any LV volume overload quickly corrected through surgical repair allowing for a normal lifespan (26). Unfortunately, secondary MR portends poor clinical outcomes with MR as a result of myocardial infarction carrying an increased risk of death. Despite the differences in prognosis and clinical outcomes, HFpEF with associated MR and HFrEF are quite evenly balanced in relation to rates of hospital admission and overall impact on hospital resources (27).

### 2.2.3 Diagnosing mitral regurgitation

#### 2.2.3.1 Echocardiography

Echocardiography is an extensively utilised, non-invasive investigative tool that can be used in the identification of MR. It is inexpensive, widely available and has no known side effects. Transthoracic (TTE) and transoesophageal echocardiography (TOE) are commonly used in combination in order to definitively diagnose the

mechanism of MR, its severity and any other underlying concomitant cardiac lesions. Both of these diagnostic tools use an integrative approach, merging qualitative, quantitative and semi-quantitative measures in the assessment of MR. Current recommendations regarding the defining features of severe MR from the American Heart Association (AHA), American College of Cardiology (ACC) (2017 and 2020), American Society of Echocardiography (ASE) (2017) and European Society of Cardiology (ESC) (2017) are outlined in Table 2.2 (28-31). A small degree of variation can be noted but general guidance is reasonably consistent between the 2017 guidelines.

**Table 2.2.** A summary of echocardiographic criteria and cut points used to define severe mitral regurgitation across a selection of guidelines including the American Heart Association (AHA), American College of Cardiology (ACC), American Society of Echocardiography (ASE) and European Society of Cardiology (ESC) (28-31).

| **Parameter** | **AHA / ACC guideline (2017)** | | **ASE guideline (2017)** | **ESC guideline (2017)** | | **AHA/ACC guideline (2021)** |
|---|---|---|---|---|---|---|
| **Quantitative** | | | | | | |
| EROA ($mm^2$) | Primary ≥40 | Secondary ≥20 | ≥40 (may be lower in secondary MR) | Primary ≥40 | Secondary ≥20 | ≥40 for both Primary and Secondary |
| PISA radius (cm) | Not defined | | ≥1.0 | Not defined | | |
| Regurgitant Volume (mL) | Primary ≥60 | Secondary ≥30 | ≥60 (may be lower in secondary MR) | Primary ≥60 | Secondary ≥30 | ≥60 for both Primary and Secondary |
| Regurgitation Fraction (%) | ≥50 | | ≥50 | Not defined | | ≥50 |
| **Semi-quantitative** | | | | | | |
| MV inflow (m/s) | Not defined | | >1.2 | E-wave dominant >1.5m/s | | Not defined |
| Pulmonary Vein Flow | Not defined | | Systolic flow reversal | Systolic flow reversal | | Not defined |
| Vena Contracta (mm) | >7 | | >7 | >7 | | ≥7 |

Of note, during the submission and revision of this thesis, AHA/ACC updated the guidelines regarding the management of patients with valvular heart disease (Table 2.2) (31). Interestingly, the 2020 AHA/ACC guideline made the decision to align criteria for both primary and second MR. The reasoning for this was based on the premise that the criteria for severe primary MR had been used in determining severe for secondary MR in foundation surgical intervention randomised controlled trials (RCTs) (31). Reviewing the RCTs in detail it appears that although in some cases an effective regurgitant orifice area (EROA) cut point of >0.4cm2 (criteria for severe primary MR) had been applied, there was also flexibility within the criteria with MR being defined as severe with an EROA <0.4cm2 but with other echocardiographic features of severe MR, indicating that this change in guidance had been supported by outcomes using integrative criteria (32-34). Alongside the change, the guideline does denote controversies surrounding the definition of severe secondary MR. It describes: 1) established data reporting a smaller EROA in secondary MR being associated with adverse outcomes when compared to primary MR; 2) secondary MR as carrying an increased risk of progression and deterioration due to adverse LV or MV annulus remodelling; and 3) secondary MR as suffering from potential underestimation due to crescentic shape of the regurgitant orifice when measured by the flow convergence method (31). Moreover, though not included in guideline reasoning, it is also well established that in the presence of LV dysfunction and concomitant low stroke volume, a smaller regurgitant volume represents a small regurgitant fraction; and that MR is dynamic and as such severity can vary depending on the phase of the cardiac cycle and the loading condition. Importantly, all guidelines emphasise that assessment of MR should be integrative and based on a combination of parameters to minimise the

impact of the intrinsic limitations of each individual method and ensure more precision in determining severity.

In addition to the parameters outlined above, guidelines further support the use of two dimensional (2D) and three dimensional (3D) imaging to provide detailed information in relation to anatomy and pathology (prolapsed or flail leaflets, ruptured papillary muscles or large coaptation defects). Leaflets should be thoroughly inspected to determine if valve anatomy is amenable to repair. The application of colour flow imaging also facilities examination of the jet size and direction. A large central jet (greater than 40-50% of the LA) or an eccentric jet adhering to the wall or inter-atrial septum and reaching the posterior wall of the LA may denote severe MR (Figure 2.5 A, B) (29). Additionally, a large flow convergence zone would be cause for concern. Furthermore, the shape and density of the continuous wave Doppler signal may assist in determining severity, with those that are dense, triangular and holo-systolic aligning with severe MR.

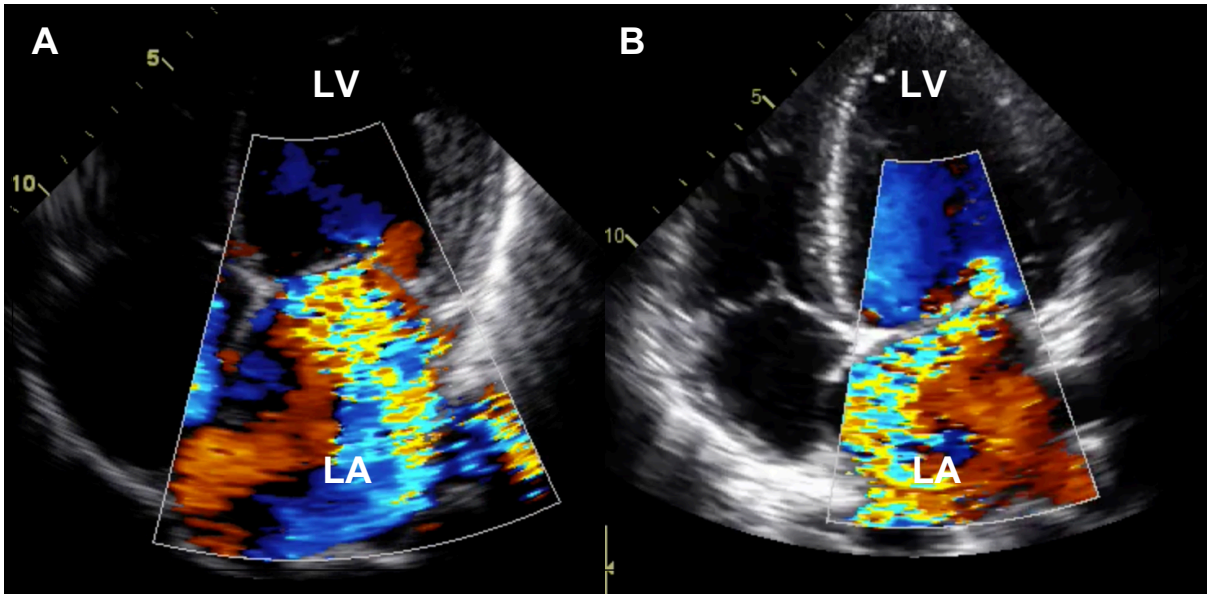

**Figure 2.5.** Two dimensional echocardiography images obtained from an apical four chamber acoustic window with the application of colour Doppler imaging. (A) shows a large central jet of mitral regurgitation which occupies greater than 50% of the left atrium; (B) shows a large eccentric jet of mitral regurgitation which is directed anteriorly towards the interatrial septum, reaching the posterior wall of the left atrium. Both of these images denote severe mitral regurgitation. Note: the mitral regurgitation jets are represented by the green/yellow/light blue disorganised, mosaic colour on the image. Abbreviations: LV: left ventricle; LA: left atrium.

Assessing the size and function of the LV is crucial for these patients and can be best performed with 2D biplane and 3D volume measurements. Across both primary and secondary aetiologies of MR, LV performance may vary from poor to hyperdynamic. Therefore, obtaining an accurate estimate of stroke volume can prove useful in determining if there is adequate forward circulation. Most current guidelines also advise on inspecting the size and/or volume of the LA as this measurement can be vital in determining eligibility for surgery. Likewise, the estimated pulmonary artery systolic pressure (PASP) contributes to the decision making process in terms of surgical intervention and this measurement is key (in conjunction with assessment of right ventricular (RV) size and function, and the presence of concomitant tricuspid regurgitation).

While echocardiography remains the first line investigation for the assessment of MR, other cardiac imaging modalities may be useful. Magnetic resonance imaging (MRI) can provide accurate information in relation to LV and RV volumes, function and MR severity and aetiology when these are not clear on echocardiography. MRI has the advantage of not being limited by body habitus or a narrowed selection of imaging

planes, and can provide additional valuable information in relation to myocardial viability and scarring.

#### 2.2.3.2 Functional testing

On the occasions when there is a discrepancy between symptoms and echocardiographic findings, or when disease severity is borderline, functional testing can provide useful additional information. The AHA/ACC, ASE and ESC guidelines all endorse the use of exercise testing, whether through the use of treadmill, exercise stress echocardiography or cardiopulmonary testing (28-30). Exercise testing may unmask symptoms in individuals who are sedentary as well as providing an overall estimate of functional capacity. Testing can also be useful as a serial comparative measure. Additional information pertaining to the LV response to exercise, as well as the PASP and degree of MR at peak exercise can assist in determining risk stratification and predicting outcomes. Yet the feasibility, practicality and usefulness of functional testing specifically within the HF and MR population requires further examination. Chapter 5 provides a systematic review and meta-analysis explicitly critiquing the role of functional testing.

#### 2.2.3.3 Biomarkers

The use of biomarkers in the setting of MR still requires further investigation. Although limited studies have shown that B-type natriuretic peptide (BNP) can independently predict outcome in asymptomatic primary MR, a greater number of large scale studies

need to be performed before BNP can be used as a definitive trigger for surgery, particularly for the HF population who may have coexisting AF (35). Current recommendations from the ESC suggest the use of brain natriuretic peptide and N-terminal pro B-type natriuretic peptide (NT-pro BNP) as predictors of outcome, particularly at symptom onset (29). Additionally NT-pro BNP can be used as a 'rule out' test, categorising patients with a normal value as low risk where follow up with close monitoring and echocardiographic surveillance is the recommended course of action.

### 2.2.4 Treating mitral regurgitation in heart failure

#### 2.2.4.1 Primary MR in heart failure

By definition, patients with HF and severe MR will be symptomatic. Therefore this section will focus primarily on treatment for symptomatic patients. Surgery is indicated in acute severe symptomatic MR. In the setting of chronic severe MR, surgery is indicated in symptomatic patients with an EF >30%. For those with an LV EF <30% or left ventricular end systolic dimension >55mm refractory to medical therapy, surgical MV repair should be considered where the likelihood of successful repair is high and comorbidity low (29, 30). MV replacement should be considered with caution within this same population where the likelihood of surgical MV repair is considered low. Finally, transcatheter edge to edge repair should be considered for patients with symptomatic severe primary MR who are high surgical risk and considered inoperable (29). Important decisions for the Heart Team to consider prior to transcatheter mitral

valve repair (TMVR) include fulfilling echocardiographic eligibility criteria (with anatomy deemed favourable for transcatheter repair) and a reasonable life expectancy (29, 30).

#### 2.2.4.2 Secondary MR in heart failure

The presence of severe secondary MR has been shown to negatively impact prognosis. However, it is unclear if prognosis is independently affected by MR or whether this is a consequence of LV dysfunction. To date, there remains debate as to whether reducing secondary MR results in survival benefit. For patients with HF, the degree of MR can be dynamic. Therefore, the first step in management of secondary MR should be to ensure that all patients are on OMT in line with recommendations for the management of HF (10, 36). This may include initiation of a beta-adrenergic receptor antagonist (more commonly known as a beta-blocker) and an angiotensin-converting enzyme (AVE) inhibitor or angiotensin II receptor blockers (ARB). Where symptoms persist a mineralocorticoid receptor antagonist (MRA) may be considered (37). In the setting of signs and/or symptoms of congestion, a diuretic may be recommended. Ongoing input from a HF specialist is fundament.

Where patients remain symptomatic on OMT, cardiac resynchronisation therapy (CRT) should be considered for patients who meeting eligibility criteria. CRT is indicated for patients who have an LVEF of 35% or less, sinus rhythm, left bundle-branch block (LBBB) with a QRS duration of $\geq$130ms, and New York Heart Association (NYHA) class II, III, or ambulatory IV symptoms on OMT (36, 38, 39). Studies have

shown that patients who undergo CRT experience a reduction in the degree of MR alongside improvement in symptoms, functional capacity and QoL (40). Improvement may occur acutely or progressively over time and is thought to be related to the degree and location of dysynchrony (41).

Conventional MV surgery should be considered for patients with an EF >30% and persistent symptoms despite OMT and CRT who are undergoing CABG and for those with an EF <30% where revascularisation is an option based on positive myocardial viability assessment. Indications for isolated MV surgery are restrictive in patients not undergoing concomitant revascularisation, owing to high rates of mortality and residual MR as well as limited evidence to suggest a survival benefit (42, 43). Conventional surgery without revascularisation may be indicated within this cohort when surgical risk is low. However, for patients with multiple comorbidities and a prohibitive surgical risk, edge to edge TMVR may be considered with the primary aim of reducing the degree of MR with additional clinical outcomes focussed on symptom relief, enhanced lifestyle and longevity.

Valve intervention is uncommon and not advised in those with an EF <15% (29). Cardiac transplantation or destination LV mechanical assist device therapy should be considered for patients who have severe refractory symptoms or irreversible severe cardiogenic shock (18).

## 2.3 Transcatheter mitral valve repair: a literature review

The first TMVR was performed in Venezuela in 2003 (44-46). Five years later this experience was shared by the UK (47). Since this time, there has been rapid progression and significant evolution in the sphere of TMVR devices, with broadening indications for their use and increased degrees of success.

As a consequence of lifelong learning from surgical colleagues and subsequent collaboration with interventional specialists, the last decade has seen the development of a significant number of TMVR devices; each with slight variations in design and alterations in anatomical approach and delivery techniques. The European approved TMVR toolbox comprises devices such as the MitraClip (Abbott Vascular, Inc., Santa Clara, California), the DS1000 device (NeoChord, Inc., St. Luis Park, Minnesota), the Carillon (Cardiac Dimensions, Inc., Kirkland, Washington), the CardioBand (Valtech Cardio, Or Yehuda, Israel), and the Mitralign device (Mitralign, Inc., Tewksbury, Massachusetts) (48). Many more are currently undergoing clinical evaluation in order to obtain approval. Transcatheter edge to edge repair using the MitraClip system (Abbott Vascular, Inc., Santa Clara, California) remains the most well established and commonly used (Figure 2.6) (49). Having treated 35 000 patients globally with MitraClip by 2016, this has now exploded to over 100 000 MitraClip patients worldwide (45, 48).

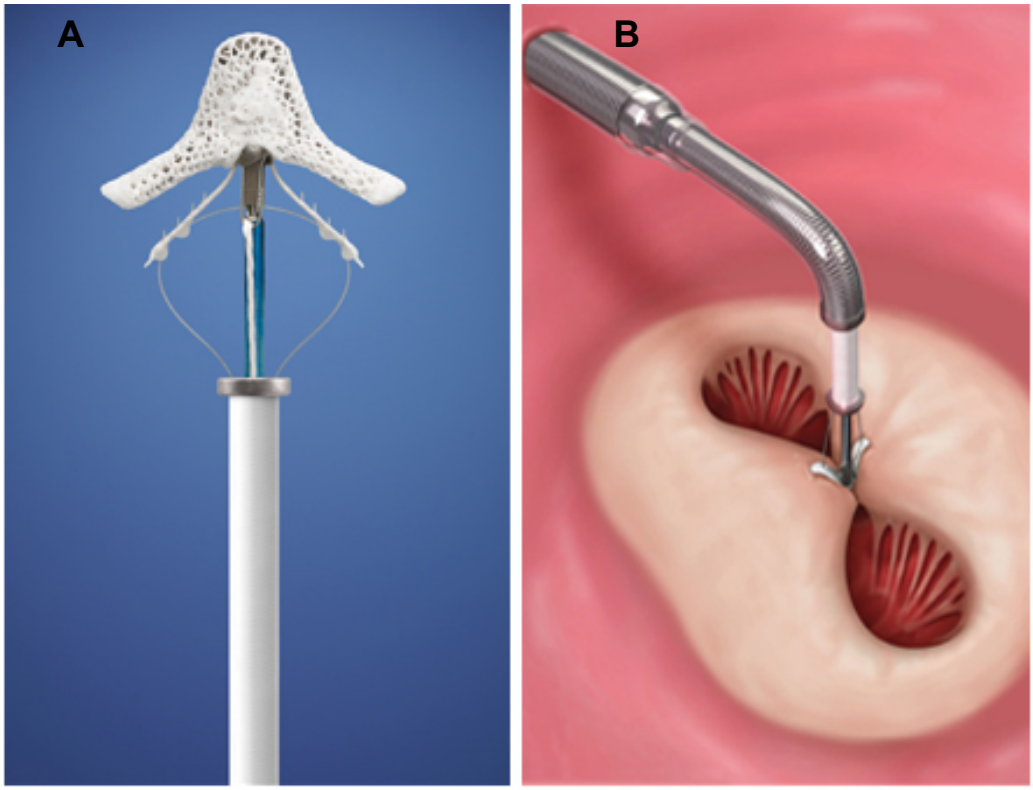


**Figure 2.6.** The Abbott MitraClip device (A). (B) shows deployment of the MitraClip device at the P2, A2 mitral leaflet scallops. Using the edge to edge repair technique a small bridge between the anterior and posterior mitral valve (MV) leaflets is created resulting in a MV with a double orifice. Taken from: Ottawaheart (50).

The excitement surrounding TMVR was based on the premise that it presented a novel and innovative alternative to conventional open heart surgery via a minimally invasive route. By 2003, we had already lived the experience and seen the benefit of transcatheter aortic valve implantation (TAVI). However, TMVR remained largely untested with unknown outcomes in a population of complex HF patients with a complicated continuum of MV anatomy. Early studies therefore focussed on the feasibility, safety and efficacy of TMVR, drawing comparisons with conventional

surgery. The Endovascular Valve Edge-to-Edge Repair Study (EVEREST II trial) set the stage for comparison by performing a randomised controlled trial (RCT) separating patients into one of two arms: 1) TMVR or 2) surgical repair or replacement (51, 52). This study showed that TMVR was feasible with low rates of mortality and a reduction in MR in the majority of patients (52). More specifically, it found that major adverse events rates were lower in those who underwent TMVR compared to MV surgery (15% vs 48%, $p<0.001$). Yet, reported findings also demonstrated that reduction in the severity of MR (to grade 1+ or less) was more common in the surgical group (100% vs 73%, $p=0.18$). The study concluded that TMVR was less effective in reducing the degree of MR compared to conventional surgery, but was safer and just as effective in improving quality of life (QoL) and symptoms. This was supported by a comparison of NYHA class at 12 months which showed only 2% of TMVR patients had NHYA class III/IV versus 13% of patients who underwent surgical intervention. By this time, other foundation studies focussing on TMVR were supporting the usefulness of percutaneous technology and also drawing comparisons with conventional surgery in relation to perceived high levels of safety and efficacy but questionable outcomes in relation to the degree of residual MR (53).

Given these findings, researchers shifted their focus to the role of TMVR amongst frail patients with multiple comorbidities considered too high risk for surgical repair. Studies consequently concentrated on comparing high risk TMVR patients with a retrospective cohort of high risk patients receiving standard care. Early outcomes demonstrated that TMVR was feasible within this cohort with additional benefits in relation to LV geometry and positive remodelling, as well as symptoms (54). The most significant conclusion

was a reduced rate of HF hospitalisation following TMVR. The study concluded that the annual rate of HF hospitalisation amongst TMVR patients reduced to 0.32 compared to 0.59 for 'matched' patients who received standard care (p=0.034) (54).

At this point, no study had looked at distinguishing outcomes of patients with primary versus secondary MR, or randomised those who underwent TMVR versus optimal HF medical therapy, or conclusively determined the effects on longevity. The ACCESS-Europe Phase I Trial did just that. With a primary focus on delivering TMVR to patients with inoperable degenerative MR, it showed significant reduction in MR and improvements in clinical condition 12 months following intervention (55). This was supported by the work of Buzzatti *et al* who showed that in octogenarians, the aging population with the highest incidence of MR, TMVR was associated with lower procedural complications and improved QoL but more residual MR compared with surgical repair. Interestingly though, recurrent MR was not significantly associated with follow up mortality (56). Five years on and rapidly moving forward, 2020 delivered the 5-year follow up results of the EVEREST II trial. This demonstrated no difference in rates of redo surgery for patients who had conventional surgery versus those who underwent TMVR where patients were event free at 12 months (TMVR 5% vs MVR 3%, p=>0.99). This evidence provided reassurance in relation to TMVR and its impact on longevity (57).

With the accumulation of relevant studies and debate surfacing regarding the patient groups for whom TMVR is most effective, Chiarito *et al* performed a meta-analysis interrogating the use of TMVR in primary versus secondary MR (2018). Based on nine

studies, this review showed no significant difference in the degree of residual MR between patients, but a higher rate of MV re-intervention required for patients with degenerative MR (58). Additionally, and as expected, a higher percentage of patients with secondary MR remained in NYHA class III/IV and required re-admission for heart failure (58). The final conclusions of this meta-analysis suggested that large randomised clinical studies were still needed to confirm the benefit of TMVR within the separate aetiological groups, with a particular focus on secondary MR (58).

In 2018, two large scale ground-breaking studies (MITRA-FR and COAPT) were published in the New England Journal of Medicine (59, 60). Each study focussed on assessing clinical outcomes following TMVR in patients with secondary MR. On first impressions, both delivered very different results, opposing clinical messages, and contradictory recommendations for treatment. However with greater inspection it is possible to provide explanation of the diverging results and see outcomes as more complementary rather than conflicting, These studies are outlined in Table 2.3 and discussed in more detail below.

**Table 2.3.** A comparison between the findings of two large scale transcatheter mitral valve repair studies: MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation); Abbreviations: GDMT: guideline directed medical therapy; CRT: cardiac resynchronisation therapy; HF: heart failure; EF: ejection fraction; LVESD: left ventricular end systolic dimension. RVol: regurgitant volume; EROA: effective regurgitant office area (59, 60).

| | MITRA-FR (2018) | COAPT (2018) |
|---|---|---|
| **Country** | France | United States and Canada |
| **Study Design** | Prospective, randomised | Prospective, randomised |
| **Arms** | Intervention: MitraClip + GDMT | Intervention: MitraClip + GDMT |
| | Control: GDMT | Control: GDMT |
| **Sample Size** | 304 | 614 |
| **Centres** | 37 | 78 |
| **Primary Outcome** | Death and HF hospitalisation at 12 months | HF hospitalisation at 24 months |
| **Inclusion criteria** | EF: 15-40% | EF: 20-50% |
| | LVESD: no specific criteria | LVESD: <70mm |
| | MR: RVol >30mL, EROA >20mm2 | MR: RVol >45mL, EROA >30mm2 |
| | RV Function: no specific criteria | RV Function: < moderate dysfunction |
| | SPAP: no specific criteria | SPAP: <70mmHg |
| | HF history: Minimum of 1 HF admission within 12/24 months preceding recruitment | HF history: At least one hospitalisation for HF in the 12 months prior to enrolment and/or a corrected BNP ≥300 pg/ml or a corrected NT-pro BNP ≥1500 pg/ml |
| **GDMT** | Received HF meds at baseline. Allowed variable adjustments in each group during follow up. No specific protocol. | Protocol approach to maximal tolerated medications. Minor changes in follow up only |
| **CRT in situ (yes)** | Not specified | 224 (36%) |
| **Combined primary outcome of death and HF hospitalisation at 12 months** | Intervention (54.6%) vs control (51.3%) (p=0.53) | N/A |

| | | |
|---|---|---|
| **Annualised HF hospitalisation rate** | Intervention (48.7%) vs. control (47.4%) at 12 months | Intervention (35.8%) vs. control (67.9%) (p=<0.001) at 24 months |
| **Death from any cause** | Intervention (24.3%) vs. control (22.4%) at 12 months | Intervention (29.1%) vs. control (46.1%) at 24 months |

The MITRA-FR study (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation), based in France, was centred on a cohort of approximately 300 HF (NYHA class II-IV) patients with severe secondary MR and an LVEF 15-40%. The primary outcome was based on the composite of death from any cause or unplanned HF hospital admission. This randomised controlled trial demonstrated that the rate of death or unplanned hospitalisation at 12 months was no different between patients who underwent TMVR in addition to OMT, and those who received OMT alone (59, 61).

However only one month later, in the US, Stone *et al* released the results of the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) study (60). This study also focused on drawing comparisons between secondary MR HF patients who received OMT and subsequently underwent TMVR, and those who received OMT alone. Based on randomisation, 600 patients were divided into the two separate treatment groups and followed up for 24 months. Patients in this study had moderate to severe or severe MR, NYHA II-IV, and an LVEF 20-50%. This study focussed on the end point of all cause HF hospitalisation and demonstrated a lower HF hospitalisation rate (reduced by 32%) and lower all-cause mortality at 24 months (reduced by 17%) in the treatment arm (TMVR + OMT) compared to OMT alone (60).

These results disputed those obtained in the MITRA-FR trial, raising questions regarding the most appropriate treatment options for patients with secondary MR going forward.

Critically evaluating the outcomes of these studies there were some inherent differences in study design and patient population. Firstly, recruitment into COAPT was larger and a larger number of centres were included in recruitment. Secondly, patient selection within the MITRA-FR trial targeted many more patients with moderate (as opposed to severe) MR with clear differences in the echocardiographic inclusion criteria. To clarify this point, the MITRA-FR trial recruited patients with an EROA >20mm$^2$/ RV >30mL compared to the COAPT trial which included those with an EROA >30mm$^2$/RV >45mL, suggesting those within the COAPT had more significant MR. Additionally there were also considerable differences in the LV volumes and EFs in those who were recruited. The COAPT trial used a LVESD cut point of <70mm as a marker for inclusion but MITRA-FR did not stipulate any maximum LVESD. Likewise, the EF range for inclusion varied between studies. MITRA-FR applied a range of 15-40% with COAPT focussing on those with an EF of 20-50%. Of note, patients with moderate/severe RV dysfunction or a SPAP >70mmHg were excluded from the COAPT trial but not from the MITR-FR trial. Thirdly, there were limited data within MITRA-FR outlining the number of patients with pre-existing CRT. Fourth, OMT was more stringently monitored within the COAPT trial with only those fulfilling strict criteria accepted into the study. By contrast, MITRA-FR was more true-to-life and medical therapy rates were not tracked throughout the trial. An additional difference was rates of hospitalisation prior to recruitment. In the MITRA-FR trial all patients had been

admitted to hospital in the subsequent 12 months. Those recruited to the COAPT trial were included based on hospital admission, but were also included based on high levels of BNP or NT-pro BNP but in the absence of recent HF admission. The end points between the studies also varied, with MITRA-FR focussing on death and unplanned hospitalisation combined, and COAPT investigating rates of hospitalisation and freedom from device related complications. Follow up times also differed between the studies and MITRA-FR had missing echocardiographic and functional follow up data.

In addition to this, the proportion of patients enrolled in the COAPT was lower than MITRA-FR (61% vs 32%). This was likely due to the echocardiography exclusion criteria for COAPT but also may have been influenced by processes for the assessment of optimal medical therapy. The COAPT trial required both a local heart team evaluation in addition to a central selection committee review (24). For the MITRA-FR study patients were screened by the local heart team only. Of note, treatment varied between groups with higher rates of renin-angiotesin-aldosterone system blockers in the MITRA-FR patients compared to the COAPT patients but unfortunately pre and post device therapy, and whether or not this was further optimised, was not possible in both groups (the MITRA_FR study did not look at medical therapy following TMVR intervention).

Following careful evaluation of the different characteristics of the two studies, what becomes apparent is whether it is in fact reasonable to compare the two. The differences reveal two very disparate patient populations with the MITR-FR study

recruiting patients with less severe MR but more severe LV dilatation and dysfunction, and more advanced HF who were proportionally more severely symptomatic. With this in mind, it may be that the LV was the main culprit in the MITRA-FR study and MR the bystander, suggesting that treatment of the MR may have therefore proved less effective in reducing symptoms and/or death. In the COAPT trial we saw quite the opposite (more MR, less LV dilatation and dysfunction), making the effects of TMVR more effective in reducing hospitalisation (62). Therefore rather than conflicting, it may be that these studies should be regarded as complementary, both evaluating MR and HF at different points along a continuum (24).

Nevertheless, the results of these two foundation studies leave the HF and intervention communities still searching for clarification; not really knowing when to refer HF patients with secondary MR for valve intervention whilst also appreciative and sympathetic that TMVR may be the only source of relief from life limiting symptoms in certain patients. One thing that both studies made clear was the importance of appropriate patient selection and increased focus on determining patients who might benefit (63). As a result of these studies, philosophies relating to ‘proportionate’ and ‘disproportionate’ MR to LV volume have been proposed (discussed further in Chapter 8) (64, 65). These frameworks suggest it may be worth homing in on patients who have undergone appropriate optimisation with medical therapy and CRT (if eligible) who still have a MV effective regurgitant orifice area $\geq$0.3cm2 without excessive LV dilatation. For these patients, reducing MR with percutaneous devices may effectively reduce mortality linked to secondary MR, and the total HF burden (66, 67).

A review of the current literature demonstrates the benefits of TMVR in relation to QoL and symptoms. For primary MR there is also a proven survival benefit. Although TMVR in secondary MR may be promising for selected patients, more research is required to ascertain if there is an impact on mortality within this patient cohort. There is a clear research gap with a dearth of information and very little scrutiny into a number of key areas including: 1) the actual burden of MR within the HF cohort; 2) the mortality risk for those without MR versus those with MR; 3) the degree to which we are failing to treat those who are suitable for TMVR; and 4) identifying parameters which may be useful in determining which patients will gain the most benefit from TMVR. Further research studies should therefore be focussed on investigating these areas, with a view to generating evidence to support greater clinical advantage in relation to patient selection and improved patient outcomes.

## 2.4 Aims and Objectives

The overall aim of this study was to determine the prevalence of HF patients with significant MR and investigate responses to treatment and methods for risk stratification.

The specific aims and objectives were to:

**Aim 1.** **Determine the proportion of patients admitted with HF who have moderate or more MR, their mortality risk, and the impact of OMT on MR, EF and symptoms.**

**Objective 1:** Perform a retrospective consecutive study of patients admitted with HF across Lambeth and Southwark over a five year period and use TTE data to determine the proportion of patients who have moderate or more MR.

**Objective 2:** Using ONS data, compare mortality 12 and 18 months following the index HF admission across patients with and without moderate or more MR.

**Objective 3:** Use TTE and clinical data to determine the effects of OMT in relation to cardiac function (MR and EF) and symptoms (NYHA), and the number of patients who remain with moderate or more MR, EF $\leq$50% and symptoms, despite OMT.

**Aim 2.** **Determine the number of high-risk patients with moderate or more MR, an EF 20-50% and symptoms despite OMT who are potentially eligible for TMVR based on echocardiographic criteria, and extrapolate this on a population level.**

**Objective 1:** Perform a retrospective consecutive study of Lambeth and Southwark patients admitted with HF and use echocardiography and

clinical data to determine those who have moderate or more MR, an EF 20-50% and symptoms, despite OMT.

**Objective 2:** Use clinical data and the Euroscore II algorithm to determine those patients who are high and intermediate risk.

**Objective 3:** For patients with HF, MR, and symptoms who are deemed high and intermediate risk, determine those who are potentially suitable for TMVR through application of the COAPT selection criteria and Heart Team review; and using national HF audit data extrapolate this on a population level.

**Aim 3.** **Perform a systematic review of the available evidence in relation to TMVR and the role of functional testing in predicting outcomes.**

**Objective 1:** Search five databases for publications related to TMVR and functional testing.

**Objective 2:** Focus on articles where functional testing is predictive of outcome and use meta-analysis to calculate effect size so as to determine the usefulness of functional testing in risk stratification for patients undergoing TMVR.

**Aim 4.** **Examine the effectiveness of TMVR for patients with MR and symptoms, and the usefulness of echocardiographic markers, functional testing and biomarkers in predicting changes in LV performance and improvements in symptoms and QoL.**

**Objective 1:** Prospectively recruit patients undergoing TMVR and draw comparisons between pre and post TTE data to determine if TTE can predict changes in LV performance following TMVR.

**Objective 2:** Perform functional tests (6MWT and exercise stress echocardiograms) to examine their usefulness in discriminating MR patients who demonstrate improved LV parameters and QoL following TMVR.

**Objective 3:** Examine the effects of residual MR (post TMVR) on LV performance and QoL using TTE and QoL questionnaires.

**Objective 4:** Using TTE, clinical, laboratory and functional data, explore and characterise the relationship between changes in LV parameters and clinical outcomes.

**Objective 5:** Assess the usefulness of TTE parameters combined with functional, clinical and biochemical parameters in providing better prediction of post-procedural outcomes following TMVR.

## 2.5 Impact Statement

It is envisaged that the presented project will provide a framework for the generation of further research in the area of HF, MR, and TMVR. By quantifying the burden of MR in HF patients within a precise geographical area, this work will allow other research

groups to plan further studies and in particular help aid more precise power calculations.

Additionally, through the dissemination and communication of abstracts and publications at a national and international level, the wider cardiology community will become more aware of the burden of MR within the HF population and the relevant treatment options available. Raising the profile of the problem and the treatment therapies means that medical professionals are more cognisant and responsive when faced with these dilemmas in the clinical context. The work should also encourage clinicians to integrate these novel treatment options into HF pathways.

This project work provides evidence that can be used by healthcare providers and NHS decisionmakers in regard to the provision of resources. More specifically, it is anticipated that this research will help support NHS specialised commissioning in planning national resources, most likely leading to further increases in the number of commissioned TMVR treatments centres, ultimately resulting in improvements in accessibility to TMVR.

Additionally, recommendations from the research may also influence commercial partners in relation to subsequent design features and deployment approaches related to TMVR devices, or when creating selection criteria parameters for subsequent research studies. I am hopeful that this research helps leads to a better understanding of risk stratification in relation to the value of functional testing for patients undergoing TMVR.

This research also highlights the importance of key echocardiographic considerations in the work up to TMVR. Through an appreciation of the necessary expertise required, it is anticipated that echocardiographers will strengthen their skills and knowledge in these areas. Training programmes should be focussed on an integrative approach to the assessment of MR as well as the role of the LV, left atrium and the right heart.

HF is one of the largest problems within cardiovascular medicine. Most of the cost, morbidity and mortality is centred around acute admissions, which is the group of patients this thesis studied. HF affects just short of a million people in the UK and has outcomes worse than most cancers. However it is often a very treatable condition and the hope is that this thesis will help contribute to improving treatment options for the subgroup of HF patients who have significant MR, leading to improvements in both their quality of life and life expectancy.

# CHAPTER 3

# ACUTE HEART FAILURE: WHAT IS THE BURDEN OF MITRAL REGURGITATION?

## 3.1 Introduction

Mitral regurgitation (MR) is common in patients with acute heart failure (AHF). However, the burden of MR within this population has not been definitively quantified across a complete geographical sector. Within the London boroughs of Lambeth and Southwark, there is limited data available regarding the prevalence and severity of MR, the impact of medical therapy in relation to symptoms and severity of MR, and the relationship between MR severity and mortality. In order to ensure we provide appropriate monitoring and treatment options for our patients on a local, London-wide and population level, further research into the true burden of MR is necessary.

## 3.2 Aims and Objectives

The primary aim of this retrospective study was to investigate those patients with heart failure (HF) and significant MR. I hypothesised that a substantial number of Lambeth and Southwark patients admitted with HF would have moderate or more MR, and that a considerable proportion of patients would experience limited improvements in MR severity, left ventricular ejection fraction (EF) and symptoms despite optimal medical therapy (OMT).

My objectives were to determine: (1) the proportion of patients with a HF admission with moderate or more MR and their survival; (2) the number of HF patients with moderate or more MR and an ≤EF 50%; 3) the effectiveness of OMT in reducing the severity of MR and symptoms for these patients; (4) the number of HF patients with moderate or more MR, an EF ≤50% and symptoms despite OMT.

## 3.3 Methods

### 3.3.1 Study Design

This retrospective observational study was performed across two tertiary care centres, involving collaboration between the Department of Cardiology at Guy's and St Thomas' NHS Foundation (GSTT), the Department of Cardiology at King's College

NHS Foundation Trust (KCH), and the Department of Life Sciences and Centre for Bioscience at Manchester Metropolitan University (MMU). The study involved collecting NICOR national audit data, UK Office of National Statistics (ONS) mortality data, patient demographics, clinical and laboratory data, and co-morbidity details for patients presenting with an AHF admission between January 2013 and December 2017. Where patients underwent a transthoracic echocardiogram (TTE) assessment six months prior to or one month following the index admission, these data were used to assess the degree of MR, using EF as a surrogate for left ventricular systolic function. Patients with an EF $\leq$50% and moderate or worse MR were then further examined with a focus on symptoms (NYHA class), and current and subsequent treatments and medical therapies. Where patients underwent subsequent TTE on maximally tolerated medical therapy, the changes in the degree of MR, EF, and symptoms (NYHA class) were re-examined. In these circumstances, only TTE performed a minimum of one month after commencement on OMT were included.

A comprehensive list of the parameters recorded and relevant data sources can be found in Table 3.1.

**Table 3.1.** A comprehensive list of parameters collected for comparison as part of a retrospective study of heart failure patients across Southwark and Lambeth. Abbreviations: MR: mitral regurgitation; PISA: proximal isovelocity surface area; EROA: effective regurgitant orifice area; RVol: regurgitant volume; MV: mitral valve; LV: left ventricle; 3D: three-dimensional; EF: ejection faction; LVESD: left ventricular end systolic dimension; RV: right ventricle; PASP: pulmonary artery systolic pressure; LA: left atrium; HF: heart failure; CRT: cardiac resynchronisation therapy; ICD: implantable cardioverter defibrillator; MI: myocardial infarction; NYHA: New York Heart Association; PND: paroxysmal nocturnal dyspnoea; EPR: electronic patient record; NICOR: National Institute for Cardiovascular Outcomes Research; NT-pro BNP: N-terminal pro B-type natriuretic peptide; ACEI: angiotensin-converting-enzyme inhibitors; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonists; OMT: optimal medical therapy.

| Category | Assessment Type | Parameter | Time points | Data Source |
|---|---|---|---|---|
| Echocardiography | Mitral assessment | Visual impression of severity of MR, vena contracta, PISA, EROA, RVol, pulmonary vein systolic reversal, MV E wave velocity, continuous wave Doppler envelope shape | (1) At the time of HF admission<br>(2) On OMT | Transthoracic echocardiography reports and digital echo images. |
| | LV assessment | LV 3D EF, LV Simpson's biplane EF, visual LV EF, LVESD, visual impression of LV systolic function | (1) At the time of HF admission<br>(2) On OMT | Transthoracic echocardiography reports and digital echo images. |

| | | | | |
|---|---|---|---|---|
| | Other | Visual impression of RV size and function, PASP, LA size | (1) At the time of HF admission<br>(2) On OMT | Transthoracic echocardiography reports and digital echo images. |
| Clinical | General | Date of HF admission, medical team allocated to follow up care (i.e. tertiary, community), presence of CRT/ICD, date of death | (1) At time of HF admission<br>(2) At 12 and 18 months | EPR records, NICOR and ONS data |
| | HF presentation parameters | NYHA classification, oedema, orthopnoea, PND, abdominal swelling, raised venous pressure, basal crackles, third heart sound | At time of HF admission | EPR records and NICOR data |
| | HF symptoms at medical optimisation | NYHA classification, oedema, orthopnoea, PND, abdominal swelling, raised venous pressure, basal crackles, third heart sound | At time of HF review | EPR records and NICOR data |
| Demographics | | Age, gender, height, weight, ethnicity | At time of HF admission | EPR records and NICOR data |
| Laboratory | | Plasma creatinine, haemoglobin, urea, serum sodium, serum potassium, NT-pro BNP | At time of HF admission | EPR records |

| | | | | |
|---|---|---|---|---|
| Co-morbidity | | Angina at rest, recent MI, extra-cardiac arteriopathy, poor mobility, previous cardiac surgery, chronic lung disease, active infective endocarditis, diabetes on insulin | At time of HF admission | EPR records |
| Medical therapy | | Date of medical optimisation, medical therapy regime including: ACEI / ARB, beta blocker, MRA, ICD or CRT, appropriate diuretic therapy | (1) At time of admission<br>(2) On OMT | EPR records and NICOR data |

### 3.3.2 Study Population

Using national audit and United Kingdom (UK) Office of National Statistics (ONS) data, 2821 AHF admissions were recorded at the two nominated tertiary care centres between the time period January 2013 – December 2017, including a population of 1884 patients local to Lambeth and Southwark, London, United Kingdom (UK). Patients were included and excluded based on the criteria below (Table 3.2). Inclusion and exclusion criteria were determined based on combined opinions from local experts specialising in HF and cardiac imaging, including HF consultants, valve consultants, clinical scientists, nurses and researchers.

**Table 3.2.** Retrospective study assessing the burden of mitral regurgitation within the heart failure population across Southwark and Lambeth: inclusion and exclusion criteria. Abbreviations: GSTT: Guy's and St Thomas' Trust; KCH: King's College Hospital; HF: heart failure; UK: United Kingdom; TTE: transthoracic echocardiogram; EF: ejection fraction; MR: mitral regurgitation.

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| **1.** Presentation to either GSTT or KCH with HF between January 2013 and December 2017<br>**2.** Resident of Southwark or Lambeth, London, UK<br>**3.** 18 years or older | 1. TTE performed either within 1 month of, or up to 6 months preceding, the index admission<br>2. Unable to estimate EF or quantify MR on TTE |

### 3.3.3 Patient Recruitment

As this was a retrospective observational study, there was no formal prospective recruitment process. Patients were recruited based on an AHF admission following presentation to one of two tertiary care centres (GSTT or KCH) between 1st January 2013 and 31st December 2017. Figure 3.1 provides an outline of retrospective patient data collection using four modalities: NICOR data, ONS data, echocardiography data, electronic patient records (individual parameters collected as outlined in Table 3.1).

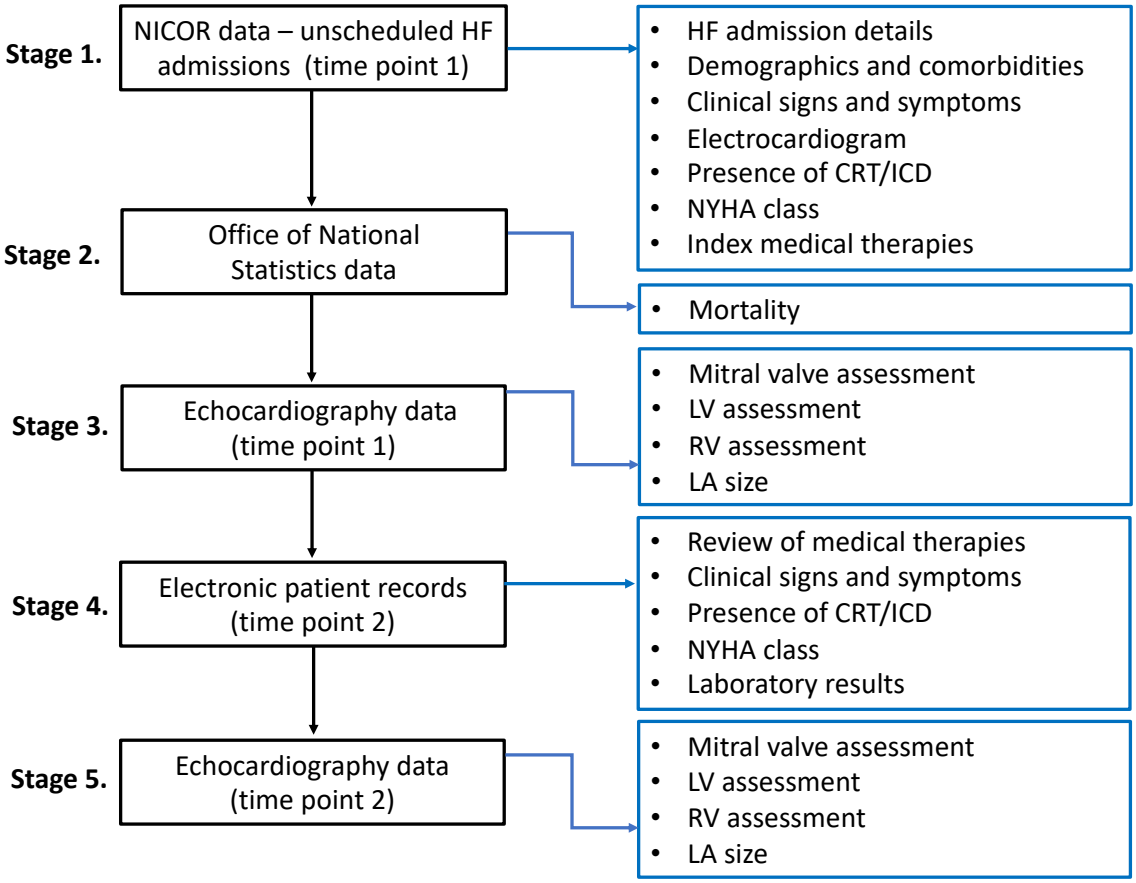


**Figure 3.1.** Flowchart demonstrating the process by which patient data were collected for the retrospective heart failure study. Abbreviations: HF: heart failure; CRT: cardiac resynchronisation

therapy; ICD: implantable cardioverter-defibrillator; NYHA: New York Heart Association; LV: left ventricle; RV: right ventricle; LA: left atrium.

### 3.3.4 National audit and UK Office of National Statistics mortality data

The National Heart Failure Audit group collects data concerning unscheduled admissions to hospital in England and Wales where a death or discharge is associated with a diagnosis of HF as the primary aetiology (1). Only patients 18 years or over are included in the audit. Patients were included based on a primary entry of death or diagnosis of HF, corresponding with episodes of care for the following NICOR discharge codes (1):

- I11.0 Hypertensive heart disease with (congestive) heart failure
- I25.5 Ischaemic cardiomyopathy
- I42.0 Dilated cardiomyopathy
- I42.9 Cardiomyopathy, unspecified
- I50.0 Congestive heart failure
- I50.1 Left ventricular failure
- I50.9 Heart failure, unspecified

Additional data obtained from the NICOR record included New York Heart Association (NYHA) classification, oedema, orthopnoea, paroxysmal nocturnal dyspnoea (PND),

abdominal swelling, raised venous pressure, basal crackles, third heart sound, medical therapy, date of HF admission, responsible follow up team (i.e. cardiology, elderly care, community care), and presence of cardiac resynchronisation therapy (CRT) or implantable cardioverter-defibrillator (ICD).

The UK Office of National Statistics (ONS) collects data on mortality. The registration of life events (i.e. deaths) is a service carried out by the Local Registration Service in partnership with the General Register Office. Mortality statistics are based on information recorded when deaths are certified and registered by the doctor certifying the death, the informant to the registrar, or the coroner to the registrar. This information is used to formulate ONS mortality data and available on request (68). Only data regarding mortality were collected using this mechanism.

### 3.3.5 Echocardiographic data

Echocardiographic data, where available, were collected at two time points. Firstly, six months prior to or one month following the index HF admission. Where patients had multiple admissions, the index admission was the first admission. If the patient did not undergo TTE six months pre- or one month post-admission, other admission dates within the study period for the same patient were reviewed for eligibility.

The second time point was once maximally tolerated HF medical treatment had been reached. To ensure this was robust, only TTEs performed a minimum of one month

post OMT were included (details regarding how OMT was determined are outlined in section 3.3.8).

Information was obtained based on review of the echocardiogram report. Where data were missing or incomplete, the digital images were reviewed by a cardiac physiologist trained and accredited in echocardiography. Where measurements were missing, these were performed by the cardiac physiologist in line with British Society of Echocardiography (BSE) recommendations (themselves based on recommendations from the American Society of Echocardiography [ASE] and the European Association of Echocardiography [EAE] 2013) (69-71).

#### 3.3.5.1 Equipment and information technology

Comprehensive TTE studies were performed across two cardiology sites using commercially available cardiac ultrasound machines including: Philips IE33, EPIQ, Affiniti, Cx50, GE E9, E95, S70, Vivid Q, Vivid I, Vivid 7. Images were obtained using a 3MHz or 5MHz fixed array ultrasound probe. Echo images were stored using digital loops and transferred to an archiving database (Echopac Imagevault, or Xcelera) to enable further offline analysis.

Studies were performed in line with recommendations of the British Society of Echocardiography (themselves based on recommendations from the American Society of Echocardiography [ASE] and European Association of Echocardiography

[EAE] (2013)). Both GSTT and KCH echocardiography departments are nationally certified and hold BSE departmental accreditation. Studies were performed by a cardiac physiologist accredited in TTE, or a trainee doctor or physiologist. Where a trainee performed the scan, all images and the clinical report were reviewed and finalised by a senior cardiac physiologist prior to formal publication on electronic medical records. Comprehensive TTE reports were uploaded to CVIS (formally known as Tomcat) or Xcelera.

#### 3.3.5.2 Measurements and technique

The degree of MR was determined using an integrative multiparametric approach. Quantitative measures such as vena contracta, effective regurgitant orifice area (EROA), proximal isovelocity hemispheric surface area (PISA) and regurgitant volume (RVol) were combined with semi-quantitative and qualitative parameters. These included increased MV E wave, the presence of reversal within the right upper pulmonary vein (RUPV) and the density, shape and duration of the MR continuous wave Doppler envelope. A visual impression of the severity of MR contributed to this integrative approach.

EF was determined based on quantitative measurement in the first instance. Where three-dimensional (3D) measurements were possible, these were considered the gold standard. In the absence of 3D, two dimensional (2D) Simpson's biplane disk method was used. In the absence of both of these measures, a visual impression of EF was

estimated. Where a range was used for EF, this was averaged (i.e. 30-35% = 32.5%). Assessment of LV systolic function was based on forward stroke volume, cardiac output and a visual impression. The left ventricular end systolic dimension (LVESD) was also collected as it is of particular importance in the timing of surgical intervention.

Right ventricular (RV) function was assessed using tricuspid annular plane systolic excursion (TAPSE) and RV tissue Doppler imaging (TDI) peak S wave (S') for the assessment of longitudinal contractility and a visual approach or fractional area change (FAC) for the assessment of radial contractility. This information was combined to give an overall impression of RV systolic function. Pulmonary artery systolic pressure (PASP) was estimated using the peak of a complete continuous wave Doppler envelope of tricuspid regurgitation (when available).

#### 3.3.5.3 Echocardiographic exclusions

When evaluating patients for the presence of moderate or more MR, those who had previously undergone surgical or transcatheter mitral valve repair, or MV replacement were excluded. Incomplete studies and those with poor image quality were excluded if they did not allow assessment of MR or EF.

### 3.3.6 Diagnosis and symptoms of heart failure

The initial diagnosis of HF was determined at admission by the HF team based on a combination of signs, symptoms and echocardiographic findings. Medical records were searched to determine NYHA class, and concomitant clinical signs and symptoms, such as evidence of oedema, orthopnoea, abdominal swelling, raised jugular venous pressure (JVP), a third heart sound or basal crackles at the lung bases.

Signs and symptoms were reassessed at a second time point marked by medical treatment at a maximally tolerated dose as determined by a HF specialist (cardiology consultant or HF specialist nurse).

### 3.3.7 Demographic, clinical, laboratory and comorbidity data

Demographic information including sex, age, ethnicity, locality, height and weight were collected as part of the NICOR data. Additionally, clinical data such as body mass index (BMI), systolic blood pressure, diastolic blood pressure, heart rate and electrocardiogram findings (rhythm, QRS width) were documented.

Biochemistry results were collected from internal electronic medical record systems. Specifically NT-pro BNP, haemoglobin, urea, creatinine, serum sodium and potassium were recorded.

Information pertaining to past medical history and comorbidities including ischaemic heart disease (IHD), valve disease, hypertension, diabetes, asthma, and chronic obstructive pulmonary disease (COPD) was also collected from internal electronic medical records.

### 3.3.8 Optimisation of medical therapy

Following a review of clinical records and medical therapies, OMT was determined by a consultant cardiologist with a specialist interest in HF specialisation. OMT was defined as:

1. Maximal tolerated dose of angiotensin-converting enzyme (ACE) inhibitors / angiotensin II receptor blockers (ARB).
2. Maximal tolerated dose of beta blocker.
3. Addition of a mineralocorticoid receptor antagonist (MRA) (spironolactone or eplerenone) where symptomatic despite maximal ACE inhibitor (or ARB) and beta blocker.
4. Implantable cardioverter-defibrillator (ICD) / cardiac resynchronisation therapy pacemaker (CRT-P) or cardiac resynchronisation therapy defibrillator (CRT-D) where appropriate as part of national guidelines.
5. Appropriate diuretic therapy.

The date of OMT was determined by one of two consultant cardiologists based on the case notes review.

### 3.3.9 Data management

All information that had been gathered as part of routine clinical practice was obtained from digital medical records within the relevant Trust. Permission to access medical records was granted by GSTT and KCH. Multiple onsite electronic hospital IT systems were accessed, including CVIS, EPR, e-noting, EPR Sunrise, and Xcelera. Access to electronic systems was via the cardiac outpatient department at both GSTT and KCH.

All collected data were stored in a password protected Excel spreadsheet. An active version was updated and adapted using secure e-mail transfer (nhs.net) and a master version stored on GSTT networked hospital IT systems. No patient data were taken outside the hospital premises.

### 3.3.10 End-points

The end-points for this study were:

1) Death
2) Change in symptoms as defined by NYHA class
3) Change in echocardiographic parameters; specifically, LV EF and degree of MR

### 3.3.11 Statistical analysis

Statistical analysis was performed using SPSS IBM software (version 25) (72). Baseline characteristics were expressed as means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. The normality of distribution was evaluated using skewness and kurtosis (-2 to +2). Bivariate analysis focussed on determining a significant difference between matched baseline and OMT data across the variables: 1) MR 2) LV EF; 3) NHYA class. This was achieved using Chi-square test for independence or McNemar's test for non-parametric comparisons. An independent T-test was used for continuous variables. Mortality at 12 and 18 months for those with and without moderate or more MR was determined using Chi-square test for independence. Kaplan Meier survival curves evaluated death across groups with and without moderate or more MR. Logistic regression was used to look at the individual and summative predictive value of EF, age, comorbidities and MR severity using mortality at 12 months following index admission. For paired data, a paired T-Test was used for continuous variables, and Chi-square and ANOVA for categorical variables. A p-value of 0.05 was used to conclude statistical significance.

### 3.3.12 Research ethics statement

This research project was submitted as a service evaluation, reviewed by the research governance teams at both Trusts and granted exemption from formal ethical approval

via REC by GSTT, UK (approval number 9161; see Appendix B for e-mail confirmation) and KCH, UK (approval granted by Dr Alexandros Papachristidis 30/01/2019, see Appendix C for e-mail confirmation).

As part of this retrospective review, all patient identifiable information was removed. All information collected was obtained as part of routine clinical practice. Patients' informed consent was not required.

### 3.3.13 Individual contributions to the research team

The entirety of this project was the responsibility of the principal investigator. Prof Bernard Prendergast was the principal supervisor. Prof Prendergast is the lead of valve services at the primary research site, GSTT. Prof Mark Monaghan and Dr Jane Hancock assisted in the interrogation of echocardiographic data. Dr Garry McDowell and Dr Fiona Wilkinson were joint academic supervisors on behalf of Manchester Metropolitan University. The lead consultant specialists for the King's, and Guy's and St Thomas' hospital heart failure, echocardiography, and non-invasive cardiology teams provided access to the NICOR, ONS, echocardiographic data and electronic patient records. Dr Vasileios Stylianidis, Dr Fatima Bangash and Mr Andrew Guilder assisted with data collection.

## 3.4 Results

### 3.4.1 General

There were a total of 2821 HF admissions to either GSTT or KCH over the five year period, 1st January 2013 – 31st December 2017. This included repeat admissions and therefore translated to 1884 HF patients who were local to Lambeth or Southwark, UK.

Of this cohort, 1733 (92%) underwent TTE either within 1 month of the index admission or up to 6 months preceding the index admission. There were 16 patients where the quality of the TTE did not allow accurate assessment of MR. A small portion of patients (n=36, 9%) with MR underwent conventional MV surgery. Both of these groups were excluded from our analysis.

This left a total of 1681 patients. Of this group, 1300 (77%) patients had a TTE which showed less than moderate MR, whilst 381 patients had moderate or more MR. This translated to one fifth (20%) of the total number of HF patients who were admitted within the specified five year period. The flowchart below (Figure 3.2) outlines the number of patients who were selected at each stage of the selection criteria pathway, as well as outlining those who were excluded (and reasons for exclusion).

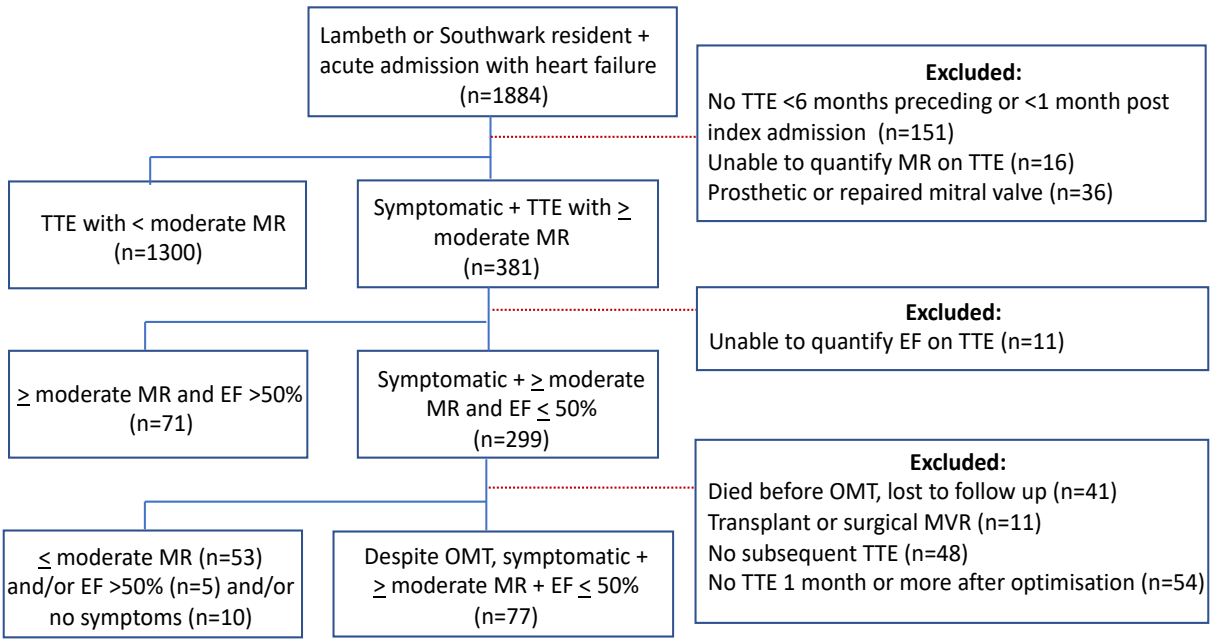


**Figure 3.2.** Flowchart outlining the pathway for patients selected in the retrospective heart failure study. This also outlines those who were excluded and the reasons for exclusion. Abbreviations: MR: mitral regurgitation; EF: ejection fraction; TTE: transthoracic echocardiogram; OMT: optimal medical therapy; MVR: mitral valve replacement.

### 3.4.2 HF patients: with and without MR

There were 1681 patients who underwent TTE as part of their HF admission. The mean age was 72.8 ± 14.8 years and a small majority were male (51.8%). Of the 1681, 58 patients died during the index admission. There were proportionally higher death rates amongst those with moderate or more MR when compared to those with less than moderate MR (n=20 [5.2%] vs. n=38 [2.9%]). There were 395 (24.34%) patients who died within 12 months and 501 (30.9%) who died within 18 months. Of the population with MR, 220 (57.7%) had moderate MR, 80 (21.0%) had moderate to severe MR and 81 (21.3%) had severe MR.

When comparing those patients with and without moderate or more MR, there was a significant difference in 12 month mortality between groups. The risk of mortality for those with moderate or more MR was 32.5% versus 25.3% for those with less than moderate MR (p=0.006; Fisher's exact 2-sided). Results were paralleled at 18 months, with a difference of 37.8% versus 31.9% mortality risk (p=0.036; Fisher's exact 2-sided). Similarly, 12 month survival curves showed a significant difference between groups suggesting a mean survival of 293.5 days (281-306 days) for those with moderate or more MR versus 312.6 days (307-318) for those with less than moderate MR (p=0.003; Kaplan-Meir survival curve) (Figure 3.3). Results were again comparable at 18 months with mean survival estimated at 413 days (≥ moderate MR) versus 444 days (< moderate MR) (p=0.015; Kaplan Meier survival curve) (Figure 3.4).

Using univariate logistic regression, both moderate or more MR and age were predictors of 12 month mortality (p=0.005 for MR, p<0.0001 for age). Gender was not found to be a significant predictor of outcome. Multiple logistic regression including age and presence of moderate or more MR showed that age was the strongest predictor of mortality, with the presence of moderate MR also an independent predictor. For each year of age, the odds of survival decreased by 3.7% (OR 0.963, 95% CI 0.955-0.971, p<0.0001). Additionally, the odds of mortality were 1.5 times higher for patients with moderate or more MR compared to those with less than moderate MR (OR 1.522, 95% CI 1.178-1.968, p=0.01).

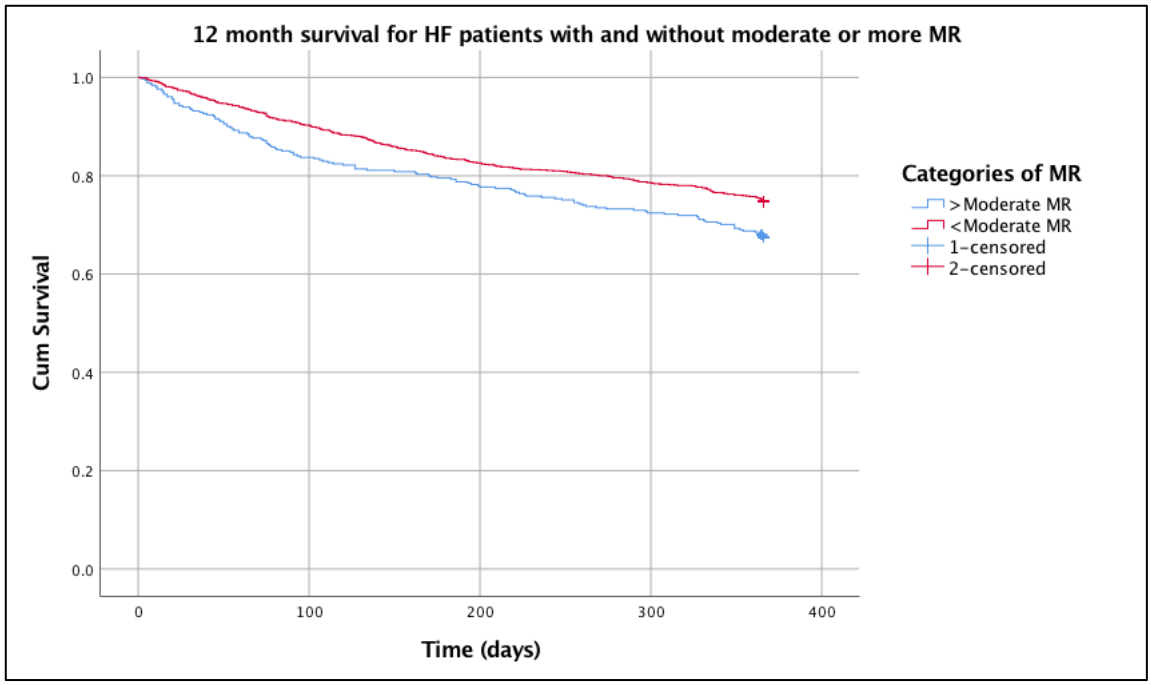


**Figure 3.3.** Kaplan-Meier survival curve based on 12 month survival for heart failure (HF) admission patients with moderate or more mitral regurgitation (MR) versus those without moderate or more MR.

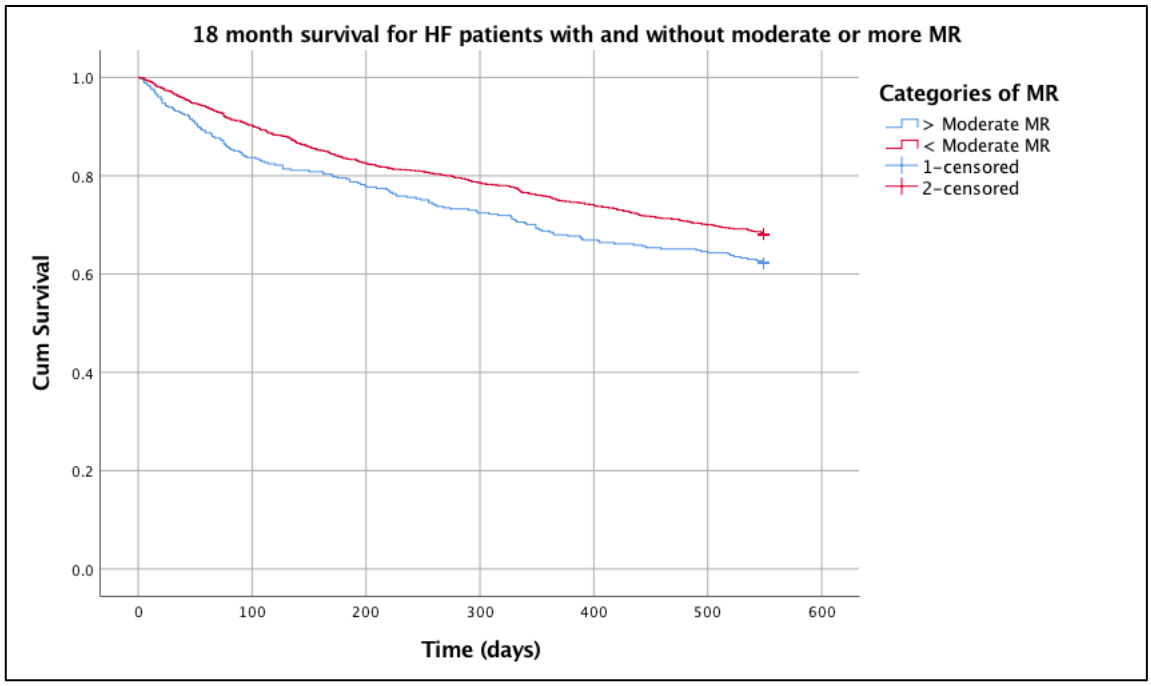


**Figure 3.4.** Kaplan-Meier survival curve based on 18 month survival for heart failure (HF) admission patients with moderate or more mitral regurgitation (MR) versus those without moderate or more MR.

### 3.4.3 Moderate or worse MR: comparing EF

Patients with moderate or more MR were subsequently categorised into two groups: those with an EF of >50% and those with an EF of ≤50%. Of the 381 patients with moderate or more MR, there were 71 with an EF greater than 50%. There were a small number of patients where the quality of the TTE did not allow quantification of EF (n=11). This resulted in a remaining pool of 299 patients with at least moderate MR and an EF of 50% or less. The baseline characteristics for this group are outlined in Table 3.3 with an additional column to outline the characteristic of those with EF >50%.

**Table 3.3.** Patients with heart failure and moderate or more mitral regurgitation (MR): comparing those with an ejection fraction (EF) of ≤50% versus those with an EF of >50%. *Ethnicity was based on limited data. Where a p-value was not reported, there were inadequate data for analysis. Abbreviations: PM: pacemaker; ICD: implantable cardioverter-defibrillator; IHD: ischaemic heart disease; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; NT-pro BNP: N-terminal pro B-type natriuretic peptide; MR: mitral regurgitation; LOS: length of stay. Statistics: Chi-square test for independence for categorical variables and independent T-test for continuous variables.

| Variables | | ≥Moderate MR + EF ≤50% | ≥Moderate MR + EF >50% | P-value |
|---|---|---|---|---|
| Patients | n (%) | 299 (80.82%) | 71 (19.18%) | |
| Age (years) | Mean ± SD | 70.44 ± 15.91 | 78.41 ± 14.66 | 0.064 |
| Sex (male) | n (%) | 165 (55.2%) | 24 (33.8%) | **0.01** |
| Ethnicity (White)* (n=139) | n (%) | 78 (43.8)* | 23 (43.4%)* | - |
| Device (PM or ICD) | n (%) | 58 (19.4%) | 11 (15.5%) | - |
| Mortality at 12 months | n (%) | 58 (19.4%) | 15 (21.1%) | 0.742 |
| LOS in hospital (days) | Mean ± SD | 13.66 ± 12.22 | 15.3 ± 19.86 | 0.15 |
| Hypertension | n (%) | 181 (60.5%) | 52 (73.2%) | 0.113 |
| IHD | n (%) | 116 (38.8%) | 17 (23.9%) | **0.048** |
| Diabetes | n (%) | 91 (30.4%) | 25 (35.2%) | - |
| COPD | n (%) | 46 (15.4%) | 8 (11.3%) | - |
| Asthma | n (%) | 25 (8.4%) | 5 (7.0%) | - |
| Atrial fibrillation | n (%) | 116 (42.5%) | 40 (61.5%) | **0.004** |
| NT-pro BNP | Mean ± SD | 5230 (IQR 11861) | 2829 (IQR 6373) | 0.23 |
| Creatine | Mean ± SD | 108.50 (IQR 63) | 104.00 (IQR 78) | 0.828 |
| NHYA class | I | 7 (2.3%) | 4 (5.6%) | |
| | II | 29 (9.7%) | 12 (16.9%) | |
| | III | 132 (44.1%) | 27 (38.0%) | |
| | IV | 129 (43.1%) | 26 (36.6%) | |
| | Unknown | 2 (0.7%) | 2 (2.8%) | |
| MR moderate | n (%) | 170 (56.9%) | 41 (57.7%) | |
| MR moderate-severe | n (%) | 66 (22.1%) | 13 (18.3%) | |
| MR severe | n (%) | 63 (21.1%) | 17 (23.9%) | 0.738 |
| Ejection fraction | Mean ± SD | 28.51 ± 10.05 | 58.26. ± 5.12 | **<0.0001** |

This showed patients were reasonably matched in terms of their age (p=0.064) although there was a difference between groups in relation to sex. There were more patients in the impaired EF group who were male (55.2%) as opposed to the preserved EF group which predominantly included females (66.2%) (p=0.01) (Figure 3.5). There was also a significant difference in the frequency of patients with IHD, with considerably more patients with IHD in the group with an EF <50% (p=0.048). There was also a significant difference in the number of patients with AF. Interestingly, more patients had AF within the EF >50% group (p=0.004).

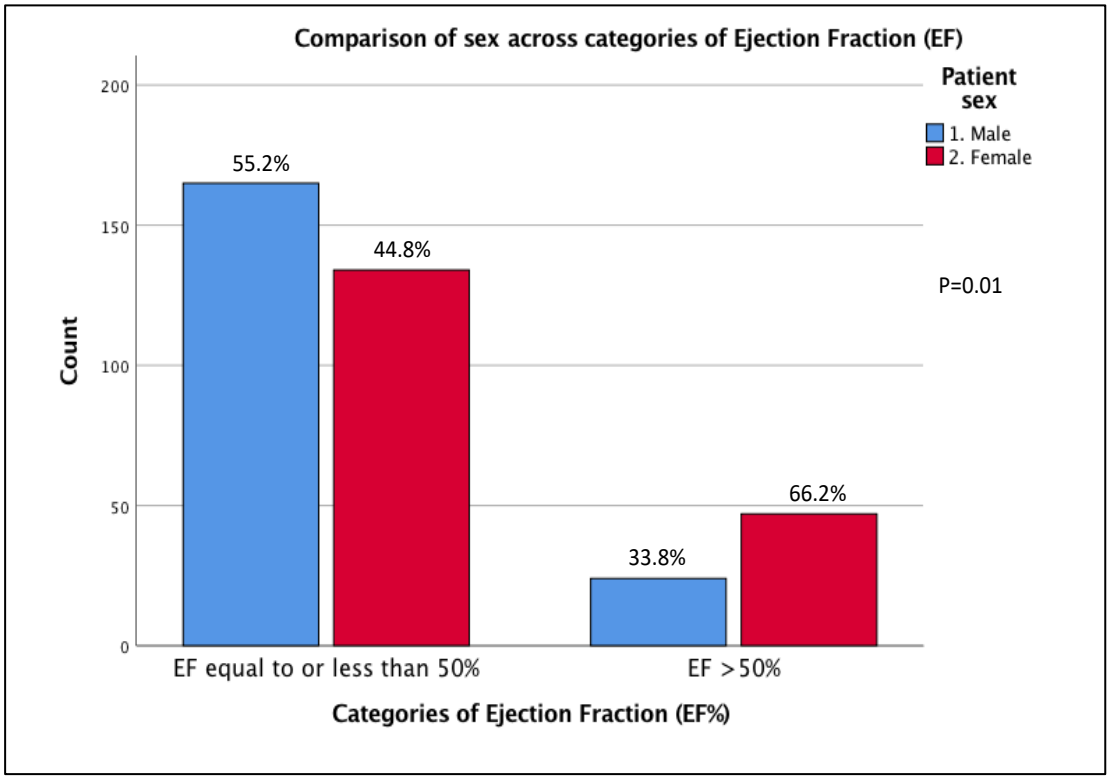


**Figure 3.5.** Patients with heart failure and moderate or more mitral regurgitation: A comparison of sex across the categories of ejection fraction (EF). Statistics: Chi square test for independence.

In total there were 69 (34.9%) patients with an intra-cardiac device. Those with an EF ≤50% were more likely to have a cardiac resynchronisation therapy defibrillator (CRT-D), cardiac resynchronisation therapy pacemaker (CRT-P) or implantable cardioverter-defibrillator (ICD) (Table 3.4).

**Table 3.4.** Patients with heart failure and moderate or more mitral regurgitation: Device therapy across categories of ejection fraction (EF). Abbreviations: CRT-D: cardiac resynchronisation therapy defibrillator; CRT-P: cardiac resynchronisation therapy pacemaker; ICD: implantable cardioverter-defibrillator; PM: pacemaker.

| Categories of EF (%) | No device | CRT-D | CRT-P | ICD | PM | Not known | Total |
|---|---|---|---|---|---|---|---|
| EF ≤50% | 241 | 21 | 4 | 11 | 18 | 4 | 299 |
| EF >50% | 60 | 0 | 0 | 0 | 10 | 1 | 71 |
| **Total** | 301 | 21 | 4 | 11 | 28 | 5 | 370 |

Within this cohort there were 73 patients who died within 12 months, 58 with an ≤50% and 15 with an EF >50%. When we compared mortality at 12 months for patients with moderate or more MR and an EF ≤50% with those with an EF >50%, there was no significant difference (p=0.742, Fisher's exact test). There was no significant difference in the length of hospital stay between groups (p=0.15, t-test) and no significant difference in NT-pro BNP levels (p=0.23, t-test). Neither the presence of IHD or AF were statistically significant predictors of death (p=0.416, p=0.497; Chi Squared test).

Multivariate logistic regression was performed to assess predictors of 12 month mortality and demonstrated that age (p=0.008; univariate logistic regression) and NYHA class (p=0.031; univariate logistic regression) were predictive of mortality in those with moderate or more MR across categories of EF. For multinominal logistical regression results see Table 3.5. This showed that age was an independent predictor of mortality in those with moderate or more MR (p=0.008). There was a trend suggesting NYHA class may have been an independent predictor but this was not statistically significant (p=0.062). The type of HF (HFpEF vs HFrEF) was not an independent predictor of outcome.

**Table 3.5.** Multinominal logistic regression for variables age, New York Heart Association (NYHA) class and ejection fraction (EF) in the prediction of mortality in those with heart failure and moderate or more mitral regurgitation (MR). Abbreviations: HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HR: hazard ratio; CI: confidence interval.

| Variable | HR | CI | P-value |
|---|---|---|---|
| Age | 0.974 | 0.956-0.993 | **0.008** |
| NYHA class | 0.704 | 0.487-1.108 | 0.062 |
| EF (HFrEF or HFpEF) | 1.001 | 0.983-1.019 | 0.955 |

### 3.4.4 Patients on OMT: MR severity, EF and symptoms

Of the 299 patients with moderate or more MR and an EF of ≤50%, 11 underwent conventional surgery or transplantation. A further 41 patients either died before medical optimisation was reached or were lost to follow up.

There were 247 patients who were on OMT. Of these, 36 had undergone CRT. There were 48 patients who did not undergo TTE following optimisation and a further 54 who did not have an echo performed a minimum of one month post optimisation. This left a pool of 145 patients.

From the total group, 68 (46.9%) patients saw an improvement in the degree of MR (to less than moderate MR) and/or an improvement in EF >50% and/or became asymptomatic on OMT. Baseline characteristics for these patients and the remaining 77 patients are outlined in Table 3.6.

**Table 3.6.** Baseline characteristics of patients with heart failure (HF), moderate or more mitral regurgitation (MR) and an ejection fraction of $\leq$50% who were on optimal medication therapy (OMT) (Group 1) compared with patients with HF on OMT with less than moderate MR +/- EF >50% +/- symptom relief (Group 2). Abbreviations: PM: pacemaker; ICD: implantable cardioverter-defibrillator; IHD: ischaemic heart disease; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; NT-Pro BNP: N-terminal pro B-type natriuretic peptide; *Ethnicity was based on a population size of 101. ^There were expected cell counts less than 5. #NT-pro BNP was based on a population of 104. Mitral regurgitation grades: 0=none or trivial; 1=mild; 1.5=mild to moderate; 2=moderate; 3=moderate to severe; 4=severe. Statistics: Chi square test for independence for categorical variables and independent T-test for continuous variables.

| Variables | | | OMT with moderate MR + EF ≤50% | OMT with < moderate MR +/- EF >50% +/- symptom relief | P-value |
|---|---|---|---|---|---|
| | | | Group 1 | Group 2 | |
| **Patients** | | n (%) | 77 (53%) | 68 (47%) | |
| **Age (years)** | | Mean ± SD | 69.95 ± 14.13 | 65.79 ± 17.21 | 0.082 |
| **Sex (male)** | | n (%) | 48 (62.3%) | 37 (54.4%) | 0.212 |
| **Ethnicity (White)* (n=101)** | | n (%) | 19 (24.7%) | 24 (35.3%) | 0.301 |
| **Device (PM or ICD)** | | n (%) | 27 (35.1%) | 9 (13.2%) | 0.04^ |
| **Hypertension** | | n (%) | 49 (64.5%) | 36 (52.9%) | 0.108 |
| **IHD** | | n (%) | 40 (53.3%) | 22 (33.3%) | **0.013** |
| **Diabetes** | | n (%) | 27 (35.1%) | 22 (32.4%) | 0.411 |
| **COPD** | | n (%) | 11 (14.7%) | 14 (20.9%) | 0.226 |
| **Asthma** | | n (%) | 10 (13.3%) | 4 (6.0%) | 0.117 |
| **Mortality at 12 months** | | n (%) | 16(20.8%) | 7(10.3%) | **0.06** |
| **Length of hospital stay (days)** | | Mean ± SD | 14.68 ± 10.98 | 12.79 ± 10.47 | 0.271 |
| **NT-pro BNP# (n=104)** | | Mean ± SD | 6637.6 ± 133447 | 4849.6 ± 8391 | 0.07 |
| **Mitral regurgitation grade** | 0 | n (%) | 0 (0%) | 12 (17.6%) | |
| | 1 | n (%) | 0 (0%) | 27 (39.7%) | |
| | 1.5 | n (%) | 0 (0%) | 16 (23.5%) | |
| | 2 | n (%) | 40 (51.9%) | 9 (13.2%) | |
| | 3 | n (%) | 20 (26%) | 2 (2.9%) | |
| | 4 | n (%) | 17 (22.1%) | 2 (2.9%) | **<0.0001** |

| | | | | | |
|---|---|---|---|---|---|
| **NHYA Class** | 1 | n (%) | 0 (0%) | 21 (30.9%) | |
| | 2 | n (%) | 35 (45.5%) | 29 (42.6%) | |
| | 3 | n (%) | 27 (35.1%) | 13 (19.1%) | |
| | 4 | n (%) | 15 (19.5%) | 5 (7.4%) | **<0.0001** |

For the group with remaining MR, EF <50% and symptoms (Group 1), the mean age was 77 years and the majority were male. Those patients with improved status (Group 2) were slightly younger (mean age 68 years). Age was not statistically different between groups. As expected, a larger number of patients in Group 1 had an intra-cardiac device (35.1% vs 13.2%).

In terms of comorbidities, hypertension was the most common across both groups (Group 1: 64.5% vs. Group 2: 52.9%), followed by IHD (Group 1: 53.3% vs. Group 2: 33.3%), and diabetes (Group 1: 35.1% vs. Group 2: 32.4%). On the whole, Group 1 had more comorbidities aside from chronic obstructive pulmonary disease (COPD). Length of stay (LOS) did not differ between groups (p=0.271; t-test). However, there was a trend suggesting greater mortality within Group 1, namely those with persistent moderate or more MR, EF $\leq$50% and symptoms despite OMT (p=0.06, Fisher's exact test). Despite OMT, over half (n=77, 53%) of HF patients with moderate or more MR, EF $\leq$50% remained symptomatic.

### 3.4.5 Patients on OMT: MR severity, EF and symptoms

In order to assess change in MR and NYHA with OMT, it was necessary to separately assess patients with moderate or more MR, EF $\leq$50% on OMT who underwent echocardiographic evaluation at two time points in line with our selection criteria (before OMT, and at least 1 month post OMT). Paired sequential comparisons of echocardiographic findings, medical therapy and symptom status pre- and post-optimisation were therefore performed.

There were 82 patients. This analysis showed that medical optimisation reduced the number of patients with moderate, moderate to severe and severe MR from 82 to 43. Following OMT, there were 12 patients with severe MR, 10 with moderate to severe MR and 21 with moderate MR. Compared to pre-OMT, there was a significant difference in MR severity suggesting that medical therapy is helpful in reducing MR (p=0.001, Pearson Chi-Square). Unfortunately, there was no significant change in NYHA class pre- and post-OMT (p=0.650, Chi-square test) (Table 3.7). This was based on analysis with cell counts less than five so the accuracy of this outcome is questionable. When repeated using ANOVA, examining the raw percentages suggested an improvement in NYHA class on OMT (63.4% showed improvement, 30.5% were unchanged and only 6.1% were clinically worse) (Table 3.8).

**Table 3.7.** Comparison before and after optimal medical therapy (OMT): change in clinical (New York Heart Association [NYHA] class) and echocardiographic (mitral regurgitation) characteristics after optimal medical therapy (OMT). [+]Based on cell counts less than 5.

| | | | Pre OMT | Post OMT | P-value |
|---|---|---|---|---|---|
| **Mitral regurgitation** | Moderate | n (%) | 42 (51.2%) | 12 (14.6%) | |
| | Moderate-severe | n (%) | 21 (25.6%) | 10 (12.2%) | |
| | Severe | n (%) | 19 (23.2%) | 21 (25.6%) | 0.001 |
| | | | | | |
| **NYHA classification** | Class I | n (%) | 0 (0%) | 14 (16.9%) | |
| | Class II | n (%) | 11 (13.3%) | 35 (42.2%) | |
| | Class III | n (%) | 36 (43.4%) | 25 (30.1%) | |
| | Class IV | n (%) | 36 (43.4%) | 9 (10.8%) | 0.650[+] |

**Table 3.8.** Changes in mitral regurgitation (MR) and New York Heart Association (NHYA) class with optimal medical therapy (OMT) based on the categories improved, unchanged and worsened.

| Variable | Change | n (%) |
|---|---|---|
| **MR severity post OMT** | Improved | 44 (53.0%) |
| | Unchanged | 31 (37.4%) |
| | Worsened | 8 (9.6%) |
| **NYHA class post OMT** | Improved | 52 (63.4%) |
| | Unchanged | 25 (30.5%) |
| | Worsened | 4 (6.1%) |

## 3.4 Discussion

This retrospective study focussed on a large consecutive unfiltered cohort of adult patients admitted with a primary diagnosis of HF and demonstrated that one fifth of all HF patients have moderate or more MR. There are limited data available in relation to the prevalence of MR specific to the HF population. Our national audit data suggest that 41% of the HF population has valvular disease although this is not specific to MR (1). Other evidence suggests significant MR within the HF population with prevalence as high as 49%. However, these data were based on filtering of recruited patients, with only those with an EF of 35% or less included (73). An EF of 35% or less is what we could consider severe according to British Society of Echocardiography guidance, thus introducing a certain degree of bias in the interpretation of MR prevalence within the HF population. Additional population based data from the UK suggest that significant MR is present in 2.3% of those over the age of 65 years (17). However, this fails to examine prevalence across the subset of HF.

Aside from these resources, robust evidence is scarce. A smaller American study suggested up to 59% of patients presenting with HF have moderate or more MR. However, this study was based on those with an EF <40% only and was not founded on the total population of HF referrals (TTE results missing) (74). Having excluded patients with an EF >40% from the examination cohort, it is plausible that this predicted number was over-estimated due to a more clinically unstable population where referral for TTE may have been more likely. Moreover, this study was published in 2002, since

when the diagnosis and management of patients with HF has changed significantly, raising uncertainty as to how a diagnosis of HF was defined in this study (74).

In the study cohort, mortality at 12 months was higher for individuals with moderate or more MR compared to those with less than moderate MR. This experience has been long supported by the literature (75-77). Studies have found a strong association between functional MR and long term risk of death (76, 78). The severity (across all grades of MR) has also been shown to inversely relate to survival. One study suggested a 12 month survival rate of 70% for those with moderate MR and 59% for those with severe MR (73). Our study assessed survival based on moderate and severe MR combined and suggested a 12 month survival rate of 67.5% which appears to align with the previous study. More than moderate MR and age were found to be independent predictors of death. This finding was corroborated by Cioffi *et al* who also identified age and degree of MR as independent predictors of mortality at 12 months, albeit with a focus on a population aged greater than 70 years (79).

The purpose of the current study was to determine the burden of MR at local population level. Therefore patients with both primary and secondary MR aetiologies were included. The current European recommendations regarding primary MR suggest that surgery should be considered in patients with symptoms and an EF $\leq$60%. Around 10% of our cohort underwent surgical MV repair or replacement and it is therefore expected that patients with primary MR were excluded from our analysis in the early stages. This does however raise the question as to whether more patients

should have been considered for surgical intervention. Over 80% of our patients with moderate or more MR had an EF ≤50% and an admission with HF (implying that they were symptomatic). However, many patients in our cohort were older (70 ± 16 years) with multiple comorbidities. A large number of patients had IHD and hypertension. It is important also to note that the mean EF for patients under scrutiny in this study was 29% (± 10%). This suggests a population of which the majority of patients had MR that was secondary in nature, alongside high, or even prohibitive, risk. Given that surgery is not currently indicated for isolated secondary MR (as it has not been shown to offer a survival benefit), this provides reasoning as to the low percentage of patients who underwent surgical intervention (30).

OMT is recommended for secondary MR in both the European HF and valve guidelines to aid in improving overall LV systolic contractility and assist in reducing the degree of MR. Our study demonstrated that 50% of patients had an improvement in symptoms (NYHA class) as a result of OMT. Additionally, there was a significant reduction in the degree of MR with OMT. It is feasible that this would have resulted in a reduced number of avoidable hospital admissions, improved quality of life for many and associated cost savings for the health service.

Despite CRT and OMT there were still 77 patients with moderate or more MR and an EF <50% with significant symptoms. Left untreated, the future for these patients will likely involve frequent hospitalisation, worsening quality of life (QoL) and premature death. It is reasonable then to consider what other options may be available to this

population. The national guidelines last updated in 2017 (prior to publication of the COAPT and MITRA-FR studies) highlighted a lack of evidence supporting improved survival as a consequence of a reduction in chronic secondary MR (10). However, over the last five years TMVR has been shown to reduce the rate of hospitalisation and lower all cause mortality for patients with LV systolic dysfunction and more than moderate MR (60). Moreover, it has been shown to improve symptoms, functional capacity and QoL as well as potentially playing a role in positive LV reverse re-modelling (80). Worldwide, the jury is still out as large scale RCTs debate the effectiveness of TMVR with one mutual, recognisable and resonating recommendation: the need for further long term studies with stringent research designs and a focus on comparable variables delivering unquestionable patient outcomes.

## 3.5 Limitations

There were a number of limitations within this study. Firstly, data obtained from NICOR was based on hospital admissions rather than patients and it is possible that there was duplication of patients who may have presented to different tertiary centres. Efforts were made to overcome this limitation by applying filtering, sorting and matching tools.

Secondly, I wanted to gain an appreciation of the burden of MR at local population level and therefore included those with both primary and secondary MR aetiologies.

Our interpretation has thus not separated the two. However, it is likely that most patients with primary MR and an EF <50% would have undergone MV surgery given the difference in treatment guidelines for patients with primary and secondary MR, and would have therefore been excluded from the analysis in the early stages.

Thirdly, survival modelling has been based on the whole population. This means we have included patients with MR of mixed aetiologies (primary and secondary MR) alike. It is possible that other underlying confounding variables biased the results of this modelling (i.e. ischaemic heart disease, dilated atria, idiopathic cardiomyopathies).

Fourthly, we did not collect data on patient's adherence to medical therapy and therefore we cannot be sure that patients' who we classified as being on OMT were in fact adhering to their medical therapy recommendations. Current guidance suggests that optimisation of medical therapy is best achieved through the supervision of a cardiologist expert (31).

Additionally, only 27% of patients had matching echocardiographic, symptom and medical therapy data to allow interrogation of the effects of medical therapy. Aside from those who underwent surgical MVR, transplant, or those who improved or did not improve, the remaining patients were either lost to follow up, died, or did not undergo a repeat TTE within one month of medical optimisation.

Finally, the inherent nature of a retrospective review limited our interpretation. Although I investigated admissions over a 5 year period, I was only able to assess the risk of mortality at a maximum of 18 months.

## 3.6 Conclusion

MR is common within the Lambeth and Southwark HF population. At least one fifth of patients demonstrate moderate or worse MR, with the large majority also having an EF of 50% or less. For those with moderate or more MR, there is an increased risk of premature death. When treated with OMT, patients experience improvement both through reduction in MR and symptom resolution. However, half of patients continue to have moderate or more MR, an EF $\leq$50% and remain symptomatic. I propose that a portion of these patients are potential candidates for TMVR according to current international guidelines and further intervention should therefore be explored.

# CHAPTER 4

# MITRAL REGURGITATION IN ACUTE HEART FAILURE: POTENTIAL PREVALENCE OF PATIENTS SUITABLE FOR TRANSCATHETER MITRAL VALVE REPAIR

## 4.1 Introduction

Mitral regurgitation (MR) is one of the most common valvular lesions with a global prevalence exceeding 6 million and an annual mortality of 5% without interventional treatment (2-4, 81). In the previous chapter, I demonstrated that one fifth of all heart failure (HF) admissions had moderate or more MR. This retrospective study combined both primary and secondary aetiologies, but it is likely that the majority of patients had secondary MR given the high incidence of ischaemic heart disease (IHD), hypertension, and impaired ejection fraction (EF) within our aging cohort. Current treatment options for secondary MR include medical therapy, cardiac resynchronisation and conventional mitral valve (MV) surgery, with transcatheter

mitral valve repair (TMVR) reserved for high surgical risk patients with multiple comorbidities, significant MR, left ventricular impairment and persistent symptoms despite optimal medical therapy (OMT).

## 4.2 Aims and Objectives

Based on the outcomes of the previous chapter and an established cohort of symptomatic HF patients with moderate or MR and an EF ≤50%, I aimed to investigate the potential for treating HF patients who have MR using TMVR. I hypothesised that a significant number of Lambeth and Southwark HF patients with moderate or more MR remain symptomatic despite OMT, and may be candidates for TMVR.

My objectives were to determine: (1) the number of patients presenting with HF who have an EF of 20-50% and moderate or more MR despite OMT; (2) the number of patients within this group who are considered high or intermediate risk using the Euroscore II risk algorithm; (3) the sub-group who may be candidates for TMVR based on Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) echocardiographic criteria, surgical risk and Heart Team review; 4) estimated projections regarding the potential to treat patients with TMVR at population level.

## 4.3 Methods

As described in Chapter 3, this was a retrospective study based on the interrogation of a large database of patients presenting with HF to two tertiary centres over a five year period. Those patients with moderate or more MR were then compared to those without MR, and those with moderate or more MR were then sub-categorised into one of two groups: those with an EF >50% and those with an EF ≤50%. Subsequent to this, patient records were reviewed to evaluate which patients were receiving OMT (and which of these remained symptomatic). Sections 3.3.1-3.3.3 provide a comprehensive outline of the methodology and Figure 4.1 provides a flowchart summarising the patient selection process.

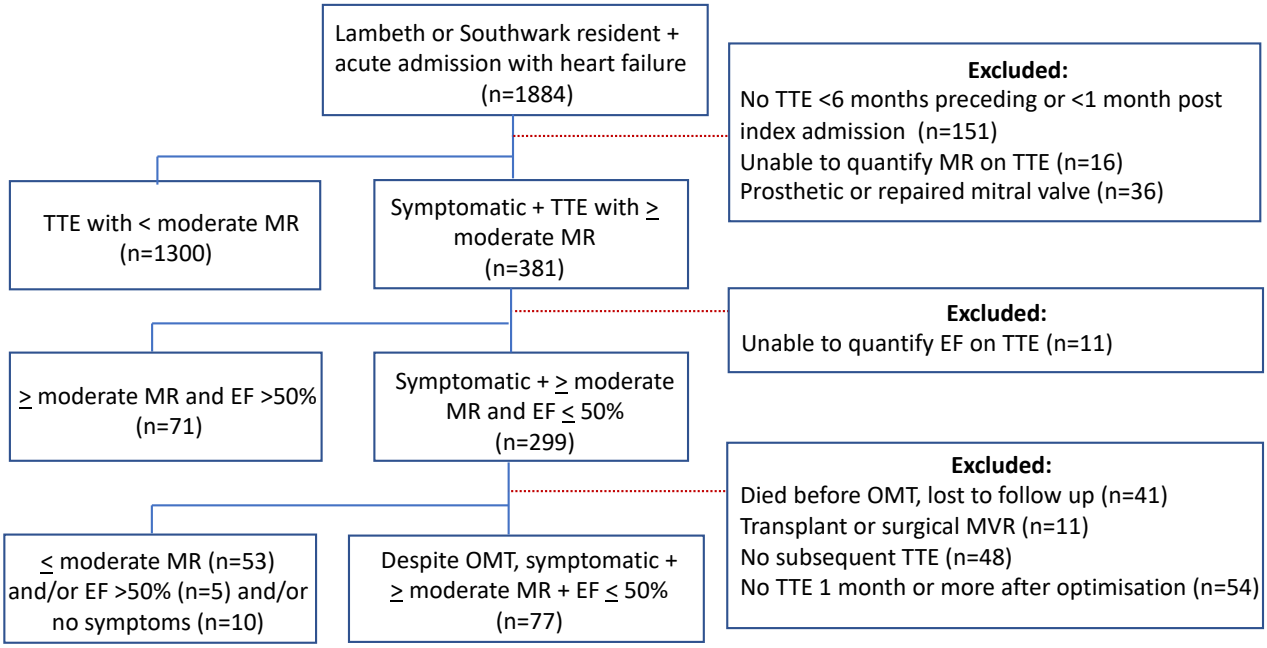


**Figure 4.1.** Flowchart outlining the pathway for patients selected in the retrospective heart failure study. This also outlines those who were excluded and the reasons for exclusion. Abbreviations: MR: mitral regurgitation; EF: ejection fraction; TTE: transthoracic echocardiogram; OMT: optimal medical therapy; MVR: mitral valve replacement.

Methods for identification of the population of symptomatic HF patients with moderate or more MR and an EF ≤50% despite OMT are outlined in Chapter 3. The methodology was extended in this chapter as outlined in Figure 4.2 (please refer to stages 6,7 and 8).

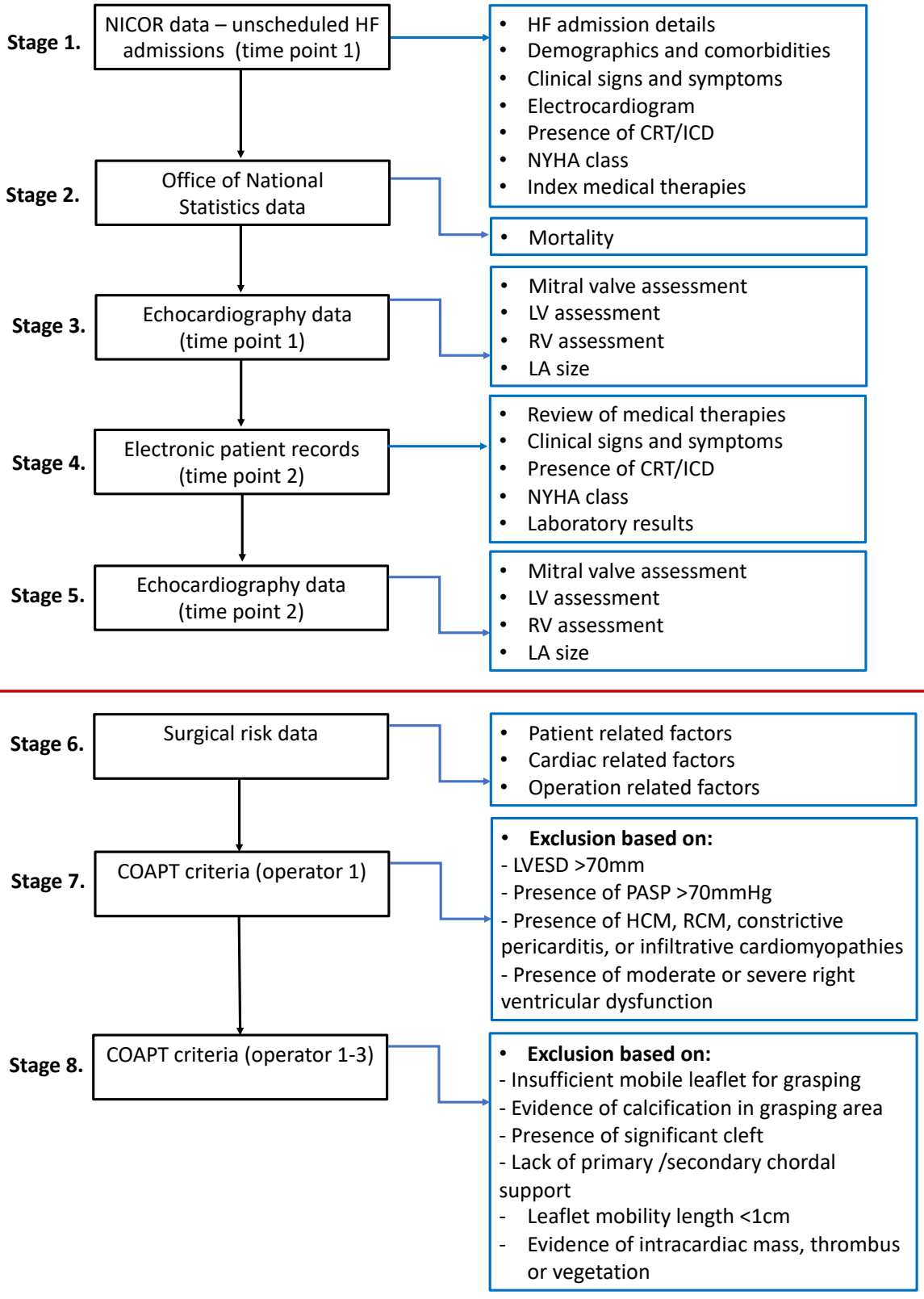
Stage 1.
NICOR data – unscheduled HF admissions (time point 1)
HF admission details
Demographics and comorbidities
Clinical signs and symptoms
Electrocardiogram
Presence of CRT/ICD
NYHA class
Index medical therapies
Stage 2.
Office of National Statistics data
Mortality
Stage 3.
Echocardiography data (time point 1)
Mitral valve assessment
LV assessment
RV assessment
LA size
Stage 4.
Electronic patient records (time point 2)
Review of medical therapies
Clinical signs and symptoms
Presence of CRT/ICD
NYHA class
Laboratory results
Stage 5.
Echocardiography data (time point 2)
Mitral valve assessment
LV assessment
RV assessment
LA size
Stage 6.
Surgical risk data
Patient related factors
Cardiac related factors
Operation related factors
Stage 7.
COAPT criteria (operator 1)
Exclusion based on:
- LVESD >70mm
- Presence of PASP >70mmHg
- Presence of HCM, RCM, constrictive pericarditis, or infiltrative cardiomyopathies
- Presence of moderate or severe right ventricular dysfunction
Stage 8.
COAPT criteria (operator 1-3)
Exclusion based on:
- Insufficient mobile leaflet for grasping
- Evidence of calcification in grasping area
- Presence of significant cleft
- Lack of primary /secondary chordal support
- Leaflet mobility length <1cm
- Evidence of intracardiac mass, thrombus or vegetation

**Figure 4.2.** Flowchart demonstrating the process by which retrospective patient data were collected for the retrospective heart failure study (stages 1-5). Additional stages 6,7 & 8 have been included to outline further components introduced as part of the Chapter 4 methodology. Abbreviations: HF: heart failure; CRT: cardiac resynchronisation therapy; ICD: implantable cardioverter-defibrillator; NYHA: New York Heart Association, LV: left ventricle; RV: right ventricle; LA: left atrium; LVESD: left ventricular end systolic dimension; PASP: pulmonary artery systolic pressure; HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathies; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation. Note: the red line denotes where the methodology was extended in Chapter 4.

### 4.3.1 Study design

All patients underwent detailed echocardiographic examinations with MR assessed using an integrative multiparametric approach. Left ventricular (LV) size and function, right ventricular (RV) size and function, and pulmonary artery systolic pressure (PASP) were also key areas for interrogation. These data were used to determine potential suitability for TMVR based on application of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial echocardiographic inclusion and exclusion criteria (21). Additionally, patient records were used to determine surgical risk (Euroscore II). Demographics, laboratory data and co-morbidity details were collected by the lead investigator (KV) using electronic patient records.

### 4.3.2 Study population

Previously examining patients with an EF ≤50%, this chapter focussed on patients with an EF between 20-50% to ensure alignment with inclusion and exclusion criteria applied in the COAPT trial. Therefore, patients with an EF of 19% or less were subsequently excluded from this Chapter. There were additional specific echo criteria which were used to define suitability (Table 4.3) and wider inclusion and exclusion criteria are outlined below (Table 4.1).

**Table 4.1.** Inclusion and exclusion criteria for patients involved in this study focussing on suitability for transcatheter mitral valve repair based on echocardiographic and surgical risk criteria. Abbreviations: GSTT: Guy's and St Thomas' NHS Foundation Trust; KCH: King's College Hospital; HF: heart failure; MR: mitral regurgitation. EF: ejection fraction; OMT: optimal medical therapy; TTE: transthoracic echocardiogram.

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| 1. Presentation to either GSTT or KCH with HF between Jan 2013 and December 2017<br>2. Resident of Southwark or Lambeth<br>3. 18 years or older<br>4. Moderate or more MR, EF ≤50% and symptoms despite OMT | 1. TTE performed either within 1 month of, or up to 6 months preceding, the index admission<br>2. Unable to estimate EF or quantify MR on TTE<br>3. Less than moderate MR, EF >50% or asymptomatic |

### 4.3.3 Demographics, laboratory and clinical information

As outlined in Chapter 3, demographics, clinical data, information relating to medical history, comorbidities, and biochemistry results were obtained from the NICOR data set and electronic patient records. This information was obtained by myself and a cardiology doctor in training (FB) using electronic patient records such as EPR and EPR Sunrise.

### 4.3.4 Surgical risk

#### 4.3.4.1 Determining surgical risk

The European System for Cardiac Operative Risk Evaluation (Euroscore) II was used to determine the risk of in-hospital mortality after major cardiac surgery. Parameters required for the calculation of surgical risk score are outlined in Table 4.2. Risk was determined by inputting the relevant data into the online Euroscore II algorithm tool (http://www.euroscore.org) (82). I performed this task assisted by a cardiology doctor in training (FB) using information that was obtained by searching through electronic patient records. In order to ensure simplicity, only one risk score was used in this study. This particular risk score most reliably relates to UK experience and the decision to use it was based on expert opinion from our internal surgical consultant body. To maintain simplicity within the calculation, all routine patients were allocated an urgency

of ‘elective’, a weight of intervention of ‘single non-CABG’ and a surgery on thoracic aorta of ‘no’.

**Table 4.2.** Parameters required for the calculation of surgical risk score using the online Euroscore II calculator. [+] Renal impairment was determined using the Cockroft-Gault creatinine clearance calculator which required plasma creatinine, age, weight, and sex. [*]CCS class 4 angina was defined by angina at rest. ^Pulmonary hypertension (as per moderate 31-35mmHg; severe > 55mmHg). [#]For this study, all routine patients were allocated an urgency of ‘elective’, a weight of intervention of ‘single non-CABG’ and a surgery on thoracic aorta of ‘no’. Abbreviations: NYHA: New York Heart Association; MI: myocardial infarction (82).

| **Patient Related Factors** | **Cardiac Related Factors** | **Operation Related Factors** |
|---|---|---|
| Age in years | NYHA | Urgency[#] |
| Gender | CCS class 4 angina[*] | Weight of the intervention[#] |
| Renal impairment[+] | LV function | Surgery on thoracic aorta[#] |
| Extracardiac arteriopathy | Recent MI | |
| Poor mobility | Pulmonary hypertension[^] | |
| Previous cardiac surgery | | |
| Chronic lung disease | | |
| Active endocarditis | | |
| Critical pre-operative state | | |
| Diabetes on insulin | | |

#### 4.3.4.2 Categories of surgical risk

Based on empirical evidence and recommendations from the literature, pre-operative risk and in-hospital mortality risk categories were defined in this study as (83, 84):

- low risk <3%
- intermediate risk 3 - < 6%
- high risk ≥6%;

### 4.3.5 Echocardiography data

I reviewed archived digital images for all intermediate and high risk patients with symptomatic HF despite OMT who had moderate or more MR and an EF ≤50%. Details regarding the lead investigator review are outlined in Section 4.3.6. Potential suitability for TMVR was determined by application of the COAPT trial echocardiographic inclusion and exclusion criteria.

#### 4.3.5.1 COAPT inclusion and exclusion criteria

Table 4.3 outlines the criteria used in the COAPT trial relating to echocardiographic measurements (21). This was used in conjunction with the COAPT algorithm for determining the severity of MR (Figure 4.3). Finally, technical suitability for TMVR was determined based on consensus amongst a group of experts (Section 4.3.6). Patients with both primary and mixed primary/secondary mitral valve disease were excluded.

**Table 4.3.** Echocardiographic inclusion and exclusion criteria used in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial (21). Abbreviations: MR: mitral regurgitation; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic dimension; PASP: pulmonary artery systolic pressure; HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy.

| Echocardiographic Inclusion | Echocardiographic Exclusion |
|---|---|
| • Functional MR (≥3+)<br>• Global or regional abnormality<br>• LVEF ≥20% and ≤50%<br>• Primary MR jet is non-commissural<br>• LVESD ≤70mm | • PASP >70mmHg<br>• Presence of HCM, RCM, constrictive pericarditis, or infiltrative cardiomyopathies<br>• Presence of moderate or severe right ventricular dysfunction<br>• Mitral valve orifice area <4.0cm2<br>• Leaflet anatomy precluding clip implantation:<br>  • Insufficient mobile leaflet for grasping<br>  • Evidence of calcification in grasping area<br>  • Significant cleft<br>  • Lack of primary / secondary chordal support<br>• Leaflet mobility length <1cm<br>• Evidence of intracardiac mass, thrombus or vegetation |

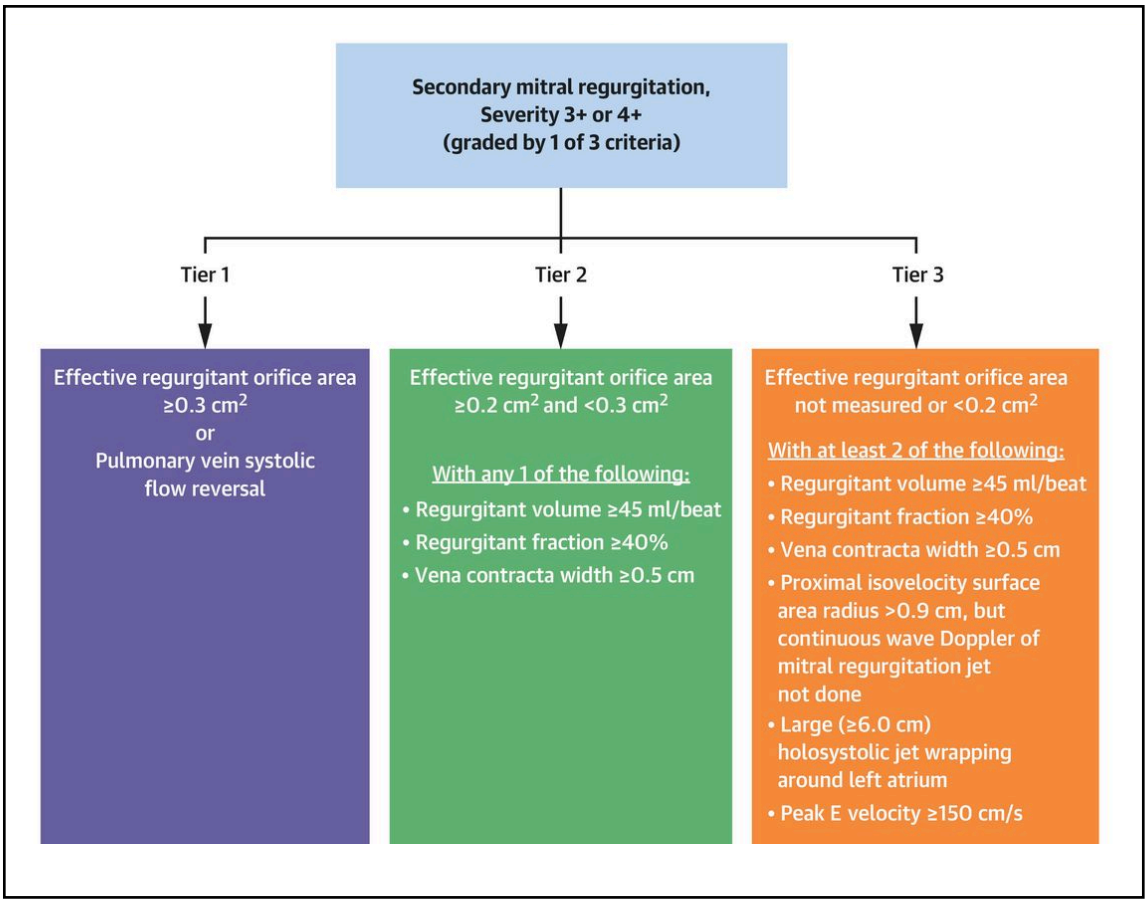


**Figure 4.3.** Echocardiography algorithm used to determine the degree of mitral regurgitation in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial. Taken from: Asch *et al* (2019) (85).

#### 4.3.5.2 Measurement and assessment technique

Digital images were interrogated with additional measurements made offline in order to determine the aetiology and severity of MR, and suitability for TMVR. Measurements were made in line with British Society of Echocardiography recommendations (themselves based upon recommendations from the American

Society of Echocardiography [ASE] and European Association of Echocardiography [EAE]) (69-71).

Mitral valve (MV) leaflets were assessed for the presence of thickening, calcification and tethering. The degree of tenting throughout systole was also examined. Each of these were graded as follows: 1) nil 2) mild 3) significant. The length of the leaflets was reviewed for appropriateness and leaflets examined for rheumatic changes, commissural fusion and the presence of stenosis. Where the MV areas were <4.0cm$^2$, this was documented.

In each case, the aetiology of the MR was determined as either primary or secondary. The severity of regurgitation was assessed using an integrative approach. Regurgitant volume was calculated one of two ways:

1) Stroke volume (SV) method using the difference between transmitral flow and flow across the left ventricular outflow tract. In this case, 2D linear measurements of both the LVOT in systole and mitral valve annulus in diastole were required (Table 4.4).
2) Proximal isovelocity surface area (PISA) method: PISA was performed with a Nyquist limit of 30-40cm/sec. When PISA was obtained and considered accurate, the radius was measured from the point of colour aliasing to the vena contracta (Table 4.4).

Effective regurgitant orifice area (EROA) was calculated based on measures of regurgitant flow and peak velocity of the MR continuous wave envelope (Table 4.4). Regurgitant fraction (RF) was determined based on MV regurgitant volume (RVol) as a proportion of total mitral volume converted to a percentage.

**Table 4.4.** Calculations used for the quantitative echocardiographic assessment of mitral regurgitation. Abbreviations: SV: stroke volume; MV: mitral valve; D: diameter; r: radius; VTI: velocity time integral; PISA: proximal isovelocity surface area; LVOT: left ventricular outflow tract.

| Measurement | Measurement Abbreviation | Calculation |
|---|---|---|
| Regurgitant volume (mL) (by SV method) | RVol | $SV_{MV} - SV_{LVOT}$ Where SV is ($0.795 \times D^2 \times VTI$) |
| Regurgitant volume (mL) (by PISA method) | RVol | $2\pi r^2$ x Va (where Va is the Nyquist limit) / regurgitation velocity of the MR jet x VTI of the MR jet |
| Effective orifice area (cm2) | EROA | RVol / Peak velocity of the MR jet |
| Regurgitant fraction (%) | RF | $SV_{MV} - SV_{LVOT}$ / 100 |

Flow reversal within the pulmonary vein was assessed based on pulsed wave Doppler with a small sample volume placed approximately 1cm into the mouth of the pulmonary vein (typically the right upper pulmonary vein).

Vena contracta width was measured when proximal flow convergence was best visualised. Where possible, this was taken from the PLAX window to allow alignment between the proximal flow convergence, vena contracta and MR jet. PISA radius was measured as outlined above in regurgitant volumes.

A large holosystolic jet wrapping around the left atrium (LA) was assessed visually using colour flow imaging (CFI) and continuous wave (CW) Doppler. A dense and uniform trace throughout systole or a biphasic CW Doppler trace was required to define moderate to severe or severe MR. A triangular jet also suggested severe MR. Colour flow imaging was also used to exclude the presence of a commissural jet.

The peak E-wave of mitral inflow was obtained using pulsed wave Doppler aligned with the MV forward flow and positioned at the tip of the valve leaflets in diastole (obtained in the four chamber view). A peak velocity $\geq$1.50m/s was deemed consistent with severe MR.

Additionally, digital images were used to exclude the presence of vegetations, masses or thrombus. Colour flow imaging was used to assess the degree of tricuspid regurgitation and 2D images were used to inspect the suitability of the interatrial septum for TMVR via trans-septal approach. Right ventricular systolic function was assessed based upon a combination of visual assessment and the interpretation of quantitative measures, such as fractional area change (FAC), tricuspid annular plane

systolic excursion (TAPSE) and tissue Doppler of the right ventricle in systole (RV S'). A 2D linear measurement of the left ventricular end systolic dimension was recorded.

### 4.3.6 Echocardiography review

In the first instance, I reviewed the echocardiographic images. I am trained and accredited in transthoracic and transoesophageal echocardiography and have more than 15 years experience working in echocardiography and valve disease.

Following initial screening by myself, TTEs of patients considered suitable for TMVR based on echocardiographic criteria and procedural risk, were reviewed by an expert valve specialist within the valve team (JH or MM), both of whom are imaging consultants trained and accredited in transthoracic and transoesophageal echocardiography with more than 25 years experience working in valve disease and echocardiography. If agreement was met, the patient was considered 'suitable based on echocardiographic and risk criteria'. Any discrepancies between investigator 1 and expert 1, were resolved by a second expert (BP) who is the chief investigator and lead for valve disease services at Guy's and St Thomas' Hospital.

Inter-operator reproducibility was examined in all patients being assessed for eligibility following exclusion of patients with LVESD >70mm, the presence of PASP >70mmHg, HCM, RCM, constrictive pericarditis, or infiltrative cardiomyopathies, or moderate or

severe right ventricular dysfunction (Stage 7 of methodology flowchart, Figure 4.2), using blinded reads by two experts.

### 4.3.7 Extrapolation of data

For the extrapolation of data, figures published within the NICOR 2017/2018 report (1) were used to determine HF incidence at the level of the English population.

### 4.3.8 End points

The end points for this chapter were:

1) Number of patients potentially suitable for TMVR based on risk criteria.
2) Number of patients potentially suitable for TMVR based on echocardiographic and risk criteria.

### 4.3.9 Statistical analysis

Limited statistical analysis was required in this Chapter. Categorical outcomes were based on frequencies and percentages, and continuous variables on standard deviations and means. Bivariate analysis was performing using Chi Square for categorical variables and ANOVA for continuous variables.

## 4.4 Results

In Chapter 3, I was able to establish that 1884 patients presented with acute HF over a five year period (Jan 2013 – Dec 2017). Of this cohort, 237 (12.6%) had moderate or more MR and an EF of <50%. Following stabilisation on OMT, 77 patients remained symptomatic with moderate or more MR and an EF <50%. Figure 4.4 provides an overview of the patient selection process.

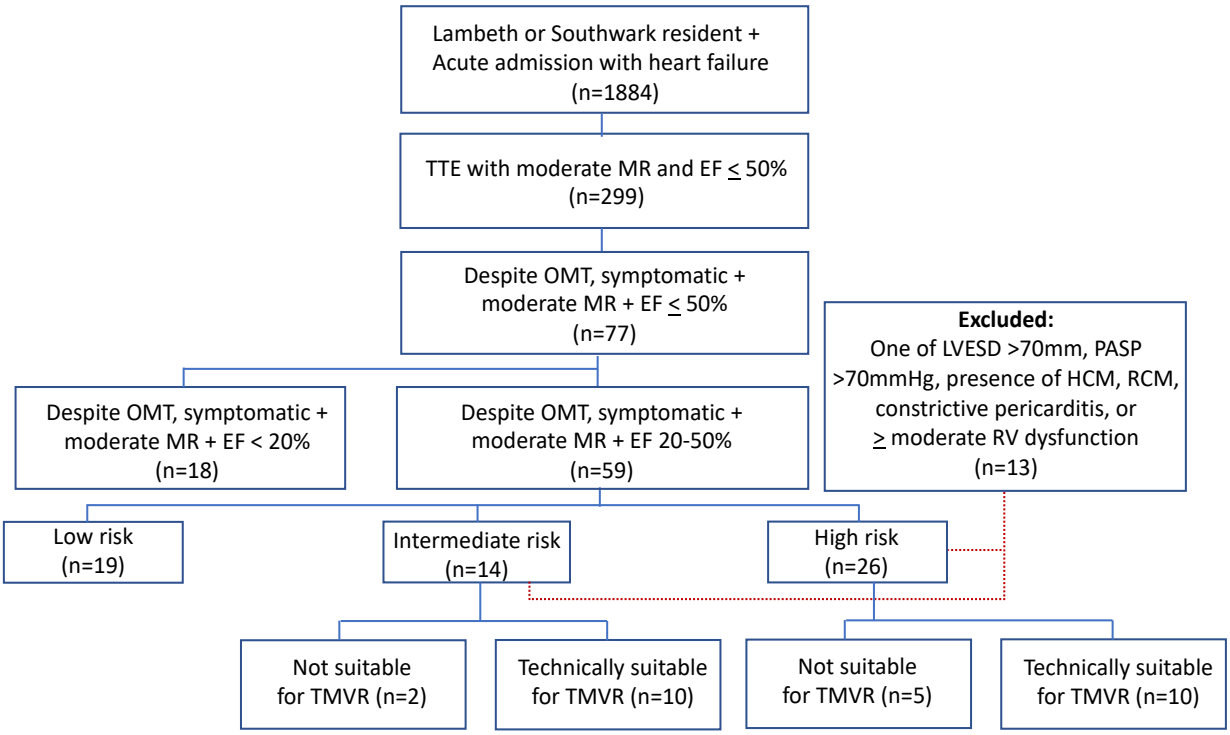


**Figure 4.4.** Flowchart outlining the selection criteria pathway for patients involved in the retrospective studies (Chapters 3 and 4). Abbreviations: MR: mitral regurgitation; EF: ejection fraction; OMT: optimal medical therapy; LVESD: left ventricular end-systolic dimension; PASP: pulmonary artery systolic pressure; HCM: hypertrophic cardiomyopathy; RCM: restricted cardiomyopathy; RV: right ventricle; TMVR: transcatheter mitral valve repair.

There were 18 patients with an EF <20% and these individuals were excluded from our population. Thus, 59 patients had an EF 20-50%, moderate or more MR and symptoms despite OMT.

For each of the 59 patients, risk was determined based on the Euroscore II algorithm. There were 26 (44%) patients with high risk (≥6%), and 14 (24%) with intermediate risk (3-<6%). Those with low risk (<3%) were examined and excluded from further analysis (n=19 (32%)). Across the groups, the mean age was 69.88 years (SD ± 13.57) and the mean EF 31.6% (SD ± 8.8%).

In the intermediate and high risk groups, the mean age and mean EF were 70 and 79 years and 30% and 33%, respectively. Variations between groups are highlighted in Table 4.5. The mean calculated risk scores across different groups were as follows: low risk 1.89%, intermediate risk 3.88%, high risk 15.67%. Two variables which were statistically different across the three risk groups were age (p=<0.001) and history of IHD (p=0.001). Of those in the higher risk group (>6%), 81% had IHD, 72% had hypertension and half (52%) were diabetic. When combining the intermediate and high risk patients (>3%), 67.8% had IHD, 72% had hypertension and 40% were diabetic. Additionally there were 10 patients in the high risk group with a CRT-D, CRT-P or pacemaker device (2 and 4 patients with CRT in the intermediate or low risk groups, respectively).

**Table 4.5.** Clinical variables stratified according to surgical risk in patients considered potentially suitable for transcatheter mitral valve repair Abbreviations: IHD: ischaemic heart disease; COPD: chronic obstructive pulmonary disease. Statistics: Chi square for categorical and one way ANOVA for continuous variables.

| Variable | | High Risk | Intermediate Risk | Low Risk | P-value |
|---|---|---|---|---|---|
| **Patients** | n (%) | 26 | 14 | 19 | |
| **Risk (%)** | Mean ± SD | 15.67 ± 7.96 | 3.88 ± 0.512 | 1.89 ± 0.723 | **<0.001** |
| **Age** | Mean ± SD | 79.46 ± 9.71 | 69.5 ± 8.14 | 57.05 ± 10.4 | **<0.001** |
| **Sex (male)** | n (%) | 16 (61.54%) | 9 (64.28%) | 10 (52.6%) | 0.07 |
| **IHD** | n (%) | 21 (80.7%) | 6 (46.15% | 4 (78.9%) | **0.001** |
| **Hypertension** | n (%) | 18 (72.0%) | 11 (78.6%) | 9 (47.3%) | 0.206 |
| **Diabetes** | n (%) | 13 (52.0%) | 3 (21.43%) | 4 (21.05%) | 0.105 |
| **Asthma** | n (%) | 4 (16.6%) | 2 (14.3%) | 2 (10.5%) | 0.447 |
| **COPD** | n (%) | 4 (16.0) | 4 (28.57%) | 0 (0.0%) | 0.07 |
| **Ejection fraction** | Mean ± SD | 30.17 ± 8.97 | 33.067 ± 9.02 | 32.0 ± 8.55 | 0.105 |

Of the 40 patients with high and intermediate risk, 13 met COAPT echocardiographic exclusion criteria. There were 15 patients with high risk and 12 patients with intermediate risk remaining. Digital echo images were reviewed by an expert panel and based upon risk and COAPT criteria, a total of 20 patients were deemed technically suitable for TMVR according to current international guidelines.

Inter-operator reproducibility showed 100% alignment between investigator 1 and expert 1 with no requirement for cases to be reviewed by a second expert (chief investigator). Therefore inter-operator variability was 0%.

Extrapolating these data to the population of England suggested a provisional requirement of approximately 400 TMVR procedures per year for the acute HF cohort with secondary MR alone (Table 4.6). In 2019 in England there were a total of 124 TMVR using MitraClip, the only currently available edge to edge mitral repair device.

**Table 4.6.** Extrapolation of study data to English population level. Abbreviation: TMVR: transcatheter mitral valve repair.

| | **Study** | **Population** |
|---|---|---|
| Total heart failure admissions over 5 years | 2 821 | 280 289<br>(based on 71 188 per year) |
| Patients deemed potentially eligible for TMVR | 20 | 2 000 |
| Predicted annualised rate for potential TMVR | 4 | 400 |

## 4.5 Discussion

Within this chapter, this study concludes that there were a large proportion of patients with increased pre-operative surgical risk (based on the Euroscore II algorithm) within a cohort of medically optimised HF patients with moderate or more MR and an EF 20-50%. Over two thirds of patients were in the high (≥6%) or intermediate risk groups (3-<6%).

Surgical risk scores have been used for many years to assist estimation of the pre-operative risk and subsequent risk of in-hospital death following cardiothoracic surgery. Once relying on the original logistic Euroscore, 2011 saw an updated Euroscore II that was designed to be more accurate as a result of updated datasets reflecting improved surgical outcomes (86). The Society of Thoracic Surgeons (STS) score is another well-known risk score which can be used for this purpose but is more widely applied in the United States. Currently, there remains debate regarding which risk score provides the best estimate with studies disagreeing whether Euroscore II is superior or inferior to STS and/or Euroscore (87, 88). Comparatively, they all perform reasonably well. The STS score is known to provide slightly higher discrimination in relation to long term outcomes for patients undergoing conventional but isolated surgery, but this needs to be weighed against practicality since additional variables make it more time consuming. Furthermore, application of these scores in the prediction of mortality for patients undergoing transcatheter valve procedures has not been well established. Indeed, multiple studies focussed on drawing a comparison

between risk scores (STS score, logistic Euroscore, Euroscore II) found that none of the scores were predictive of 30 day mortality across populations of patients who had undergone transcatheter aortic valve implantation (TAVI) (89, 90). Similarly, these tools were found to be insufficient in predicting mortality in patients undergoing TMVR, with recommendations suggesting the need for validated surgical risk tools for transcatheter intervention (91). Although most studies have suggested that these tools overestimate the risk of mortality due to the less invasive nature of transcatheter interventions, the combination of potential for real complications and failure to consider frailty, porcelain aorta and previous radiation makes absolute risk interpretation challenging. Regardless of these findings, the value of surgical risk tools in defining patients who are high risk and thus ineligible for conventional surgical intervention still holds strong. Moreover, these tools are useful in determining patients candidacy for transcatheter interventions, assisting the decision making process and also determining when even transcatheter interventions may be futile and unlikely to improve quality of life and longevity. The challenge here lies in determining where the precise cut points rest, an issue still under debate and perhaps best made within a collaborative Heart Team incorporating interventional and surgical representation. Defined cut points would be very helpful but are only one piece in the puzzle determining suitability for transcatheter intervention.

In our study there were 13 patients who met COAPT exclusion criteria due to left ventricular end systolic dimensions >70mm, pulmonary artery systolic pressure >70mmHg, moderate or worse right ventricular dysfunction, or a combination of two

or more of these parameters. Seven patients were excluded based on moderate or worse right ventricular dysfunction. The COAPT criteria excluded patients with ‘physical evidence of right-sided congestive heart failure with echocardiographic evidence of moderate or severe right ventricular dysfunction as assessed by site‘. Firstly, physical evidence does not always align with echocardiographic findings, and it was not possible to combine the two in our retrospective study. Additionally, designation of RV dysfunction as mild, moderate or severe is somewhat subjective given national and international recommendations that RV function should be assessed using an integrative approach (including visual estimation of longitudinal and radial contractility, TAPSE, RV S’ and FAC). Of note, patients were not excluded based on RV function in the EVEREST HHR study (which focussed on high risk patients) or RESHAPE-HF trial. In theory, if patients with moderate or severe RV dysfunction based on echo criteria but without physical evidence of right heart congestion were eligible, the potential for treatment in our cohort may have been underestimated. With that said, in our study, given the established utility of transcatheter aortic valve interventions, we did not exclude patients with significant aortic valve disease. Additionally, in light of recent advances in transcatheter tricuspid valve procedures, we did not excluded patients with significant tricuspid valve regurgitation. Patients with both primary and mixed primary/secondary mitral valve disease were excluded.

In a conceived variation with the COAPT trial, my study included patients with moderate MR. However ‘reported’ moderate MR using 2013-2017 national guidelines

aligned with the classification of moderate-severe or severe MR using EROA and regurgitant volume ranges in current guidelines (mainly due to the addition of a subcategory for secondary MR) (71, 92). Fortunately for intermediate and high risk patients, review of echocardiographic images meant that additional measurements were performed where possible to ensure alignment with current guidelines and classification of moderate-severe and severe MR categories.

In total, there were 20 patients deemed potentially suitable for TMVR based on risk and echocardiographic criteria. When assessing these patients there was very high inter-operator reproducibility which should allow for a robust multidisciplinary team (MDT) approach to the assessment of these patients.

Projecting these data to population level (using national HF audit data numbers) suggested a total of approximately 400 patients per year across England. It is important to note that these figures are based on patients with HF and secondary MR only – those with primary MR and mix primary/secondary MR potentially requiring TMVR were not taken into consideration, making our estimate particularly conservative. This clearly highlights a gap between existing provision and demand. Presently there are only three institutions in England commissioned to perform TMVR using the MitraClip edge to edge system. It is possible that initial hesitation in commissioning was due to uncertainty as to whether reduction in the severity of MR resulted in a survival benefit. In 2018, the final conclusions of a 'Commissioning Through Evaluation Report' supported a causal link between TMVR using MitraClip

and clinically important reductions in MR and improved quality of life (93). The availability of MitraClip is currently being reviewed at national level with plans to establish TMVR treatment centres outside the present designation. However, in light of a very uncertain health climate, it remains unclear whether decisions to extend the accessibility of TMVR will be made with sufficient time to cater for the aging UK population.

## 4.6 Limitations

There were a number of limitations in this study. Firstly, surgical risk was determined based on Euroscore II alone and comparison with STS score was not possible.

Secondly, as mentioned above there are inherent limitations in the use of the Euroscore II risk score, both in relation to the absence of additional co-morbidities (such as frailty and previous radiation) and its applicability in the sphere of transcatheter interventions.

Thirdly, we based the selection of suitable patients upon echocardiographic criteria and Euroscore II alone. To be completely in line with COAPT recommendations, patients considered for TMVR should undergo both TTE and TOE. Our study was based on the assessment of MV aetiology and MR severity using TTE alone. Use of TOE may have resulted in different outcomes in relation to mechanism and/or suitability. Moreover, based on COAPT criteria a number of additional parameters

would have required consideration before a patient was deemed suitable. These include (but are not limited to) NT-pro BNP, creatine kinase-MB, coronary artery status, aortic valve disease, carotid stenosis, haemodynamic instability, and a life expectancy less than 12 months.

Finally, this study was based on a real patient population with hypothetical assumptions. Patients were not formally turned down for conventional surgery and there is no way of knowing whether patients were prepared to consider conventional surgery or transcatheter options.

## 4.7 Conclusion

A substantial proportion of acute HF patients remain symptomatic with significant MR despite OMT. Based on echocardiographic and risk criteria, many are potential candidates for TMVR according to current international guidelines. However, there is a need to ensure that the appropriate funding and resource are in place to cater for this aging population.

Although calculated risk score can assist in determining eligibility for intervention, additional clinical, imaging and haemodynamic variables need to be considered. The role of biomarkers and functional testing in the risk stratification of patients being considered for TMVR is poorly understood, demonstrating the need for further

characterisation of these markers in this cohort. These parameters, especially those relating to proportionate and disproportionate MR, may prove useful in selecting patients who will gain the greatest improvements following TMVR.

# CHAPTER 5

# FUNCTIONAL TESTING IN TRANSCATHETER MITRAL VALVE REPAIR: A SYSTEMATIC REVIEW AND META-ANALYSIS

## 5.1 Introduction

International experience of transcatheter mitral valve repair (TMVR) in patients with secondary mitral regurgitation (MR) continues to grow and its application has become more widespread as a result of numerous large multicentre trials vindicating the potential advantage of TMVR for patients with secondary MR who remain symptomatic despite optimal medical therapy (OMT) and/or cardiac resynchronisation therapy (CRT) (44, 60). Positive outcomes such as reduced rates of hospital admission and improvements in quality of life have been reported (60). However, there remains some degree of unpredictability in terms of symptomatic relief across the breadth of the population treated, with some patients gaining very little or no improvement in symptoms whilst others experience a new lease of life. It is therefore vital that clinical teams correctly determine which patients are likely to gain the greatest improvement,

in turn offering our patients more clarity and certainty in relation to the balance of risk and benefit. Patient selection therefore needs to focus on an individual yet integrative approach, including combined assessment of clinical signs, symptoms and echocardiographic findings, with further investigation needed into the value of functional testing within the TMVR population.

## 5.2 Functional testing: background

Aside from risk scores, echocardiographic criteria and clinical thresholds, the presence of symptoms is fundamental in identifying patients who require intervention. However, reported symptoms can be subjective, or minimal in those patients who progressively, incidentally or inadvertently reduce their activity. Functional testing therefore provides a more objective approach to the estimation of exercise tolerance and offers an opportunity for the assessment and unmasking of symptoms. It can also assist clinicians in assessing prognosis and evaluating potential response to treatment. Commonly used methods to determine functional capacity in patients with MR include exercise stress testing, exercise stress echocardiography, cardio-pulmonary exercise testing and six minute walk tests.

Exercise stress echocardiography (ESE) is invaluable in the assessment of structural heart disease, especially lesions affecting the mitral valve (MV). For patients with MR, ESE is of particular benefit in the assessment of symptoms, functional capacity and

when there is a mismatch between the degree of MR and perceived level of symptoms (94). The dynamic nature of MR means that ESE can provide pertinent information in relation to loading and cardiac haemodynamics (95). In the past, an inadequate increase in ejection fraction (EF) and a larger end systolic volume on exercise was shown to indicate limited contractile reserve, with potential for pre-operative EF to serve as a predictive marker following surgical MV repair (96). Today, we view EF as just the tip of the predictive iceberg, with concomitant markers such as exercise induced change in MR, cardiac output, right ventricular functional reserve and systolic pulmonary artery pressure all being viewed as important predictors of symptoms or early indicators for intervention.

Moreover, a combination of both primary and secondary aetiologies means that assessing MR can be complex. As such, the reliability of exercise stress echocardiography in the assessment of dynamic MR offers incremental value. In a study investigating patients with primary MR, an increase in MR as a consequence of exercise was associated with lower symptom free survival. This was evaluated on exercise stress echocardiography using quantitative changes in effective orifice area and/or regurgitation volume, with conclusions suggesting a more aggressive treatment strategy within this patient cohort (97).

Cardiopulmonary exercise testing (CPET) plays a critical role in prognostic assessment of heart failure (HF) patients (98). Said to be the ‘gold standard’, it is an established tool in the management of those HF patients with reduced ejection fraction

(EF), highlighting warning signs in symptomatic patients and discriminating exercise limitation in those who are functionally asymptomatic. A recent review paper which focussed on the application of CPET in HF emphasised differences in CPET results across specific groups (98). These included comparisons within genders, the aging population, those with increasing body mass index (BMI) and those with arrhythmias and comorbidities. CPET was useful in determining prognosis in these populations and the review questioned whether this learning could be useful in risk stratification for patients undergoing TMVR. Unfortunately, the limited availability of CPET in some centres means that pre-procedural testing may not be widely accessible.

Perhaps a better reflection of routine daily activity, the six minute walk test (6MWT) is a commonly used tool in the assessment of functional capacity. It is simple to perform, reproducible and inexpensive, and requires limited or no equipment. The design allows participants to stop or pause as required, which means the test can be used for a wider (and potentially more symptomatic) patient population. An important marker of prognosis, studies have shown good correlation between 6MWT and peak $VO_2$, with one study demonstrating equivalent predictive value (99, 100). Previous studies have suggested that patients with congestive HF and reduced EF with a 6MWT distance of less than 340m have a 3.5 times higher risk of death (101). Similarly, a recent large European multicentre registry demonstrated that HF patients with reduced 6MWT distance (<360m) experienced more frequent hospital admissions and a 14% increase in the risk of death (102). Findings within this study correlated with those outlined above - patients who were female, of older age, and with an increased heart rate and

comorbidities performed worst. The study reported that addition of the 6MWT did not improve predictive modelling in relation to prognosis in this cohort (c-index: 0.71 for primary outcomes, 0.73 for death) (102). It did, however, suggest that a 6MWT distance of 240m or less carried a much higher risk of death and/or hospitalisation (adjusted HR 2.41 [1.76–3.29] and 1.73 [1.38–2.18], respectively) (102).

Drawing parallels with evidence in the HF population, there is optimism that functional testing in patients requiring TMVR may (A) assist in patient selection, (B) discriminate patients most likely to demonstrate improved left ventricular (LV) parameters, reduction in symptoms, and improved quality of life following intervention, (C) facilitate more careful risk stratification and interventional planning, and (D) help to avoid high risk procedures which may prove futile. However, the current role of functional testing in patients undergoing TMVR is poorly understood.

Current European Society of Cardiology (ESC) guidelines state that functional capacity and symptoms assessed by CPET may be useful in asymptomatic patients (29). ESE is useful to quantify exercise-induced changes in MR, systolic pulmonary artery pressure and LV function. The guidelines suggest that ESE may be particularly helpful where the patient is symptomatic and there is uncertainty regarding the severity of MR at rest. For asymptomatic patients, rises in systolic pulmonary artery pressure with exercise (> 60mmHg) are thought to be of prognostic value (29). These recommendations are supported by the American College of Cardiology / American Heart Association 2020 guideline (31). Additionally the ACA / AHA recommend

exercise stress testing with a focus on symptoms, exercise capacity and blood pressure response which are of prognostic value in asymptomatic patients (31).

## 5.3 Aims and Objective

The primary aim of this systematic review and meta-analysis was to provide a qualitative and quantitative presentation of current evidence from original studies focussed on the role of functional testing in predicting outcomes of TMVR. I hypothesised that the literature would support the use of functional testing for risk stratification and prognostication in patients undergoing TMVR. The research question was to determine if functional testing was appropriate for risk stratification and determination of prognosis in patients undergoing TMVR.

My objectives were to determine: (1) the number of articles in existence focussed on functional testing in relation to TMVR; (2) the number of articles involving TMVR and functional testing as a predictor of outcome; (3) the breakdown of different modes of functional testing; (4) the reported value of functional testing in risk stratification for patients undergoing TMVR.

## 5.4 Methods

### 5.4.1 Search Strategy

A systemic review of the literature was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) methodology and registered with PROSPERO (ID192319, approval number CRD42020192319) (103). Three databases were used - Medline, Scopus and Google Scholar (US). In addition, clinical trials were identified through searches of the Cochrane Library and clinicaltrials.org (five databases in total). The search was focussed on all articles in existence involving humans up to May 25$^{th}$ 2020. Searches were performed in keeping with established search methods and MeSH strategy where possible. Key words and search strategies are outlined in Tables 5.1 and 5.2.

**Table 5.1.** Search terms used across five databases to determine articles relevant to our research question focussing on the use of functional testing for risk stratification and determination of prognosis in patients undergoing transcatheter mitral valve repair.

| Concept | Search terms |
|---|---|
| Medical diagnosis | Mitral insufficiency, mitral regurgitation, mitral |
| Procedural approach | Percutaneous, transcatheter |
| Exercise capacity | Six minute walk test, 6 minute walk test, exercise test, stress test, stress echocardiography, stress echocardiogram, exercise echocardiography, exercise echocardiogram, cardiopulmonary test, $VO_2$ max, CPET, CPEX. |
| Other limits | Adult, human, published in English |

**Table 5.2.** Search terms and strategy across five databases (Medline, Scopus, Google Scholar, Clinicaltrials.org and Cochrane library) and the number of results returned prior to filtering and exclusion of duplication.

| Database | Search terms and strategy | Results |
|---|---|---|
| Medline | (MeSH 'mitral valve insufficiency' OR (mitral or mitral regurgitation or mitral valve or mitral insufficiency).ti,ab,kw.) AND ((transcatheter or percutaneous).ti,ab,kw.) AND (exercise test* or stress test* or stress echo* or exercise echo* or minute walk test* or 6MWT or six minute walk test or cardiopulmonary test* or cardiopulmonary exercise test* or CPET or CPEX or VO2 max* OR MeSH 'echocardiography, stress/ or | 80 |

| | | |
|---|---|---|
| | exercise test/ or walk test/.) Limited to English and humans.<br>Duplicates removed. | |
| Scopus | MeSH 'mitral regurgitation'<br>( TITLE-ABS-KEY ( "exercise test*" OR "stress echo*" OR "minute walk test*" OR "cardiopulmonary test*" OR "stress test*" OR "exercise echo*" OR "cardiopulmonary exercise test*" OR "6MWT" OR "CPEX" OR "CPET" OR "VO2 max" OR "6 minute walk test*" OR "six minute walk test*" ) ) AND ( TITLE-ABS-KEY ( "Mitral regurgitation" OR "mitral insufficiency" ) ) AND ( TITLE-ABS-KEY ( percutaneous OR transcatheter ) ) AND ( LIMIT-TO ( LANGUAGE , "English" ) ) AND ( LIMIT-TO ( EXACTKEYWORD , "Human" ) ) | 264 |
| Google Scholar | ("Transcatheter mitral valve" OR "percutaneous mitral valve") AND ("exercise testing" OR "minute walk test" OR "exercise stress echo" OR "stress testing")<br>Limited to English language | 647 |
| Clinicaltrials.org | MeSH 'mitral insufficiency' AND ('percutaneous' OR transcatheter')<br>Limited to 'with results' | 8 |
| Cochrane Library | MeSH 'mitral insufficiency' AND ('percutaneous' OR transcatheter') | 65 |

Once duplications had been excluded, two independent reviewers (KV, MHH) screened the retrieved citations, firstly using the title and secondly by reviewing the

abstract. Any pertinent articles were then reviewed in full according to pre-determined selection criteria (Table 5.3). Any trials without results were excluded. Discrepancies were resolved by consensus following input from a third reviewer (CC). We employed backward snowballing by examining the list of references in those articles that met selection criteria and subsequently including relevant and eligible articles. For articles involving pooled data and clear overlapping populations, we included only those that were most recent, had the longest follow up period or largest number of recruits. There was no direct patient involvement in this study. Microsoft Excel was used to collect data and Endnote for referencing.

**Table 5.3.** Inclusion and exclusion criteria for selected articles related to functional testing in patients undergoing transcatheter mitral valve repair.

| Inclusion criteria | Exclusion criteria |
|---|---|
| 1. Observational and randomised clinical trials in patients treated with transcatheter mitral valve intervention<br>2. Evaluation of functional capacity by exercise testing (including six minute walk test, exercise test, stress echocardiography or cardiopulmonary exercise test)<br>3. Outcomes showing that functional testing was predictive of outcome<br>4. Studies including adult human participants<br>5. Peer reviewed studies | 1. Duplicate reports<br>2. Duplication of the sample size<br>3. Case series with sample size <10 subjects or case reports<br>4. Articles not written in English<br>5. Abstracts, posters or presentations<br>6. No original data or trial in progress<br>7. Opinion papers, letters or editorials<br>8. Review papers<br>9. Guidelines or protocols |

### 5.4.2 Data Extraction

Two unblinded reviewers (KV, MHH) extracted data comprising publication-related characteristics, patient-related characteristics and data related to functional testing, hospitalisation and mortality. More specifically this included: authors, year of publication, country of origin, methodology and design, sample size, patient demographics (age, sex), medical history and comorbidities (diabetes mellitus, coronary artery disease, COPD, previous myocardial infarction, atrial fibrillation, surgical risk score), cardiac imaging data (MR aetiology and severity, LV function, LV dimensions, left atrium (LA) volumes). Additionally, the end-points, outcomes and limitations of each study were recorded alongside data related to functional testing, device type, mortality, and rates of hospitalisation.

### 5.4.3 Quality

The quality of selected articles was evaluated using Methodological Items for NOn-Randomised Studies (MINORS) methodology (104) - an established tool in the assessment of non-randomised trials that has demonstrated validity across comparative and non-comparative studies (104).

### 5.4.4 Statistical analysis

Meta-regression analysis was performed to evaluate the value of 6MWTs in predicting outcomes only. The primary safety end point was a composite of all cause death, cardiac death, length of stay, re-hospitalisation for HF, and re-interventions during follow up. The primary efficacy end point was mean 6MWT distance. Where the 6MWT data were reported using categorical variables, the authors were contacted, and a request was made for continuous variable data. Hazard and/or odds ratios and sample sizes were used to calculate effect size. The studies were analysed using a forest plot, with a random effects model to assess differences in the means. Heterogeneity was expressed as an $I^2$ statistic which describes the percentage variation across studies that is due to heterogeneity rather than chance. Analysis was performing using STATA 13 (Statacorp, College Station, Texas 77845 USA).

### 5.4.5 Individual contribution to the research team

The entirety of this project was my responsibility. Prof Bernard Prendergast is the lead of valve services at the primary research site (Guy's and St Thomas' NHS Foundation Trust) and was the principal supervisor. Prof Mark Monaghan and Dr Jane Hancock assisted in conceptualisation of this chapter. Dr Garry McDowell and Dr Fiona Wilkinson were joint academic supervisors on behalf of Manchester Metropolitan University. Dr Matthew Hammond-Haley, Dr Chiara Cirillo and Dr Georgios

Georgiopoulos assisted with article screening, data extraction, interpretation of findings and statistical analysis.

## 5.5 Results

### 5.5.1 Systematic Review

Our systematic review identified 43 studies involving TMVR and functional testing. The primary purpose of the majority of these studies was to assess the safety and efficacy of TMVR. There were only 6 studies that used functional testing as a means of predicting outcome. Samples varied from 46 to 326, with 3 of the 5 studies reporting a sample size greater than 100 participants. Figure 5.1 provides an overview of the article selection process.

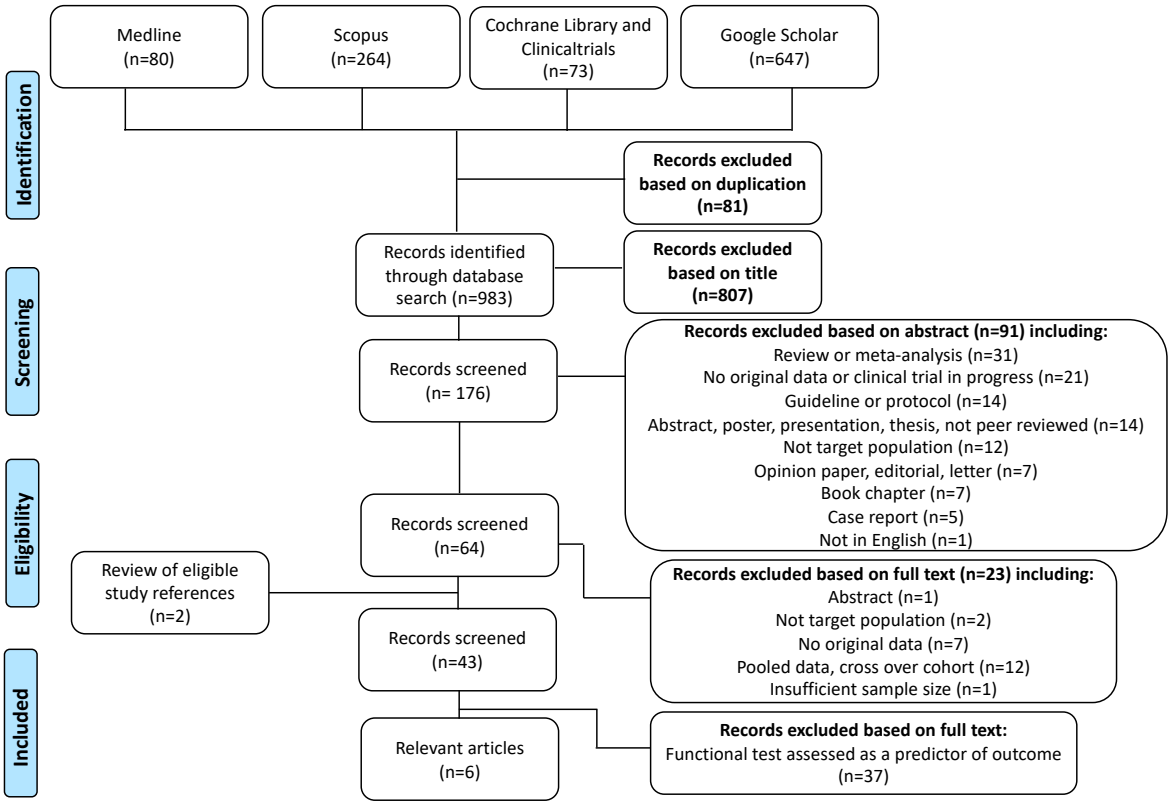


**Figure 5.1.** Flowchart outlining selection process for the systematic review of patients undergoing functional testing and transcatheter mitral valve repair.

All six of the studies of interest focussed on use of the MitraClip edge to edge device system, and five concentrated on application of the 6MWT. The remaining study examined the role of stress echocardiography using isometric handgrips and compared patients with severe MR against those with moderate MR that increased to severe on static exercise (105). Patients with moderate MR that increased to severe MR on exercise had smaller LV and LA cavity sizes, and lower all cause mortality, less frequent HF hospitalisation and less residual MR following TMVR compared to those with severe MR at rest. Although limited details were provided regarding the isometric exercise protocol and degree of heart rate change or workload, these findings suggest

that exercise stress echocardiography may have a role in discriminating patients likely to gain the greatest improvement from TMVR.

The remaining five studies were based on the role of the 6MWT in the prediction of outcomes following TMVR. Table 5.4 provides an overview of the publication-related, patient-related and study-related outcomes, following which each study is then summarised. There was variation across the studies in relation to study design, sample size, defined end points, statistical approach and outcomes.

**Table 5.4.** Overview of publication-related, patient-related and study-related outcomes for articles focussed on the role of the six minute walk test (6MWT) in predicting outcomes following transcatheter mitral valve repair (TMVR). Abbreviations: TRAMI: TRAnscatheter Mitral valve Intervention; P: primary; S: secondary; MR: mitral regurgitation; HF: heart failure; Pts: patients; f/u: follow up; CPET: cardiopulmonary exercise test; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LAD: left atrial dimension; LVEF: left ventricular ejection fraction; LVEDVi: left ventricular end diastolic volume indexed; LVESVi: left ventricular end systolic volume indexed; LAVi: left atrial volume indexed; DM: diabetes mellitus; CAD: coronary artery disease; AF: atrial fibrillation: ESII: euroscore II; NHYA: New York Heart Association; MI: myocardial infarction; NT-pro BNP: N-terminal pro B-type natriuretic peptide; COPD: chronic obstructive pulmonary disease; PASP: pulmonary artery systolic pressure; QoL: quality of life; [+]MINORS: Items were scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate) - global ideal score 16 for non-comparative studies, 24 for comparative studies (104).

| ID | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| **Reference (Year)** | **Triantafyllis *et al* (2015) [106]** | **Ledwoch *et al* (2018) [107]** | **Saji *et al* (2018) [108]** | **Lee *et al* (2019) [109]** | **Baldi *et al* (2019) [110]** |
| **Country** | The Netherlands | Germany | United States | Taiwan | Italy |
| **Methodology / design** | Retrospective, consecutive high risk patients.<br>Examined long term predictors of outcomes. | Subset of TRAMI trial registry. Large multicentre real world population (21 sites).<br>Pt assigned to either arm: <200m or > 200m based on 6MWT distance pre-procedure. | 3 groups:<br>6MWT >219m<br>6MWT <219m or unable to walk.<br><br>Consecutive recruitment.<br><br>Retrospective design. | Consecutive but retrospective recruitment.<br><br>Compared pts aged <80 years and those >80 years | Consecutively and prospectively enrolled.<br><br>No details regarding how 6MWT was performed.<br><br>No comparison group<br>Investigators blinded to clinical details for CPET |
| **Sample size** | 136 | 326 | 162 | 46 | 74 |
| **MR aetiology** | Mixed P and S MR; (moderate-severe or severe MR) | Not specified (moderate, moderate-severe and severe) | Mixed P and S MR (75% P MR).<br>Moderate-severe and severe MR | Mixed P and S MR (severe MR) | P MR (moderate-severe and severe) |
| **Mean age and sex (%)** | Mean age:<br>75 ± 9 years<br>Sex (male): 68% | Mean age:<br>76 years;<br>Age:<br><200m: 78 years<br>>200m: 74 years<br><br>Sex (male):<br>Arm 1: 61%<br>Arm 2: 69% | Overall mean age:<br>79 ± 11 years.<br><br>Unable to walk: mean age: 79 years, sex (male): 48%.<br>Walk <219m: mean age: 80 years, sex (male): 32%<br>Walk >219m: mean age: 76years, sex (male): 57%. | Arm 1:<br>mean age: 84 years<br>Sex (male): 63%<br><br>Arm 2:<br>mean age 73 years<br>Sex (male): 81% | Mean age: 72 ± 8 years<br>Sex (male): 78% |

| Reference (Year) | Triantafyllis *et al* (2015)[106] | Ledwoch *et al* (2018) [107] | Saji *et al* (2018) [108] | Lee *et al* (2019) [109] | Baldi *et al* (2019) [110] |
|---|---|---|---|---|---|
| **Comorbidities** | Hypertension 52%; DM 23%, CAD 63%; AF 53%, ESII 9.6±7; NYHA III/IV: 89% | Hypertension 79%; DM 35%; CAD 40%; prev MI Arm 1 32%, Arm 2 20%; AF 40%; Log ES Arm 1 22%, Arm 2 17%. NYHA class III/IV Arm 1 94%, Arm 2 74%. | Hypertension 74%, DM 23%, CAD 56%, prev MI 25%, AF 65%,<br><br>NYHA III/IV differed between groups: unable to walk 79%, <219m 90%, >219m 90%. | No significant difference between groups. Hypertension 63%; DM 27%, CAD 53%, AF 61%, mean ESII 10.1%, NYHA III/IV 94%. | Hypertension (39%), DM 36%, CAD 37%, prev MI 35%, AF 42%, COPD 29%, ESII 6.1(mean), NYHA class III/IV 92%. |
| **Echo Data** | Baseline only:<br>P MR 17%, S MR 78%, mixed 5%.<br>Average LVEF 36% | Baseline only: no difference in MR between groups<br>EF<30%: Arm 1 28%, Arm 2 37%<br><br>EF30-50%: Arm 1 EF35%, Arm 2 32%<br><br>EF>50%: Arm 1 37%, Arm 2 31% | Baseline only: no difference between groups.<br><br>Mean LVEDD 52mm, mean LVESD 38mm, mean LAD 48mm, mean LVEF 48%. | Baseline only:<br>>80 years: P MR 68%, S MR 32%<br><80 years: P MR 37%, S MR 63%.<br><br>LVEF: >80 years mean 55%; <80 years mean 44% | Baseline only (mean data):<br>LVEF 33%, LVEDVi 97 mL/$m^2$, LVESVi 65.9mL/$m^2$, LAVi 60 mL/$m^2$ |
| **End point** | End points not clearly defined | P MR: 1 year all-cause mortality;<br><br>S MR: in-hospital mortality, in-hospital complications, re-hospitalisation and symptom status at 1 year | Prolonged hospital admission defined as total length of stay >4 days (including death in hospital and discharge to rehabilitation centre). | P MR: procedural success with reduced MR<br><br>S MR: procedure-related complications, conversion to surgery, prolonged intubation, acute kidney injury | P MR: Cardiac death<br><br>S MR: All-cause death, composite of cardiac death or re-hospitalisation for HF |

| Reference (Year) | Triantafyllis *et al* (2015) [106] | Ledwoch *et al* (2018) [107] | Saji *et al* (2018) [108] | Lee *et al* (2019) [109] | Baldi *et al* (2019) [110] |
|---|---|---|---|---|---|
| **Research Question** | Evaluate long term survival and identify pre-procedural predictors of long term mortality | Assess potential of 6MWT to predict 1 year mortality in pts undergoing TMVR | Can 6MWT predict prolonged hospitalisation | Compare outcomes in pts undergoing TMVR: >80 years vs. <80 year | Identify baseline predictors of long term outcomes in S MR pts undergoing TMVR |
| **Outcomes** | TMVR has good survival rates in high risk pts.<br>Functional tests, NT pro-BNP and advanced age predict long term cardiac mortality | 1 year outcome: pts with walking distance <200m had higher all-case mortality<br>After adjustment for baseline risk factors: strong trend towards increased risk of all-cause mortality<br>Cardiac mortality higher in those with <200m walk distance | 6MWT independently associated (after adjustment) with prolonged hospitalisation . | Baseline 6MWT distance predicted all-cause mortality 95% vs. 93% success rate across groups<br>Improved NYHA class and severity of MR in both groups | 6MWT is a predictor of all-cause mortality<br>LAVi and low peak $O_2$ uptake increase the risk of death at f/u<br>AF associated with all-cause mortality<br>Low $VO_2$ independent predictor of mortality |
| **Confounding variables** | Univariate analysis alone. Multivariate did not include 6MWT (only NYHA class). | Multivariate analysis adjusted for age, gender, NYHA class, LVEF<30%, COPD, DM, smoker, renal failure, previous MI. | Multivariate analysis adjusted for age, haemoglobin, NHYA class, unsuccessful procedure. | Multivariate analysis adjusted for age, sex, LVEF, PASP, ESII, FMR, NT-pro BNP, creatinine. | Univariate analysis alone |
| **Limitations** | Observational, single centre trial.<br>Selection bias as a result of 'Heart Team'<br>Problems with f/u data (no QoL) | Pts in the <200m group were more symptomatic, with lower EF, higher risk and higher comorbidities | Retrospective study<br>Small patient cohort | Retrospective, observational, single centre experience. Follow up limited to 1 year. No control group. | Small sample; did not distinguish between AF types (persistent vs paroxysmal).<br>Only hard outcomes used. Uncertain improvement in QoL<br>Pts with post-procedural MR>2+ |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | excluded from analysis. |
| **Quality of Evidence (+MINORS)** | 2+2+1+0+1+1+0+0 = 7/16 | 2+1+1+2+0+2+1+0 = 9/16 | 2+2+1+1+1+1+1+0 = 9/16 | 2+2+1+2+1+2+1+0 = 11/16 | 2+1+2+2+1+2+2+0 = 12/16 |

In 2015, a group from the Netherlands retrospectively recruited 136 consecutive high risk patients with a mix of primary and secondary MR who underwent TMVR (106). Their mean age was 75 years with a mixture of comorbidities (predominantly hypertension, atrial fibrillation and coronary artery disease). The study found that TMVR was associated with good survival rates in high risk patients at one and two years, and demonstrated that the 6MWT predicted long term cardiac mortality in univariate analysis (p=0.05). Unfortunately 6MWT was not included in the multivariate analysis. The study therefore concluded that New York Heart Association (NYHA) class, N-terminal pro B-type natriuretic peptide (NT-pro BNP) and advancing age were predictors of outcome in this cohort with little focus on the contribution of the 6MWT. Of note, the study had limited data in relation to quality of life, inherent limitations due to its observational and single centre design, and lack of clarity regarding end points.

Ledwoch *et al* and Saji *et al* subsequently used a slightly different approach. Both of these retrospective studies categorised patients into groups based on 6MWT distance (107, 108). Ledwoch *et al* separated patients into one of two groups (<200 metres (m) 6MWT distance vs ≥200m 6MWT distance), based upon retrospective collection of data from the TRAnscatheter Mitral valve Interventions (TRAMI) registry (49). This

study suggested that patients with a 6MWT distance <200m were at increased risk of mortality at 1 year compared to those able to walk ≥200m (p=0.07). Cardiac death and hospitalisation were also higher in this group. Interestingly, a 6MWT distance <200m did not impact on symptom improvement 1 year following TMVR. This study excluded patients who did not undergo a 6MWT but failed to clarify whether this was because patients did not have the test performed or because patients were unable to perform the test due to poor health (which would have introduced positive bias into the analysis).

Saji *et al* took this into consideration by separating patients into three groups: 1) 6MWT distance ≥219m; 2) 6MWT distance ≤219m; and 3) those unable to walk (102). This study focussed on assessing whether 6MWT distance was predictive of prolonged hospital admission. The study found that 6MWT distance was independently associated with prolonged hospital admission (defined as ≥4 days or discharge to a rehabilitation facility within 3 days, or death) and an effective discriminator (p<0.001). Only 162 patients were included and recommendations were made to investigate this further within a larger patient population.

Although again limited by small sample size, a subsequent study from Taiwan showed that baseline 6MWT was a predictor for all cause mortality after TMVR (p=0.026) (109). This study compared patients by age, with those >80 years showing no difference in survival at 1 year following TMVR compared to their younger

counterparts. This study combined patients with both primary and secondary MR, and was limited by its retrospective single centre design.

The final study to focus on 6MWT as a predictor of outcome was that of Baldi *et al* (110) that enrolled patients with secondary MR only and showed that 6MWT was a predictor of all cause mortality (p=0.023). Moreover, this study also demonstrated the utility of peak $VO_2$ (obtained via cardiopulmonary functional testing) in the prediction of cardiac and all-cause mortality (p=0.018 and p<0.001, respectively). Furthermore, left atrial volume indexed for body surface area >65mL/$m^2$ and atrial fibrillation were also predictors of worse prognosis following TMVR. Unfortunately, this study excluded patients with >moderate residual MR following TMVR and failed to report quality of life outcomes and comparisons, thereby limiting its capacity for translation to real world practice.

### 5.5.2 Meta-analysis

Overall, five studies documented that 6MWT was predictive of outcome. Two of these reported a hazard or risk ratio based on categorical variables. Ledwoch *et al* reported a trend for patients who walked <200m on a 6MWT to have higher mortality risk than those who walked 200m or more (p=0.71). Saji *et al* showed that patients who were unable to walk or those who walked <219m were more likely to have a prolonged length of stay (p<0.001). Fortunately, on contacting the authors, Saji *et al* were able to provide additional supplementary data to allow us to interrogate these parameters

as continuous variables. The authors quoted an odds ratio of 0.992 (95% CI 0.988-0.996) for 6MWT as a continuous variable.

My meta-analysis was therefore based on four studies. Three of these examined the ability of the 6MWT to predict all cause mortality, while the remaining study focussed on an end point of prolonged hospital admission. After synthesising the four studies, I found that a reduced 6MWT distance was significantly predictive of the combined end point of increased mortality or prolonged hospital admission (pooled HR 0.935 per 10m increase in walking distance, 95% CI 0.891-0.980, p=0.005) (Figure 5.2). However, severe heterogeneity was observed in the pooled analysis ($I^2$ 67.7%, p=0.023) and none of the studies included a control group.

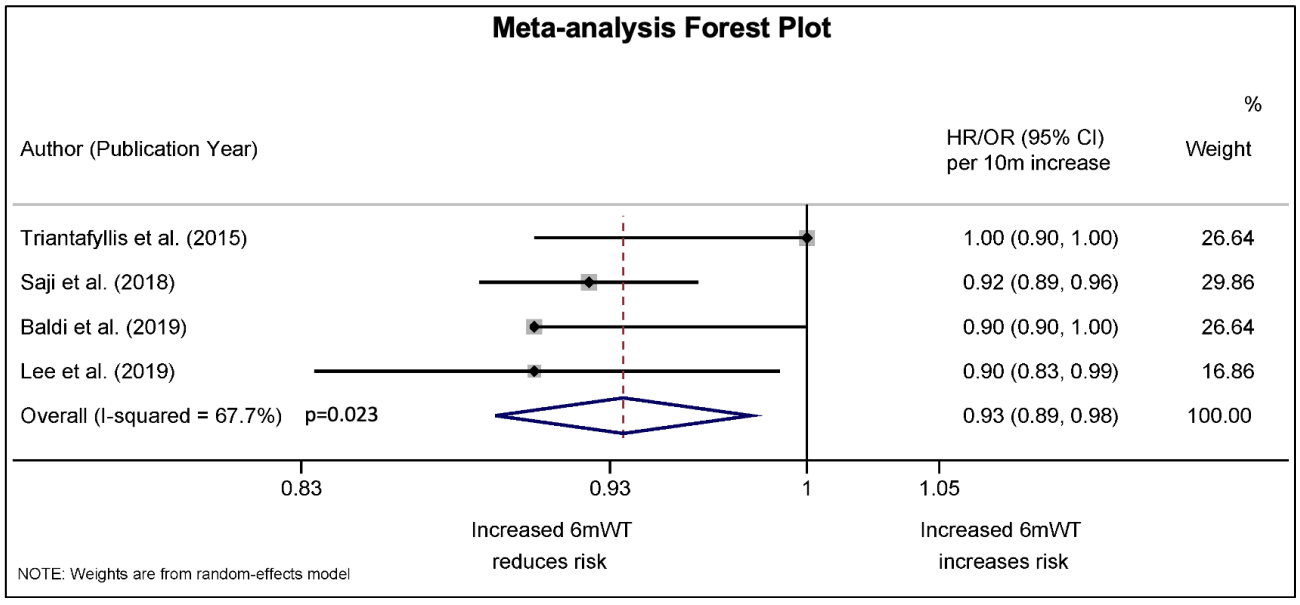


**Figure 5.2.** Forest plot using a weighted for random-effects model demonstrating that the six minute walk test (6MWT) is predictive of a combined end point of all cause mortality and prolonged hospital admission). The blue diamond on the left side of the vertical axis suggests that increased 6MWT

distance predicts reduced risk. Abbreviations: HR: hazard ratio; OR: odds ratio; CI: confidence interval; m: metres.

## 5.6 Discussion

This systematic review concluded that although many studies incorporate functional testing in their research design, very few examine their discriminatory power to predict outcomes in patients undergoing TMVR. The finding of my meta-analysis supports the value of the 6MWT in predicting outcomes for patients undergoing TMVR.

Findings from the study performed by Curio *et al* highlighted valid and pertinent questions relating to the role of exercise stress echocardiography (105), suggesting that patients with moderate MR that worsened on static exercise had lower rates of all cause mortality. It also suggested that these patients had smaller LV and LA cavity sizes. It may be that improved outcomes in patients with moderate MR at rest and severe MR on exercise who have smaller LV and LA volumes are related to intervention at an earlier stage of the disease process. Based on current guidelines, TMVR would not be routinely indicated in this cohort of patients. On the other hand, this is perhaps the exact population to whom we should be offering TMVR. Additionally, Curio *et al* suggested that lower residual MR is commonly associated with better long term outcomes in those with exercise induced severe MR. Interestingly, recent evidence in patients undergoing surgical mitral valve intervention suggests that

favourable outcomes are seen when MR is treated at an earlier stage (111, 112). Perhaps this early disease stage learning needs to be adopted for patients undergoing the transcatheter alternative, guided by the use of exercise stress echocardiography to assist in determining those patients with worsening MR on exertion.

There is a growing body of evidence suggesting that 6MWT distance predicts outcomes for patients undergoing TMVR. Arbitrary cut points of 200m and 219m have been used to determine outcome based on mean walking distance within this high risk population. Previously, a threshold of 300m has proved effective in providing additional prognostic information for pre-operative patients undergoing aortic valve replacement (113). Other studies in patients with HF suggest that thresholds of 300m (but also up to 490m) were predictive of capacity (114). In patients with COPD, a threshold <350m has been associated with increased mortality (115). Regardless of numerical variation, this suggests that 6MWT distance is valuable in the prediction of end points. In this context, it is noteworthy that the ongoing RESHAPE-HF trial examining the use of MitraClip in a high risk functional MR population is applying 6MWT distance as one of the exclusion criteria. Nevertheless, no test is without limitations and 6MWT distance can be influenced by HF status, LV function and participant motivation. Despite these limitations, it offers an objective, reliable and reproducible parameter that is easy to incorporate into daily practice.

As suggested by Baldi *et al*, there may also be value in performing sub-maximal functional testing using CPET. However, CPET requires specialised equipment and

appropriately trained personnel in order to perform the test, making it less likely to be adopted in the setting of randomised controlled trials or daily practice (102). Usefully, 6MWT distance has demonstrated moderate correlation with peak $VO_2$ in multiple studies and systematic reviews (114).

Predicting risk within this TMVR population is complicated. Using parameters such as 6MWT distance and exercise induced MR alongside surgical risk score may assist in discriminating those who are most likely to improve. Future studies should focus on implementing these tools routinely with the hope that more defined thresholds can be determined. More holistically, these tools will facilitate better understanding of the prognosis for TMVR patients and provide a more solid foundation for optimal medical decision making.

## 5.7 Limitations

There were a number of limitations within this systematic review and meta-analysis. In some cases, internationally pooled data were difficult to decipher from other international studies. Although attempts were made to ensure that duplicated data were excluded, I cannot be absolutely sure there was no duplication within the pooled data.

My meta-analysis was based on only five studies. Therefore inference and generalisability within our discussion may be skewed. Although attempts were made to contact authors who had reported categorical data in a request for continuous data, it was only possible to obtain this information from one of the two lead authors.

## 5.8 Conclusion

Many studies perform functional tests in order to evaluate symptoms and exercise capacity. Less commonly, however, do these studies use functional testing as a means of determining outcome. There is a growing body of evidence suggesting that 6MWT distance may assist in discriminating between patients who see an improvement with TMVR and those who do not. Exercise stress echocardiography has also proven effective in the assessment of patients with early stage exercise induced severe MR. These observations suggest that such tests may be useful in providing enhanced diagnostics in the TMVR population.

Unfortunately, the evidence in relation to this is scarce and further studies into the use of 6MWT and exercise stress echocardiography are required before their value can be determined. The hope is that these functional parameters alongside imaging, laboratory and clinical data will prove useful in further defining the characteristics of patients who gain the greatest improvement following TMVR, whilst simultaneously ensuring careful patient selection to prevent high risk futile procedures.

# CHAPTER 6

# TRANSCATHETER MITRAL VALVE REPAIR: PREDICTING IMPROVEMENT IN LEFT VENTRICULAR PERFORMANCE

## 6.1 Introduction

Based on retrospective data, my thesis has been able to demonstrate mitral regurgitation (MR) is a common problem within the heart failure (HF) population, and many patients remain symptomatic despite optimal medical therapy (OMT). Additionally, for those patients in intermediate and high risk groups, trials have demonstrated that transcatheter mitral valve repair (TMVR) is safe and feasible, with potential to improve quality of life (QoL) and reduce subsequent hospital admissions. However, outcome data are varied with some patients experiencing vast improvement and others feeling no different. A review of the literature suggests that functional testing may be a useful tool to predict those that may benefit, but this is based on limited evidence.

In this Chapter, I describe a prospective pilot study aimed at assessing the role of cardiac imaging, functional testing, and clinical and laboratory data in predicting changes in left ventricular (LV) performance, symptoms and QoL following TMVR in order to facilitate more careful risk stratification, interventional planning and avoidance of high risk futile procedures. I hypothesised that the combination of echocardiography with clinical, functional and laboratory data would help to identify those patients who experience the greatest relief from symptoms.

## 6.2 Aims and Objective

The primary aim of this study was to determine the usefulness of clinical, imaging, functional and laboratory markers (in isolation and combined) in predicting patients who demonstrate improvement following TMVR.

The principal objective of this prospective study was to determine whether transthoracic echocardiography (TTE) could predict changes in left ventricular (LV) size and function following TMVR.

The secondary objectives were to: (1) evaluate the feasibility and usefulness of functional testing and its role in discriminating MR patients who demonstrate improved LV parameters and QoL following TMVR; (2) assess the relationship between improvements in LV performance and the degree of residual MR; (3) explore and

characterise the relationship between changes in LV parameters and clinical outcomes; (4) assess the usefulness of TTE parameters combined with functional, clinical and biochemical parameters in providing better prediction of post-procedural outcomes following TMVR.

## 6.3 Methods

### 6.3.1 Study design

This prospective longitudinal cohort pilot study was performed across two tertiary care centres, involving collaboration between the Department of Cardiology at Guy's and St Thomas' NHS Foundation (GSTT), Department of Cardiology at King's College NHS Foundation Trust (KCH), and the Department of Life Sciences and Centre for Bioscience, Manchester Metropolitan University (MMU). The study involved prospective recruitment of patients who had been accepted for TMVR on clinical grounds and following review by the Heart Team. Routine clinical data collected during work up, peri-procedural care and follow up were collected. In addition, the patients underwent a pre- and post-procedural blood test, six minute walk test (6MWT), QoL questionnaire, and a pre-procedural exercise stress echocardiogram (ESE). Figure 6.1 provides an outline of the investigations performed and their timing. Pre-procedural tests were performed approximately 3 months (maximum 6 months) prior to

intervention. Assessment at follow up was performed approximately 3-6 months post procedure.

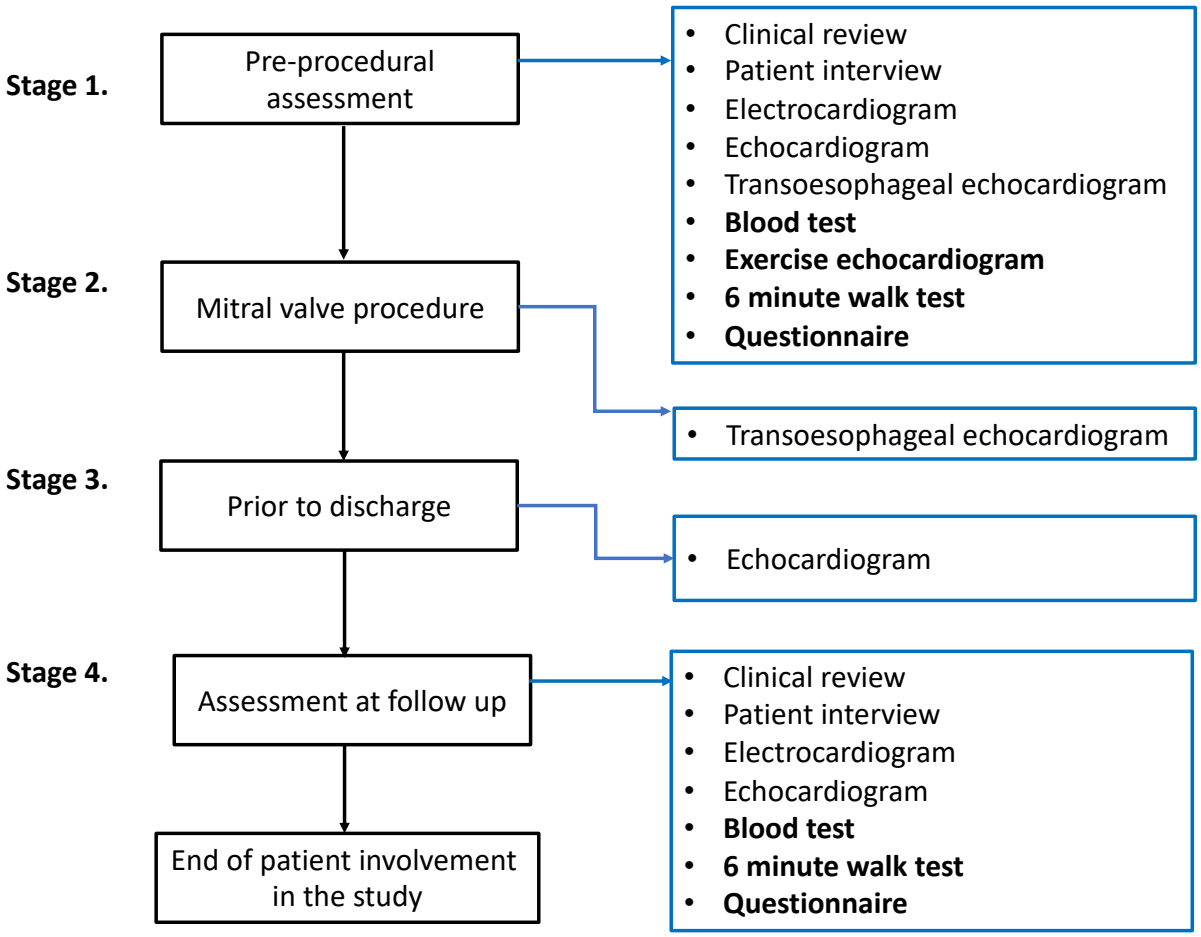


**Figure 6.1.** Flow diagram of the patient journey during the prospective transcatheter mitral valve research study. Activities beyond routine clinical care are highlighted in bold.

A comprehensive list of parameters recorded and relevant data sources is provided in Table 6.1.

**Table 6.1.** Parameters recorded for the prospective transcatheter mitral valve research study including sub-category, relevant data sources and time points. MR: mitral regurgitation; EROA: effective regurgitant office area; RVol: regurgitant volume; VC: vena contracta; MV: mitral valve; 2D: two dimensional; PISA: proximal isovelocity surface area; LVOT: left ventricular outflow tract; MVA: mitral valve area; TTE: transthoracic echocardiogram; TOE: transoesophageal echocardiogram; LV: left ventricle; EF: ejection fraction; LVEDD: left ventricular end diastolic dimension; LVESD: left ventricular end systolic dimension; GLS: global longitudinal strain; TDI: tissue Doppler imaging; VTI: velocity time integral; AV: aortic valve; SV: stroke volume; CO: cardiac output; PW: pulsed wave; LA: left atrium; RA: right atrium; RWMAs: regional wall motion abnormalities; RV: right ventricle; PASP: pulmonary artery systolic pressure; NYHA: New York heart association, EPR: electronic patient record; HR: heart rate; LVH: left ventricular hypertrophy; MI: myocardial infarction; BP: blood pressure; $O_2$: oxygen; BMI: body mass index; BSA: body surface area; NT-pro BNP: N-terminal pro B-type natriuretic peptide; CRP: C-reactive protein: eGFR: estimated glomerular filtration rate.

| Category | Assessment Type | Parameter | Time points | Data Source |
|---|---|---|---|---|
| Demographics | General | Age, gender, height, weight, ethnicity, BSA, BMI | <6months prior to intervention and 3-6 months post-intervention | EPR/EPR Sunrise/E-noting |
| Clinical | General | Evaluation of symptoms, medical history, comorbidities, medication, NHYA class, Euroscore II, heart rate, heart rhythm, BP, $O_2$ saturation, peripheral oedema, orthopnoea, | <6months prior to intervention and 3-6 months post-intervention | EPR/EPR Sunrise/E-noting |

| | | | | |
|---|---|---|---|---|
| | | date of initial review, date of follow up review, death | | |
| Echocardiography | Mitral assessment | Visual impression of severity of MR, EROA, RVol, VC area, mechanism of MR, concomitant valve disease, MV leaflet thickening, annular diameter, tenting height, flail gap, flail width, coaptation length, coaptation depth, central jet area, pulmonary vein reversal, 2D PISA, 2D vena contracta, regurgitant volumes, LVOT angle, MVA, MV gradients, mobile length of posterior leaflet | TTE: Pre-intervention (<6months before), immediately post-intervention (1-2 days) and approximately 3 months later. TOE: Pre-intervention (<6months before) and peri-procedural | Transthoracic and transoesophageal echocardiography (reports and digital images). |
| | LV assessment | LV 3D EF, LV Simpson's biplane EF, visual LV EF, first phase ejection fraction (EF1), LVEDD, LVESD, visual impression of LV systolic function, GLS, strain, speckle tracking, TDI, LVOT VTI, AV VTI, SV, CO, | TTE: Pre-intervention (<6months before) and approximately 3 months post. TOE: Pre-intervention (<6months before) and peri-procedural | Transthoracic and transoesophageal echocardiography (reports and digital images). |

| | | | | |
|---|---|---|---|---|
| | | PW MV, LA volume, RA volume, assessment of RWMAs. | | |
| | Other | Visual impression of RV function, TAPSE, RV S', PASP | TTE: Pre-intervention (<6months before) and approximately 3-6 months post. TOE: Pre-intervention (<6months before) and peri-procedural | Transthoracic and transoesophageal echocardiography (reports and digital images). |
| Functional testing | Exercise stress echocardiogram | Exercise duration, total Watts, symptoms on exertion, severity of MR (colour flow imaging and spectral Doppler), 2D LV volumes (Simpson's biplane), 2D ejection fraction (Simpson's biplane), cardiac output (LVOT VTI), PASP, heart rate (HR) at rest and peak, percentage of age-predicted maximal HR | <6 months prior to intervention | Exercise stress echocardiography (reports and digital images). |
| | Six minute walk test | Distance, symptoms, timing of symptom onset, distance of symptom onset, duration (if other than 6 mins), number of pauses | <6 months prior to intervention and 3-6 months post-intervention | Recorded in research site visit file. |

| | | | | |
|---|---|---|---|---|
| | | required, scoring for breathless and fatigue pre- and post-test, percentage change between pre- and post-intervention | | |
| Laboratory | General | NT-Pro BNP, ST2, galectin-3, CRP, haemoglobin, eGFR, creatinine | <6 months prior to intervention and 3-6 months post intervention | EPR/EPR Sunrise/E-noting and Viapath reports, Cyberlab |
| Electrocardiogram | General | HR, rhythm, QRS duration, evidence of LVH, myocardial infarction or atrial enlargement | <6 months prior to intervention and 3-6 months post-intervention | EPR/EPR Sunrise/E-noting |
| Quality of Life | SF-36 questionnaire | Physical function, role limitations due to physical health or emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health, total score, comparison between pre- and post | <6 months prior to intervention and 3-6 months post-intervention | Recorded in research site visit file. |
| Intervention | Procedural details | Device type and size, complications, approach, success | Time of intervention | EPR/EPR Sunrise/E-noting, cardiovascular information system (CVIS) |

### 6.3.2 Study population

This study was performed across two sites - Guy's and St Thomas' (GSTT) and King' College Hospitals (KCH). Patients were recruited based on referral to GSTT or KCH, a diagnosis of mitral valve (MV) disease and clinical eligibility for TMVR. Study approval was granted by the Health Research Authority (HRA) on 17 June 2019.

Based on power calculations using data from the Everest I and II trials, the expected change in left ventricular ejection fraction (LVEF) was approximately 5.5% (standard deviation 11%), providing an estimated sample size of 32 participants to achieve sufficient power (53). Therefore, the proposed target sample size was 50 participants to allow for unexpected deaths or complications, and those patients lost to follow up.

### 6.3.3 Inclusion and exclusion criteria

Patients were included and excluded based on the selection criteria below (Table 6.2).

**Table 6.2.** Inclusion and exclusion criteria for patients recruited to the prospective transcatheter mitral valve repair study. Abbreviation: MR: mitral regurgitation.

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| 1. 18 years or older<br>2. At least moderate to severe symptomatic MR<br>3. Life expectancy >1 year post-intervention<br>4. Able to provide informed consent | 1. Patients not eligible for transcatheter mitral valve repair. |

### 6.3.4 Patient recruitment

Study participants were recruited via two arms:

1) Participants already involved in another MV research study were also invited to take part in this study. The invitation was extended to the participant by a member of the direct care team with access to identifiable information as part of routine clinical care. The invitation was either in person or via the telephone. Interested patients were given or sent the research patient information sheet (PIS) and contacted via telephone to confirm interest. At this time, a date was organised for the lead investigator (KV) to receive consent and begin pre-procedural research assessments. Data between studies were shared to reduce unnecessary repeat investigations.

2) Participants not involved in an additional MV research study, were identified as eligible by a member of the direct care team at KCH or GSTT, either in the course of direct clinical care or following review at an MDT meeting. The participant was contacted by a member of the direct care team via telephone. If interested, they received a PIS and initial contact letter, and a follow up telephone call to confirm interest. If they were still interested, a date was organised to allow consent and begin pre-procedural assessments.

Informed consent was obtained from patients by a clinical scientist, researcher, doctor or other medical professional with appropriate training (Valid Informed Consent, Human Tissue Act training and Consent training). Informed valid consent was received in person. There were no patients considered vulnerable or unable to provide consent, and no children involved in this study. There was no direct payment for participation in the research project. All consented patients spoke English so there was no need for an interpreter.

### 6.3.5 Clinical review and patient interview

All participants were assessed clinically within six months prior to the procedure date. This included an evaluation of symptoms and New York Heart Association (NYHA) class. The patient interview was performed by either a Cardiologist, specialist registrar or HF specialist nurse. Additional recorded clinical parameters included heart rate and rhythm, blood pressure, oxygen saturation, the presence and extent of peripheral oedema, and assessment of orthopnoea. Additional demographic data included gender, age, ethnicity, height, weight, body surface area (BSA) and body mass index (BMI). A repeat clinical assessment and review was performed 3-6 months following intervention when these parameters were reassessed.

### 6.3.6 Transthoracic and transoesophageal echocardiography

All patients underwent both transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) as required in the diagnosis, peri-operative and follow up phases of the study. These investigations included comprehensive two-dimensional (2D), colour flow (CFI), spectral and tissue Doppler (TDI), strain and three-dimensional (3D) imaging. MR was assessed using an integrative approach aligned with the algorithm outlined in the COAPT trial (Chapter 4, Table 4.3, Figure 4.3). Measurements were performed in accordance with recommendations from the British Society of Echocardiography (BSE), American Society of Echocardiography and European Association of Cardiovascular Imaging (69, 71). Ultrasound systems used were from a variety of vendors, including Philips EPIQ and IE33, GE E9 and E95, and Siemens SC2000 scanners. Images were obtained using a 3MHz or 5MHz fixed array ultrasound probe, stored using digital loops and transferred to an archiving database to enable further offline analysis. Imaging and measurements were performed by BSE TTE and TOE accredited operators.

TTE was performed at three time periods:

1. Pre-intervention: approximately 3 months (maximum 6 months) prior to intervention.

2. Immediately following intervention (approximately day 1-4; prior to discharge).
3. Assessment at follow up: approximately 3-6 months after intervention.

TOE was performed as per routine practice (pre-procedure and intra-operative assessment).

### 6.3.7 Functional testing

Functional testing was performed using both exercise stress echocardiography and 6MWT.

#### 6.3.7.1 Exercise stress echocardiography

Stress echocardiography was performed approximately 3 months (maximum 6 months) prior to MV intervention on a bicycle using a standard protocol recommended and endorsed by the American Society of Echocardiography and European Association of Cardiovascular Imaging (95, 116). Study parameters included an assessment of exercise duration, total workload, symptoms on exertion, blood pressure response, percentage of age-predicted maximum heart rate and cardiac function (including the degree of MR using CFI and spectral Doppler, cardiac output using the left ventricular outflow tract velocity time integral, left ventricular volumes and EF, strain, and estimated pulmonary artery systolic pressure [PASP]). The reason for termination of the test was documented.

#### 6.3.7.2 Six minute walk test (6MWT)

This assessment of functional capacity was performed in accordance with recommendations from the American Thoracic Society (117). Data collected included distance, symptoms (at baseline and end of test), scoring of symptoms and timing/distance of onset, and duration (if other than 6 mins) and compared (as a percentage) against age-predicted standards. The test was performed at approximately 3 months (maximum 6 months) prior to the procedure date with follow up evaluation approximately 3-6 months following MV intervention. In this instance, an additional calculation of percentage change between tests was performed.

### 6.3.8 Laboratory biochemical sampling

Blood sampling was performed as per routine clinical practice less than 6 months prior to cardiac intervention. Additionally, a post procedure follow up blood sample was acquired (approximately 3-6 months). These tests were used to measure N-terminal pro B-type natriuretic peptide (NT-pro BNP), C-reactive protein (CRP), haemoglobin, estimated glomerular filtration rate (eGRF), and creatinine.

Aside from routine blood tests, a small volume of additional blood was obtained and analysed for troponin T, ST2 and galectin-3 before (<6 months before) and after (3-6 months) intervention. Details regarding blood sample collection and storage are further detailed in Section 6.3.13.

### 6.3.9 Electrocardiogram

Participants underwent an electrocardiogram within 6 months prior to the procedure. This was repeated in the follow up phase, approximately 3-6 months following MV intervention. Details of the rate, rhythm, QRS duration, and evidence of myocardial infarction, left ventricular hypertrophy or LA enlargement were noted.

### 6.3.10 Quality of life questionnaire

All patients completed the RAND Health 36-item short form survey (SF-36) pre- and post-TMVR. Total scores and percentage change before and after intervention were determined across all categories (physical functioning, role limitations due to physical health or emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health).

### 6.3.11 Intervention

All participants underwent TMVR. Data concerning device type and approach as well as the relative success of the procedure and any complications were collected. Patients who subsequently required conventional MV surgery for complications were noted but excluded from further analysis.

### 6.3.12 End points

Given the descriptive nature of this study, a number of variables were used as end points and collected 3-6 months following MV intervention. Global longitudinal strain (GLS), tissue Doppler, first phase ejection fraction (EF) (EF1), 3D and 2D EF were used to assess improvement in LV systolic function. Residual MR was assessed using quantitative and qualitative parameters. Overall outcomes were assessed by death, improvement in QoL, 6MWT, NHYA class, reduction in symptom severity and biochemical markers. Our aim was to demonstrate that TTE combined with clinical, demographic, biochemical and functional parameters could be used to predict outcomes for patients undergoing TMVR. End points were determined based on consensus from an expert panel of specialists, including Consultant Cardiologists with expertise in imaging and intervention, researchers, clinical scientists and specialist nurses.

**Table 6.3.** Imaging and clinical endpoints for the transcatheter mitral valve study. Abbreviations: LV: left ventricle; LVEDD: left ventricular end diastolic dimension; LVEDV: left ventricular end diastolic volume; 2D: two dimensional; 3D: three dimensional; GLS: global longitudinal strain; EF: ejection fraction; EF1: first phase ejection fraction; NYHA: New York Heart Association; 6MWT: six minute walk test.

| No | End points | Parameters |
|---|---|---|
| 1. | Improvement in LV size and systolic function (evidence of reverse remodelling) | LVEDD, LVEDV (2D and 3D), 2D and 3D GLS, EF (3D and 2D), EF1 |
| 2. | Improvement in clinical outcomes | Death, NYHA classification, quality of life assessment, 6MWT, symptoms, biomarkers |

### 6.3.13 Blood sample collection and storage

Blood tests were performed as per routine clinical practice less than 6 months prior to cardiac intervention. A post-procedure follow up blood test was performed at approximately 3-6 months. Additional blood was taken for troponin T, ST2 and galectin-3 assays. Samples were collected by medical professionals trained in phlebotomy using BD vacutainer tubes at room temperature. As soon as possible after phlebotomy, the sample was transported at room temperature and hand delivered to Viapath for analysis. Viapath falls under the host Trust licence. Samples were accompanied in transit by a study-specific sample request form with instructions and labelled with a unique pseudoanonymised coding, meaning that the sample was not traceable to the patient except by the investigators. Samples taken at GSTT were transferred to KCH via internal transport. Storage was at -20 degrees Celsius in a temperature-controlled suite monitored with Comark Probes in a contract research and development (R&D) suite with restricted access (2nd floor, Cheyne Wing, KCH).

For ST2 and galectin-3, samples were batched prior to analysis. For troponin T, samples were stored for analysis using Roche analysers.

### 6.3.14 Data Management

All information collected during the course of this study was kept strictly confidential according to the Data Protection Act 2018. Data were transferred electronically via e-mail from an NHS.net to the same NHS.net account so that the results could be placed into a single encrypted spreadsheet. The patient's hospital number, name and other identifiable data were removed prior to transfer. A master spreadsheet was kept at GSTT. Access required password entry and the individual document was password protected. The recording of these data from a collection, recording and quality perspective was maintained by the primary researcher but remained the responsibility of the chief investigator. E-mail access required password entry. There are two investigator binders containing details of GSTT and KCH patients that were kept separately at the host institutions. All blood samples and reports were pseudoanonymised using a study number (i.e. KCH_001) and all patient identifiable information was removed at this point. Results were made available electronically using a secure results online service (Cyberlab). Access to Cyberlab was only granted to authorised users and all information encryted and stored within a secure password protected spreadsheet on secure Trust servers. The researchers adhered to rules regarding confidentiality as outlined in Trust policy.

All patient data were handled according to NHS information governance procedures. All personal identifiable data were anonymised before analysis and publication to ensure confidentiality. No other individuals other than the research team had access to the data outside the direct care team. Professor Prendergast was custodian of the data.

### 6.3.15 Statistical analysis

In this study I aimed to identify significant change between two time points, and relationship between the primary outcome (change in TTE pre- and post-intervention), functional testing and clinical assessment variables. Continuous variables were summarised using means and standard deviations and categorical variables as frequencies and percentages. TTE change was examined using a one sample T-Test with the null hypothesis being no difference pre- and post-intervention (change = 0). A univariate linear regression model was used to compare predictive variables with changes in TTE. Paired T-Test was used to compare QoL pre- and post-intervention. Similarly, paired T-Test and simple linear regression was used to assess QoL change in relation to predictive variables. Variables that showed an association with the outcome (either TTE or QoL) were entered into a multivariate linear regression analysis. Outcomes which showed a non-normal distribution were dichotomized and logistic regression analyses performed. An alpha of $<0.05$ was used for all analyses. Based on power calculations using data from the Everest I and II Trials the expected

change in LVEF was approximately 5.5% (standard deviation 11%) (53), providing an estimated sample volume of 32 participants.

I performed statistical analysis using IBM SPSS Statistics Version 25.0 (72) Statistics on a personal computer or laptop following anonymisation.

### 6.3.16 Research ethics statement

This research project was granted formal approval by the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) (IRAS 248271, REC reference 19/LO/0619) (Appendix D). The project underwent proportional review with R&D at GSTT, and following 'capacity and capability' with the GSTT research team, GSTT provided sponsorship (Appendix E) that was agreed and supported by Manchester Metropolitan University (Appendix F). Additionally, the project was granted 'capacity and capability' status and registered as a study at King's College NHS Foundation Trust (reference KCH19-100) (Appendix G). Finally, the project was verified by Manchester Metropolitan University (review reference 2020-20464-14239).

### 6.3.17 Individual contribution to the research team

This entire project was my responsibility. Prof Bernard Prendergast (valve service lead at the primary research site, GSTT) was the principal supervisor. Prof Mark Monaghan and Dr Jane Hancock assisted in the logistical planning and conceptualisation. Dr

Garry McDowell and Dr Fiona Wilkinson were joint academic supervisors on behalf of Manchester Metropolitan University. Dr Jon Bryne and Prof Simon Redwood were the lead structural interventionalists at KCH and GSTT, respectively. Karen Wilson and Jonathan Breeze assisted with patient consent and data collection.

## 6.4 Results

A total of eight patients were recruited to this research study. We calculated that we would need approximately 50 patients (minimum 32 patients) for adequate power to achieve statistical significance. Unfortunately, all research ceased in March 2020 due to the COVID-19 pandemic. As a result, no further recruitment was permitted and patients were barred from attending the hospital for research purposes alone. Where patients were scheduled for clinical follow up, this was undertaken virtually, thereby precluding the possibility of scheduled research activity aligned with clinical face to face appointments. However, I was able to obtain follow up QoL data via post.

The findings of this pilot research study will therefore be presented descriptively. My hope is that research can continue in this area once the COVID-19 pandemic is resolved.

### 6.4.1 Demographic and clinical data

The recruited cohort was split evenly between men and women with an average age of 77 years (± 13.5 years) and all were of white ethnicity. Three quarters of the cohort (75%) had either coronary artery disease (CAD) or atrial fibrillation (AF), and half (50%) had hypertension. Two patients had previously undergone cardiac surgery, two patients had intra-cardiac devices (pacemaker or ICD) and one patient had undergone both cardiac surgery and device implantation. Table 6.4 outlines the demographic and clinical data.

All patients presented to GSTT or KCH with shortness of breath. Two had a previous diagnosis of HF and four had pulmonary and/or peripheral oedema. All patients were in NYHA classification IV at presentation and five of the seven patients (1 death) reported symptomatic improvement at follow up after TMVR.

**Table 6.4.** Demographic and clinical characteristics of patients recruited to the transcatheter mitral valve study. *Analysis based on eight patients only. Abbreviations: BMI: body mass index; IHD: ischaemic heart disease; COPD: chronic obstructive pulmonary disease; ICD: implantable cardioverter defibrillator; NYHA: New York Heart Association.

| **Variables** | | | |
|---|---|---|---|
| **Patients** | | n | 8* |
| **Age (years)** | | Mean ± SD | 77 ± 13.45 |
| **Sex (male)** | | n (%) | 4 (50%) |
| **Ethnicity (white)** | | n (%) | 8 (100%) |
| **BMI (kg/m$^2$)** | | Mean ± SD | 24 ± 3.2 |
| **Comorbidities** | Hypertension | n (%) | 4 (50%) |
| | IHD | n (%) | 6 (75%) |
| | Diabetes | n (%) | 2 (25%) |
| | COPD | n (%) | 2 (25%) |
| | Asthma | n (%) | 0 (0%) |
| | Atrial fibrillation | n (%) | 6 (75%) |
| | Prior cardiac surgery | n (%) | 2 (25%) |
| **Pacing or ICD** | | n (%) | 3 (37.5%) |
| **NYHA class (III/IV)** | | n (%) | 8 (100%) |
| **Device** | Edge to edge | n (%) | 8 (100%) |
| | MitraClip | n (%) | 5 (62.5%) |
| | No of devices >1 | n (%) | 5 (62.5%) |
| **Mortality at 30 days** | | n (%) | 1 (12.5%) |
| **Readmission at 30 days** | | n (%) | 2 (25%) |

### 6.4.2 Intervention

All eight patients underwent transcatheter edge to edge repair using at least one device without immediate complications. Four patients received two devices and one received three. Five patients had MitraClip devices deployed and three patients were treated with a Pascal device. Following the procedure one patient developed urinary retention and another had confusion and acidosis. A separate patient was re-intubation and required transfer to the intensive care unit on day 2 of recovery due to a hospital acquired pneumonia. This patient was known to have underlying COPD.

Unfortunately, one patient died approximately 4 weeks post TMVR. The cause of death was documented as: 1) multiple organ failure, 2) right heart failure, 3) mitral valve disease, 4) COPD. A further patient elected to undergo subsequent high risk mitral valve replacement at a different institution. Two patients were re-admitted to hospital with symptoms of breathlessness within one week - on both occasions the TMVR was deemed satisfactory based on echocardiographic examination, and discharge was possible within three days after optimisation of medical therapy.

### 6.4.3 Quality of life

Quality of life (QoL) was assessed using eight different categories integrating physical and emotional function. Eight patients completed the pre-procedural questionnaire but matching data were only available for six (1 death and 1 lost to follow up). Analysis

showed that three patients reported an improvement in quality of life, two patients experienced deterioration and one saw no real change (Table 6.5, Figure 6.1).

**Table 6.5.** Absolute and total quality of life scores for each patient across sub-categories of the SF-36 questionnaire. Abbreviations: Pt: patient; Pre: prior to intervention; F/U: follow up.

| | **Pt 1** | | **Pt 2** | | **Pt 3** | | **Pt 4** | | **Pt 5** | | **Pt 6** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Categories** | **Pre** | **F/U** | **Pre** | **F/U** | **Pre** | **F/U** | **Pre** | **F/U** | **Pre** | **F/U** | **Pre** | **F/U** |
| **Physical functioning** | 25 | 15 | 20 | 5 | 20 | 45 | 0 | 55 | 20 | 20 | 35 | 20 |
| **Role limitations due to physical health** | 0 | 0 | 0 | 0 | 0 | 25 | 0 | 50 | 25 | 25 | 0 | 0 |
| **Role limitations due to emotional problems** | 100 | 100 | 33 | 0 | 100 | 100 | 0 | 0 | 100 | 33.3 | 0 | 0 |
| **Energy/ fatigue** | 15 | 0 | 15 | 10 | 20 | 45 | 0 | 45 | 45 | 50 | 0 | 40 |
| **Emotional well-being** | 92 | 88 | 48 | 32 | 88 | 96 | 68 | 92 | 80 | 88 | 4 | 60 |
| **Social functioning** | 50 | 25.5 | 50 | 12.5 | 12.5 | 50 | 0 | 87.5 | 62.5 | 50 | 0 | 0 |
| **Pain** | 35 | 22.5 | 57.5 | 22.5 | 100 | 100 | 20 | 57.5 | 55 | 90 | 27.5 | 32.5 |
| **General health** | 35 | 30 | 45 | 15 | 25 | 40 | 80 | 55 | 65 | 65 | 10 | 15 |
| **Total** | **352** | **281** | **268.5** | **97** | **365.5** | **501** | **168** | **442** | **452.5** | **421.3** | **76.5** | **167.5** |

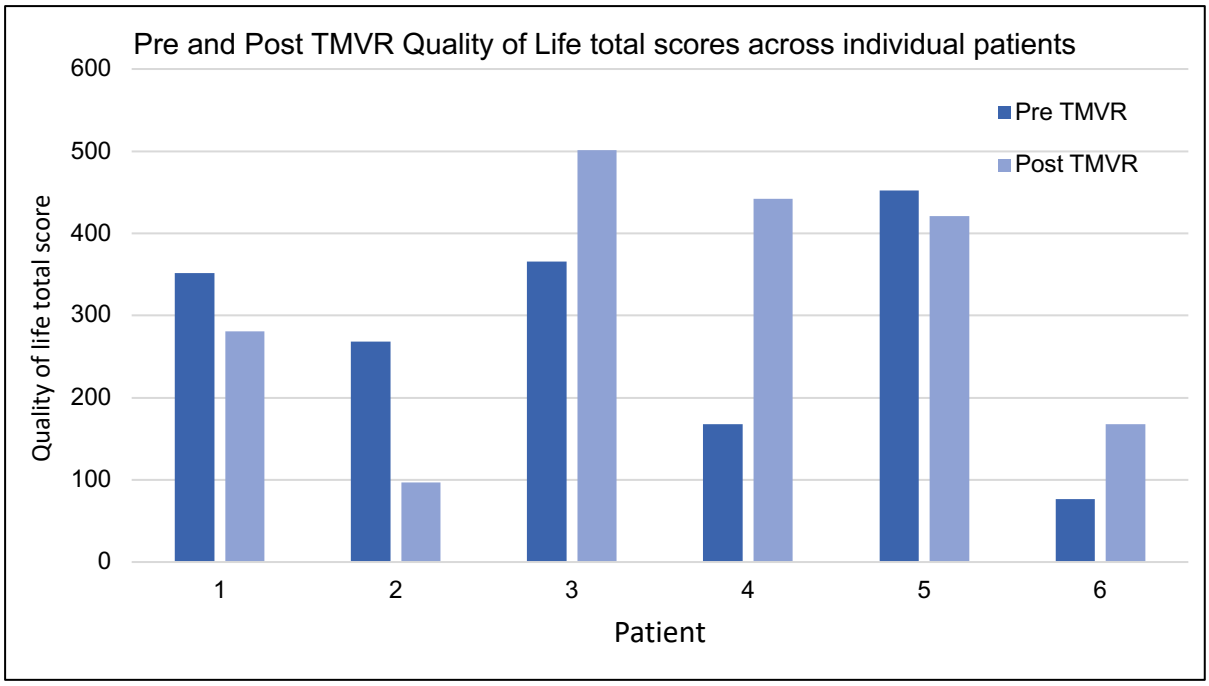


**Figure 6.2.** Quality of life scores before and after transcatheter mitral valve repair (n=6).

There was no clear relationship between improvement in QoL in primary or secondary MR. The degree of improvement or deterioration varied across the cohort and given the small sample size and risk of bias, further analysis was not performed. Similarly, there was no significant difference in individual QoL domains before and after intervention (Table 6.6).

**Table 6.6.** SF-36 quality of life questionnaire scores (individual domains and overall total) before (left) and after (right) transcatheter mitral valve repair. Statistics: paired t-test. Abbreviations: TMVR: transcatheter mitral valve repair. SD: standard deviation.

| Categories | Before TMVR | Before TMVR | After TMVR | After TMVR | P-value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| **Physical functioning** | 20.00 | 11.40 | 26.66 | 19.15 | 0.586 |
| **Role limitations due to physical health** | 4.16 | 10.21 | 16.16 | 20.41 | 0.203 |
| **Role limitations due to emotional problems** | 55.5 | 50.21 | 38.88 | 49.07 | 0.204 |
| **Energy/ fatigue** | 15.83 | 16.56 | 31.67 | 21.13 | 0.175 |
| **Emotional well-being** | 63.33 | 33.12 | 76.0 | 25.04 | 0.271 |
| **Social functioning** | 29.17 | 28.17 | 37.58 | 31.58 | 0.676 |
| **Pain** | 49.17 | 29.01 | 54.17 | 34.27 | 0.679 |
| **General health** | 43.33 | 25.82 | 36.67 | 20.66 | 0.394 |
| **Total** | **280.50** | **138.81** | **318.3** | **162.72** | **0.589** |

### 6.4.4 Echocardiography

All patients underwent baseline TTE in addition to pre- and peri-procedural TOE (Table 6.7).

**Table 6.7.** Baseline echocardiographic parameters prior to transcatheter mitral valve repair. Abbreviations: MR: mitral regurgitation; RUPV: right upper pulmonary vein; MV: mitral valve; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; BSA: body surface area; EF: ejection fraction; RV: right ventricle; TAPSE: tricuspid annulus plane systolic excursion; PASP: pulmonary artery systolic pressure.

| **Variables** | | | |
|---|---|---|---|
| **Patients** | | n | 8 |
| **Mitral Valve** | Mechanism (functional) | n (%) | 4 (50%) |
| | MR severity (severe) | n (%) | 8 (100%) |
| | RUPV flow reversal | n (%) | 4 (50.0%) |
| | MV E peak (≥1.5m/s) | n (%) | 3 (37.5%) |
| **Left Atrium** | Biplane volume indexed (mL/m$^2$) | Mean ± SD | 65.97 ± 17.6 |
| **LV size and function** | LVEDD (cm) | Mean ± SD | 5.56 ± 1.1 |
| | LVESD (cm) | Mean ± SD | 3.86 ± 1.7 |
| | LVEDV (mL) | Mean ± SD | 137 ± 72.4 |
| | LVEDV indexed for BSA (mL/BSA) | Mean ± SD | 81.34 ± 40.1 |
| | LVESV (mL) | Mean ± SD | 75.0 ± 55.0 |
| | EF (%) | Mean ± SD | 46.7 ± 13.7 |
| | EF <50% | n (%) | 3 (37.5%) |
| **Right ventricle** | RV dilated (≥4.3cm) | n (%) | 3 (37.5%) |
| | RV function (TAPSE, cm) | Mean ± SD | 1.9 ± 0.47 |
| | PASP (mmHg) | Mean ± SD | 60 ± 16 |

All patients had severe MR based upon integrative TTE and TOE assessment and half of the cohort had secondary MR. There were three patients with MV leaflet prolapse

(2 posterior, 1 anterior). The last patient had undergone previous MitraClip implantation and the residual MR jet was complex. Accurate quantitative measurements were not possible in all patients due to MR jet eccentricity.

Three patients had a dilated left ventricle (LV) and three had impaired systolic function (EF <50%, range 31-65%). The mean indexed LV volume in diastole was 81.34mL/$m^2$ and biplane left atrial volume was increased in all patients with a mean indexed volume of 65.97mL/$m^2$. Three patients had a dilated right ventricle but the majority (80%) had normal right ventricular systolic function. The mean pulmonary artery systolic pressure was 60mmHg.

Post-procedural TTE (0-4 days) demonstrated moderate to severe residual MR in two patients. This had been noted on the peri-procedural TOE, but no further transcatheter intervention was possible.

### 6.4.5 Functional testing

At baseline, seven patients were able to perform a 6MWT. One was unable to perform the test due to severe fatigue and breathlessness at rest, and one walked 5:32 mins before terminating the test. The mean walking distance was 187m (range 120-245m). Patients were permitted pauses throughout (range 0-4) and asked to score their breathlessness and fatigue at rest and upon completion of the test. Scores are outlined in Table 6.8.

At follow up, only two patients performed a 6MWT. One was the patient who was unable to perform the test at baseline so no comparison could be drawn. The other reported a significant deterioration in walking distance (from 180m to 118m) accompanied by a decline in QoL scores and reduced LV systolic function (EF 30-35% to 10-15%) despite reduction in the severity of MR (severe to moderate). Unfortunately, the remaining five patients were unable to attend for follow up assessment as a result of the COVID-19 pandemic.

**Table 6.8.** Six minute walk test outcomes prior to transcatheter mitral valve repair. Abbreviations: m: metres.

| | **Pre Intervention** | | | | |
|---|---|---|---|---|---|
| **Pt** | **Baseline dyspnoea score** | **Baseline fatigue score** | **Distance walked (m)** | **Post dyspnoea score** | **Post fatigue score** |
| **1** | 0 | 3 | 180 | 5 | 5 |
| **2** | 2 | 0 | 244 | 10 | 3 |
| **3** | 5 | 5 | 120 | 9 | 9 |
| **4** | 3 | 6 | 189 | 8 | 8 |
| **5** | 6 | 0 | 246 | 8 | 7 |
| **6** | 2 | 2 | 173 | 5 | 5 |
| **7** | 1 | 0 | 160 | 5 | 0 |

Regrettably, no exercise stress echocardiograms were performed for a variety of reasons (artificial legs, extreme breathlessness and fear).

### 6.4.6 Laboratory results

Baseline blood results were obtained for all patients (Table 6.9) but additional research assays (ST2, galectin-3) could not be processed due to batching and the reallocation of resources during the COVID-19 pandemic. Therefore, these results are not available. Post-intervention results were also limited due to reduced face to face follow up, batching and reallocation of resources.

**Table 6.9.** Laboratory results prior to transcatheter mitral valve repair. ^n=5, *n=4. Abbreviation: eGFR: estimated glomerular filtration rate; CRP: C-reactive protein.

| **Variables** | | | |
|---|---|---|---|
| **Patients** | | n | 8 |
| **Pre-intervention biochemistry** | NT-pro BNP | Mean ± SD | 6943 ± 5525 |
| | Troponin T | Mean ± SD | 34 ± 25.2 |
| | eGFR | Mean ± SD | 51.3 ± 20.7 |
| | Creatinine | Mean ± SD | 128.6 ± 72.4 |
| | CRP^ | Mean ± SD | 16.4 ± 22.62 |
| | Haemoglobin* | Mean ± SD | 128.8 ± 13.9 |

Post intervention NT-pro BNP was available for three patients. In one patient with no significant improvement in MR severity, worse QoL, reduced EF and 6MWT distance, NT-pro BNP increased from 2978ng/L to 9276ng/L. In the other two patients with reduced MR severity, no change in EF and improved or equivocal QoL, NT-pro BNP fell by an average of 8414ng/L.

## 6.5 Discussion

Despite limited data collection due to unforeseen circumstances, this Chapter highlights important concepts that need to be considered in relation to symptomatic improvement, and parameters useful in the selection of TMVR candidates.

Current recommendations suggest that an integrative echocardiographic approach should be used in the assessment of MR severity incorporating a constellation of qualitative and quantitative measures alongside characteristics features commonly seen in severe MR (e.g. LV size and function, systolic reversal in the pulmonary vein) (85, 118). Aside from the renowned methodological errors associated with echocardiographic measurements, experiences and learning related to data extraction in this pilot study support the importance of using an integrative approach. Limitations associated with eccentric and multiple jets meant that certain measurements were not accurate or reliable and decisions regarding the assessment of MR need to incorporate a multifaceted approach. The presence of atrial fibrillation or frequent ectopy also meant that it was not always possible to perform every measurement precisely or with consistency. Furthermore, the effects of sedation and its bearing on blood pressure needed to be considered when TOE was used in combination with TTE to determine MR severity. Put simply, defining severe MR is complex and certainly not defined by one or two parameters in isolation. There is an argument that specific training should be provided to specialist echocardiographers undertaking evaluation of these patients to ensure rigid adherence to the COAPT algorithm

(Chapter 4, Table 4.3 and Figure 4.3), thereby correctly identifying high risk patients who are most likely to respond and thrive after TMVR. Going forward, it would be interesting to better understand the role of the LA, annular dilation and the proportional ratio between the LV and LA within this population, and whether these parameters also play a role in the integrative approach to defining MR severity.

A novel and interesting component of this pilot study was the incorporation of functional testing. We requested that patients undergo a 6MWT in addition to a bicycle exercise stress echocardiogram. Seven of the eight patients were able to perform a 6MWT and the results offered a useful, objective parameter of sub-maximal functional capacity. By comparison, no patients were willing to undergo a bicycle exercise stress echocardiogram, often because of extreme breathlessness, fear or anxiety. All but one patient had breathlessness at rest, questioning the feasibility of performing a more 'maximal' exercise test in symptomatic HF patients. In a Belgian multi-centre trial, Van de Heyning *et al* recruited 31 patients to perform exercise pre and post TMVR. Although enrolling a slightly younger population (mean age 72 years), they were able to demonstrate haemodynamic improvement in secondary MR patients following TMVR (119). Similarly, as outlined in Chapter 5, Curio *et al* were able to achieve similar findings using a novel isometric handgrip exercise protocol (105). Other studies have examined the impact of exercise in HF, albeit in less symptomatic patients (NYHA I/II) with less severe MR (120, 121). Ongoing investigations in this population include a COAPT sub study assessing the feasibility of cardiopulmonary exercise

testing - however data from this component of the trial are limited and recruitment is ongoing (NCT01626079) (122).

An empirical observation in my study relates to two patients with moderate to severe residual MR despite device deployment who reported deterioration in overall QoL. Theoretically, it is possible that this relates to increased left atrial pressure resulting from the combination of residual MR paired with mitral stenosis. One patient had a mean MV gradient of 6mmHg on TOE whilst under sedation following device deployment. The other had a mean gradient of 3 mmHg at follow up TTE in the context of a poor LV and significantly reduced stroke volume (28mL). Moderate or more residual MR after TMVR is associated with lower survival, reduced symptom relief and an increased likelihood of further recurrent MR (123-125). However, the solution - an additional device - may lead to iatrogenic mitral stenosis and further symptomatic deterioration (126). A recent study compared TMVR patients with greater than moderate residual MR against those with less than moderate residual MR but with a mean MV gradient >5mmHg, demonstrating that those with less than moderate MR and an MV gradient >5mmHg were less likely to require subsequent hospitalisation (127). Operators need to be cautious when making decisions regarding the deployment of multiple devices, particularly when further improvement of MR is unlikely. Similarly, industry partners should bear this conundrum in mind when considering future device design.

## 6.6 Limitations

Unfortunately, the study outlined in this Chapter was significantly curtailed by the effects of the COVID-19 pandemic. Firstly, restrictions on research project activity meant that no further patients could be recruited. Although in-patient recruitment was technically feasible, this would have had no bearing on the study since all TMVR procedures were cancelled.

Secondly, all patients scheduled for routine clinical follow up were advised to avoid hospital attendance, meaning that follow up tests including TTE, 6MWTs and blood tests could not be performed. This restricted my capacity to draw pre- and post-intervention comparisons.

Thirdly, no research blood samples were processed due to limited recruitment and follow up, and as a consequence of the reallocation of blood centre resources (personnel and equipment).

Fourthly, patients were reluctant and/or unable to undergo exercise stress echocardiography evaluation. Furthermore, follow up QoL questionnaires were sent to recruited patients for completion during the national COVID-19 lock down when the prevailing circumstances would have had significant impact on responses relating to physical and emotion health and assessment of social interactions.

Finally, this was a small dual-centre observational prospective pilot study that did not randomise or enrol consecutive patients.

## 6.7 Conclusion

This pilot study was unable to successfully meet the proposed objectives as a result of the COVID-19 pandemic and limited recruitment. As a consequence, no solid conclusions could be determined from this work.

Reflecting on the small patient cohort recruited, I assessed a combination of patients with primary and secondary MR who underwent TMVR. There was variation across the cohort in terms of comorbidities and underlying LV function. As reported in the literature, there was variation in the extent of symptom relief and QoL following intervention. I hope that continuation of this project work will result in the identification of echocardiographic and functional parameters that enable better selection of patients for TMVR.

# CHAPTER 7

# FINAL DISCUSSION AND FUTURE APPLICATIONS

Transcatheter mitral valve repair (TMVR) presents a novel option for patients with symptomatic heart failure (HF) and prohibitive surgical risk. For those with secondary mitral regurgitation (MR) who undergo TMVR there is variation in the degree of symptom improvement and inconsistent impact on quality of life. A consensus view and unequivocal evidence regarding its effect on survival is yet to be determined. What is clear is that there is a population of HF patients who remain plagued by limiting symptoms despite optimal medical and device therapy. Accordingly, the existing evidence base needs prompt attention and resolution.

For those patients undergoing TMVR, appropriate selection and eligibility is vital. The first step is ensuring that patients are considered following an appropriate period of maximal medical optimisation with additional device therapy where applicable. Ensuring adherence to medical therapy should be made a priority. The use of objective measures to evaluate symptoms, frailty and functional capacity will also assist in the determination of risk and prediction of outcomes. Research into the application and amalgamation of biomarkers into the patient selection algorithm is ongoing and

integrative echocardiographic approaches continue to evolve. Importantly, focussing on the appropriate timing of intervention and more collaborative working in the early stages of HF to facilitate better risk stratification and patient selection will be needed for these advances to be useful in the future.

The outcomes of the COAPT and MITRA-FR trials and their subsequent interrogation has led to a rethink in terms of how we consider MR in the setting of HF. As briefly mentioned in Chapter 2, the concept of proportionate versus disproportionate MR has been generating momentum with the understanding that proportionality is part of the explanation behind the complementary findings of the COAPT and MITRA-FR trials (65, 128). The theory surrounds inadequacies in the traditional evaluation of effective regurgitant orifice area (EROA) and its knock-on effect in relation to an assumed association with clinical outcomes. The concept suggests that far too much emphasis is being placed at the level of the mitral valve (MV) with little attention given to the critical contribution of left ventricular (LV) volumes, pressure and function in determining the impact on haemodynamics and prognosis (65). Thus the proposal is that EROA is dependent on LV end diastolic volume, and that using the Gorlin hydraulic orifice equation, LV volume and the regurgitant fraction (RF), an EROA can be determined, independent of MV interrogation (65). This focus on an EROA:EDV ratio therefore overcomes challenges associated with the traditional direct MV EROA measurement. Proportionate MR is hence defined by characteristics including larger LV volumes (LV >97mL/$m^2$), and smaller EROAs at approximately 0.3cm2, therefore suggesting no need for intervention with treatment focussed on medical therapy (65,

129). Disproportionate MR is defined by a greater than expected EROA (0.3-0.4cm2) exceeding any enlargement of LV volume (LV <97mL/$m^2$), indicating a population of patients who following optimisation of medical therapy may benefit from additional MV directed intervention. Although this concept has been considered as a possible next step in understanding secondary MR, much of the attention was gained as a result of news media and Twitter rather than citations, and as such there are also those who oppose the concept (130). Hagendorff et al disputes that the concept of 'disproportionate MR' is questionable as disproportionateness of flow in communicating vessels can by definition not exist (131). The authors argue that regurgitant volume (RV) must be proportional to EROA in a system of communicating vessels at a single beat to beat measurement to align with the physical laws of conservation of mass and energy, with disproportionate MR written off as a consequence of measurement error (131). Rather, a quantitative approach with accurate measurement of LV stroke volume (SV) (total and effective), regurgitant volume (MV level) and individual RF by echocardiography is recommended (131). Hagendorff et al's reasoning has been supported by other groups with a focus on promoting the use of RF (132, 133). Of note, the algorithm used for proportionate and disproportionate MR does not take into consideration LV EF, LV/LA pressure and compliance, the presence of atrial fibrillation, pulmonary venous/arterial pressure, pulmonary vascular compliance, tricuspid regurgitation, and right ventricular size and function. Moreover, determining disproportionately and TMVR candidacy may be irrelevant depending on the exact anatomy and MR mechanism.

The model described above is not the only one that has recently come to light. Alternative models suggest the primary use of echocardiography to define secondary MR, and its underlying pathophysiology, into one of four sub-types according to disease staging. This approach assesses the relationship between LV and LA remodelling in the setting of hypertension, cardiomyopathy, ischaemia or atrial fibrillation (134). Assessment of SV and RF is also recommended in this model.

Whether secondary MR is based on proportions, stages of disease or chronicity, thresholds defining severity and indications for intervention are clearly required. Further prospective validation should therefore be performed in order to achieve and outline recommendations for widespread clinical adoption.

Beyond the paradigm shift of how we treat MR, comes a rethink in relation to when. Since its generation, TMVR has been considered an end stage treatment for HF patients looking to extend longevity or gain quality of life. Some may argue that given TMVR may be less effective in the setting of proportionate MR, do we need to consider referral for TMVR at an earlier stage, before LV dilatation becomes prohibitive? Early referral of patients with severe MR despite optimal medical therapy (OMT) may prevent irreversible LV remodelling. Maybe TMVR should no longer be viewed as a last resort option, but as a complementary prevention device that prevents (or delays) ventricular decline, worsening symptoms and deteriorating quality of life? Of course, to determine if this approach would be beneficial for patients, further research with carefully planned studies primarily focussed on the concept of ‘outcomes with early

MV referral and/or MV intervention' are required. In addition to this it is highly recommended that further studies also focus on the benefits of TMVR across different clinical settings such as acute vs chronic HF; ischaemic vs non-ischaemic HF; the range of MR aetiologies including AF induced MR; and demographics including age, gender and ethnicity. It goes without saying that synergistic collaboration between interventional and valve teams, HF and care of the elderly specialists will be just as necessary in the research phase as in the clinical phase. With clear outcomes, these partnerships would allow for research findings to beget prompt clinical diagnosis, consideration of all treatment options and optimal timing of intervention for the benefit of patient.

This pilot study has established the framework for the generation of future investigation, demonstrating that the protocol is feasible with capacity to perform such a project. My hope is that a return to 'normal' NHS services will facilitate the re-initiation of recruitment once more elective work is underway. Pandemic or not, we will still have patients with HF and significant MR so the demand will continue to grow. Timeframes for ethical approval have been extended and this project will be continued by the valve and intervention teams at Guy's and St Thomas' and King's College Hospitals.

Should the analysis of functional testing, novel biomarkers, echocardiographic parameters (or the combination thereof) yield promising results in terms of patient outcomes our plan would be to further extend the project. This would involve a national registry for patients undergoing TMVR allowing assessment of the utility of the patient

selection algorithm on a wider level. If effective, our vision would be to undertake a European-wide randomised controlled trial, enrolling patients randomised into groups based upon inclusion and exclusion criteria developed on the basis of the patient selection algorithm.

# CHAPTER 8

# CONCLUSION AND FUTHER WORK

Mitral regurgitation (MR) in the heart failure (HF) population is a common and growing concern but further research is needed in order to fully understand the breadth of the problem, effectiveness of treatment and strategies for the selection of best treatment option for individual patients. These concepts underlie the framework used to develop my research question and this thesis.

The thesis opened with a retrospective investigation of patients with HF. By combining HF admission data with echocardiographic findings, I concluded that one fifth of all patients presenting with HF have moderate or more MR and that this sub-group have a greater risk of mortality. Patients receiving optimal medical therapy (OMT) reported relief from symptoms and a proportion also experienced reduction in the severity of MR. However, one half of patients with left ventricular (LV) dysfunction and MR remained symptomatic despite OMT.

Concentrating on a sub-group within the HF population, I then interrogated HF patients with moderate or more MR and reduced ejection fraction (EF) who remained symptomatic despite OMT. I demonstrated that a large proportion of patients at high and intermediate surgical risk (defined by Euroscore II) were suitable candidates for TMVR but that lack of resources and funding presented obstacles to the availability and accessibility of this treatment option at national level.

My systematic review and meta-analysis of TMVR and the role of functional testing demonstrated that functional testing in this setting was very much focussed on use of the six minute walk test (6MWT), and that although commonly used in study design, the 6MWT was not readily applied in the extrapolation of data relating to outcome. A meta-analysis including all five available studies showed that the 6MWT was not only objective, fast and reliable, but also predictive of outcome for patients undergoing TMVR. Aside from this, the assessment of severe exercise-induced MR using a novel isometric handgrip protocol presented a useful and interesting concept for further interrogation.

Finally, I presented an observational prospective study in patients undergoing TMVR to determine whether echocardiographic imaging combined with functional testing, clinical status and serum markers could assist in identifying patients most likely to benefit from intervention, thereby facilitating more careful risk analysis and device selection. Unfortunately, limited conclusions were possible due to the onset of the COVID-19 pandemic, although preliminary observations demonstrated considerable

variations in outcomes related to LV performance, symptoms and end points, even within a small cohort of patients.

More widely, these findings confirm that the burden of MR within the HF population is significant and although medical optimisation assists in reducing symptoms and the degree of MR, high risk patients with LV systolic dysfunction remain symptomatic and may be candidates for TMVR. Further research into the utility of functional assessment and serum biomarkers, and the application of different echocardiographic models to re-define the relationship between MR and the LV are required to enhance patient selection and optimise clinical outcomes. The benefits of TMVR across a range of clinical settings (acute vs chronic HF; ischaemic vs non-ischaemic HF; the range of MR aetiologies; and demographics including age, gender and ethnicity) should form the focus of these studies, thereby ensuring reduction (or abolition) of symptoms, improved quality of life and increased longevity for HF patients across the spectrum.

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# APPENDICES

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# APPENDIX A

**Modules completed as part of the Doctorate of Clinical Science**

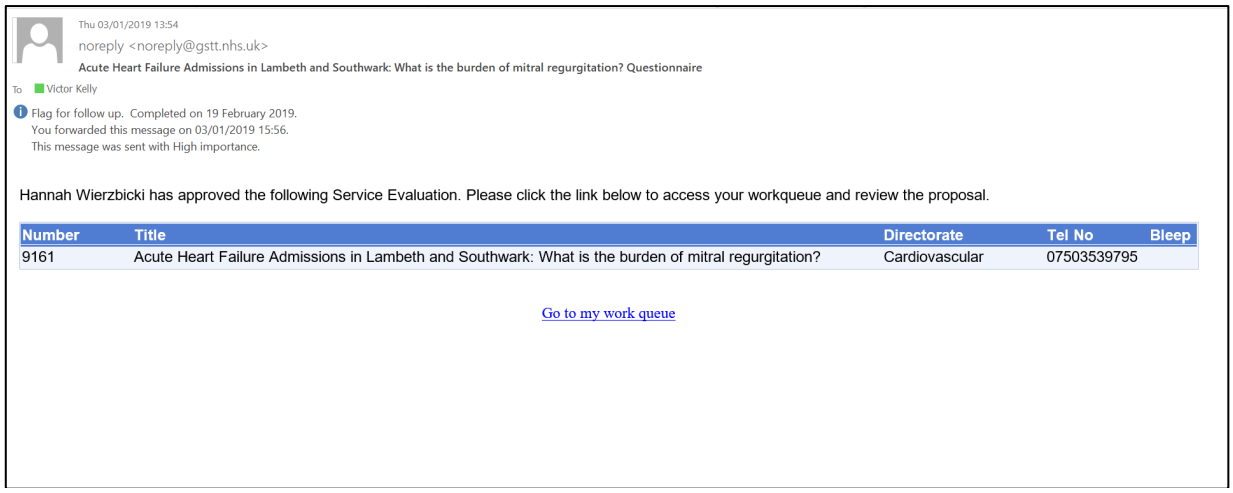
A list of A, B and C modules completed as part of the DClinSc including information with regards to total number of credits and final mark.

| Module | Unit Title | University | Internal Code | Mark | Credits |
|---|---|---|---|---|---|
| A1 | Professionalism and Professional Development in the Healthcare Environment | University of Manchester | 6ACP7160 | 68%<br>**Pass** | 30 |
| A2 | Theoretical Foundations of Leadership | University of Manchester | 6ACP7161 | 75%<br>**Pass** | 20 |
| A3 | Personal and Professional Development to Enhance Performance | University of Manchester | 6ACP7162 | 79%<br>**Pass** | 30 |
| A4 | Leadership and Quality Improvement in the Clinical and Scientific Environment | University of Manchester | 6ACP7163 | 77%<br>**Pass** | 20 |
| A5 | Research and Innovation in Health and Social Care | University of Manchester | 6ACP7164 | 82%<br>**Pass** | 20 |

| | | | | | |
|---|---|---|---|---|---|
| B1 | Advanced History Taking, Clinical & Communication Skills | University of Manchester | 6ACP8000 | 65%<br><br>**Pass** | 15 |
| B2/B4 | Clinical Presentation and Management of Cardiac Disorders | Manchester Metropolitan University | 6ACP8010 | 83%<br><br>**Pass** | 25 |
| B3 | Therapeutics | University of Manchester | 6ACP8002 | 96%<br><br>**Pass** | 10 |
| B5 | Contemporary Issues in Healthcare Science | Manchester Metropolitan University | 6ACP8001 | 82%<br><br>**Pass** | 20 |
| B6 | Diagnostics and Monitoring in Cardiology | Manchester Metropolitan University | 6ACP8011 | 82%<br><br>**Pass** | 20 |
| B7 | Teaching, Learning and Assessment in Healthcare Science | Manchester Metropolitan University | 6ACP8003 | 95%<br><br>**Pass** | 20 |
| B8-B10 | Specialist Option Adult Practice | Manchester Metropolitan University | 6ACP8030 | 88%<br><br>**Pass** | 45 |
| C1 | Doctoral Research and Innovation in Clinical Science | Manchester Metropolitan University | 6ACP8024 | <br>**Pass** | 40 |

# APPENDIX B

## E-mail evidence of registration and approval of the retrospective heart failure study as a service evaluation at Guy's and St Thomas' Hospital



Thu 03/01/2019 13:54

noreply <noreply@gstt.nhs.uk>

**Acute Heart Failure Admissions in Lambeth and Southwark: What is the burden of mitral regurgitation? Questionnaire**

To Victor Kelly

Flag for follow up. Completed on 19 February 2019.
You forwarded this message on 03/01/2019 15:56.
This message was sent with High importance.

Hannah Wierzbicki has approved the following Service Evaluation. Please click the link below to access your workqueue and review the proposal.

| Number | Title | Directorate | Tel No | Bleep |
|---|---|---|---|---|
| 9161 | Acute Heart Failure Admissions in Lambeth and Southwark: What is the burden of mitral regurgitation? | Cardiovascular | 07503539795 | |

Go to my work queue

# APPENDIX C

## E-mail evidence of registration and approval of the retrospective heart failure study as a service evaluation at King's College Hospital

From: PAPACHRISTIDIS, Alexandros (KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST) Sent: Wed 30/01/2019 00:34
To: Victor Kelly
Cc: MONAGHAN, Mark (KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST); Carr-White Gerry
Subject: RE: HF and MR service evaluation

Dear Kelly,

Thank you very much for sending both documents.
The audit is now registered at King's.

Please let me know should you need any help with your audit.
I would be more than happy to help.

Kind regards
Alexandros

Dr. Alexandros Papachristidis
Consultant Cardiologist
King's College Hospital NHS Foundation Trust
Denmark Hill, London, SE5 9RS
E-mail: alexandros.papachristidis@nhs.net

# APPENDIX D

## Evidence of HRA and Health Care Research Wales Approval for the prospective transcatheter mitral valve research project

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Bernard Prendergast
Director of Valvular Heart Disease and Consultant Cardiologist
Guy's and St Thomas' Foundation Trust
Lower Ground Floor, South Wing, St Thomas' Hospital
Westminster Bridge Road
London
SE17EH

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

17 June 2019

Dear Professor Prendergast

**HRA and Health and Care Research Wales (HCRW) Approval Letter**

| | |
|---|---|
| **Study title:** | **Percutaneous Mitral Valve Intervention: Predicting improvements in left ventricular performance** |
| **IRAS project ID:** | **248271** |
| **Protocol number:** | **248271** |
| **REC reference:** | **19/LO/0619** |
| **Sponsor** | **Guy's and St Thomas NHS Foundation Trust** |

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

**How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?**
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

**How should I work with participating non-NHS organisations?**
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

**What are my notification responsibilities during the study?**

The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

**Who should I contact for further information?**
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **248271**. Please quote this on all correspondence.

Yours sincerely,

Natalie Wilson
Approvals Specialist

Email: nrescommittee.london-londonbridge@nhs.net

*Copy to:* *Ms Elizabeth Bruna, Guy's and St Thomas NHS Foundation Trust, Sponsor contact*

**List of Documents**

The final document set assessed and approved by HRA and HCRW Approval is listed below.

| *Document* | *Version* | *Date* |
|---|---|---|
| GP/consultant information sheets or letters [GP_letter] | 1.0 | 11 March 2019 |
| HRA Schedule of Events | 1 | 02 April 2019 |
| HRA Statement of Activities | 1 | 02 April 2019 |
| IRAS Application Form [IRAS_Form_19032019] | | 19 March 2019 |
| IRAS Checklist XML [Checklist_06062019] | | 06 June 2019 |
| Letter from funder [Finance Support] | | 11 March 2019 |
| Letter from sponsor [Sponsorship support] | | 11 March 2019 |
| Letters of invitation to participant [Patient_Letter_for_KCH] | V1.1 | 30 May 2019 |
| Letters of invitation to participant [Patient_Letter_KCH_tracked_changes] | V1.1 | 30 May 2019 |
| Letters of invitation to participant [Patient_Letter_for_GSTT] | V1.1 | 30 May 2019 |
| Letters of invitation to participant [Patient_Letter_GSTT_tracked_changes] | V1.1 | 30 May 2019 |
| Other [Response_to_REC] | V1.1 | 30 May 2019 |
| Participant consent form [ICF] | V1.1 | 30 May 2019 |
| Participant consent form [ICF_tracked_changes] | V1.1 | 30 May 2019 |
| Participant information sheet (PIS) [PIS_GSTT] | V1.1 | 30 May 2019 |
| Participant information sheet (PIS) [PIS_GSTT_tracked_changes] | V1.1 | 30 May 2019 |
| Participant information sheet (PIS) [PIS_KCH] | V1.1 | 30 May 2019 |
| Participant information sheet (PIS) [PIS_KCH_tracked_changes] | V1.1 | 30 May 2019 |
| Referee's report or other scientific critique report | | |
| Research protocol or project proposal [Protocol] | 1.0 | 11 March 2019 |
| Summary CV for Chief Investigator (CI) [CV for CI] | | 11 March 2019 |
| Summary CV for student [CV for student] | | 11 March 2019 |
| Summary CV for supervisor (student research) [CV for Academic Supervisor] | | |
| Validated questionnaire | | |

| IRAS project ID | 248271 |
|---|---|

## Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

| Types of participating NHS organisation | Expectations related to confirmation of capacity and capability | Agreement to be used | Funding arrangements | Oversight expectations | HR Good Practice Resource Pack expectations |
|---|---|---|---|---|---|
| All participating organisations will undertake the same activities, as detailed in the protocol and supporting documents. | Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study. | A statement of activities has been submitted and the sponsor is intending to use a separate site agreement. The agreement is unmodified. | Sponsor is not providing funding to participating organisations. | A Principal investigator is expected to be in place at all participating organisations. | No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance. For research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate. |

**Other information to aid study set-up and delivery**

| *This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.* |
|---|
| The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.<br>Given this is a pilot study with much of the data a result of tests considered routine practice, the project is unlikely to generate new IP. However any new IP generated by the research will be owned by Guy's and St Thomas' NHS Foundation Trust. We will not share the data we collect as we have not consented for this however we aim to publish and disseminate our anonymised findings so that the value of this information can be used and applied by others working in the same field. |

# APPENDIX E

## Confirmation of capacity and capability from Guy's and St Thomas' Hospital for the transcatheter mitral valve research study.

**From:** Walker Dan
**Sent:** 17 June 2019 15:18
**To:** Prendergast Bernard <Bernard.Prendergast@gstt.nhs.uk>
**Cc:** Victor Kelly <Kelly.Victor@gstt.nhs.uk>; Wilson Karen <Karen.Wilson@gstt.nhs.uk>; 'Black, Stephen' <stephen.black@kcl.ac.uk>; Fedele Fiammetta <Fiammetta.Fedele@gstt.nhs.uk>; Munim Abdul <Abdul.Munim@gstt.nhs.uk>; Edgeworth Jonathan <Jonathan.Edgeworth@gstt.nhs.uk>; 'MARE, Tracey (VIAPATH LLP)' <tracey.mare@nhs.net>; 'ABBASI, Mariam (KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST)' <mariam.abbasi@nhs.net>
**Subject:** IRAS 248271 GSTT confirmation of capacity and capability (GSTT research team)

Dear Dr Prendergast,

| | |
|---|---|
| **Study Title:** | **Predicting improvements in left ventricular performance** |
| **IRAS ID:** | **248271** |
| **Sponsor:** | **GSTT** |
| **Chief Investigator:** | **Dr Bernard Prendergast** |

Guy's and St Thomas' NHS FT has agreed to host your research study.

Please note your responsibilities detailed below and in the attached 'Conditions of GSTFT participation'. These conditions must be adhered to for the Trust to host and support your research.

Requesting Green Light Approval:

If your study involves a study trial manager, Clinical Trials Unit, or any other sub-contracted party (for example a database held by a third party) please confirm with them whether they need to issue a separate green light.

Recruitment target/timelines:

- You have committed to recruit 15 participants between now and the planned study end date of 20/03/2022
- The Trust is performance managed nationally by the NIHR and as such you will be expected to recruit your first participant by 12/07/2019 to meet your performance target.

It is a Trust requirement that recruitment data is uploaded to the EDGE database; please refer to the attached document for capturing recruitment activity. Please also get in touch with edgesupport@gstt.nhs.uk for further information on how R&D can assist with uploading recruitment data.

Documents approved:

| Document title | Version | Date |
|---|---|---|
| Protocol | 1.0 | 11th March 2019 |

| | | |
|---|---|---|
| PIS | 1.1 | 30th May 2019 |
| ICF | 1.1 | 30th May 2019 |
| Validated questionnaire | NA | NA |

If you wish to make any changes to the approved documents, please contact the R&D department or refer to our guidance on submitting amendments.

If you would like to provide any feedback on your experience of working with the non-commercial R&D team at GSTT please email this to: RDfeedback@gstt.nhs.uk

Kind Regards,

**Dan Walker**

**R&D Governance Facilitator (non-commercial)**
NIHR GSTFT/KCL Biomedical Research Centre
16th floor, Tower Wing, Guy's Hospital
Great Maze Pond,
London
SE1 9RT

Tel: 020 7188 7188 ext: 56030 F: 0207 188 3472

*Guy's and St Thomas' and King's College London working together with our partners to deliver better health through research www.guysandstthomasbrc.nihr.ac.uk*

NHS
Guy's and St Thomas'
NHS Foundation Trust

**Our values: Put patients first | Take pride in what we do | Respect others | Strive to be the best | Act with integrity**

# APPENDIX F

**Letter from Manchester Metropolitan University demonstrating support for sponsorship through Guy's and St Thomas' Hospital.**

Manchester Metropolitan
University

**Manchester Metropolitan University**
Research and Knowledge Exchange
Directorate

Ormond Building,
Cavendish Street, Manchester,
M15 6BG, UK

Ethics@mmu.ac.uk

**19th November 2018**

To whom it may concern,

I have been advised that one of our students, Kelly Victor, is undertaking research within Guy's and St Thomas NHS Foundation Trust as part of her Doctor of Clinical Science Programme at Manchester Metropolitan University, and that you will be acting as sponsor.

Please accept this letter as confirmation that Manchester Metropolitan University are happy for you to sponsor the study. Please can you ensure that the application, including approval letters are forwarded to us for our records.

Please don't hesitate to contact me if you have any questions about this.

Yours sincerely,

**Alison Lloyd**
Research Ethics and Governance Manager
Ethics@mmu.ac.uk

# APPENDIX G

## E-mail evidence confirming King's College capacity and capability approval for the prospective transcatheter mitral valve repair research study.

**From:** ASSEFA-KEBEDE, Hosanna (KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST) [mailto:hosanna.assefa-kebede@nhs.net]
**Sent:** 20 August 2019 16:36
**To:** MONAGHAN, Mark (KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST) <mark.monaghan@nhs.net>; Victor Kelly <Kelly.Victor@gstt.nhs.uk>
**Cc:** MARE, Tracey (VIAPATH LLP) <tracey.mare@nhs.net>; BROWNE-MORGAN, Melrose (KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST) <m.browne-morgan@nhs.net>; BREEZE, Jonathan (KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST) <jonathan.breeze@nhs.net>; MCDONAGH, Theresa (KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST) <t.mcdonagh@nhs.net>; Prendergast Bernard <Bernard.Prendergast@gstt.nhs.uk>
**Subject:** IRAS 248271: Confirmation of Capacity and Capability at King's College Hospital NHS Foundation Trust

Dear Kelly,

**IRAS Ref: 248271**
**Full Study Title: Percutaneous Mitral Valve Intervention: Predicting improvements in left ventricular performance**
**KCH Ref No: KCH19-100**
**Sponsor: Guy's and St Thomas' NHS Foundation Trust**
**Location: Denmark Hill [CPMS code: RJZ01]**
**Target Recruitment: 25**
**Protocol Version: V1.0 11/03/2019**

This email confirms that **KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST** has the capacity and capability to deliver the above referenced study. Please find attached our signed Organisation Information Document as confirmation.

We agree to start this study when the sponsor gives the green light to begin.

**NB: Principal Investigator and research team, please note that *capacity and capability* has been issued; however, recruitment must not start until you receive confirmation from the sponsor that you are able to begin.**

Dear Professor Monaghan,

The study has been registered as **KCH19-100**. Please quote this reference in any communications with the R&I Office regarding your project.

A condition of the approval is to upload your recruitment data in real time into the study record in EDGE. Please contact your research facilitator or our data central email address kch-tr.data@nhs.net if you need assistance with training or EDGE account activation.

If you would like help from the R&I office, have any concerns regarding the study and/or want advice, please contact us. I have enclosed the R&I structure with contact details for you.
The R& I facilitator allocated to your study is: **Hosanna Assefa-Kebede**
The R&I Lead for your clinical area, who can also provide support is: **Professor**

**Theresa McDonagh**

Wishing you all the best with your research; we thank you for leading research at KCH for the benefit of patients and families. We look forward to working with you on this study.

Kind regards,

Hosanna Assefa-Kebede
**Assistant Research Facilitator**
King's College Hospital NHS Foundation Trust
The R&I Officel 161 Denmark Hill l London SE5 8EF

☎DL: +44 (0) 20 3299 2763 (internal 32763) l ✉: hosanna.assefa-kebede@nhs.net
R&I: kch-tr.research@nhs.net Contracts: kch-tr.researchcontracts@nhs.net
QA: kch-tr.researchqualityassurance@nhs.net Data: kch-tr.data@nhs.net

R&I: +44 (0) 203 299 1980 l www.kch.nhs.uk/research

# END OF THESIS