Can routine cardiovascular measures when combined with patient demographics better determine the extent of exercise capacity in patients with heart failure?

A thesis submitted for the degree of

Doctor of Medicine (MD)

Rashed Hossain

Hull York Medical School

University of York

August 2019

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List of Abbreviations

ACE	*Angiotensin-Converting Enzyme*
ACS	*Acute Coronary Syndrome*
BACPR	*British Association for Cardiovascular Prevention and Rehabilitation*
BHF	*British Heart Foundation*
BMI	*Body Mass Index*
CAD	*Coronary Artery Disease*
CABG	*Coronary artery bypass graft*
CHD	*Coronary Heart Disease*
CI	*Confidence Interval*
CKD	*Chronic kidney disease*
COPD	*Chronic obstructive pulmonary disease*
CR	*Cardiac Rehabilitation*
CVD	*Cardiovascular Diseases*
HF	*Heart Failure*
HRQL	*Health Related Quality of Life*
ISWT	*Incremental shuttle walk test*
MI	*Myocardial Infarction*
MLHFQ	*Minnesota Living with Heart Failure Questionnaire*
NACR	*National Audit of Cardiac Rehabilitation*
NHS	*National Health Service*
NICOR	*National Institute for Cardiovascular Outcomes Research*
NICE	*National Institute For Health and Care Excellence*
NYHA	*New York Heart Association*
PCI	*Percutaneous coronary Intervention*
REACH-HF	*Rehabilitation Enablement in Chronic Heart Failure*

Acknowledgments

Many thanks to my main research supervisor, Professor Patrick Doherty from the Department of Health Sciences, who has been a tremendous support and motivation helping me, navigate a meaningful clinical research route for my MD.

To the NACR team, Alexander Harrison, Corinna Petre, Nerina Onion, Karen Cardy and Jessica Hemingway who supported me with my first study using National Audit of Cardiac Rehabilitation (NACR) data. I am ever so grateful to them all.

Thank you to my second supervisor, Dr Sanjay Gupta without whom I would not have been able to carry out this research. His constant mentorship and tutoring in clinical areas and life in general helped me a great deal to achieve this task.

My dearest thanks to Dr Maurice Pye for his exceptional support and encouragement to let me take time to do the MD besides hectic clinical work.

I am very grateful to the REACH-HF team for including my project (sub-study of baseline fitness) as part of their NIHR programme of research which informed one of my MD studies.

I cannot thank enough my wonderful research team at York Hospital namely Lorraine Wright, Yvonne Mcgill, Heidi Redfearn and Mark Fearnley for their continued support and cooperation.

My thanks to my secretaries Jeanette Kuba and Linda Brook-shields for tolerating me so much and to adhere to my erratic timetable and lifestyle and supporting me mentally always.

Finally my mum and dad, my brother and his wife, my nephews and niece without whom I am nobody and their unconditional love always energise me and makes me complete.

Author's Declaration

I declare that this thesis is a presentation of my own original work, of which I am the sole author. This work has not previously been presented for an award at this, or any other, university. All sources are acknowledged as references.

- **Publications arising from this thesis**

1. **The review of literature is being prepared for submission to the European Journal of Preventive Cardiology. Hossain R is the lead author.**

2. Doherty P, Harrison AS, **Hossain R.** Determinants of walking fitness in patients with heart failure attending cardiac rehabilitation Open Heart 2019;6:e000866. doi: 10.1136/openhrt-2018-000866.

   ***All three authors involved in this paper had equal involvement in generating the concept, design, analysis, interpretation and all equally contributed to the write up*.**

   Resources for this particular study utilised BHF funding and resources secured by Prof Doherty (Department of Health Sciences, University of York) for service based research that aims to enhance service quality.

1. Introduction

1.1 Background to the study

Less than 20% of patients with heart failure access cardiac rehabilitation (CR) services which have proven benefits in terms of quality of life (QoL), fitness and reduced hospital admissions (NACR 2017, Taylor 2014, NICE CG108). One of the barriers to offering heart failure patients an exercise-based intervention is the uncertainty about their capacity to exercise safely around exercise training (BACPR 2017). Access to cardiac rehabilitation (CR) heart failure services is poor yet patients are known to benefit in terms of quality of life (QoL), fitness and reduced hospital admissions. Uncertainties about the extent by which patients can exercise safely around exercise training are known barriers to participation. Although some early guidelines suggested that left ventricular ejection fraction (LVEF) is a possible determinant of a patient's exercise ability in isolation LVEF and exercise ability are poorly correlated. This thesis seeks to evaluate the extent by which cardiac related measures, when combined with patient demographics, determine exercise ability in patients with heart failure.

Cardiac rehabilitation (CR) for patients with coronary heart disease (CHD) and those with heart failure is a clinically effective intervention that has yet to achieve optimal uptake in routine clinical practice (Anderson et al NACR 2015). The stated ambition of NHS England and that of NICE quality standard (QS99) is to improve uptake from 45% to > 65% in the next five years (CVD Outcomes, NICE CG172, NICE CG 108). Cardiologists play a fundamental role in treating and managing heart disease, especially following a heart attack, and represent, alongside cardiac nurse specialists, the primary source of referral to CR. National audit data (NACR 2015) shows that uptake to CR is at 47% for conventional CHD patients which is reasonable when compared to European rehab programmes where uptake is around 30%. The situation is very different for patients with heart failure where uptake is estimated to be less than 15% of all eligible patients (NICOR 2017). It makes sense that if most patients are not being referred then uptake will inevitably be poor. One of the reasons suggested for the lack of referral by cardiologists and GPs is that they somehow believe that patients with low ejection fraction are either at greater risk during exercise or are unlikely to cope with exercise.

There is a strong physiological link between cardiac output (i.e. stroke volume x heart rate) and exercise capacity in healthy populations with a similar, albeit modest relationship, found in patients with mild to moderate cardiovascular disease (CVD) (Vanhees et al 2013). The amount of blood ejected from the heart, at rest, known as left ventricular ejection fraction (LVEF), has in many respects become a clinical surrogate for cardiac function/output yet LVEF is, at best, moderately associated with exercise capacity in patients with cardiac disease. Despite the low level of evidence supporting this association LVEF is used as a fundamental part of clinical decision making when advising patients about exercise risks. Guidance from professional associations, for instance the British Association for Cardiac Rehabilitation (BACPR), has stressed the need to include a measure of exercise capacity and not just LVEF when deciding on patient risk during exercise training. The problem facing heart failure services and cardiac rehab programmes generally is that exercise capacity assessment, albeit recommended, is not routinely carried out (BACPR 2017, NACR 2017). This study intends to investigate the relevant cardiovascular parameters including transthoracic echocardiogram (TTE) alongside the patient characteristics to better determine the ability of heart failure patients to exercise.

The relationship between LVEF and related patient characteristics in determining exercise capacity, as measured in clinical practice, has not been established in patients with heart failure. Due to the severe lack of uptake to routine cardiac rehab programmes and clinical trials there is an urgent need to assess the ability of cardiovascular measures to determine exercise capacity. We believe our findings will improve clinical decision making, beyond that of just using LVEF, in respect of the appropriateness of referral to exercise based cardiac rehab. We know from REACH-HF and other exercise-based trials, in patients with CVD, that many clinicians and patients are unsure about promoting or taking up the offer of exercise in trials. This sub-study will clarify, for recruiting clinicians, the types of patient demographics that are associated with high levels of fitness thus giving a degree of reassurance that patients would be exercising within their scope of fitness for trials. For instance, a patient might be deemed as not suited due to a measure of heart output less than normal (e.g. LVEF < 45) however when this measure is combined with resting heart rate, normal BP or ideal weight then the ability of a patient to exercise may change substantially. Knowing the patient characteristics could also help in generating more appropriate study information sheets and help reassure patients, thinking about volunteering, that the study is well thought out and that the researchers are aware of the risks and issues about exercising patients with cardiac conditions.

Aims of the MD thesis:

To examine the impact of cardiovascular measures when combined with patient demographics in determining the extent of exercise capacity in patients with heart failure.

This will be achieved through meeting the following objectives:

a. A review of literature
b. Implement an observational study using data from routine clinical practice
c. Evaluate the determinants of exercise capacity in a clinical trial population

1.2 Background to the disease (Heart Failure)

Heart failure (HF) is a syndrome that comprises symptoms of exertional shortness of breath, fatigue and fluid retention and becoming more prevalent worldwide. In the UK around 900,000 people have HF (BHF 2015).

Diagnosis of HF relies on clinical judgement based on a combination of history, physical examination and appropriate clinical investigations. Patient symptoms and functional exercise capacity are routinely used to classify the severity of HF, often using the New York Heart Association (NYHA) functional classification. These same measures are used to judge responsiveness to treatment. There is no single diagnostic test to identify HF but echocardiographic assessment of ejection fraction can be used as quantified objective measures for severity of the symptoms. People with HF experience marked reductions in their exercise capacity, which has detrimental effects on their activities of daily living, health-related quality of life (HRQoL), and ultimately their hospital admission rate and mortality (Taylor et al 2014, WGCR 2001). HF has a poor prognosis, as 30% to 40% of people diagnosed with HF die within one year but survival after HF diagnosis has improved (AHA 2014). People with HF may be categorised as having either systolic HF or diastolic HF (NICE CG 108, NICE NG106). Systolic HF is due to impaired left ventricular contraction, which results in a reduced ejection fraction (usually <45%) and diastolic HF is due to stiffness of the ventricle wall delaying filling of the heart chamber. Although maximizing pharmacological therapies and recent advances in device implantation, mainly CRT-D or P (Cardiac resynchronization therapy with defibrillator or biventricular pacing options) have improve physiological parameters and quality of life, reduce symptoms and decrease mortality and readmission rates HF continues to have significant negative impacts on the quality of life of patients. Despite significant advances, HF remains a common cause of hospitalisation, and accounts for a substantial personal and economic burden. Ongoing challenges of HF management include multiple hospital admissions causing financial costs, of up to £1 billion per year.

Cardiac rehabilitation (CR) in the management of heart failure

Cardiac rehabilitation (CR) is a process by which patients with heart disease, in partnership with health professionals, are encouraged and supported to achieve and maintain optimal physical health. Cardiac rehabilitation programmes have historically relied on ejection fraction as surrogate determinant of physical fitness and the assessment of risk of a cardiac event during exercise.

The Cochrane systematic review of exercise based cardiac rehabilitation in conventional CVD patients (Anderson et al 2016) for HF patients (Taylor et al 2014) identified important quality of life benefits in participants, as well as reductions in HF admissions compared with usual care. 33 randomized trials in 4740 individuals with HF showed that participation in exercise-based CR was associated with a significant reduction in the risk of overall hospitalization (relative risk: 0.75; 0.62 to 0.92, p=0.005) and HF-specific hospitalization (relative risk: 0.61; 0.46 to0.80, p=0.0004) and improvements in patient health-related quality of life. Data from the NACR indicates that around 16% of those surveyed offer a specific CR programme for those with HF. (NACR 2014)

Cardiac rehabilitation plays a major role in lives of patients with coronary artery disease (CAD). CAD is a long term, progressive and often debilitating condition with enormous mental and psychosocial implications. Appropriate rehabilitation in cardiac care enables the recipients to gain the knowledge, skills and support necessary to live as normal a life as possible alongside their cardiac condition. CR has been defined by various organisations and national entities and can be encompassed by:

"The coordinated sum of activities required to influence favourably the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their own efforts, preserve

or resume optimal functioning in their community and through improved health behaviour, slow or reverse progression of disease" (BACPR 2017).

CR has incorporated other additional components include health education, advice on the reduction of cardiac risk factors and stress management to optimise the reduction of risk factors and improve adherence to healthy behaviours among recipients although traditionally, exercise training was the core component of CR.

The main objective of CR is to continue to help patients to regain their autonomy by improving regular physical activity after a cardiac event, in addition to controlling the modifiable risk factors and therefore reducing the negative effects of CAD.

To achieve optimal outcome CR programme should also be more comprehensive by educating patients about their conditions so as to allow them to become responsible for their medical treatment and lifestyle changes (Dalal et al. 2015). These are best delivered in a structured workshop-based teaching programme and by a skilled and experienced multidisciplinary team such as dieticians, psychologists, exercise specialists, etc. (BACPR 2017). Anxiety and depression have been reported to be associated with lower exercise capacity, fatigue and sense of wellbeing. Use of an skilled and experienced psychiatrist to educate recipients about stress management and self-control tools can help recipients to have a better control of other risk factors (SIGN 150 2017).

CR programmes should have favourable impact on patients' quality of life, making the benefits of CR more tangible to recipients (Dalal et al. 2015) by controlling disease symptoms and the side effects of medications. This would in turn limit the physiological and psychological effects of heart disease on patients.

Although generally accepted indications for CR include MI, CABG, PCI, valve repair or replacement and angina, there are special patient groups like heart failure where significant potential exists to obtain a positive outcome from a tailored CR programme. (Taylor et al. 2017). The recently completed REACH trial (Dalal et al 2018) has verified the efficacy of exercise based rehab in heart failure patients.

The most recent Cochrane review on exercise in patients with Heart failure (Taylor R et al 2014) focused on providing an overall review of exercise-based rehabilitation in heart failure to determine the effectiveness of exercise-based rehabilitation on the mortality, hospitalisation admissions, morbidity and health-related quality of life for people with HF. The authors found 33 RCTs comprised of 4740 participants. Important benefits of exercise-based rehabilitation were shown on reduction in the risk of hospital admissions due to HF and improvements in health-related quality of life compared with no exercise. (RR 0.88; 95% CI 0.75 to 1.02, fixed-effect analysis) compared with control, exercise training reduced the rate of overall (RR 0.75; 95% CI 0.62 to 0.92, fixed-effect analysis) and HF specific hospitalisation (RR 0.61; 95% CI 0.46 to 0.80, fixed-effect analysis).It has been previously discussed in this chapter that the main two challenges in modern cardiology are cost and capacity. It can therefore be assumed that CR, by reducing the number of hospital admissions, is a significant tool in facing the challenges in modern cardiology. It can thus also be said that the outcomes of CR go beyond the benefits to individuals and encompass improvements to the complete cardiac care system.

A Cochrane review of exercise-based CR for CHD patients reported 20 trials, with a total population of 5,060 subjects that assessed Health Related Quality of Life (HRQL). Fourteen of the 20 trials (65%) documented an increase in HRQL in one or more domains in patients subsequent to a CR programme compared to controls. Within these 14 trials, five reported a higher level of HRQL in at least one-half of the subscales (Anderson et al. 2016).

In particular relevance to my study this is supported by another Cochrane systematic review that was conducted on heart failure patients. Sagar et al (2015) reviewed a total of 18 trials which reported a validated HRQL measure. Thirteen of those 18 trials (72%) reported higher HRQL scores in patients following exercised-based CR programmes compared with control subjects (Sagar et al. 2015). All 13 trials used the same validated HRQL scoring measure, the disease-specific Minnesota Living with Heart Failure Questionnaire (MLHFQ) and therefore provided a valuable insight into the clinical relevance of CR in HF patients.

As explained earlier another major aim of CR is to provide mental support and improve the psychological state of the patient by stress reduction and promote psychosocial wellbeing. A meta-analysis of 23 RCTs with a total population size of 3,180 CAD patients was conducted to evaluate the impact of including a psychosocial component within a standard exercise-based CR programme. Patients who received psychosocial intervention showed greater reductions in psychological status with effect size differences of 0.34 (Linden et al. 1996). In view of HF and CR an American observational study assessed depression in patients with HF after receiving a comprehensive CR programme. A standard questionnaire (Kellner Symptom Questionnaire) was used to assess depressive symptoms at baseline and following CR. In patients who completed CR depressive symptoms decreased by 40% ($p < 0.0001$). Depressed patients who completed CR had a 59% lower mortality ($p < 0.05$) compared to depressed dropout subjects (Milani et al. 2011). These findings need to be treated with caution as they are based on a small sample size of 38 patients.

2. Review of literature

2.1 Introduction

In order to determine which factors influence exercise capacity (physical fitness) in patients with heart failure there was a need to review the literature. There is a huge volume of literature published on CR for patients with HF all using many different research approaches such as randomised controlled trials (RCTs), surveys, prospective and retrospective studies. The aim was to identify potential determinants of physical fitness in the HF population to help inform two studies that also underpin thesis MD thesis. Previous studies on determinants of physical fitness have tended to default to classic factors such as age and gender with some mention of comorbidity (Cardoso et al 2017, Alotaibi & Doherty 2016).

This MD wanted to learn from the literature and try to utilise as many determinants as feasible in the future studies.

2.2 Method

Literature search results

The electronic databases searches found a total of 8,715 studies. The main search was conducted in December 2016 with an updated search in May 2019. The search included

- MEDLINE (Ovid)
- CINHAL Plus (EBSCO)
- Cochrane library (CENTRAL)
- AMED (Ovid)
- EMBASE (Ovid)
- PsycINFO (Ovid)
- Scopus

Search findings were uploaded to ENDNOTE (version 7.8 Thomson Reuters). Duplicates (10%) were removed by ENDNOTE duplicate removal tool. Review by paper title removed over half of papers due to not meeting specific focus of the study (Figure 2.1). Abstract review removed a further 660 papers after which formal review of papers lead to the selection of 22 papers for inclusion in this specific review.

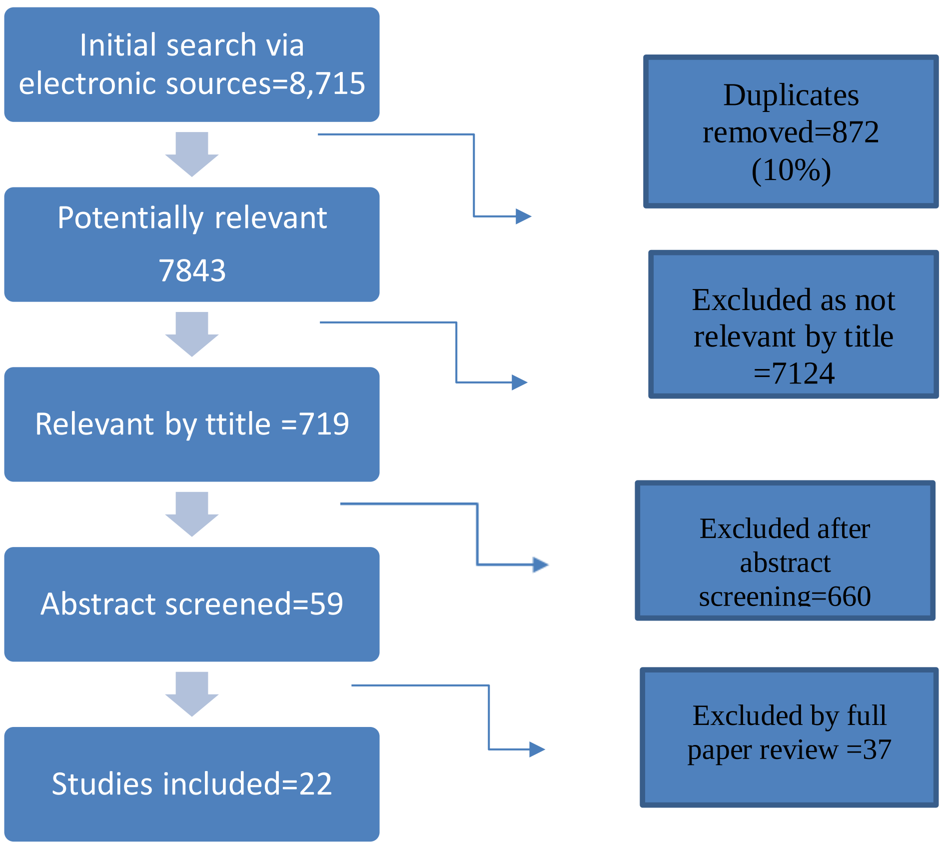

Figure 2.1. Study selection and process

2.3 Results

The following section reviews these papers in more detail in terms of methodology and findings and aims to identify which factors are likely to determine fitness in patients with HF. The reason this is important is that many studies have tended to use rather simple analyses when trying to identify factors that might determine fitness. In such an analysis it is important to control for multiple factors at the same hence the major rationale of this part of the review is to identify which factors may act as co-variables and potential confounding variables when investigating determinants of fitness. Table 2.1 summarises the key features of the included studies.

Table 2.1. Included papers identifying determinants of fitness in heart failure

	Author/study/country	Number of participants	Population	Age (years)	Fitness measure	Determinants
1	Ahmad T et al 2014 RCT	928	Chronic HF patients	59 (mean)	CPEX 6MWT	NYHA class
2	Alpert M et al 2014 Review of literature	Review of multiple studies Primary study for fitness 2066 patients	Chronic HF patients	54-55	CPEX	Obesity Age
3	Chiong JR et al 2010 Prospective cohort	243	Chronic HF patients	79.3	METS	Age

4	Comin-Colet J et al 2013 Post-hoc analysis	552	Chronic HF patients	72	Minnesota Living with Heart Failure questionnaire	Iron deficiency
5	Fenk S et al 2015 Prospective longitudinal study	188	Chronic HF patients	42 to 51	6MWT	Weight
6	Fitzsimons S et al 2014 Non-systematic Descriptive review	six studies with a range of 37 to 1506 patients	Chronic HF patients	53 – 71	CPEX	Iron deficiency

7	Gutzwiller FS et al 2013 RCT FAIR-HF sub-analysis	459	Chronic HF patients	67.8 ± 10.3	6MWT	Iron deficiency NYHA class CKD
8	Hajdusek P et al 2016 Cohort study	103 (25 healthy controls and 78 patients)	Healthy + Chronic HF patients	52.4 ± 8.1	METs using bicycle ergometry	beta-blocker use, NYHA class NT-ProBNP
9	Ingle L et al 2014 A Regional study	1667	Chronic HF patients	72	6MWT	age, NYHA, NT pro-BNP, diastolic BP, renal function
10	Kallistratos MS et al 2012 Prospective study	160	Chronic HF patients	58 ± 13	Treadmill test	SBP

11	Kommuri NV 2010 Prospective study	265	Chronic HF patients	56 -72	6MWT	Low levels of fitness
12	Adedoyin RA et al. 2010	65	HF in Nigeria	57	6MWT and CPET	Baseline walking distance
13	Reibis R et al 2010 Cohort study	1346	Chronic HF patients	64 ± 10	6MWT	Atrial fibrillation Valvular heart disease
14	Yoshihisa A et al 2018 Prospective Observational study	1079 3 groups split by zinc tertiles	Chronic HF patients	62.4 ± 14.9, 65.9 ± 13.2, 71.4 ± 13.4	Cycle ergometer	Zinc
15	Nyolczas N et al 2017 Book chapter	642 men over a 5-year period in V-HeFT I 804 men 5-year period in V-HeFT II	Chronic HF patients	18 to 75	Exercise capacity	Medicines (nitrates+hydralazine)

16	Mentz R J et al 2013 HF-ACTION RCT	2311	Chronic HF patients	No COPD 59 (51, 68) COPD 64 (56, 71)	CPEX 6MWT	COPD
17	Ahmeti A et al 2017 Prospective study	118	HFpEF HFrEF	62+/- 10	6MWT	LA size
18	Chen Y et al 2018 RCT	36	Chronic HF patients	60+/-16 61+/11(inter)	CPET/6MWT MLHFQ	Physical inactivity
19	Diaz Molina B et al 2013	122	Chronic HF patients	59+/-8	Modified Bruce test	COPD
20	McCabe N et al 2017	71	Acute heart failure	52.6+/-12.3	6MWT	NYHA
21	Enjuanes E et al 2016	538	Chronic HF	71+/- 12	6MWT	Iron deficiency/status
22	Marco B et al 2019	Review article (RA)	Chronic HF	RA	RA	All comorbidities

1. **Ahmad T et al 2014**

The effects of exercise on cardiovascular biomarkers in patients with chronic heart failure

This study investigated determinants of fitness, which highlighted a role for heart failure severity, measured by BNP, in a cohort of 928 subjects from the HF-ACTION study. This was a randomized clinical trial of exercise training versus usual care in chronic HF patients with reduced left ventricular ejection fraction (<35%).

The LVEF cut off for inclusion was strict compared to other studies where 45% has been used (Taylor et al 2015) which might explain the strength of their findings. The situation clinically is that a LVEF of 45% is used for defining the HFrEF, which is why the REACH-HF study is highly relevant.

2. **Alpert M et al 2014**

Obesity and heart failure: epidemiology, pathophysiology, clinical manifestations, and management

This review of literature, albeit non-systematic in its approach, does put across a compelling case for the role of obesity in determining fitness. Their findings, from multiple studies with variable sample sizes, confirm that obesity is a major risk factor for heart failure and substantial weight loss in severely obese persons can reverse the cardiac hemodynamic instability and improve cardiac performance and thereby exercise capacity. The review explores various epidemiological studies and cardiac pathophysiology in addition to clinical manifestations and management which indicate that clinicians and health services consider obesity as an important variable.

This can be highly relevant in our REACH-HF sub-study as increased BMI with other co morbidities may be an important parameter in reducing individuals' fitness.

3 Chiong JR et al 2010

Impact of exercise capacity among elderly (≥ 75) with systolic heart failure

This study prospective cohort study assessed the relationship between physical fitness, expressed as metabolic equivalents (METs), ECG changes and all-cause mortality in 243 severe HF patients (LVEF <40%) over the age of 75 years (mean 79.3 years) of which 76% were men. With a mean follow up of 4.7 years, 149 (61%) died. The median fitness achieved was 5.8 METs. Low levels of fitness (≤5.8 METs) were predictive of all-cause mortality (adjusted HR 0.77, 95% CI: 0.68–0.88, p = <0.001) but not ECG ischemic changes.

They conclude that higher survival rates were observed in patients age 75 years and older with fitness levels greater than 5.8 METs which represents a strong rationale for age as a determinant of fitness in HF related studies.

This is an important observation and may be an important parameter in our HF sub-study as our recruited patients were mainly younger population with mean age 69 years.

4. Comin-Colet J et al 2013

Iron deficiency is a key determinant of health-related quality of life in patients with chronic heart failure regardless of anaemia status

This post-hoc analysis of a cohort of chronic heart failure patients demonstrates that iron deficiency not anaemia was associated with reduced health related quality of life. With a total of 552 patients observed in the study Minnesota living with heart failure questionnaire scores was significantly worse in patients with iron deficiency.

As with most post-hoc analyses there are concerns about sample bias and representativeness of findings. The analysis was not sufficiently powered statistically especially as part of a post-hoc analysis where there is limited scope to account for confounding variables in a sample of this size. That said testing for iron status is increasingly important and has become a routine part of clinical practice in recent years. Studies of fitness levels in HF patients should strive to investigate this measure or take it in to account when interpreting their findings. For later discussion in this MD thesis the REACH-HF sub-study failed to include iron deficiency as it was not routine practice at the time of the study development (2001/2002).

5. **Fenk S et al 2015**

Successful weight reduction improves left ventricular diastolic function and physical performance in severe obesity.

This prospective longitudinal study followed 188 obese patients on a long-term weight reduction programme in severe obese patients (mean BMI >40) found that weight reduction does improve LV diastolic function and exercise capacity. Patients with BMI around 40 underwent 1-year weight reduction programme (diet and lifestyle change). 6-minute walk test and echocardiography were performed at baseline and after 1 year. Patients with successful weight reduction demonstrated significant echocardiographic parameter improvement thereby suggesting obesity is an important factor in reducing exercise capacity. This study suggests that being obese is associated to fitness in this non-cardiac population and that weight reduction has potential to improve left ventricular function in around one-third of people following such programmes.

6. **Fitzsimons S et al 2014**

Iron deficiency in patients with heart failure

This non-systematic descriptive review article emphasizes that iron replacement in patients with heart failure with reduced ejection fraction has been shown to improve symptoms and exercise capacity. The review, based on six studies with a range of 37 to 1506 patients, highlights the prevalence of iron deficiency in patients with HF independent of the presence of concomitant anaemia which is an important clinical finding that requires clinicians to think more broadly about when interpreting factors may affect patient fitness and daily physical activity status. Iron deficiency is clearly a factor that future research and regression analyses should investigate although the ability collect reliable and valid data from clinical practice is likely to create challenges for researchers.

7. **Gutzwiller FS et al. 2013**

Determinants of quality of life of patients with heart failure and iron deficiency treated with ferric carboxymaltose: FAIR-HF sub-analysis

There have been many studies that have shown benefits of any iron therapy in heart failure patients; this study is of no exception in demonstrating that intravenous iron therapy not only improves quality of life but also increases exercise tolerance. In this randomized, double-blind placebo-controlled trial of 459 patients it was found that in addition to intravenous iron, lower NYHA class and a better result in 6 min walk test had a positive influence on the health related quality of life (HRQoL) of heart failure patients.

This is relevant in our sub-study as these parameters are thoroughly examined in our patient group to assess their exercise capacity.

8. **Hajdusek P et al 2016**

Heart rate response to exercise in heart failure patients: the prognostic role of metabolic-chronotropic relation and heart rate recovery

This recent cohort of 25 healthy controls and 78 patients with advanced systolic heart failure underwent maximal cardiopulmonary exercise test and found to have impaired exercise performance compared to control. They had lower peak workload, peak VO_2 and higher VE/VCO_2 slope.

This study took account of the heart failure patients who are already on optimized medical therapy including beta blockers, ACE $_{(i)}$/ARBs and mineralocorticoid receptor antagonists as well as device therapy. It was also evident in follow up that patients with impaired exercise performance had higher NT pro-BNP level. In heart failure patients metabolic-chronotropic relation (MCR) slope was inversely associated with beta-blocker use, NYHA class and heart failure duration.

9. **Ingle L et al 2014**

The long-term prognostic significance of 6-minute walk test distance in patients with chronic heart failure

This is one of the largest studies that have focused on the prognostic value of the 6-minute walk test during extended follow up. 1667 patients with left ventricular systolic impairment undertook a 6 MWT as part of baseline assessment and were followed up for 5 yrs and results showed that patients who had managed lower distance 6 MWT had higher mortality rates. Higher NT pro-BNP level and NYHA class, increasing age and lower diastolic pressure were independent predictors of all cause morality.

This study forms the base of our discussion point in our sub-study as REACH-HF trial too used incremental shuttle test to assess exercise capacity of heart failure patients and the above parameters like Pro-BNP level and blood pressure.

10. **Kallistratos MS et al 2012**

Prognostic significance of blood pressure response to exercise in patients with systolic heart failure (HF)

Hypertension remains a major risk factor for the development of heart failure and higher systolic blood pressure (SBP) has traditionally been related to heart failure, myocardial infarction and overall cardiovascular mortality and morbidity and European guidelines also recommend lower SBP to reduce the risk.

160 patients with systolic heart failure were studied and blood pressure was taken at rest and at peak exercise during cardiopulmonary exercise test. Patients were followed up for a period and found that patients with higher blood pressure at rest

and peak exercise had the most favorable prognosis. There was an inverse relationship between SBP and cardiac mortality in patients with systolic HF and thereby concluded that BP response to exercise could risk stratify HF patients. The sample size was too small to allow higher level statistical analysis which would have made the findings more informative by including potential co-variates. (Field A. 2017)

11. Kommuri NV 2010

Six –Minute walk distance predicts 30-day readmission in hospitalized heart failure patients

This prospective study of 265 patients (40% of the original sample of 666 patients) showed low levels of fitness as measured via 6MWT distance predicts early hospital readmission in patients with HF. Patients walking greater than 400 m had half the admissions in 30 days than patients walking less than 400 m ($p = 0.016$). The analysis failed to take account for missing data as only 210 patients were included in the final analysis which is also a very low sample size considering 22 variables were included in the multiple regression. Statistical guidance suggests around 30 participants per item entered into a regression analysis which would need to be in the region of 700 patients to account for so many variables (Field A 2017).

12. Adedoyin RA et al. 2010

Prediction of functional capacity during six-minute walk among patients with chronic heart failure

This small prospective study of 65 patients with HF in Nigeria concluded that age and weight were not strong predicting of fitness as measured through a 6MWT and

CPET. In the absence of sophisticated equipment, they proposed an equation that aims to predict functional capacity in form of oxygen consumption (VO_2) in chronic HF patients. The equation includes age and weight because the authors felt they were important, yet these two factors were not significant predictors of fitness. Distance walked on the 6MWT was the only significant variable in predicting fitness. The study findings lack generalizability as they use a very small sample size for regression analysis would normally include a few hundred or more patients. The HF patients were also much younger than with a mean age of 57 years compared to UK HF patients were the mean age is 78 years (NICOR 2017) which makes the equation less pertinent to patients attending routine clinical practice.

13. Reibis R et al 2010

Exercise capacity is the most powerful predictor of 2-year mortality in patients with severe ventricular systolic dysfunction

This German cohort study of 1,346 patients, mean age of 64.3 years (27% women) with left ventricular systolic dysfunction (LVEF <45%) showed that symptom limited exercise capacity and walking distance performed via 6 MWT were good prognostic tools in cardiovascular mortality and morbidity. Mean LVEF was 36.3 ± 8% and across the patient group LVEF was non predictive of prognosis with a mean follow-up was 731 ± 215 days. Atrial fibrillation (AF) and valvular heart disease in LVSD carries poorer prognosis. The REACH-HF and MD sub-study investigated these parameters further in terms of fitness prediction.

14. Yoshihisa A et al. 2018

Association of Serum Zinc Level with Prognosis in Patients with Heart Failure

Using a prospective observational study with 1079 HF patients Yoshihisa et al demonstrated that low zinc levels are associated with associated with high mortality accompanied by impaired exercise capacity. Zinc levels were measured in 968 patients admitted to hospital with decompensated heart failure. Patients were recruited 2010 and 2015 and followed up in 2017 with cardiac function and exercise capacity examined. 322 (33.3%) of patients underwent incremental symptom-limited exercise testing using an upright cycle ergometer with a ramp protocol with breath-by-breath gas analysis including oxygen consumption. The results were analysed in the Cox proportional hazard analysis, serum zinc level was predictor of cardiac and all-cause mortality. Although the sample size was large the authors noted a reluctance from HF patients to take part in breath-by-breath gas analysis exercise tests which clearly impacted their results. Increasingly HF based CR studies are preferring to use sub-maximal field tests such and the 6MWT or ISWT as patients are able to tolerate these tests as they do not require patients to wear restrictive face masks (Singh et al 2005, Taylor et al 20154, Taylor et al 2015).

15. Nyolczas N et al. 2017

Combination of Hydralazine and Isosorbide-Dinitrate in the Treatment of Patients with Heart Failure with Reduced Ejection Fraction

Nyolczas et al have demonstrated in a recent study published in Advances in Experimental Medicine & Biology that the combination of hydralazine and isosorbide dinitrate in heart failure with reduced ejection fraction (HFrEF) can improve the signs and symptoms of heart failure, exercise capacity and quality of life, and, most importantly, reduce morbidity and mortality in HFrEF patients. These are particularly beneficial in patients who cannot receive either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers due to intolerance or contraindication or self-identified African-American race. The Hy+ISDN combination can decrease preload and afterload, decrease left ventricular end-diastolic diameter and the volume of mitral regurgitation, reduce left atrial and left ventricular wall tension, decrease pulmonary artery pressure and pulmonary arterial wedge pressure, increase stroke volume, and improve left ventricular ejection fraction, as well as induce left ventricular reverse remodeling. The combined drugs also have antioxidant property thereby affecting endothelial dysfunction and improve Nitric Oxide bioavailability. This particular property improves the patients' exercise capacity. These findings are based on a book chapter only and should be treated with caution.

16. Mentz RJ el al 2013

Clinical Characteristics, Response to Exercise Training and Outcomes in Heart Failure Patients with Chronic Obstructive Pulmonary Disease: Findings from HF-ACTION

An investigation of 2,331 HF patients with ejection fraction ≤35% with and without chronic obstructive pulmonary disease (COPD). This study was a sub-study of the HF-ACTION trial which randomised patients to usual care with or without aerobic exercise training. The study included two groups categorised as No COPD (N=2311), mean age 59 (51-68) years and HF+COPD (N=249) mean age 64 (56-71) years the percentage of female patients of 29% and 25% respectively. Using data from CPEX and 6MWT measurements COPD was one of the strongest determinants of distance walked. One of the limitations was the relatively small sample size for patients with documented COPD which represented 11% of the overall sample. The prevalence of COPD in HF is around 30% (Valk MJ et al 2015, Hawkins NM el al 2009) which suggests that the sample recruited as part of HF-ACTION was perhaps non-representative.

17. Ahmeti A et al. 2017

Quality of life questionnaire predicts poor exercise capacity only in HFpEF and not in HFrEF

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is the most widely used measure of quality of life (QoL) in HF patients. The MLHFQ is a disease-specific HRQoL questionnaire with 21 items focusing on core dimensions (e.g. physical, emotional, social and mental) of an individual's quality of life with a range of scores from 1 to 105 where high scores suggest poor QoL.

This prospective study aimed to assess the relationship between HRQoL and exercise capacity in HF patients. Ahmeti and the team have studied 118 consecutive patients with chronic HF with NYHA I-III. 57 of the patients were female and age range was 62+/- 10 yrs. Patients answered a MLHFQ questionnaire, had an echocardiogram which grouped them into 2 groups namely preserved EF (HFpEF) and reduced EF (HFrEF). They also underwent a 5 min walk test (6-MWT), in the same day. Interestingly despite conventional belief the total scale and the physical and emotional functional MLHFQ scores did not differ between HFpEF and HFpEF.

Group I patients were older (p = 0.003), had higher NYHA functional class (p = 0.002), faster baseline heart rate (p = 0.006), higher prevalence of smoking (p = 0.015), higher global, physical and emotional MLHFQ scores (p < 0.001, for all), larger left atrial (LA) diameter (p = 0.001), shorter LV filling time (p = 0.027), higher E/e' ratio (0.02), shorter isovolumic relaxation time (p = 0.028), lower septal a' (p = 0.019) and s' (p = 0.023), compared to Group II. Independent predictors of 6-MWT distance for the group as a whole were increased MLHFQ total score (p = 0.005), older age (p = 0.035), and diabetes (p = 0.045), in HFpEF were total MLHFQ (p = 0.007) and diabetes (p = 0.045) but in HFrEF were only LA enlargement (p = 0.005) and age (p = 0.013. A total MLHFQ score of 48.5 had a sensitivity of 67% and specificity of 63% (AUC on ROC analysis of 72%) for limited exercise performance in HF patients. Quality of life, assessment by MLHFQ, is the best correlate of exercise capacity measured by 6-MWT, particularly in HFpEF patients. Despite worse ejection fraction in HFrEF, signs of raised LA pressure independently determine exercise capacity in these patients.

18. Chen Y et al. 2018

Home-based cardiac rehabilitation improves quality of life, aerobic capacity, and readmission rates in patients with chronic heart failure

Chen et al. have shown in a recent published study that home-based cardiac rehabilitation offered the most improved results in functional capacity, QOL, and a reduced the rate of readmission within 90 days. This study was an RCT with 18 patients in the control group and 19 in the interventional group all with LVEF < 50%. We randomly assigned patients to the). patients with a LVEF of less than 50%.

Within the interventional group CR programmes, including home-based cardiac rehabilitation, diet education, and management of daily activity over a 3-month period were incorporated. Cardiopulmonary Exercise Test (CPET), Six-minute Walk Test (6MWT), and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) were measured before and after the intervention. Patients enrolled in home-based CR had significant improvement in peak fitness (18.2 +/- 4.1 vs 20.9 +/- 6.6 mL/kg/min, P = .02), 6MWT (421 +/- 90 vs 462 +/- 74 m, P = .03) and QOL. The 90-day readmission rate for patients reduced to 5% from 14% after receiving CR. This is very relevant to part two of this MD thesis as we aimed to used data from facilitate home based CR for these heart failure patients (REACH-HF study).

The sample size was small limiting generalizability to the wider HF population.

19. Diaz Molina, B., et al. (2013).

Exercise capacity in patients with heart failure and COPD.

Chronic obstructive pulmonary disease (COPD) is a frequent co morbidity in heart failure which was identified in paper one of this MD thesis.

The study by Diaz Molina et al compare exercise capacity of CHF patients with and without COPD. 122 patients underwent a modified Bruce test with spirometry. Their analysis considered age, sex, height, weight, BMI, aetiology of the CHF, COPD previously diagnosed, and six ventilatory measures plus heart rate. Nine patients were unable to complete the test. The mean age was 59+/-8 years. 78% were male. 27% had previously COPD. Their findings conclude that CHF patients with COPD have diminish exercise tolerance.

20. McCabe N et al. 2017

Six-minute walk distance predicts 30-day readmission after acute heart failure hospitalization

In a recent journal article published by McCabe and team looked at the relationship between 6-min walk test distance (6MWD) and 30-day readmission in hospitalized heart failure (HF) patients. Seventy-one hospitalized HF patients with NYHA Class II/III (mean age 52.6 +/- 12.3 years, 42.3% female, 73.2% African American) performed 6MWD prior to discharge. 30-day readmission occurred in 14 (19.7%) patients. Average 6MWD was 756.4 +/- 403.2 feet. Higher 6MWD significantly decreased risk of 30-day readmission, even after adjusting for sociodemographic and clinical characteristics (OR = .84, 95% CI [.71, .99]). For each additional 100 feet walked odds of a 30-day readmission decreased by 16%. 6MWD predicted 30-day readmission in this study prompting further investigations into this field.

21. Enjuanes C et al. 2016

Iron Status in Chronic Heart Failure: Impact on Symptoms, Functional

Class and Submaximal Exercise Capacity

Enjuanes and colleagues have evaluated effect of iron deficiency and anaemia on exercise capacity in patients with chronic heart failure. 538 patients with average age of 71 years and NYHA class of III-IV (33% of the patients) were included in the single centre cross-sectional study. 6 minute walk test was used to evaluate the exercise capacity of these patients. Stable heart failure patients with ferritin of <100 ng/ml or transferrin saturation <20% when ferritin level <800 ng/ml were considered as iron deficient patients. The results showed the mean distance walked by patients with impaired iron status is lower compared to ones without impairment. In addition patients with impaired iron status complained of more exercise induced symptoms predominantly fatigue. Multivariate regression analysis showed a significant independent and linear association between iron status and advanced NYHA class ($p<0.05$) and submaximal exercise capacity ($p=0.03$ for both) respectively. On the other hand anaemia had no associations with the 6 minute walk test distance.

This analysis clearly emphasize the key fact yet similar to previous four other studies as described above that impaired iron status or reduced iron level or iron deficiency remains a key determinant of fitness in patients with heart failure.

22. Marco et al. 2019

Exercise intolerance in patients with heart failure

This very recently published JACC state-of-the-art review gives an excellent and comprehensive overview of the pathophysiology of exercise and functional intolerance in patients with HF. This review not only details the different modalities used to quantify exercise tolerance in these patients groups but also multiple comorbidities that may co-exist that impairs and contributes towards their exercise intolerance. The review starts with discussing the pros and cons of different methods and tests used to quantify exercise intolerance in heart failure. The review then discusses determinants of exercise intolerance in patients with heart failure more from pathophysiological point of view that includes factors that reduces cardiovascular and pulmonary reserve. As discussed in the initial part of the thesis these are systolic and diastolic impairment, chronotropic incompetence and valvular disease such as functional mitral regurgitation, reduced pulmonary reserve impaired ventilation-perfusion and reduced O2 diffusion respectively. The review then talks about other significant comorbidities that include range of diseases from anemia/iron deficiency, diabetes, obesity, malignancy, muscle disorders and presence of COPD with concomitant heart failure may contribute to diminished exercise and functional capacity. The review concludes with current pharmacological and non-pharmacological methods used in these patient groups that includes essential medications that includes conventional ACE, ARBs, Aldosterone antagonists, beta blockers and more newer Sacubitril-valsartan and Ivabradine and role of CRT devices and iron replacement. The review finally emphasized tight control of co-morbidities and tailor-treat the mechanisms of reduced exercise and functional capacity to achieve the relevant goal in these patient group.

In summary there were 14 variables derived from the literature that are seen as determinants of fitness inpatients with HF (Table 2.2). Although angina was considered as a possible determinant there were no studies verifying this in patients with HF.

Table 2.2. Summary of determinants influencing exercise capacity in HF

	Determinant	Number and details of papers supporting each determinant
1	Age	5:22 Chiong JR et al 2010, Ingle L et al 2014, Adedoyin RA et al. 2010, Ahmeti A et al. 2017, McCabe N et al. 2017
2	Gender	1:22 McCabe N et al. 2017
3	LVEF	2:22 Ahmad T et al 2014, McCabe N et al. 2017
4	Iron deficiency anaemia	5:22 Comin-Colet J et al 2013, Fitzsimons S et al 2014, Gutzwiller FS et al. 2013, Enjuanes C et al 2016, Marco B et al 2019
5	NYHA class	5:22 Ahmad T et al 2014; Gutzwiller FS et al 2013; Ingle L et al 2014; McCabe N et al 2017, Marco B et al 2019
6	COPD	3:22 Diaz B et al 2013, Mentz, RJ et al 2013, Marco B et al 2019
7	Hypertension	2:22 Kallistratos MS et al; Ingle L et al 2014
8	Diabetes	1:22 Marco B et al 2019
9	CKD	3:22 Gutzwiller F et al 2013; Ingle L et al 2014, Marco B et al 2019
10	Obesity	3:22 Fenk S et al 2015; Alpert M et al 2014, Marco B et al 2019
11	Physical inactivity	2:22 Kommuri NV 2010; Chen Y et al 2018
12	NT-proBNP	2:22 Hajdusek P et al 2016, Ingle L et al 2014
13	Zinc	1:22 Yoshihisa A et al 2018
14	LA size	1:22 Ahmeti A et al 20170

2.4 Discussion

This review is the first to systematically identify and summarise determinants of fitness in patient with HF. This review identified 14 factors determining fitness and in doing so highlights the complexity of drawing conclusions about fitness from singular characteristics such age or gender which has been a trend in most studies, recommendations and reference values. This review also highlights that at any one-time multiple factors may be playing a role in defining fitness which further supports the approach I have taken as part of this MD and underpinning analyses where I have tried to account for possible confounding variables.

One of the biggest gaps in the literature and studies investigating determinants is that the sample sizes used to identify determinants of fitness in patients with HF are small and, in many cases, insufficient to meet statistical requirements. Nine of the studies (numbers 5,6,8,10,12,17,18,19 and 20) representing (45% of total) reviewed relied on small cohorts recruited as part of larger trials and cohorts which question the day-to-day clinical representativeness of these groups when compared to what is seen in routine practice.

The small sample sizes for the multiple variables included in these studies and recruitment of patients through voluntary take up of studies questions the validity and generalizability of these studies.

One of the other key points to draw from the literature is that the term fitness and fitness assessment is subject to interpretations and can be misleading. What is clear is that cardiopulmonary exercise testing (CPEX) is the criterion measure of fitness in research and in clinical practice especially where diagnosis and prognosis are being evaluated (Thomas et al 2019, Del Buono et al 2019). However, when it comes to field based exercise tests, often referred to as sub-maximal tests, there is greater uncertainty about the extent by which they measure fitness (BACPR 2017, Thomas et al 2019, Del Buono et al 2019). For instance the 6MWT and ISWT are both often reported as measures of walking fitness and seen as interchangeable as both tests conclude on total distance walked expressed in metres (Thomas et al 2019). However these two tests measure very different aspects of walking ability especially in patients with HF. The ISWT, developed by Singh and colleagues in 1992, is a measure of fitness (exercise tolerance/capacity) achieved via a protocol that is externally paced and gets harder through increases in walking speed each minute from very slow 0.50 m/s (1.1mph) to the final level of very fast walking of 2.37m/s (5.3mph). As a context the average walking speed for healthy 70 year old people is 1.2m/s (2.6mph) and even lower for HF patients at 0.84 m/s (1.8 mph). The final stages of the ISWT test extend to a level of exertion that virtually no HF can ever achieve hence the ISWT protocol has no ceiling effect. The ISWT, is strongly recommended in the clinical guidelines and national standards and meets all the key attributes of fitness test (BACPR, 2017), On the other hand the 6MWT simply asks patients to walk at their natural or comfortable cadence for as long as they can up to 6 minutes. Many patients (~ 40%) can achieve the protocol end point of 6 minutes (NACR 2019) which means there is a significant ceiling effect. This test assesses how far a patient can walk at their natural cadence up to six minutes and requires no additional increments of exertion (e.g. such as speed). Although the 6MWT does not fulfill the attributes of a fitness test (Fleg et al 2000) it nevertheless retains a place in clinical practice as part of the evaluation of treatment efficacy and prognosis (Del Buono et al 2019). The inability to walk 300 metres at a self-directed pace during the

6MWT is seen as an independent prognostic marker of cardiovascular death in patients with moderate degrees of HF (Del Buono et al 2019).

This review is highly relevant to my MD as it explored and concludes on determinants other than ejection fraction influencing exercise capacity in patients with heart failure.

Based on this review and its findings the MD thesis sought to carry out a study that would tackle many of the issues of sample size and relevance to clinical practice by carrying out an observational study of determinants of fitness in HF patients using routine clinical data as part of the National Audit of Cardiac Rehabilitation. This could potentially compliment the literature giving a more balance perspective to that of the existing literature which uses predominately RCT and prospective cohort studies which are known, through recruitment and exclusion criteria¸ to attract a younger and less comorbid population (Anderson et al 2016, NACR 2017).

2.5 Conclusion

The review fulfilled the aim of identifying determinants of physical fitness in patients with HF by identifying 14 potential determinants with varying levels of evidence underpinning their selection.

These findings have helped increase our understanding around which factors should be considered when drawing conclusions about physical fitness. The findings also highlight the need for further studies to validate these potential determinants in larger populations especially in routine clinical practice populations.

3. Determinants of walking fitness in patients with heart failure

Abstract

Introduction: Patients with heart failure (HF) attending cardiac rehabilitation (CR) benefit in terms of mortality, quality of life and hospital admissions however too few HF patients attend CR. There is a shortage of quality data and analyses on the characteristics of those patients that do take up CR and this is even more the case in respect of physical fitness. This study, using routine clinical data, evaluated the extent by which clinical and patient demographics determine walking fitness in HF patients.

Methods: Clinical data from the British Hear Foundation National Audit of Cardiac Rehabilitation identified patients with HF who completed an incremental shuttle walk test (ISWT). Stepwise regression accounting for age, gender and multiple potential confounders, informed by the literature, were assessed for their contribution to fitness expressed in distance walked.

Results: 1519 patients (68% male) with a mean age was 64.5 years (12.7 SD) and an average ISWT distance of 266.6 m (156.4 SD). Walking distance reduced by 4.9 metres for each year increase in age above mean age ($p < 0.001$). After accounting for confounders females walked 42.1 metres < males ($p = <0.001$). Pulmonary disease was associated with a 39 metre reduction walking distance. BMI > 30 and being unemployed were associated with 28 metre and 50 metre reduction in walking distance respectively ($p<0.005$). HF severity failed to improve the regression model fit or achieve significance in the analysis

Conclusions: Age, gender, depression and the presence of pulmonary disease were highly significant factors in predicting walking fitness in HF patients. To aid clinical practice this study also produced a table of reference values aligned with age, gender and key comorbidities which has the potential to aid the interpretation of walking fitness and gaol setting in patients with heart failure.

Keywords: physical fitness, heart failure, cardiac rehabilitation

3.1 Introduction

Cardiac rehabilitation (CR) for patients with coronary heart disease (CHD) and those with heart failure is a clinically effective intervention that has yet to achieve optimal uptake in routine clinical practice [Anderson et al 2016, Taylor et al 2017, Rauch et al 2017]. The stated ambition of NHS England is to improve uptake from 45% in 2014 to greater than 65% by 2020 which is an initiative that aligns with NICE guidance recommendations in the UK [CVD Outcomes Strategy 2013, NICE CG108] and international guidance [Piepoli et al 2016]. Cardiologists and cardiac nurses play a fundamental role in the early treatment and management of heart disease and they represent the primary source of referral to CR (BACPR 2017).

National audit data from the UK (NACR 2017) shows that uptake to CR is around 50% for acute coronary syndrome patients and equivalent to one-third in European and American CR programmes (Bjarnason-Wehrens et al 2010, Peters & Keeley 2018). The situation is much worse for patients with HF where uptake is less than 20% of all eligible patients in the UK (NACR 2018, NICOR 2018). Referral to CR for patients with HF has yet to become routine practice with most programmes already stretched by the sheer volume of patients attending CR through conventional cardiology referral pathways (NACR 2018, Dalal et al 2015).

The study hypothesis was that one of the reasons so few HF patients attend CR and many programmes are unable to recruit HF patients is, in part, due to a perception that 'exercise training and rehabilitation' are at odds with the diagnosis of HF. There is an urgent need to create a more realistic view of what a patient with HF can achieve in terms of physical exercise and fitness. Although clinical trial data on HF exists suggesting what is possible in terms of maximal exercise capacity, obtained from cardiopulmonary exercise testing (CPET), this tends to be based on an exclusive population that are much younger, by as much as 11 years, and have fewer comorbidities (Anderson et al 2016) compared to patients that attend routine practice CR (NACR 2017).

The incremental shuttle walk test (ISWT) is the most commonly used test of functional physical fitness in the UK (NACR 2017). Although the ISWT does not represent a ‘criterion maximal test’, of exercise capacity it is a recommended sub-maximal surrogate measure of exercise capacity (BACPR 2017) that is positively validated against CPET (Fowler et al 2005). Some studies have used the ISWT to investigate potential determinants of walking fitness in conventional cardiac patients (Pepera et al 2010, Cardoso et al 2017) identifying age, height, body mass index (BMI) and the presence of diabetes as significant predictors of distanced achieved. The New York Heart Association (NYHA) Functional Classification is an established symptom and function aligned measure, classifying the extent of HF severity in patients, yet not been investigated for its role in determining walking fitness as measured by the ISWT in HF.

This study aims to investigate and assess the strength of association between walking fitness and relevant patient demographics, risk factors, comorbidities and severity of HF. Our findings aim to create new knowledge to guide clinical decisions about the characteristics of patients with HF taking part in exercise-based CR.

3.2 Method

This study applied a robust observational methodology to evaluate the potential contribution of individual patient characteristics in defining physical fitness in patients with HF attending a CR assessment. Data for the NACR is imputed by clinicians and collected routinely throughout the patient journey from acute management through to outpatient CR (Figure 3.1 with permission from NACR).

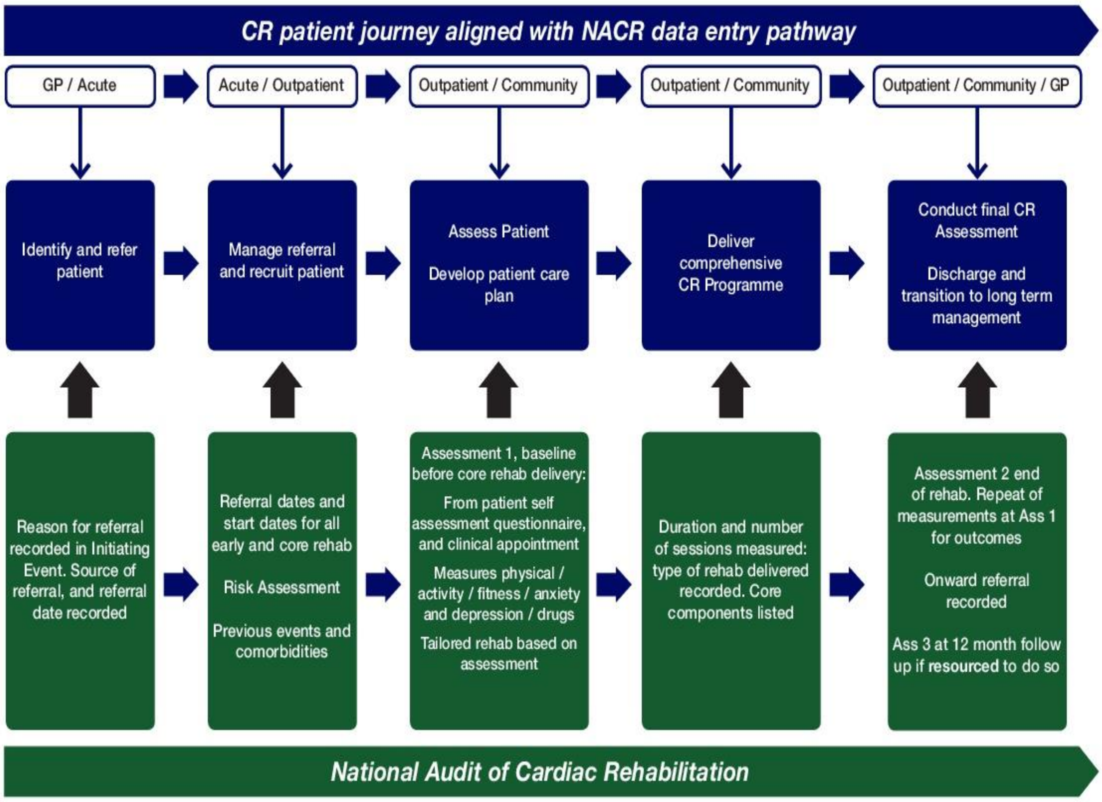

Figure 3.1. Cardiac rehabilitation data collection (NACR 2017)

The NACR collects an extensive range of patient and service level information through an electronic data entry database hosted by NHS Digital (BACPR 2017).

The data collected includes:

- demographics (age, sex, marital status, ethnicity)
- initiating event, e.g. myocardial infarction (MI), a treatment such as percutaneous coronary intervention (PCI) or a combination of MI and PCI; additional information includes comorbidities, acute events during CR; previous cardiac events; and reason for CR
- referral times (date of initiating event, date referred to CR, date started CR, date completed CR)
- clinical data on BMI, Waist measures, cholesterol and to a small degree on medications)
- Hypertension is an important variable in CVD management which is collected as follows:
    - Systolic blood pressure (SBP)
    - Diastolic blood pressure (DBP)
    - BP >140/90 mmHg is considered to represent hypertension (NICE, 2013a).
- Health status such as smoking status, level of physical activity, physical fitness (ISWT and 6MWT)
- health-related quality of life (HRQoL) using the Dartmouth COOP questionnaire)
- psychosocial health using the Hospital Anxiety and Depression Scale
- CR duration which has a mean of 9 weeks base don NACR 2017 data
- reason for not completing CR are also collected

Cardiac rehabilitation uptake

NHS England CVD Outcomes Strategy (2013) set an ambition of 33% uptake of CR in patients with HF. The NACR has shown increasing numbers of CR programmes now offering CR with over 90% of programmes now stating that do not exclude HF patients which is a marked improvement compared to 2010 when less than 30% of programmes included HF patients. Data from the National Cardiology HF Audit run by the National Institute for Cardiovascular Outcomes Research (NICOR 2017) suggests that 20% of patients with a HF diagnosis are referred to CR with wide variation in referrals between hospitals. Using NICOR data for CR referral patients referred to CR, demonstrated improved survival of around 12% compared to patients not referred to CR (National Heart Failure Audit, NICOR 2017).

In real terms, CR programmes are dealing with a wide range of patient populations. The 2017 NACR report shows the types of patients taking up CR by country (Table 3.1). Patients with HF represent just over 5% of the total population attending CR in 2015 to 2016 which is estimated to be less than 10% of the eligible HF population.

Based on NACR data uptake to CR remains roughly the same year-on-year as last year at around 30% and 70%, for females and males respectively (NACR 2017). 25% of older women below 75 years took up CR versus 40% for women above 75 years of age (NACR 2017, Al Quait and Doherty 2016).

Table 3.1. CR utilisation by patient group 2015 to 2016 (NACR 2017)

	Number of patients			
	England	**Northern Ireland**	**Wales**	**Other**
MI	14182	363	730	42
MI + PCI	23554	985	1506	96
MI + CABG	1945	69	151	27
CABG	9248	363	531	30
PCI	13893	554	480	45
MI With HF	170	3	7	2
HF	**4313**	**46**	**174**	**8**
Angina	2362	127	526	7
Valve Surgery	4186	137	340	13
Other Surgery	445	9	44	0
Cardiac Arrest	111	0	3	1
Pacemaker	248	3	19	6
ICD	578	11	28	6
Other	2850	136	406	2
Unknown	1661	5	40	-
Total	**79,746**	**2,811**	**4,985**	**285**

CR patients present around an average age of 67 years with a range of comorbidities (Table 3.2) which are known to impact uptake and outcomes. Analysis of NACR data has shown that patients with more comorbidities benefit less, in terms of physical health outcomes, than those patients with fewer comorbidities (NACR 2013).

Table 3.2. Comorbidity profile for patients attending CR (NACR, 2018)

MORBIDITIES PROFILE FOR CR

MORBIDITY CATEGORY	WITH 2 OR MORE MORBIDITIES %
Angina	23
Arthritis	18
Cancer	9
Diabetes	32
Rheumatism	3
Stroke	7
Osteoporosis	2
Hypertension	63
Chronic bronchitis (COPD)	5
Emphysema (COPD)	4
Asthma	10
Claudication	3
Chronic Back Problems	10
Anxiety	7
Depression	8
Family History	31
Erectile Dysfunction	3
Hypercholesterolaemia/Dislipidaemia	42
Other Comorbid Complaint	35

N= 43,399

With regards to smoking status the NACR response categories are:

- Never smoked
- Ex-smoker
- Stopped smoking since event
- Currently smoking

Physical activity status

Physical activity status is obtained through the Chief Medical Officer (CMO) Physical Activity Questionnaire which is a patient self-report questionnaire on weekly physical activity (NACR, 2017). The CMO recommends regular 'moderate' physical activity of at least 30 minutes duration on at least 5 times a week which is equivalent to 150 minutes over 7 days or 75 minutes of vigorous exercise a week (GOV.UK 2016).

Physical Fitness measurement

Sub-maximal field tests such as the ISWT and 6MWT are used to assess physical fitness in CR patients (Gremeaux et al., 2011).

Incremental shuttle walking test as a measure of fitness

The ISWT is an externally paced sub-maximal walking test that evaluates physical fitness based on the distance walked or incremental level achieved. The test was adapted from the idea of the shuttle run test and introduced by Prof Singh 1992 in patients with COPD. The test involves walking on the flat over a 10 metres course with a cone at each end. An audio beat sets the pace which increases each minute until the patient is unable to make the turning points before the beat sounds. There are 12 stages that start slow (0.05 m/s) which suits patients with heart failure by enabling most of them to progress through the stages 1 to 8. The final stages of the ISWT (11 and 12) are very fast walking and rarely reached by patients with HF. The reliability and validity of the test has been established (Fowler et al 2005) and found to be a good sub-maximal test of fitness with a strong correlation with CPEX findings.

For this MD analysis ISWT distance was used as the measure of walking fitness.

Psychosocial health measurement in CR

The Hospital Anxiety and Depression Scale (HADS) is now a routine measure anxiety and depression in a general medical population of patients developed by Zigmond & Snaith in 1983 and validate in cardiac patients in 1994. The HADS is seen as quick and easy to used and a recommended tool for diagnosis of depression and anxiety (NICE, 2011) and is valid in multiple diagnostic groups and sensitive to progression of psychological symptoms (Snaith 2003).

The HADS questionnaire can be analysed on a continuous scale 0 to 21 or categorised into three severity groups or normal (mild), borderline (moderate) or probable (severe) (Table 3.3)

Table 3.3. HADS categories

0–7	Mild
8–10	Moderate
11–21	Severe

Data acquisition and approval

The study used data from a routinely collected audit of CR, the National Audit of Cardiac Rehabilitation (NACR) in funded by the British Heart Foundation (BHF) has is hosted by the Department of Health Sciences, University of York in collaboration with NHS Digital.

The NACR aims to:

- Monitor and support CR teams and providers/commissioners to deliver high-quality to evidence-based standards, for the benefit of all eligible patients.
- Monitor the extent of provision and highlight inequalities and insufficiencies in delivery against key service indicators through the National Certification Programme for CR(NCP_CR)
- Design and implement research to determine the effectiveness of routinely delivered CR services on patient agreed outcomes, cardiovascular disease risk profiles and health and social care utilisation.
- Use audit and research data generated through the NACR to inform NICE clinical guidance, service specification, clinical practice standards for national associations and NHS healthcare commissioning processes and decision making

https://www.york.ac.uk/healthsciences/research/cardiac/nacr/

The NACR collects data from CR programmes across the UK and has 74% coverage for electronic data entry (NACR 2017). The electronic data was acquired in a link-anonymised format from 224 programmes, which collect data on patient's demographics, risk factors and baseline measures prior to starting CR. Patients were included if they had an initiating event (primary diagnosis of heart failure) between 1st January 2013-31st December 2017. To account for potential reporting bias through missing data, the HF population without an ISWT score were compared with the ISWT group in the context of age and gender. A planned sub-analysis investigated the extent by which HF severity, defined by the NHYA functional classification, determined walking fitness.

The primary variable of interest (dependant variable) is maximum distance walked in metres measured by the ISWT as part of a pre-rehabilitation assessment. The ISWT is an externally paced (via audio player) and graded walk test with 12 levels of speed that has been validated in cardiac and pulmonary rehabilitation populations (Fowler et al 2005). Although the test result can be reported by the speed level achieved our planned analysis used distance walked as a continuous variable in the linear regression model which also enabled us to pursue reference values using a measure (metres walked) which are more relevant to clinicians and patients.

As with all registry-based studies missing data is very likely and can be in excess of 20% (Wells, Chagin, et al 2013). Missing data can lead to bias in sampling and a substantial loss of statistical power. In this MD thesis the population included in the analysis was compared to the population excluded to check for differences in patient characteristics including age and gender.

Statistical Analysis

The analyses were conducted in IBM statistical package SPSS V.23. (SPSS, Chicago, Illinois, USA) Correlation and group comparisons utilised t-tests and Pearson correlation respectively. Subject to having sufficient data to fulfil statistical distribution assessments (N>30) all potential covariates were investigated in the analysis. Backwards Stepwise linear regression models were built to investigate whether, accounting for covariates, the patient level factors were associated with walking fitness as measured by ISWT distance.

Relevant important covariates were included in the analysis, where they were evidenced in the literature or significant in preliminary analysis. Age (years), gender (male/female), marital status (single/not) and employment status have been shown to influence the outcomes following a variety of different rehabilitation interventions, including CR. Employment status was coded as employed/retired or unemployed, this is because previous research found that employed and retired states have similar effects on outcomes. Other risk factors such as BMI, physical activity, smoking status and comorbidity were included as they are routinely reported in the NACR annual report (NACR 2017).

Statistical level for significance was $p<0.05$ and actual significant values were expressed as reported up to 0.001. Data model checking was performed to ensure that the models were a good fit through assumptions associated with the regressions.

Ethical and data governance approval

NHS Digital hosts the NACR and is approved on an annual to collect patient-identifiable data without explicit consent from individual patients from the Health Research Authority's Confidentiality Advisory Group through NHS Digital (under Section 251 of the NHS Act 2006) (NACR, 2017). Patients are informed by clinical teams about the purposes of the audit and they have a right to request that their data is not used, and they understand that doing this will not impact on their care. Section 251 approval enables NHS Digital to collect the highest quality data during then patient journey from acute to community settings. NHS Digital then transfers data in an anonymised format to NACR staff at the Department of Health Sciences, University of York.

Research studies that seek to benefit patient uptake, completion and outcomes from CR are supported as part of the 251 approvals. See www.cardiacrehabilitation.org.uk

The MD research proposal was reviewed by the NACR team and considered a good fit with its mission and study inclusion criteria and was therefore supported by the NACR team. The main rationale for inclusion was that it is in public interest to better understand the characteristics of patients with HF attending CR and identify the factors that determine fitness so that recruitment to CR services could be improved. In 2015-2016 fewer than 10% of all eligible HF patients attended CR (NACR 2017). Understanding what type of patients with HF who are assessing CR and the better understanding the barriers and facilities will help clinicians promote CR within a population of patients who, despite strong clinical guidance (NICE CG108), fail to attend such services. There is a need to publish data that shows patients with HF are able to carry out the fitness test and exercise regimes as part of CR. This will help overcome uncertainties about the appropriateness of CR for patients, carers, clinicians and health care providers.

3.3 Results

This study consisted of 1519 patients (68% male) with HF who had completed an ISWT. The mean age for total population was 64.5 (SD 12.7) with males slightly older with a mean age of 65 years (12.5) and females 64 years (13.5). Table 3.4 shows the average ISWT distances in metres for each of the included variables.

The overall mean distance was 266.6 m (156.4 SD). Pearson correlation indicates that there is a significant negative relationship between age and ISWT distance of −0.40 ($p \leq 0.001$), which was stronger for females ($r = -0.436$) than males ($r = -0.391$).

Males had a significantly larger ISWT distance on average 55.7 metres greater than females ($p = <0.001$). Patients with a history of achieving moderate physically active status had on average a statistically significant 60.85 metres greater distance than those who were not ($p = <0.001$). Patients with BMI greater than 30 demonstrated shorter ISWT distances by on average 30.05 metres ($p = <0.001$). No other variables were associated with differences in ISWT distance. Additionally, the study included as subset analysis the inclusion of NYHA class I-IV, the preliminary analysis suggests that in routine populations there are no significant differences between the NHYA class and ISWT distance ($p > 0.05$).

Table 3.4. Walk test (ISWT) distances by patient demographics

Patient Characteristics		ISWT distance (m)					
		Mean	**SD**	**N**	**%**	**test ***	**P**
	Age	64.51	12.70	15.19		-0.40 (PC)	<0.001
Gender	Male	284.3	162.65	1035	68	55.71 (MD)	<0.001
	Female	228.6	134.94	482	32		
Ethnicity	White	263.7	151.47	1136	75	-11.74 (MD)	0.204
	Non-White	275.4	170.15	383	25		
Smoking Status	No	266.5	153.31	1304	93	-10.61 (MD)	0.503
	Yes	277.1	179.31	104	7		
Physical activity status	No	246.5	153.92	887	68	-60.85 (MD)	<0.001
	Yes	307.4	149.56	408	32		
Body Mass Index (BMI)	<30	276.2	163.18	827	68	25.42 (MD)	0.002
	>30	250.8	138.64	586	32		
Employment Status	Employed	262.5	152.63	995	59	-9.53 (MD)	0.366
	Unemployed	272.1	156.78	266	41		
Marital Status	Single	246.9	157.08	359	79	-19.36 (MD)	0.039
	Partnered	266.2	143.44	799	21		
HADS Score: Anxiety	Not Anxious	271.6	155.81	1082	31	36.79 (MD)	0.002
	Anxious	234.8	145.82	209	69		
HADS Score: Depression	Not Depressed	274.2	154.71	1082	86	64.78 (MD)	<0.001
	Depressed	209.4	143.38	169	14		
IMD Score	Lowest quintile	265.5	173.68	263	22.1	0.43 (F)	0.789
	Second quintile	256.6	163.18	277	23.3		
	Third quintile	259.6	144.28	221	18.6		
	Fourth quintile	267.9	157.85	232	19.5		
	Fifth quintile	274.3	161.18	196	16.5		

*Statistical tests used = Pearson correlation (**PC**): mean difference (**MD**): F stat ANOVA (**F**)

Table 3.5 shows the ISWT distance, analysed for 18 comorbidities reported by the NACR along with a single variable coding multi-morbidity of <=3 or 3+.

Table 3.5. Walk test (ISWT) distance reported by comorbidity category

	ISWT distance (m)					
	Mean	**SD**	**Count**	**%**	**Mean Difference**	**P Value**
Angina						
No	270.0	158.5	1419	93	51.6	0.001
Yes	218.5	114.1	110	7		
Arthritis						
No	276.3	158.3	1262	83	57.1	<0.001
Yes	219.2	137.5	257	17		
Cancer						
No	268.6	158.7	1383	91	22.0	0.117
Yes	246.6	30.2	136	9		
Diabetes						
No	276.7	161.1	1207	79	48.8	<0.001
Yes	227.9	129.9	312	21		
Stroke						
No	270.0	158.0	1424	94	53.1	0.001
Yes	216.9	120.6	95	6		
Hypertension						
No	276.6	164.1	982	65	28.2	0.001
Yes	248.4	139.6	537	35		
Chronic obstructive pulmonary disease						
No	270.6	157.8	1409	93	55.3	0.001
Yes	215.4	126.9	110	7		
Asthma						
No	269.2	157.8	1394	92	31.4	0.031
Yes	237.8	137.1	125	8		
Chronic Back Problems						
No	272.0	158.5	1306	86	38.1	0.001
Yes	233.8	138.7	213	14		
Anxiety						
No	265.8	156.0	1402	92	-11.4	0.449
Yes	277.2	161.9	117	8		
Depression						
No	268.3	158.8	1372	90	16.8	0.217
Yes	251.5	131.4	147	10		
Family History						
No	266.0	159.1	1253	82	-3.5	0.741
Yes	269.5	143.1	266	18		
Erectile dysfunction						
No	267.3	157.4	1436	95	12.9	0.466
Yes	254.5	138.5	83	5		
Hypercholesterolaemia/dislipidaemia						
No	269.0	159.0	1280	84	15.3	0.166
Yes	253.8	141.7	239	16		
Comorbidities grouped						
≤3	282.0	166.0	967	64	42.2	<0.001
>3	239.8	134.1	552	36		

Osteoporosis, claudication, rheumatism were removed due to insufficient subset sample sizes (n≤25)

The results showed that patients having arthritis, diabetes, rheumatism, stroke, hypertension, emphysema, asthma, and chronic back problems demonstrated significantly lower ISWT distance (mean difference range 33-105 p value <0.05).

Grouping of comorbidities was also significant with a 56 metre reduced mean difference with having more than three comorbidities. Table 3.6 shows the results from the linear regression evaluating the association between ISWT distance against patient characteristics and related risk factors.

Table 3.6. Linear regression findings for the ISWT by patient characteristics

Patient Characteristics	B	SE	t	P Value	95% CI
Gender (Female)	-42.123	10.658	−3.952	<0.001	−63.055 to −21.191
Age	-4.868	0.477	−10.888	<0.001	−5.746 to −3.990
Ethnicity (Non-white)	-23.347	13.340	−1.750	0.081	−49.545 to 2.852
Physical activity status (150 min/week)	43.467	10.543	4.123	<0.001	22.761 to 64.173
BMI (>30)	-28.645	10.203	−2.808	0.005	−48.682 to −8.607
Employment status (Unemployed)	-50.336	12.951	−3.887	<0.001	−75.771 to −24.901
Diabetes	-33.448	12.318	−2.715	0.007	−57.639 to −9.257
Chronic back problems (Yes)	-36.855	13.392	−2.752	0.006	−63.155 to −10.554
COPD (Yes)	-39.310	18.937	−2.076	0.038	−76.501 to −2.119
HADS score: Depression (Depressed)	-52.194	14.842	−3.517	<0.001	−81.342 to −23.045
IMD score	11.624	3.801	3.058	0.002	4.160 to 19.088
Intercept	276.703	13.339	20.744	<0.001	250.506 to 302.899

R=0.530. R2=0.281. Adj R2=0.266. BMI, body mass index; COPD, chronic obstructive pulmonary disease; HADS, Hospital Anxiety Depression Scale; IMD, Index of Multiple Deprivation.

The model confirms that age, after accounting for multiple potential confounders, was negatively associated ISWT distance (B = -5.338 p <0.001). The effect of age is centralised around the mean suggesting that for each single year increase in age, above the mean, there is an associated 4.9 metre reduction in distance walked.

Gender plays a significant part in determining walking fitness with female patients having a 42.1 metre reduced walking distance (p <0.001). Other covariates of statistical significance associated were ethnicity, employment status, marital status, physical activity and BMI. Patients being non-white, unemployed, single, greater BMI and not achieving physical activity status at were all associated with a lower ISWT score between 25-54 metres (p = 0.024-0.001).

Variables that were not significant such as smoking status, other covariates and multi-morbidity were automatically removed from the backward stepwise analysis.

The model was of good fit and the residuals met the assumptions of uniform variance, linearity and the adjusted r^2 value was 0.245. Three comorbidities stroke, chronic obstructive pulmonary disease (COPD) and back pain were found to be significant determinants of ISWT distance. The grouping of comorbidities into less than or greater than three was not significantly associated with walking fitness. Subset analysis showed that the model with NYHA was not of greater fit. The inclusion of NYHA class was not statistically significant.

The ISWT distances were used to develop reference values (Table 3.7) based on age and gender. Younger age HF patients were defined as <67 years whereas older HF patients 65+ years and reported in the context male and female gender. Within each of the younger and older categories is an additional reference value for patients with HF + COPD. The comorbidity of COPD was included based on the strength of its contribution in determining walking fitness. Younger age HF patients (<67 years) with COPD had a mean ISWT distance of 237 metres whereas older HF patients (67+ years) with COPD had a mean ISWT distance of 197 metres representing a difference of 40 metres which in 30% of cases also included a change in intensity of one level of the ISWT.

Table 3.7. Walk test reference values for heart failure patients (HF)

	Incremental shuttle walk test (ISWT)							
HF + comorbidity category	**Age and gender**	**Mean difference (metres)**	**SD**	**Percentile**				
				05	**25**	**75**	**95**	**Count**
HF Only	***<67 years***							
	Male	338	180	70	200	460	630	443
	Female	285	145	70	190	350	520	190
	67+ years							
	Male	243	138	60	140	330	480	434
	Female	184	109	40	100	250	390	211
HF + COPD	<67 years	237	133	40	120	330	430	51
	67+ years	197	120	40	90	270	470	59
HF +Depression	<67 years	261	143	30	150	340	520	95
	67+years	223	107	70	155	295	420	52

3.4 Discussion

Reassuringly our findings showed that patients with HF, referred to CR, were capable of levels of walking fitness, achieved through challenging incremental test, comparable to the 25^{th} to 50^{th} centiles of conventional CVD patients attending CR (Alotaibi & Doherty 2016). Although the extent of walking fitness was greater in the group with fewer comorbidities (<= 3) a good mean distance was achieved in the group having greater than three additional comorbidities. These findings help establish a positive picture in terms of physical fitness associated with the diagnosis of heart failure in patients attending CR.

Using mean age of the study population (64.35 ±12.72) as a reference value, being older by one year was significantly associated with reduced walking distances in the region of 5.3 metres for each year above mean age. This relationship is not a new finding as it is evident in the convectional CR patient populations (Cardoso et al 2017, Alotaibi & Doherty 2016) however, the ability to reference the extent of loss, with increasing age, represents a novel finding in patients with HF.

After accounting for comorbidities gender continues to play a significant part in determining, walking fitness with female patients having a 42 metre reduced walking distance. The CR literature and routine practice data, captured in national reports (NACR 2018), highlight that around 80% of patients with HF are missing out on CR (NACR 2018, NICOR 2017). Over 90% of CR programmes offer services to patients with HF and around one-third has a recorded physical fitness assessment (NACR 2018). National clinical guidance worldwide recommend assessment of physical fitness prior to starting CR (Piepoli et al 2014, Sdes et al 2016, BACPR 2017) yet two-thirds of programmes in the UK fail to evidence this for patients with HF. The role of age and gender differences in walking fitness is evident on ISWT physical fitness levels (Table 3.4 and 3.6) which have been used in-part to inform reference values (Table 3.7). These reference values should allow clinicians to better appreciate the fitness levels achievable for patients with HF and these values have potential to aid goal setting as part of CR programme tailoring.

The presence of COPD in the form of chronic bronchitis or emphysema is significant in predicting fitness in HF patients with an associated 57 metres reduction walking distance. COPD dominated by the symptom of breathlessness, often at rest, easily exacerbated by physical effort, coupled with the diagnosis of HF possibly explains such lower levels of fitness. The severity of heart failure as measured by NYHA did not reach significance as a determinant which might be explained by accounting for the percentage of COPD. Within the NYHA class groups the proportion with COPD was 4% for class 1, 5% for class 2, 11% for class 3 and 31% for class 4. The inter-relation between HF and COPD is becoming increasingly important clinically leading to a call for a service provision aimed at managing breathlessness in patients with these comorbidities (Man et al 2016).

The final regression analysis (Table 3.6 and 3.7) incorporated the impact of comorbidity on walking fitness reference values for younger and older patients with HF alone, combination of HF + COPD and HF+ Depression. The reference age is 67 years which is the median for the HF population in the NACR. This is the first set of reference values to account for the presence of two major comorbidities (COPD and depression) alongside HF which now enable clinicians to better understand physical fitness differences and or expectations of their patients. Males and females below 67 years with HF alone were on average able to walk 101metres and 48 metres further respectively than patients of a similar age with HF+COPD.

An additional novel finding was that higher levels of depression, measured using HADS at the start of CR, were strongly associated with lower walking distances in the ISWT. To date this has not been investigated previously in HF however,

our findings do concur with a systematic review in healthy and depressed adult populations where depression and exercise capacity were found to be inversely related (Papasavvas T, et al 2016). Females and males below 67 years with HF alone were on average able to walk 62 metres and 77 metres further respectively than patients of a similar age with HF plus depression.

Index of multiple deprivation (IMD) was included in the regression as it has been investigated as a determinant in previous studies (Harrison and Doherty 2018). In this present study IMD, which is an evidenced based approach for accounting for socio-economic factors influencing access to health care, explained a small amount of variance (11.6 metres) in walking fitness.

Our findings have generated new knowledge to help guide clinical decisions about the suitability of patients with HF to take part in exercise-based CR. The study also produced a set of reference values aligned with age, gender, COPD and level of depression to aid the interpretation of walking fitness in patients with heart failure in the hope that this new knowledge will help improve referral and uptake to CR.

Limitations

Although the study investigated a large number of covariates, we were unable to account for medications such as diuretics and beta-blockers that may have accounted for some variation within the population in terms of weight gain and walking fitness respectively. The NACR does not capture medication as part of its core data.

Concerning our sub analysis of heart failure severity using NYHA there was a potential reporting/selection bias as the sample represented a relatively small proportion of the total eligible population. Missing data was also an additional limitation for some of the analyses. Although we cannot rule this out our analysis of the population with and without a recorded NHYA classification showed no significant differences for age and gender.

There is a further limitation between the mean age of patients recruited to this study (64.5 years SD 12.7) compared to the general HF population (NICOR 2017) with a mean age of 78 years. One of the main reasons for this difference is that NICOR data is based on hospitalised HF patients including those acute patients, many older patients, near the end of life. The NACR data set only records patients that were previously discharged from hospital as stable and were then willing to attend cardiac rehabilitation. When we compare the age of all NACR recorded HF patients with those that carried out a fitness test (ISWT) the difference is 5 years which is much less than the general HF population. To accommodate this difference and to make our findings more generalisable our approach to ISWT reference values utilised the median distribution above and below 67 years which better reflects the full range of HF patients recorded in NACR.

3.5 Conclusion

The observational study concludes that patient age, gender alongside depression status and the presence of COPD as comorbidity were significant determinants in predicting walking fitness in patients with HF. To the authors knowledge this is the first study to clarify the extent by which patient characteristics determine walking fitness in patients with HF. These findings which have been published have the potential to aid clinical practice through enabling clinicians to understanding of the levels of fitness patients within patients HF. The study also produced a novel set of reference values, aligned with age, gender, COPD and depression, to aid the interpretation of walking fitness by clinicians and patients. Through dissemination of these findings we believe this new knowledge has potential to improve referral to CR by clinicians leading to a greater number of patients undergoing a physical fitness assessment and thereafter enabling an appropriate exercise prescription as part of cardiac rehabilitation.

4. REACH-HF Sub-study

Abstract

Introduction: Access to cardiac rehabilitation (CR) heart failure services is poor yet patients are known to benefit in terms of quality of life (QoL), fitness and reduced hospital admissions. Uncertainty about the extent by which patients can exercise and safely around exercise training are known barriers to participation. Although some early guidelines suggested that left ventricular ejection fraction (LVEF) is a possible determinant of a patient's exercise ability in isolation LVEF and exercise ability are poorly correlated. This study seeks to evaluate the extent by which LVEF and other cardiac related measures, when combined with patient demographics, determine exercise ability in patients with heart failure.

Methods & analysis: Anonymised data from the four REACH-HF sub-study sites was approved through Exeter Trials Unit and the REACH-HF Steering Group. The data was anonymised and undergoing analysis using exploratory correlations leading to multi-regression which will help determine which combination of factors best determine a patient exercise ability.

Results: The study included 216 heart failure patients with a mean age was 69.8 years (SD10.9) with a mean BMI of 29.47 and LVEF of 31.23%. ISWT distance was 304.27 metres for men and 252.25 metres for women. Age, gender and NYHA functional class explained 40% of walking fitness as measured by ISWT.

Conclusion: The findings show that age, gender and NYHA classification strongly and significantly predict patient fitness. COPD and CKD were predictive but did not achieve statistical significance. LVEF and Pro-BNP failed to be predictive of fitness.

4.1 Introduction

Less than 20% of patients with heart failure access cardiac rehabilitation (CR) services which have proven benefits in terms of quality of life (QoL), fitness and reduced hospital admissions (NACR 2017, Taylor 2014, NICE CG108). One of the barriers to offering heart failure patients an exercise-based intervention is the uncertainty about their capacity to exercise safely around exercise training (BACPR 2017). Although some early guidelines suggested that left ventricular ejection fraction (LVEF) is a possible determinant of a patient's exercise ability in isolation LVEF and exercise ability are poorly correlated. This study seeks to evaluate the extent by which LVEF and other cardiac related measures, when combined with patient demographics, determine exercise ability in patients with heart failure.

Related literature underpinning the REACH-HF sub-study

NICE guidance and the new NICE quality standard (QS99) is to drive CR uptake to above 65% over a five-year period (CVD Outcomes 2013, NICE CG172, NICE CG 108). National audit data (NACR 2017) shows that uptake to CR is at 51% for conventional CHD patients which is reasonable when compared to European rehab programmes where uptake is around 30%. The situation is very different for patients with heart failure where uptake is estimated to be less than 20% of all eligible patients. One of the reasons suggested for the lack of referral by cardiologists and GPs is that they somehow believe that patients with HF and poor heart function (low LVEF and high Pro-BNP**)** are either at greater risk during exercise or are unlikely to cope with exercise.

The association between LVEF, Pro-BNP and related patient characteristics in determining exercise capacity has not been established in patients with HF. Given the level of poor uptake to CR services there is an urgent need to assess the ability of cardiovascular measures to determine exercise capacity. This sub-study will improve clinical decision making, beyond that of just using cardiology measures, in respect of the appropriateness of referral to exercise based CR.

4.2 Method

Setting

The Rehabilitation EnAblement in CHronic Heart Failure (REACH-HF) sub study forms part of my MD project therefore, it is crucial to illustrate the methods of the main study before proceeding to the sub-study. REACH-HF that aims to capitalize on an existing NIHR funded project (REACH-HF) that has one of four arms of the trial running at York Hospital. REACH-HF trial is part of a research programme designed to develop and evaluate a health professional facilitated, home-based, self-help rehabilitation intervention to improve self-care and health-related quality of life in people with heart failure and their caregivers. (Taylor et al 2015) REACH-HF is a multicentre randomised controlled trial with 1:1 individual allocation to the REACH-HF intervention plus usual care (intervention group) or usual care alone (control group) in 216 patients with systolic heart failure (ejection fraction <45%) and their caregivers. The intervention comprises a self-help manual delivered by specially trained facilitators over a 12-week period. The duration of the study was 26 months (11 months recruitment, 12 months follow up, 2 months analysis). Three-pronged approach to patient identification via primary care; secondary care and specialist HF nurse service has been used. The primary outcome measure is patients' disease-specific health-related quality of life measured using the Minnesota Living with Heart Failure questionnaire at 12 months follow-up.

The MLHFQ is reported in respect of its total score with a range of scores from 1 to 105 where high scores suggest poor QoL. MLHFQ below 24 is a good QOL, 24–45 is moderate QOL and greater than 45 is poor QOL (Di Mauro et al. 2018).

Secondary outcomes include survival and heart failure related hospitalisation, blood biomarkers, psychological well-being, exercise capacity, physical activity, other measures of quality of life, patient safety and the quality of life, psychological well-being and perceived burden of caregiver at 4, 6 and12 months follow-up (Taylor et al 2015, Greaves et al 2016)..

York Hospital was one of four RCT sites running the REACH-HF trial which involves cardiology support from the MS student (Dr Rashed Hossain) and the nurse researchers, working with Prof Doherty, to screen heart failure patients for inclusion and collect data on cardiovascular metrics including LVEF, medications and heart failure status using the four NYHA categories where class I ~ breathlessness with moderate exertion to class IV ~ being breathless at rest.

This REACH-HF sub-study proposal was submitted in June 2016 and approved in 22nd July 2016 by the REACH-HF Research leads (See Appendix one). The aims of the sub-study was to investigate and correlate relevant cardiovascular parameters that would enable us to better determine exercise ability of heart failure patients in contrary to the use of conventional transthoracic echocardiogram alone. Our findings will help to guide clinical decisions about the ability of patients with heart failure to take part in exercise interventions which may aid referral to cardiac rehabilitation.

REACH-HF Method

The duration of the study is 26 months (11 months recruitment, 12 months follow up, 2 months analysis) and 216 patients with heart failure. The study used a three-pronged approach to patient identification via primary care, secondary care and specialist HF nurse service.

Inclusion criteria includes adults (aged ≥18 years); patients who have been clinically stable for at least 2 weeks and on medical treatment for heart failure; have confirmed diagnosis of systolic HF on echocardiography (i.e. left ventricular ejection fraction <45%) within the last 5 years and patients deemed suitable for exercise; and informed consent to participate. (Taylor et al 2015).

The primary outcome measure is patients' disease-specific health-related quality of life measured using the Minnesota Living with Heart Failure questionnaire at 12months' follow-up. Secondary outcomes include survival and heart failure related hospitalisation, blood biomarkers, psychological well-being, exercise capacity, physical activity, other measures of quality of life, patient safety and the quality of life, psychological wellbeing and perceived burden of caregivers at 4, 6 and 12months' follow-up. A process evaluation will assess fidelity of intervention delivery and explore potential mediators and moderators of changes in health-related quality of life in intervention and control group patients. Qualitative studies will describe patient and caregiver experiences of the intervention. An economic evaluation will estimate the cost-effectiveness of the REACH-HF intervention plus usual care versus usual care alone in patients with systolic heart failure.

REACH-HF Ethical approval

REACH-HF had HRA IRAS ethics approval in accordance with the ethical principles and Research Governance overseen by Royal Cornwall Hospitals NHS Trust Research, Treliske, Truro, Cornwall, TR1 3LJ. IRAS reference 14/NW/1351.

REACH-HF patient inclusion and exclusion criteria (Figure 4.1). Exclusion criteria were extensive as this study involved exercising HF patients at home.

Inclusion criteria

- Provision of informed consent to participate.
- Adults (aged ≥18 years).
- Patients who have a confirmed diagnosis of systolic heart failure (HF) on echocardiography (ie, left ventricular ejection fraction <45% within the past 5 years).
- Patients who have experienced no deterioration of HF symptoms in the past 2 weeks resulting in hospitalisation or alteration of HF medication

Exclusion criteria

- Patients who have undertaken cardiac rehabilitation (CR) within the past 12 months
- Patients who have received an intracardiac defibrillator (ICD), Cardiac Resynchronisation therapy (CRT) or combined CRT/ICD device implanted in the last 6 months.
- Patients who have any of the following contraindications to exercise testing or exercise training documented in their medical notes:
  - Early phase after acute coronary syndrome (up to 2 days)
  - Untreated life-threatening cardiac arrhythmias
  - Acute HF (during the initial period of haemodynamic instability)
  - Uncontrolled hypertension (systolic blood pressure >200 and/or diastolic blood pressure >100)
  - Advanced atrioventricular block
  - Acute myocarditis and pericarditis
  - Symptomatic aortic stenosis
  - Severe hypertrophic obstructive cardiomyopathy
  - Acute systemic illness
  - Intracardiac thrombus
  - Progressive worsening of exercise tolerance or dyspnoea at rest over previous 3–5 days
  - Significant ischaemia during low-intensity exercise (<2 Metabolic equivalents, <50 Watts)
  - Uncontrolled diabetes (blood glucose >16 mmol/L or glycated hemoglobin >9% or equivalent unit)
  - Recent embolism
  - Thrombophlebitis
  - New-onset atrial fibrillation/atrial flutter
- Patients who are in a long term care establishment or who are unwilling or unable to travel to research assessments or accommodate home visits.
- Patients who are unable to understand the study information or unable to complete the outcome questionnaires.
- Patients judged to be unable to participate in the study for any other reason (eg, psychiatric disorder, diagnosis of dementia, life threatening co-morbidity)
- Patients participating in concurrent interventional research which may over-burden the patient or confound data collection.

With permission from REACH-HF as per Taylor et al 2015.

Figure 4.1. REACH-HF trial inclusion – exclusion criteria.

Outcomes: The findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences with a final report will be submitted to the National Institute for Health Research and a summary report to the NIHR.

This RCT will report on the clinical and cost-effectiveness of the REACH-HF intervention, a manualised home-based rehabilitation intervention designed to improve self-care and HRQoL in people with systolic HF. The study results will benefit multiple stakeholders and beneficiaries and add to current literature about the provision and uptake of rehabilitation services for people with HF and caregiver support.

The agreement as part of this MD sub-study was not to submit a journal paper until the main trial is published. This MD thesis was only ever going to use baseline data as that was appropriate for the study of determinants of fitness, which is where the uncertainty resides about factors that may determine fitness in patients with HF and potentially lead to better understanding and concomitant increases in uptake to CR.

Sample size

The sample size was based on an effect size that represents a clinically important difference in the MLHFQ questionnaire in the order of five points considered a minimal clinically important difference. This value continues in research and clinical practice as it defines the point patients perceive a noticeable change. http://qol.thoracic.org/sections/instruments/ko/pages/mlwhfq.html

The level of drop out from the study was set at 20% as per the levels seen in previous trials (Taylor et al 2014). The sample size for the primary outcome was seen as adequate to detect an important difference in the secondary outcomes.

The study was conducted in four investigator centres in the UK: Birmingham (Sandwell and West Birmingham Hospitals NHS Trust), Cornwall (Royal Cornwall Hospitals NHS Trust), Gwent (NHS Wales) and York (York Teaching Hospital NHS Foundation Trust).

Participants were recruited at each of the four sites and a total of 216 patients have been added to the REACH-HF database. York hospital contributed 54 patients that meet inclusion and exclusion criteria of the trial.

After the completion of initial recruitment for the main trial, as part of my MD sub study I had identified few routine cardiovascular measures which I felt when combined with patient demographics better determine the extent of exercise capacity in patients with heart failure. I had then approached the investigators of Exeter for database on 216 patients (total number from REACH HF database). It was approved and the anonymised data from the other three recruiting centres derived from the Exeter Trials Unit plus York hospital data formed base of my MD.

Data collection as it pertains to the REACH-HF sub-study

At the baseline clinic visit, at one of the four RCT sites, written informed consent was obtained by the research nurse. The following information was collected:

- Medical history including comorbidities (number and severity scored with Charlson Co-morbidity Index), New York Heart Association class, HF aetiology, concomitant HF medication and presence of implantable HF devices).
- Healthcare resource utilisation over the prior 6 months;
- Sociodemographic information (ie, date of birth, ethnicity, height, weight, employment status, education level, smoking status).

Participating patients were asked to complete:

- The primary and secondary outcome questionnaires
- Perform an the incremental shuttle walk test
- Provide a blood sample for measurement of NT pro-BNP levels
- Wear a wrist-worn accelerometer for 7 days and either post to the trials unit at Exeter or hand into the trial coordinator at the local REACH-HF trial site.

Table 4.1 shows the selected baseline data used as part of REACH-HF and considered as possible factors in determining fitness.

Table 4.1. Baseline data for the analysis

	Baseline data
Demographics	Age, gender, BMI & smoking status
Medical history	NYHA class, Hypertension, diabetes, CAD, previous MI or angina, AF, valvular heart disease, cardiac devices
Co-morbidity	Charlson index score
HADS questionnaire (psychosocial)	Hospital anxiety and depression scores
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NYHA	New York Heart Association (NYHA) functional classification
Pro-BNP level (biomarker)	B-type natriuretic peptide
Incremental shuttle walk test (fitness)	Test 1 and 2: distance walked, peak HR, RPE
Accelerometry (physical activity status)	Absolute values and categories
LVEF	Left ventricular Ejection fraction
HR and BP	Pulse rate Blood pressure at baseline ISWT visit
Current Medications	E.g. Beta-blocker, ACE, ARBs, loop diuretics, aldosterone receptor antagonists

An important aspect of this MD thesis was to investigate the ability of cardiovascular clinical measures in predicting a patient's level of fitness. One of the most used routine measures is the New York Heart Association (NYHA) functional classification (Table 4.2). This measure, albeit subjective, is a core routine measure in clinical practice that is easy to complete and, in some respects, easy to interpret for patients and carers.

Table 4.2. New York Heart Association (NYHA) functional classification

Class	Description
I	No limitation of activity; Ordinary activity does not cause symptoms
II	Slight limitation of activity; Ordinary activity results in symptoms
III	Marked limitation of activity; Less than ordinary activity results in symptoms
IV	Unable to carry on any physical activity without discomfort; symptoms at rest

The NYHA classification was developed and validated by interviewing HF patients regarding the limitation of activity and the presentation of symptoms (e.g. dyspnoea) during their normal daily activities. The NYHA system is simple, inexpensive and has demonstrated a small degree of predictive validity (Fletcher et al 2013). The use of the NYHA functional classification within chronic arrhythmia and heart failure patients has increased as more patients are implanted with ICDs and CRT. Although the NYHA functional class has been criticised for its subjective nature and imprecision when distinguishing between class II & III (Fleg et al 2000) the system is well used and easily understood (Gibbons et al 2001). The subjectivity of the NYHA functional class is less of a concern when considered alongside other measures such as LVEF and Pro-BNP.

4.3 Results

Descriptive statistics of the REACH-HF sub study population

Table 4.3 shows the mean age was 69.8 (SD10.9) for 216 heart failure patients with a mean BMI in the overweight category with most patients in NYHA class II. Mean LVEF was 31.263% for 156 patients measures via echocardiography.

When split by gender the REACH-HF patient demographics remain similar except for age where males were on average 2 years older (Table 4.3). As with many cardiac studies, the proportion of males to females recruited was much larger (78% male).

Table 4.3. Patient baseline demographics by gender

Patient baseline demographics by gender

Gender		Age (years)	BMI	Ejection Fraction %	NYHA classification
Male	Mean	70.24	29.81	30.99	2.01
	Std. Deviation	10.80	6.84	8.34	.67
	N	169	168	118	169
Female	Mean	68.23	28.27	32.11	2.06
	Std. Deviation	11.26	5.49	8.21	.60
	N	47	47	38	47
Total	Mean	69.81	29.47	31.26	2.02
	Std. Deviation	10.91	6.59	8.30	.66
	N	216	215	156	216

Comorbidity profile

The baseline data shows an even split between with atrial fibrillation or flutter (Table 4.4) highlighting that this condition is a significant comorbidity for up to 50% of patients with reduced LVEF in the REACH-HF cohort. The proportion of atrial fibrillation or flutter between males and females was 54.4% and 34% respectively.

Patients with HF are known to carry a significant burden in terms of comorbidity which is confirmed in the REACH-HF population (Table 4.4).

Table 4.4. Comorbidities for REACH-HF patients

		Gender					
		Male		Female		Total	
		Sample	%	Sample	%	Sample	%
Angina pectoris	No	137	81.1%	38	80.9%	175	81.0%
	Yes	32	18.9%	9	19.1%	41	19.0%
Atrial fibrillation or atrial flutter	No	77	45.6%	31	66.0%	108	50.0%
	Yes	92	54.4%	16	34.0%	108	50.0%
Valvular heart disease	No	126	74.6%	37	78.7%	163	75.5%
	Yes	43	25.4%	10	21.3%	53	24.5%
Hypertension	No	100	59.2%	29	61.7%	129	59.7%
	Yes	69	40.8%	18	38.3%	87	40.3%
Myocardial infraction	No	109	64.5%	40	85.1%	149	69.0%
	Yes	60	35.5%	7	14.9%	67	31.0%
Stroke	No	145	85.8%	42	89.4%	187	86.6%
	Yes	24	14.2%	5	10.6%	29	13.4%
Chronic kidney disease	No	147	87.0%	41	87.2%	188	87.0%
	Yes	22	13.0%	6	12.8%	28	13.0%
Diabetes mellitus	Uncomplicated	36	21.3%	8	17.0%	44	20.4%
	End Organ	6	3.6%	1	2.1%	7	3.2%
	No	127	75.1%	38	80.9%	165	76.4%

The proportion of patients with hypertension in this REACH population was 40.3% (Table 4.4). As expected the data showed that the percentage within gender is only 2 % and concludes that this comorbidity is almost equal in both males and females.

The proportion of patients with MI was 31% (Table 4.4). The distribution of MI within gender was vastly different at 35.5% to 14.9% for males and females respectively. This clearly demonstrates the conventional belief that males are more prone to MI than females. Cerebrovascular attack (CVA) or in simple terms, stroke was not quite prevalent in the REACH population (Table 4.4). Interestingly the percentage within gender differ around 4% with males 14.2% and females 10.6% respectively.

Table 4.4 shows 24.5% of the patients in the REACH trial had some form of valvular heart disease. The association between valve disease and its effect on the LV function is well known, so not surprisingly it is prevalent in both males and females. The margin of difference is only 4% in the percentage within gender (Table 4.4).

Diabetes mellitus is one of the most significant comorbidities in the REACH population or any population evaluation of heart failure. Although 20.4% of the population in REACH had diabetes but only 3.2% had end organ damage. Percentage within gender is around 4% and 2% in the uncomplicated and end organ damage respectively in these diabetes group (Table 4.4).

The use of ICD was evident in 9.7% of the total population in REACH trial with about 7% variation between males and females (Table 4.5). This shows more male patients (11.2%) had met the criteria or had the device compared to females (4.3%) (Table 4.5).

Table 4.5. Proportion of cardiac devices in REACH-HF at baseline

		Gender					
		Male		Female		Total	
		Sample	%	Sample	%	Sample	%
Implantable cardioverter defibrillator (ICD)	No	150	88.8%	45	95.7%	195	90.3%
	Yes	19	11.2%	2	4.3%	21	9.7%
Cardiac syncho therapy device (CRT)	No	156	92.3%	45	95.7%	201	93.1%
	Yes	13	7.7%	2	4.3%	15	6.9%
Combined CRT/ICD device	No	161	95.3%	46	97.9%	207	95.8%
	Yes	8	4.7%	1	2.1%	9	4.2%
Heart transplant	No	169	100.0%	47	100.0%	216	100.0%
	Yes	0	0.0%	0	0.0%	0	0.0%
Pacemaker	No	152	89.9%	42	89.4%	194	89.8%
	Yes	17	10.1%	5	10.6%	22	10.2%

The use of CRT like ICD was evident in 6.9% of the total population in REACH trial with about 3% variation between males and females (Table 4.5). This also shows more males had the device compared to females and that they had met the full criteria and guidelines for the device (Table 4.5).

The use of combined CRT/ICD was proportionately higher in male population than females (Table 4.5). Percentage within gender was 4.7% males and 2.1% females.

The proportion of patients who had pacemakers was 10.2% with distribution

Medications

The proportion of patients taking medications is shown in table 4.6.

With regards to ARB 25.5% females have remarkably higher percentage within gender (40.4%) compared to males (21.3%).

In complete contrast to the above the use of similar class of drugs between males and females percentage within gender is widely apart with males (71%) and females (46.8%) and the difference between percentages are as high as 24.2% (Table 4.6). The proportion of patients taking aldosterone receptor antagonist was 53.7%. Interestingly females have much higher percentage within gender (61.7%) compared to males (51.5%). The proportion of patients taking anticoagulant was just less than half at 49.1% with females having a much lower percentage (34.0%) compared to males (53.3%).

Both males and females have significantly lower percentage of beta-blocker with a gender split of males 84.0% compared to females 80.9%. In total 83.3% of the patients taking beta-blocker (Table 4.6).

The proportion of patients taking digoxin was low about 16%. Males have higher percentage within gender, 17.2% compared to females 15.7%. The proportion of patients taking ivabradine was as low as 5%. Females have much higher percentage (12.8%) compared to males 3%.

Table 4.6 proportion of patients taking medications

		Gender					
		Male		Female		Total	
		Sample	%	Sample	%	Sample	%
Is the Patient Taking Receptor Antagonist	No	133	78.7%	28	59.6%	161	74.5%
	Yes	36	21.3%	19	40.4%	55	25.5%
Is the Patient Taking ACE Inhibitor	No	49	29.0%	25	53.2%	74	34.3%
	Yes	120	71.0%	22	46.8%	142	65.7%
Is the Patient Taking Aldosterone Receptor Antagonist	No	82	48.5%	18	38.3%	100	46.3%
	Yes	87	51.5%	29	61.7%	116	53.7%
Is the Patient Taking Anti-Coagulant	No	79	46.7%	31	66.0%	110	50.9%
	Yes	90	53.3%	16	34.0%	106	49.1%
Is the Patient Taking Beta-Blocker	No	27	16.0%	9	19.1%	36	16.7%
	Yes	142	84.0%	38	80.9%	180	83.3%
Is the Patient Taking Digoxin	No	140	82.8%	42	89.4%	182	84.3%
	Yes	29	17.2%	5	10.6%	34	15.7%
Is the Patient Taking Ivabradine	No	164	97.0%	41	87.2%	205	94.9%
	Yes	5	3.0%	6	12.8%	11	5.1%
Is the Patient Taking Loop Diuretic	No	59	34.9%	19	40.4%	78	36.1%
	Yes	110	65.1%	28	59.6%	138	63.9%
Is the Patient Taking Nitrate	No	147	87.0%	42	89.4%	189	87.5%
	Yes	22	13.0%	5	10.6%	27	12.5%
Is the Patient Taking Thiazide Diuretic	No	167	98.8%	47	100.0%	214	99.1%
	Yes	2	1.2%	0	0.0%	2	0.9%

Loop diuretic remains the first line treatment for the heart failure patients across the world. 63.9% of the patients have been taking loop diuretics with minimal variation between male and females in percentage within gender around 6%.

The proportion of patients taking nitrates was low 12.5%. Females have much lower percentage within gender, 10.6% compared to males 13%.

The proportion of patients taking thiazide diuretics was as low as 0.9%). Within such a smaller proportion of patients taking thiazide diuretics the female consumption compared to male percentage within gender is 0%.

Quality of life and fitness

MLHFQ mean score was for the REACH-HF population was 30.65 (Table 4.7) indicating moderate QoL. Di Mauro et al 2018 defined moderate QoL in the range of 24 to 45. Females reported poorer QoL (higher scores) than males with scores of 38 and 28 respectively.

Table 4.7. Descriptive Statistics: MLHFQ and ISWT distance

Gender		Best ISWT measure	MLHFQ total sum of items
Male	Mean	304.275	28.714
	N	138	161
	Std. Deviation	170.1947	22.803
Female	Mean	252.250	38.475
	N	40	40
	Std. Deviation	127.4299	21.671
Total	Mean	292.584	30.657
	N	178	201
	Std. Deviation	162.7033	22.865

Mean walking distance was 292 metres with males walking 52 metres more than females. The correlation between HRQoL and ISWT distance was poor (Figure 4.2) with only 11.9% shared variance.

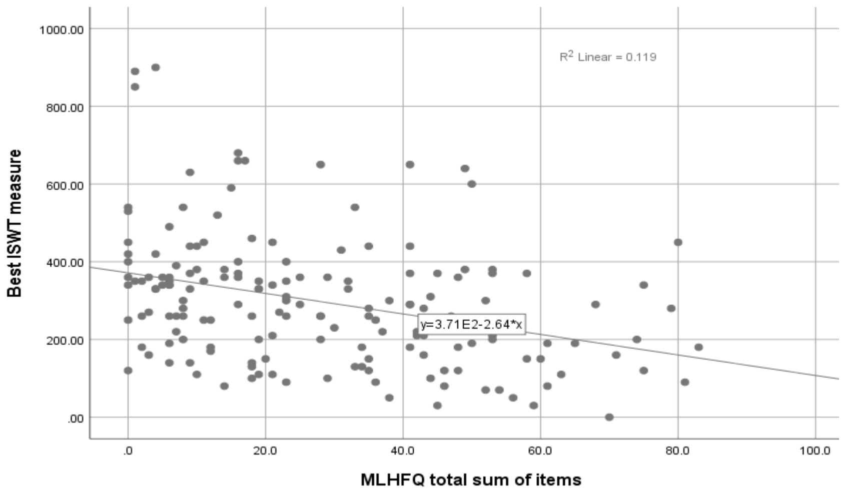

Figure 4.2. Relationship between patient HRQoL and ISWT distance

The relationship between fitness (ISWT distance) and LVEF (figure 4.3) is poor with less than 1% shared variance. There was a slightly higher value for fitness vs pro-BNP (5% shared variance) although this value is far from significant statistically or clinically (figure 4.4).

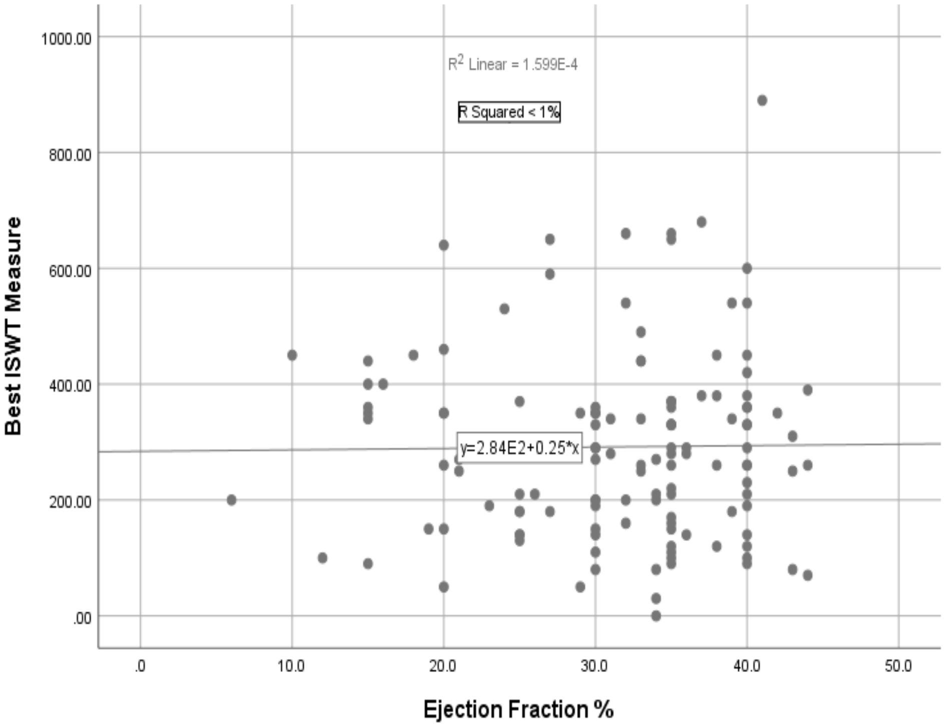

Figure 4.3. Relationship between fitness and LVEF

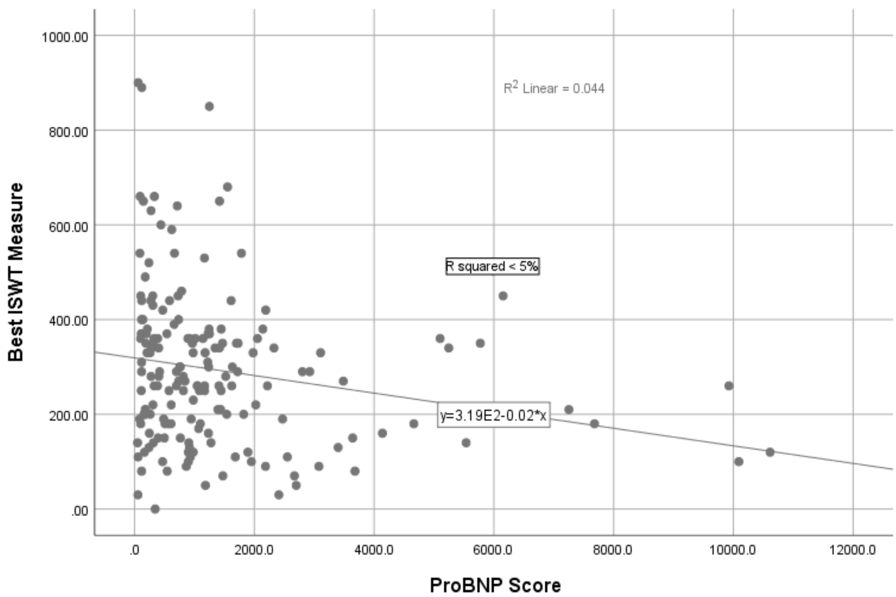

Figure 4.4. Relationship between fitness and Pro-BNP

REACH-HF sub-study regression analysis

The dependent variable was the highest maximum ISWT distance achieved during test one or two, which reflects a patient's best effort. Seventeen co-variables were included in the initial regression analysis and six variables made it through statistical modelling which excluded weaker variables (Table 4.8) where the statistical significance was greater than 0.10.

Table 4.8. Regression findings for all six patient characteristics

	Unstandardized Coefficients			95.0% Confidence Interval for B		Collinearity Statistics	
	B	Std. Error	Sig.	Lower Bound	Upper Bound	Tolerance	VIF
Centralised age	-5.144	1.080	0.000	-7.282	-3.006	0.883	1.132
Gender	-51.236	25.365	0.046	-101.453	-1.019	0.962	1.040
BMI	-3.684	1.966	0.063	-7.575	0.208	0.853	1.172
NYHA classification	-103.217	16.949	0.000	-136.772	-69.662	0.891	1.122
COPD	-85.440	47.916	0.077	-180.302	9.422	0.978	1.023
Combined CRT/ICD * device	-109.093	62.127	0.082	-232.089	13.904	0.993	1.007
(Constant)	680.713	67.973	0.000	546.142	815.283		

Table 4.9 shows the regression for the three statistically significant characteristics. Although COPD did not achieve significance, it was associated with a large decrease in walking distance.

Table 4.9. Regression findings for the three significant characteristics.

	Unstandardized Coefficients					95.0% Confidence Interval for B			
Model	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound	Tol	VIF
(Constant)	602.75	39.98		15.07	.000	523.84	681.67		
Gender	-56.21	23.00	-.146	-2.44	.016	-101.62	-10.80	.97	1.025
Central Age	-4.58	.89	-.308	-5.11	.000	-6.35	-2.81	.95	1.043
NYHA classification	-122.23	14.94	-.490	-8.18	.000	-151.73	-92.74	.97	1.031

- Based on this analysis and after accounting for all other co-variates three variables were significant
    - Age centralised around the mean, so every increase or decrease from 70 will result in 5.14 metre change +/-
    - Gender, moving from male to female results in a 51.236 metre reduction in baseline walking result

    - NYHA classification, as the patient moves up a group there is a reduction in fitness by 103.217 metres

- The VIF indicates there is no significant collinearity within the model

- The model included COPD*NYHA interaction term which was not significant

- The final model had an inclusion of 0.10 p value, this is why the BMI, COPD and CRT/ICD are presented here but are not significant.

The table 4.10 shows the model summary The R squared is 0.436 and the Adjusted is 0.408 which indicates that the model accounts for 41% of the variance in the baseline ISWT score. The data from REACH-HF met statistical checks in that data observed correlated with the distribution expected through statistical models. This was also confirmed visually by the P-P plot and scatter plot showing normality of residuals, uniform variance of residuals and predicted values (Figure 4.5).

Table 4.10. Regression model summary

Model Summary									
					Change Statistics				
Model	R	R Square	Adjusted R Square	Std. Error	R Square	F	df1	df2	Sig. F
11	.660[m]	0.436	0.408	121.86	-0.011	2.39	1	120	0.125

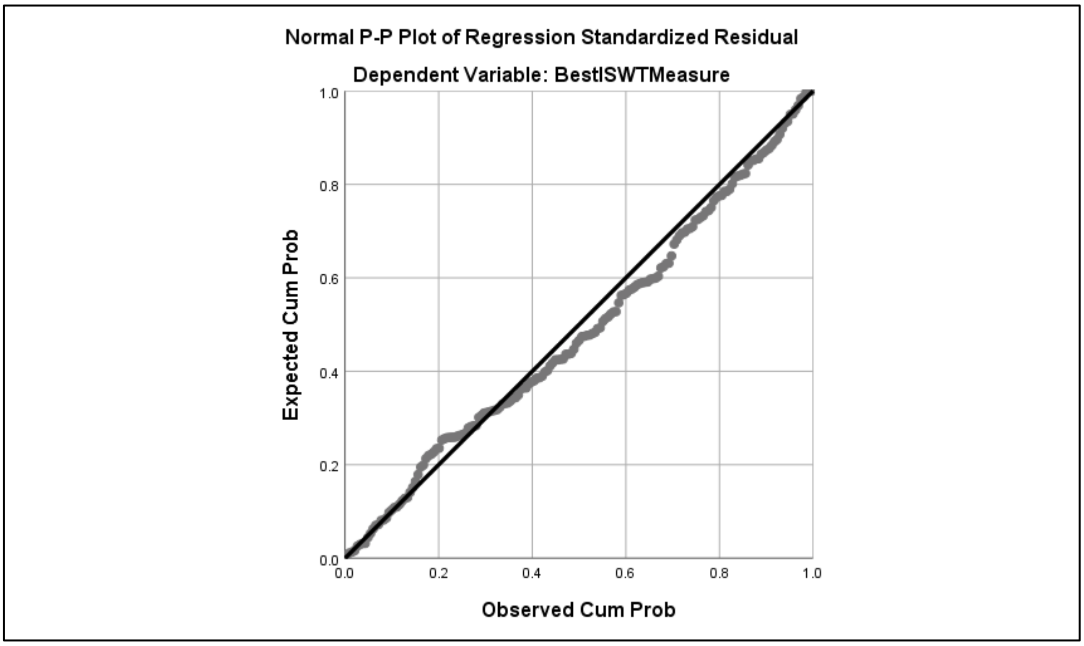

Figure 4.5. P-P plot for normality of data and uniform variance

4.4 Discussion

The REACH-HF trial successfully recruited 216 patients enabling this MD sub-study to progress with sufficient sample size to run the regression analysis. This REACH-HF sub-study was agreed by the REACH-HF Steering Group (see Appendix one)

The REACH-HF sample had a mean age of 69.8 years whereas NICOR clinical data shows a mean age of 78 years (NICOR 2017) confirming that RCTs recruit a much younger population. This is a similar difference to that seen in conventional CVD rehab population as collected through the NACR and Cochrane trials where the means age is 67 years and 56 years respectively (NACR 2017, Anderson et al 2016).

The distribution of atrial fibrillation or flutter in the 216 patients in the REACH HF population (Table 4.4) could lead to possible conclusion that dysrhythmias might have had contributed towards moderate to severe heart failure in these patients. Although the mean IWST distance did not differ between patients with AF/flutter and those without the combined burden of comorbidities like hypertension (40%), MI (31%), stroke (13%), valvular heart disease (24%) and diabetes (20%) may well create the context for a greater burden on a patient's ability and the possibility of reduced exercise capacity. CR programmes are increasing opening their doors to AF patients with early trials suggesting an improvement in exercise capacity (Risom et al 2017).

A combination of atrial fibrillation (Afib) and HF is the common cardiovascular co-existing condition that results in significant morbidity and mortality. Our baseline data shows an even split between with atrial fibrillation or flutter (Table 4.4) highlighting that this condition is a significant comorbidity for up to 50% of patients with reduced LVEF in the REACH-HF cohort. The proportion of atrial fibrillation or flutter between males and females was 54.4% and 34% respectively. The prevalence of AF in patients with HF ranges from 10 to 30%, and has been observed to increase in proportion to the severity of HF from <10% in those with New York Heart Association (NYHA) functional class I HF to approximately 50% in those with NYHA functional class IV HF. Most evidence suggests that patients with both AF and HF have a worse prognosis than HF patients who are in SR.

Most recently published National Heart Failure Audit (April 2014-March 2015) suggests that 21% of the HF-REF (heart failure with reduced ejection fraction) population had AF thereby carrying a significant comorbidity burden. Unfortunately, one of the limitations of the REACH trial is that we have not investigated further to see whether REACH population patients have been rate or rhythm controlled or both as part of their management. This audit also noted that just less than 20% of the HF-REF population has chronic obstructive pulmonary disease (COPD).

Although device trials states that newer development of device therapies have contribute towards improvement in LV function (Moss et al 2002, Bardy el at 2005) the extent of take up of these devices in REACH-HF was relatively low {ICD (9%), CRT (6%) or combined (4%) and pacemaker (10%)} and tended to reside in NYHA II. Despite only having nine patients with combined CRT/ICD this variable came close to being a significant determinant of poorer walking fitness with a means score of 271.25 m compared to 293.58 in the non-CRT/ICD group. One could argue that low fitness levels in patients with combined therapy is likely to remain low as these patients carry a significant burden complicated by dyssynchrony which will predispose them to poorer fitness levels. Future studies with larger sample sizes are required to investigate these issues.

The results found that CKD was evident in 13% of the REACH-HF population which is an important finding but unfortunately, the sample size was too small to meet the regression requirements. However, CKD remains and important characteristic as it is associated with poorer exercise capacity (Table 4.11). Those patients with CKD had lower levels of fitness by 50 metres compared to those without CKD. Although inferential statistical analysis is not appropriate, due to the small sample size of 26, the proportion of patients with CKD was greatest in NYHA class II and III.

Table 4.11. ISWT distance in patients with and without CKD and COPD

ISWT fitness by COPD and CKD

Best ISWT measure

COPD	CKD	Mean	Std. Dev	N
No	No	**304.93**	168.39	144
	Yes	268.10	137.28	21
	Total	300.24	164.84	165
Yes	No	210.00	74.07	8
	Yes	**172.00**	116.06	5
	Total	195.38	89.78	13
Total	No	299.93	166.01	152
	Yes	249.62	136.84	26
	Total	292.58	162.70	178

COPD = Chronic bronchitis or Emphysema)

CKD = Chronic kidney disease (moderate to severe)

The other comorbidity that associated with differences in fitness was COPD (ie. Chronic bronchitis and emphysema) which showed over 100 metres difference between those with and without COPD (Table 4.11). Although there was insufficient sample size for COPD to reach statistical significance in the regression analysis it nevertheless carries significant clinical importance.

As was found for CKD the proportions of patients with COPD was greatest in NYHA class II and III. Once again there was insufficient sample size (N=13) to warrant inferential statistical analysis (Field 2017). Collectively CKD and COPD, albeit in small numbers, appear to co-exist within the NYHA classifications (II to III) suggesting that any finding regarding the ability of NYHA to predict fitness should viewed within this context.

Table 4.6 highlighted the extent of drug treatment in the heart failure population. It is very reassuring that 65% people were on ACE (i) as this class of drug has shown to improve mortality in heart failure patients (CTS 1987). 83% of the patients were on beta-blocker and 53% were on aldosterone antagonist. Both classes of drug are known to benefit patients with poor LV dysfunction and improve prognosis and exercise tolerance. Only 63% and 0.9% of the people were on loop or thiazide diuretics which could in theory explain their reduced ability to exercise due to excessive weight gained from fluid overload or retention. Fluid congestion is the most common symptom for heart failure admissions and plays a major role in acute decompensation in HF and the progression. Although there are three main classes of diuretics (loop diuretics, thiazide diuretics with metolazone and potassium-sparing diuretics), loop diuretics are most commonly used, because they have the most potent natriuretic. Please refer to 63.9% of the patients (Table 4.6) have been taking loop diuretics with minimal variation between male and females in percentage within gender around 6%. Recent data from National Heart Failure Audit clearly shows 91% of HF-REF patients were discharged on loop diuretics besides prescription of ACEI, BB and MRAs – the key disease modifying medications for patients with REACH-HF.

These patients with moderate to severe heart failure (patients in REACH population) not taking loop diuretic clearly are stable patients with reduced hospital admissions or lesser exacerbations and therefore they don’t feel they need to take diuretics regularly to offload them.

It is routine cardiology practice for heart failure patients with moderate-severe heart failure are strongly advised by secondary heart failure team to take loop diuretics in addition to three other disease modifying drugs daily despite of their symptoms of congestion or weight gain; however, it remains at discretion of primary care physicians and willingness of patients whether they adhere to this advice. Unfortunately, REACH trial has not investigated in detail as to the reasons for not achieving 100% in this patient group. We cannot therefore assume as to the exact circumstances for non -compliance.

The study also revealed that fewer patients were prescribed and have been taking nitrates and digoxin despite many successful outcome trials on benefit of these drugs in preventing fluid retention and symptoms and overall prognosis. Newer class of drugs like ivabradine has not been used in abundance despite new NICE guidelines (NICE CG 108) in reducing heart rate in non- atrial fibrillation patients. This class of drug particularly has shown to improve left ventricular dysfunction and exercise capacity (SHIFT trial[i]). These drugs when not used in suitable patients as in our study population can overall effect morbidity and wellbeing.

Our preliminary analysis (Table 4.6) of loop diuretic medication found that patients taking loop were on average heavier by 9kg and the corresponding ISWT score was in favour of greater distance in those patients not taking loop.

Quality of life and fitness

MLHFQ is the primary outcome measure for REACH-HF and our analysis found a mean of 30.65 across a range from 0 to 88. This equates to a moderate HRQoL score suggesting that REACH-HF patients do have issues with HRQoL. Di Mauro et al 2018 study helped set cut points for the MLHFQ where they defined poor QoL as a score above 45, moderate QoL is 24 to 45 with a good QoL score below 24. In the REACH-HF sub-study females reported poorer QoL than males with scores of 38 and 28 respectively. Mean walking distance was 292 metres with males walking 52 metres more than females. The correlation between HRQoL and ISWT distance was poor (Figure 4.2) with only 11.9% shared variance meaning that greater levels of fitness are not associated with higher levels of QoL as measured by the MLFHQ.

Clinical measures of heart failure severity, in this study LVEF and Pro-BNP, were not related to fitness (ISWT distance) (figures 4.3 & 4.4) as they collectively had 1% than 5% shared variance in terms of explaining fitness. Clinically there is tendency to view LVEF and Pro-BNP as surrogate expressions of a patient's ability to exercise. Our REACH-HF findings challenge this assumption and propose alternative determinants of fitness in patients with HF.

The initial linear regression analysis found that age, gender, BMI, NYHA classification, COPD and Combined CRT/ICD devices had strong association with ISWT scores (Table 4.8). After controlling for the presence of each of the six variables only three remained significant namely gender, age and NYHA class (Table 4.9). The shared variance (ie. the power by which these variables explain fitness) was 40.8% which indicates a highly predictive model (Table 4.10). The benefit is that all three variables are routinely collected as part of clinical practice. This is good news for clinical teams as it means decisions on determinants of fitness do not required additional expensive clinical measures.

In the time frame of this MD the NIHR REACH-HF project has completed showing that it is clinically effective and value for money (Taylor R et al 2019, Dalal H et al 2018). This outcome confirms the benefits of CR in a UK population and reiterates need for patients with HF to access CR services. In addition the BACPR recommends that all patients should undergo a test of physical fitness prior to starting CR (BACPR 2017). This MD has shown physical fitness assessment is determined by many different factors which should be taken into account when interpreting fitness test results and setting goals for cardiac rehabilitation.

Limitations

The sample size of REACH-HF was sufficiently powered for an effectiveness analysis (n=216) which was approved by NIHR statisticians as part of the award application and award of the grant. This sub-study was able to utilise the full 216 patients which allowed for regression analysis to be conducted. There were six variables in the main analysis which represents an average of 36 patients per variable which albeit sufficient in overall mathematical terms for sample size as part of regression it was limited in terms of gender distribution. Caution is required when interpreting these associations when gender is the focus.

The HF populations in the NACR study was much larger than that for REACH-HF (1227 vs 216) however the use of only patients with a valid measure of fitness makes the MD thesis sample from the NACR study potentially less representative of the overall HF population. The MD NACR study population had a mean age 64 years (12.72 SD) whereas the mean age of patients attending CR and captured on the NACR is 68 years (range 40 to 97). A difference of 4 years remains important however our recently published ISWT reference values (Doherty, Harrison and Hossain 2019) have, in part, accounted for this by presenting distance walked in respect of patients above and below the age of 67 years which was the median age of the population with an ISWT fitness measurement.

4.5 Conclusion

The REACH-HF main study was successful in recruiting 216 patients thus allowing the REACH-HF sub-study, underpinning the second part of this MD thesis, to complete its analysis.

This MD thesis sought to determine the strength by which cardiology measures, such as LVEF and Pro-BNP, and patient demographics helped explained (or determine) physical fitness in patients with HF. The findings from the REACH-HF sub-study convincingly show that cardiology measures play a minor role in determining fitness as measured by the incremental shuttle walk test (ISWT).

The three primary variables of age, gender and NHYA classification collectively explain 40% of fitness in HF which represents a significant level of prediction. There were two additional comorbidities, namely COPD and CKD, suggestive of a role determining fitness but lacking sufficient sample size to allow these variables to be thoroughly tested using linear regression.

The findings from the REACH-HF sub-study, based on a robust study and analytical approach, have helped clarify that conventional thinking about the potential role of LVEF and Pro-BNP, in determining exercise capacity in HF patients, need reviewing. The REACH-HF sub-study has identified age, gender and NYHA classification as significant determinants of exercise capacity.

Key findings

The key findings from the NACR study and the REACH-HF sub-study highlight that age and gender were core determinants of walking fitness in HF patients.

In the NACR routine clinical data study, COPD was found to be an additional determinant (along with age and gender) associated with significant differences in walking fitness. After account for over 15 different baseline characteristics and comorbidities (including back pain and arthritis) COPD was the only comorbidity to achieve significance as a determinant of fitness.

In the REACH-HF sub-study NYHA classification was an additional determinant (along with age and gender) of walking fitness in HF patients with reduced ejection fraction.

In respect of the research question and thesis title cardiology measures such as LVEF and Pro-BNP failed to add anything to decision making about factors determining fitness in patients with HF.

Implications for clinical practice

Findings from this MD thesis have the potential to influence clinical guidance by confirming that LVEF has no role in determining fitness of patients with HF and this measure should not be used as a criterion for exclusion from CR. This message also needs to be shared with cardiologists, GP specialists and heart failure nurse specialists who often reside at the point patients are making decisions about what is important for their ongoing care and QoL.

The reference values produced in study one, based on age, gender and COPD, will aid the interpreting ISWT scores and give clinicians and patients guidance on how well they have done in their fitness test.

The REACH-HF sub-study confirms that NYHA, which is a patient level measure, is a powerful determinant of walking fitness. In the absence of actual fitness test scores, due to limited resources or significant comorbidity, the combination of age, gender and NYHA can act as a surrogate measure of fitness which may aid advice given to patients.

Recommendations

All eligible patients with HF, irrespective of their level of fitness and LVEF values, should be referred to cardiac rehabilitation for initial baseline assessment of fitness.

The reference values produced by this thesis and its planned publications should be used to evaluate fitness as measured by the incremental shuttle walk test (ISWT).

Albeit more research is required in a larger sample of patients this thesis suggests that higher NYHA classifications, chronic obstructive pulmonary disease (COPD) and the presence of chronic kidney disease (CKD) should be considered as import clinical determinants of walking fitness in patients with HF.

Future research

The two studies underpinning this MD thesis have explored the role of obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) however the sample in each case was insufficient to carry out a robust evaluation of their role in determining fitness in patients with HF.

One of the important elements from the updated review of literature was the potential role of iron deficiency in determining mortality and exercise capacity in patients with HF. REACH-HF was conceived prior to 2003 to 2006 when the first studies emerged on iron deficiency. Future research on exercise capacity in HF patients needs to evaluate the impact of iron deficiency and its treatment.

This thesis focused on heart failure with reduced ejection fraction (HFrEF) however heart failure with preserved ejection fraction (HFpEF), which is now more clearly defined clinically, remains relatively unexplored.

I would like to thank the REACH-HF team for supporting this aspect of my MD thesis.

5. Thesis summary

This MD thesis carried out three studies that collectively add value to the literature around determinants of physical fitness in patients with heart failure. In summary the studies and findings include:

I. **Review of literature to identify determinants of physical fitness in patients with HF:**
The review 14 potential determinants with varying levels of evidence underpinning their selection. These findings question previous assumptions and should help increase our understanding about which factors should be considered when drawing conclusions about physical fitness.

II. **Observational study of determinants of physical fitness in patients with HF using national audit data:** Using patient level data from routine practice this study concludes that patient age, gender alongside depression status and the presence of COPD as comorbidity were significant determinants in predicting walking fitness in patients with HF. The study also produced a novel set of reference values, aligned with age, gender, COPD and depression, to aid the interpretation of walking fitness by clinicians and patients.

III. **An embedded study of determinants of physical fitness in patients with HF as part (formal sub-study) of the REACH-HF clinical trial:**
The findings from the REACH-HF sub-study convincingly show that cardiology measures play only a minor role in determining fitness as measured by the incremental shuttle walk test (ISWT). The three primary variables of age, gender and NHYA classification collectively explain 40% of fitness in HF which represents a significant level of prediction with two additional comorbidities, namely COPD and CKD, suggestive of a role determining fitness.

Together the three studies underpinning this MD combine a literature review (including clinical trials and cohort studies) with a randomised controlled trial sub-study alongside a large real-world routine practice observational study. This therefore represents one of the most comprehensive evaluations of determinants of fitness in patients with HF and has led to the identification of 14 determinants from the literature (Table 2.2) with confirmation of age and NYHA from the REACH-HF sub-study and the addition of depression from the NACR observational study.

The net result is that 15 factors have been identified as having the potential to determine physical fitness in patients with HF which is important information for clinicians, patients and carers. The development and publication of reference values to aid clinical decision making and help set realistic patient goals is a further outcome from this MD.

6. References

Adedoyin RA, Adeyanju SA, Balogun MO, Adebayo RA, Akintomide AO, Akinwusi PO. Prediction of functional capacity during six-minute walk among patients with chronic heart failure. Nigerian Journal of Clinical Practice. 2010; 13:379-81.

Ahmad T, Fiuzat M, Mark DB, Neely B, Neely M, Kraus WE, et al. The effects of exercise on cardiovascular biomarkers in patients with chronic heart failure. Am Heart J. 2014; 167:193-202.e1.

Ahmeti A, Henein MY, Ibrahimi P, Elezi S, Haliti E, Poniku A, et al. Quality of life questionnaire predicts poor exercise capacity only in HFpEF and not in HFrEF. BMC Cardiovasc Disord. 2017; 17:268.

Alpert MA, Lavie CJ, Agrawal H, Aggarwal KB, Kumar SA. Obesity and heart failure: Epidemiology, pathophysiology, clinical manifestations, and management. Translational Research. 2014; 164:345-56.

Al Quait, A. et al., 2017. In the modern era of percutaneous coronary intervention: Is cardiac rehabilitation engagement purely a patient or a service level decision? European Journal of Preventive Cardiology, p.204748731771706. Available at: http://journals.sagepub.com/doi/10.1177/2047487317717064.

Al Quait, A. & Doherty, P., 2016. Does cardiac rehabilitation favour the young over the old? Open Heart, 3(2), p.e000450. Available at: http://openheart.bmj.com/lookup/doi/10.1136/openhrt-2016-000450.

Anderson, L. et al., 2016. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease. Journal of the American College of Cardiology, 67(1), pp.1–12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26764059.

Anderson, L. et al., 2017a. Home-based versus centre-based cardiac rehabilitation. In R. S. Taylor, ed. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd. Available at: http://doi.wiley.com/10.1002/14651858.CD007130.pub4 [Accessed July 6, 2019].

Anderson, L. et al., 2017b. Home-based versus centre-based cardiac rehabilitation. Cochrane Database of Systematic Reviews. Available at: http://doi.wiley.com/10.1002/14651858.CD007130.pub4 [Accessed July 6, 2019].

Field A., 2013. Discovering Statistics Using IBM SPSS Statistics, SAGE Publications.

Anglemyer, A., Horvath, H.T. & Bero, L., 2014. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. The Cochrane database of systematic reviews, 4(4), p.MR000034.

Arena, R. et al., 2012. Increasing referral and participation rates to outpatient cardiac rehabilitation: The valuable role of healthcare professionals in the inpatient and home health settings: A science advisory from the American Heart Association. Circulation, 125(10), pp.1321–1329.

Alotaibi, JFM & Doherty, PJ 2018, 'Evaluation of determinants of walking fitness in patients attending cardiac rehabilitation' BMJ Open Sport & Exercise Medicine, vol 2, e000203, pp. 1-6. DOI: 10.1136/bmjsem-2016- 000203

BACPR, 2017. The BACPR Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation, 3rd ed. , p.28. Available at: http://www.bacpr.com/resources/AC6_BACPRStandards&CoreComponents2017.pdf [Accessed July 6, 2019].

Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005 Jan 20;352(3):225-37.

Beauchamp, A. et al., 2013. Attendance at cardiac rehabilitation is associated with lower all-cause mortality after 14 years of follow-up. Heart, 99(9), pp.620–5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23213175.

Bhaskaran K. & Smeeth L. 2014. What is the difference between missing completely at random and missing at random? International Journal of Epidemiology, 43(4), pp.1336–1339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24706730 [Accessed August 7, 2017].

Bhatnagar P. et al., 2015. The epidemiology of cardiovascular disease in the UK 2014. Heart, 101(15), pp.1182–1189. Available at: http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2015-307516.

Cardiovascular Disease Statistics 2015 BHF. https://www.bhf.org.uk/informationsupport/publications/statistics/cvd-stats-2015 Accessed July 6, 2019

Bjarnason-Wehrens, B. et al., 2010. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology, 17(4), pp.410–418.

Cardoso FM, Almodhy M, Pepera G, et al. Reference values for the incremental shuttle walk test in patients with cardiovascular disease entering exercise-based cardiac rehabilitation. J Sports Sci 2017;35:1–6

Carlson, M.D.A. & Morrison, R.S., 2009. Study design, precision, and validity in observational studies. Journal of palliative medicine, 12(1), pp.77–82. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19284267 [Accessed July 6, 2019].

Centre for Reviews and Dissemination, 2009. Systematic reviews: CRD's guidance for undertaking reviews in health care, CRD, University of York. Available at: https://gate2.library.lse.ac.uk/login?url=http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2524.2003.00433.x/abstract%5Cnhttp://zw4gk5cr3l.search.serialssolutions.com?sid=Central

Search:null&genre=article&atitle=Scoping+the+field&volume=11&issue=4&title=H [Accessed July 6, 2019].

Chen YW, Wang CY, Lai YH, Liao YC, Wen YK, Chang ST, et al. Home-based cardiac rehabilitation improves quality of life, aerobic capacity, and readmission rates in patients with chronic heart failure. Medicine (Baltimore). 2018; 97:e9629.

Chiong JR, Aguilar T. Impact of exercise capacity among elderly (>75) with systolic heart failure. J Card Fail. 2010; 1):S102.

Clark, A.M. et al., 2012. A qualitative systematic review of influences on attendance at cardiac rehabilitation programs after referral. American Heart Journal, 164(6), p.835–845.e2. Available at: http://dx.doi.org/10.1016/j.ahj.2012.08.020.

Collet, J.P., 2000. Limitations of clinical trials. La Revue du praticien, 50(8), pp.833–837. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10874859 [Accessed July 6, 2019].

Collins, G.S. et al., 2014. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. BMC medical research methodology, 14(1), p.40. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3999945&tool=pmcentrez&rendertype=abstract [Accessed July 6, 2019].

Comin-Colet J, Enjuanes C, Gonzalez G, Torrens A, Cladellas M, Merono O, et al. Iron deficiency is a key determinant of health-related quality of life in patients with chronic heart failure regardless of anaemia status. European Journal of Heart Failure. 2013; 15:1164-72.

CTS. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429-35.

Cupples, M.E. et al., 2010. Cardiac rehabilitation uptake following myocardial infarction: Cross-sectional study in primary care. British Journal of General Practice, 60(575), pp.431–435.

Dalal, H.M., Doherty, P. & Taylor, R.S., 2015. Cardiac rehabilitation. BMJ (Clinical research ed.), 351(sep29_11), p.h5000. Available at: http://www.bmj.com/content/351/bmj.h5000.full.pdf+html [Accessed July 6, 2019]

Dalal H, Taylor RS, Jolly K, Davis RC, Doherty PJ, Miles J, Van Lingen R, Warren FC, Green C, Wingham J, Greaves CJ, et al 2018, 'The effects and costs of home-based rehabilitation for heart failure with reduced ejection fraction: The REACH-HF multicentre randomized controlled trial', European journal of preventive cardiology, pp. 1-11. https://doi.org/10.1177/2047487318806358

David Hosmer, Stanely Lemeshow, R.S., 2013. Applied Logistic Regression 3rd ed., New Jersey: John Wiley & Sons, Inc.

Davis, J.W., 2008. Medical Statistics: A Textbook for the Health Sciences, Wiley.

Del Buono et al. Exercise Intolerance in Patients with Heart Failure JACC State-of-the-Art Review. JACC VOL. 73, NO. 17, 2019:2209 – 2 5

DH Cardiovascular Disease Team, 2013. Cardiovascular Disease Outcomes Strategy; improving outcomes for people at risk or with cardiovascular disease, Available at: https://www.gov.uk/government/publications/cardiovascular-disease-outcomes-strategy-improving-outcomes-for-people-with-or-at-risk-of-cardiovascular-disease.

Department for Communities and Local Government. The English indices of deprivation, 2015, statistics release, https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015, accessed 9 July 2019).

Diaz Molina B, Iscar M, Lambert JL, Quezada CA, Renilla A, Benito E, et al. Exercise capacity in patients with heart failure and COPD. European Journal of Heart Failure. 2013; 12:S159.

Dickstein K, Cohen-Solal A, Filippatos G,et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008:the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail2008; 10:933–89

Di Mauro M, Petroni R, Clemente D, Foschi M, Tancredi F, Camponetti V, et al. Clinical profile of patients with heart failure can predict rehospitalization and quality of life. Journal of cardiovascular medicine (Hagerstown, Md). 2018; 19:98-104.

Doherty, P. & Lewin, R., 2012. The RAMIT trial, a pragmatic RCT of cardiac rehabilitation versus usual care: what does it tell us? Heart, 98(8), pp.605–606. Available at: http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2012-301728 [Accessed July 6, 2019].

Doherty P, Harrison AS, Hossain R Determinants of walking fitness in patients with heart failure attending cardiac rehabilitation Open Heart 2019;6:e000866. doi: 10.1136/openhrt-2018-000866

Doll, J.A. et al., 2015. Effectiveness of cardiac rehabilitation among older patients after acute myocardial infarction. American Heart Journal, 170(5), pp.855–864.

Dressler, C. et al., 2012. Interventions to increase the uptake of cardiac rehabilitation: Systematic review. British Journal of Cardiac Nursing, 7(7), pp.338–346. Available at: http://www.magonlinelibrary.com/doi/abs/10.12968/bjca.2012.7.7.338 [Accessed July 6, 2019].

Dunlay, S.M. et al., 2014. Participation in cardiac rehabilitation, readmissions, and death after acute myocardial infarction. The American journal of medicine, 127(6), pp.538–46. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4035431&tool=pmcentrez&rendertype=abstract.

Evenson, K., Rosamond, W. & Luepker, R., 1998. Predictors of outpatient cardiac rehabilitation utilization: the Minnesota Heart Surgery Registry. Journal of cardiopulmonary rehabilitation, 18(3), pp.192–8. Available at: http://journals.lww.com/jcrjournal/Abstract/1998/05000/Predictors_of_Outpatient_Cardiac_Rehabilitation.2.aspx%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/9632320.

Fenk S, Fischer M, Strack C, Schmitz G, Loew T, Lahmann C, et al. Successful weight reduction improves left ventricular diastolic function and physical performance in severe obesity. International Heart Journal. 2015; 56:196-202.

Enjuanes C et al. 2016. Iron Status in Chronic Heart Failure: Impact on Symptoms, Functional Class and Submaximal Exercise Capacity. Rev Esp Cardiol.2016; 69(3):247–255.

Fletcher F, Balady G, et al. Exercise Standards for Testing and Training A Statement for Healthcare Professionals From the American Heart Association. November 2001. Circulation 104(14):1694-740. DOI10.1161/hc3901.095960

Field, A., 2017. Discovering statistics using IBM SPSS Statistics (fifth edition), Available at: https://books.google.co.uk/books?id=QMI-DwAAQBAJ&printsec=frontcover&dq=discovering+statistics+using+ibm+spss+statistics&hl=en&sa=X&ved=0ahUKEwi16p6Du5TaAhWIKsAKHad7BWMQ6AEILzAB#v=onepage&q&f=false

Fitzsimons S, Doughty RN. Iron deficiency in patients with heart failure. Eur Heart J. 2015; 1:58-64.

Fleg JL, Pina IL, Balady GJ., Chaitman BR, Fletcher B, & Lavie C. (2000) Assessment of Functional Capacity in Clinical and Research Applications. *Circulation*, **102**, 1591-1597.

Fowler SJ, Singh SJ, Revill S. Reproducibility and validity of the incremental shuttle walking test in patients following coronary artery bypass surgery. Physiotherapy 91 (2005) 22–27

French, D.P. et al., 2005. Do illness perceptions predict attendance at cardiac rehabilitation and quality of life following myocardial infarction? Journal of Psychosomatic Research, 59(5), pp.315–322.

Gibbons R, J. Balady G, et al. ACC/AHA 2002 Guideline Update for Exercise Testing: Summary Article.

Goff, D.C. et al., 2014. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American college of cardiology/American heart association task force on practice guidelines. Circulation, 129.

GOV.UK (2016) Health matters: getting every adult active every day https://www.gov.uk/government/publications/health-matters-getting-every-adult-active-every-day/health-matters-getting-every-adult-active-every-day (accessed July 6, 2019)

Grace, S.L. et al., 2016. Cardiac Rehabilitation Program Adherence and Functional Capacity Among Women: A Randomized Controlled Trial. Mayo Clinic Proceedings, 91(2), pp.140–148. Available at: http://dx.doi.org/10.1016/j.mayocp.2015.10.021.

Grace, S.L. et al., 2008. Contribution of patient and physician factors to cardiac rehabilitation referral: a prospective multilevel study. Nature clinical practice. Cardiovascular medicine, 5(10), pp.653–662.

Greaves CJ, Wingham J, Deighan C, Doherty P, Elliott J, Armitage W, et al. Optimising self-care support for people with heart failure and their caregivers: development of the Rehabilitation Enablement in Chronic Heart Failure (REACH-HF) intervention using intervention mapping. Pilot and Feasibility Studies. 2016; 2:37.

Gutzwiller FS, Pfeil AM, Comin-Colet J, Ponikowski P, Filippatos G, Mori C, et al. Determinants of quality of life of patients with heart failure and iron deficiency treated with ferric carboxymaltose: FAIR-HF sub-analysis. Int J Cardiol. 2013; 168:3878-83.

Hajdusek P, Kotrc M, Kautzner J, Melenovsky V, Benesova E, Jarolim P, et al. Heart rate response to exercise in heart failure patients: The prognostic role of metabolic-chronotropic relation and heart rate recovery. Int J Cardiol. 2016; 228:588-93.

Hannan, E.L., 2008. Randomized Clinical Trials and Observational Studies. Guidelines for Assessing Respective Strengths and Limitations. JACC: Cardiovascular Interventions, 1(3), pp.211–217. Available at: http://linkinghub.elsevier.com/retrieve/pii/S1936879808001702 [Accessed July 6, 2019].

Harrison, AS & Doherty, P 2018, 'Does the mode of delivery in routine cardiac rehabilitation have an association with cardiovascular risk factor outcomes?', European journal of preventive cardiology, vol. 25, no. 18. https://doi.org/10.1177/2047487318798923

Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail. 2009;11(2):130-9.

Humphrey, R., Guazzi, M. & Niebauer, J., 2014. Cardiac rehabilitation in Europe. Progress in Cardiovascular Diseases, 56(5), pp.551–556. Available at: http://dx.doi.org/10.1016/j.pcad.2013.08.004.

Ingle L, Cleland JG, Clark AL. The long-term prognostic significance of 6-minute walk test distance in patients with chronic heart failure. BioMed Research International. 2014; 2014:505969.

Kallistratos MS, Poulimenos LE, Pavlidis AN, Dritsas A, Laoutaris ID, Manolis AJ, et al. Prognostic significance of blood pressure response to exercise in patients with systolic heart failure. Heart & Vessels. 2012; 27:46-52.

Kommuri NVA, Johnson ML, Koelling TM. Six-minute Walk Distance Predicts 30-Day Readmission in Hospitalized Heart Failure Patients. Arch Med Res. 2010; 41:363-8.

Lawler, P.R., Filion, K.B. & Eisenberg, M.J., 2011. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: A systematic review and meta-analysis of randomized controlled trials. American Heart Journal, 162(4), p.571–584.e2. Available at: http://dx.doi.org/10.1016/j.ahj.2011.07.017.

Ligthelm, R.J. et al., 2007. Importance of Observational Studies in Clinical Practice. Clinical Therapeutics, 29(6 PART 1), pp.1284–1292. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0149291807001841 [Accessed July 6, 2019].

Linden, W., Stossel, C. & Maurice, J., 1996. Psychosocial interventions for patients with coronary artery disease: a meta-analysis. Archives of internal medicine, 156(7), pp.745–52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8615707 [Accessed July 6, 2019].

Long-Sutehall, T., Sque, M. & Addington-Hall, J., 2011. Secondary analysis of qualitative data: a valuable method for exploring sensitive issues with an elusive population? Journal of Research in Nursing, 16(4), pp.335–344. Available at: http://eprints.soton.ac.uk/193035/1/Sec_analysis_paper_[final]_03.06.10.doc [Accessed July 6, 2019].

Man, WD-C, Chowdhury, F, Taylor, RS, Evans, RA, Doherty, P, Singh, SJ, Booth, S, Thomason, D, Andrews, D, Lee, C, Hanna, J, Morgan, MD, Bell, D & Cowie, MR 2016, 'Building consensus for provision of breathlessness rehabilitation for patients with chronic obstructive pulmonary disease and chronic heart failure' Chronic respiratory disease. DOI: 10.1177/1479972316642363

Marco et al. 2019. Exercise intolerance in patients with heart failure JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 17, 2019.

McCabe N, Butler J, Dunbar SB, Higgins M, Reilly C. Six-minute walk distance predicts 30-day readmission after acute heart failure hospitalization. Heart Lung. 2017; 46:287-92.

Menezes, A.R. et al., 2014. Cardiac Rehabilitation in the Elderly. Progress in Cardiovascular Diseases, 57(2), pp.152–159. Available at: http://dx.doi.org/10.1016/j.pcad.2014.01.002.

Milani, R. V. et al., 2011. Impact of exercise training and depression on survival in heart failure due to coronary heart disease. American Journal of Cardiology, 107(1), pp.64–68. Available at: http://dx.doi.org/10.1016/j.amjcard.2010.08.047.

Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002 Mar 21;346(12):877-83.

NACR, 2018. National Audit of Cardiac Rehabilitation Annual Statistical Report 2018. Available at: https://www.bhf.org.uk/informationsupport/publications/statistics/national-audit-of-cardiac-rehabilitation-quality-and-outcomes-report-2018.

National Institute for Health and Care Excellence, 2013. Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease, Available at: https://www.nice.org.uk/guidance/cg172/resources/myocardial-infarction-cardiac-rehabilitation-and-prevention-of-further-cardiovascular-disease-35109748874437.

NHS, 2015. Physical activity guidelines for adults - Live Well - NHS Choices. Available at: http://www.nhs.uk/Livewell/fitness/Pages/physical-activity-guidelines-for-adults.aspx [Accessed July 7, 2019].

NICE, 2015. [Secondary prevention after a myocardial infarction]. Secondary prevention after a myocardial infarction (QS99), 61(5–6), pp.380–385. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16910265.

NICE, 2013. MI – secondary prevention care for patients following a myocardial. NICE Guidelines, (November). Available at: https://www.nice.org.uk/guidance/cg172/resources/myocardial-infarction-cardiac-rehabilitation-and-prevention-of-further-cardiovascular-disease-pdf-35109748874437 [Accessed July 7, 2019].

NICE commissioning guides, 2013. Cardiac rehabilitation services | Guidance and guidelines | NICE. Available at: https://www.nice.org.uk/guidance/cmg40#ftn.footnote_1 [Accessed July 6, 2019].

NICOR (National Institute for Cardiovascular Outcomes Research). National Heart Failure Audit 2017 [July 6, 2019]. Available from: http://www.ucl.ac.uk/nicor/audits/heartfailure

National Institute for Health and Care Excellence. Management of chronic heart failure in adults in primary and secondary care ((clinical guidance 108). NICE, 2010. www.nice.org.uk/guidance/cg108

Nichols, M. et al., 2014. Cardiovascular disease in Europe 2014: Epidemiological update. European Heart Journal, 35, pp.2950–2959. Available at: http://eurheartj.oxfordjournals.org/content/35/42/2950.long.

Nielsen, K.M. et al., 2008. Cardiac rehabilitation: Health characteristics and socio-economic status among those who do not attend. European Journal of Public Health, 18(5), pp.479–483. Available at: https://academic.oup.com/eurpub/article-lookup/doi/10.1093/eurpub/ckn060.

Nyolczas N, Dekany M, Muk B, Szabo B. Combination of Hydralazine and Isosorbide-Dinitrate in the Treatment of Patients with Heart Failure with Reduced Ejection Fraction. Adv Exp Med Biol. 2017.

Mentz RJ, Schulte PJ, Fleg JL, Fiuzat M, Kraus WE, Piña IL, Keteyian SJ, Kitzman DW, Whellan DJ, Ellis SJ, O'Connor CM. Clinical characteristics, response to exercise training, and outcomes in patients with heart failure and chronic obstructive pulmonary disease: findings from Heart Failure and A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION). Am Heart J. 2013 Feb;165(2):193-9. doi: 10.1016/j.ahj.2012.10.029. Epub 2012 Nov 28.

Papasavvas T, Bonow RO, Alhashemi M, et al. Depression Symptom Severity and Cardiorespiratory Fitness in Healthy and Depressed Adults: A Systematic Review and Meta-Analysis. Sports Med. 2016;46:219–30.

Pepera G, McAllister J, Sandercock G. Long-term reliability of the incremental shuttle walking test in clinically stable CVD disease patients. Physiotherapy 2010;96:222–7.

Piepoli, M.F., Hoes, A.W., Agewall, S., Albus, C., Brotons, C., et al., 2016. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. European Journal of Preventive Cardiology, 23(11), p.NP1-NP96. Available at: http://journals.sagepub.com/doi/10.1177/2047487316653709 [Accessed July 6, 2019].

Piepoli, M.F., Hoes, A.W., Agewall, S., Albus, C., Brotons, C., et al., 2016. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. European Heart Journal, 37(29), pp.2315–2381.

Piepoli, M.F. et al., 2015. Challenges in secondary prevention of cardiovascular diseases: A review of the current practice. International journal of cardiology, 180C, pp.114–119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25438230.

Piepoli, M.F.M.F. et al., 2016. Challenges in secondary prevention after acute myocardial infarction: A call for action. European Journal of Preventive Cardiology, 23(18), pp.1994–2006. Available at: http://journals.sagepub.com/doi/10.1177/2047487316663873 [Accessed July 6, 2019].

Polgar, S. & Thomas, S.A., 2013. Introduction To Research In The Health Sciences,

Ponikowski P, Anker SD, Al Habib KF, et al. Heart failure: preventing disease and death worldwide. ESC Heart Fail2014;1:4–25.

Pulz C, Diniz RV, Alves AN,et al. Incremental shuttle and six-minute walking tests in the assessment of functional capacity in chronic heart failure. Can J Cardiol2008; 24:131–5

Rauch, B. et al., 2016. The prognostic effect of cardiac rehabilitation in the era of acute revascularisation and statin therapy: A systematic review and meta-analysis of randomized and non-randomized studies – The Cardiac Rehabilitation Outcome Study (CROS). European Journal of Preventive Cardiology, 23(18), pp.1914–1939. Available at: http://eprints.whiterose.ac.uk/106630/ [Accessed July 6, 2019].

Rector T et al. Patients' self-assessment of their congestive heart failure. Part 2: content, reliability and validity of anew measure, the Minnesota Living with Heart Failure questionnaire. Heart Fail1987; 3:198–209

Risom S, Zwisler A, Johansen P, Sibilitz K, Lindschou J, Gluud C, et al. Exercise-based cardiac rehabilitation for adults with atrial fibrillation (Review). Cochrane Database Syst Rev. 2017;(2):Art No: CD011197.

Rosenbaum, P., 2002. Observational Studies 2nd ed., Springer. Available at: http://dx.doi.org/10.1007/978-1-4757-3692-2_1 [Accessed July 6, 2019].

Sagar, V.A. et al., 2015. Exercise-based rehabilitation for heart failure: systematic review and meta-analysis. Open Heart, 2(1), p.e000163. Available at: http://openheart.bmj.com/lookup/doi/10.1136/openhrt-2014-000163.

Sign 150, 2017. SIGN 150, Available at: http://www.sign.ac.uk/assets/sign150.pdf [Accessed December 30, 2017].

Silverman, S.L., 2009. From Randomized Controlled Trials to Observational Studies. American Journal of Medicine, 122(2), pp.114–120. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0002934308009522 [Accessed July 6, 2019].

Snaith, R. P. (2003). The Hospital Anxiety And Depression Scale. *Health and Quality of Life Outcomes*, *1*, 29. http://doi.org/10.1186/1477-7525-1-29

Suaya, J.A. et al., 2007. Use of Cardiac Rehabilitation by Medicare Beneficiaries After Myocardial Infarction or Coronary Bypass Surgery. Circulation, 116(15), pp.1653–1662.

Sumner, J., Harrison, A. & Doherty, P., 2017. The effectiveness of modern cardiac rehabilitation: A systematic review of recent observational studies in non-attenders versus attenders. PLoS ONE, 12(5). Available at: http://eprints.whiterose.ac.uk/116754/ [Accessed July 6, 2019].

Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, et al. Exercise-based rehabilitation for heart failure. Cochrane Database Syst Rev 2014;4:CD003331

Taylor et al. REACH: rationale and protocol for a multicentre randomized controlled trial.BMJ Open2015;5: e009994. Doi: 10.1136/bmjopen-2015-009994

Taylor RS, Sadler S, Dalal H, Warren F, Jolly K, Davis RC, Doherty PJ, Miles J, Greaves C, Wingham J, et al 2019, 'The cost effectiveness of REACH-HF and home-based cardiac rehabilitation in the treatment of heart failure with reduced ejection fraction: a decision model-based analysis', European journal of preventive cardiology, pp. 1-10. https://doi.org/10.1177/2047487319833507

Thomas R et al. Home-Based Cardiac Rehabilitation: A Scientific Statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. J Am Coll Cardiol. 2019 May 7. pii: S0735-1097(19)33874-4. doi: 10.1016/j.jacc.2019.03.008. [Epub ahead of print]

Townsend, N. et al., 2015. Cardiovascular Disease Statistics 2014, London.

Vanhees L, Rauch B, Piepoli M, Van Buuren F, Takken T, Börjesson M, Bjarnason-Wehrens B, Doherty P, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular disease (Part III). Eur J Prev Cardiol published online 23 January 2012; DOI: 10.1177/2047487312437063http://cpr.sagepub.com/content/early/2012/01/23/2047487312437063

Valk MJ, Broekhuizen BD, Mosterd A, Zuithoff NP, Hoes AW, Rutten FH. COPD in patients with stable heart failure in the primary care setting. Int J Chron Obstruct Pulmon Dis. 2015;10:1219-24. Published 2015 Jun 26. doi:10.2147/COPD.S77085

Vanhees L, De Sutter J, Geladas N, Doyle F, Prescott E, Cornelissen V, Kouidi E, Dugmore D, Vanuzzo D, Börjesson M, **Doherty P**, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health within the general population: recommendations from the EACPR (Part I). Eur J Prev Cardiol. 2012; DOI: 10.1177/2047487312437059

Wells, G. et al., 2013. An introduction to methodological issues when including non-randomised studies in systematic reviews on the effects of interventions. Research Synthesis Methods, 4(1), pp.1–11. Available at: http://doi.wiley.com/10.1002/jrsm.1068.

Wells, G.A. et al., 2013. Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews. Research Synthesis Methods, 4(1), pp.63–77.

Wells, B. J., Chagin, K. M., Nowacki, A. S., & Kattan, M. W. (2013). Strategies for Handling Missing Data in Electronic Health Record Derived Data. *eGEMs*, *1*(3), 1035. http://doi.org/10.13063/2327-9214.1035

West, R.R., Jones, D.A. & Henderson, A.H., 2012. Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. Heart, 98(8), pp.637–644. Available at: http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2011-300302 [Accessed March 2018].

WHO, 2015. WHO Cardiovascular diseases (CVDs). Available at: http://www.who.int/mediacentre/factsheets/fs317/en/ [Accessed July 6, 2019].

Wilkins, E. et al., 2017. European Cardiovascular Disease Statistics 2017 edition. European Heart Network, Brussels, p.192.

Yohannes AM, Yalfani A, Doherty P, B.C., 2007. Predictors of drop-out from an outpatient cardiac rehabilitation programme. Clin Rehabil., 21(3), pp.222–9.

Yoshihisa A, Abe S, Kiko T, Kimishima Y, Sato Y, Watanabe S, et al. Association of Serum Zinc Level With Prognosis in Patients With Heart Failure. J Card Fail. 2018.

7. Appendices

Appendix 1: Proposal to REACH-HF for sub-study

REACH-HF sub-study request

Can routine cardiology measurements, when combined with patient demographics, better determine the exercise ability of patients with heart failure?

Submitted 29nd June 2016

Approved 22nd July 2016 by the REACH-HF Steering Group

Dr Rashed Hossain

MD Supervisors:

Professor P Doherty (Health Sciences, University of York)

Dr S Gupta (Consultant, York NHS Trusts)

Proposed writing group for sub-study paper:

Hossain, Doherty, Gupta Dalal, Taylor et al on behalf of REACH-HF

Abstract:

Introduction and aims: Too few patients with heart failure access cardiac rehabilitations (CR) services which are proved to benefit in terms of QoL, fitness and reduced hospital admissions. One of the routine clinical measures used to assess heart function namely left ventricular ejection fraction (LVEF) traditionally been used as a determinant of patient risk and patient exercise ability by clinicians and CR programmes. In isolation LVEF and exercise ability are poorly correlated yet clinical decisions about referral are still influenced by the presumed relationship. This study seeks to (1) evaluate the ability of LVEF to determine exercise ability in patients with heart failure and (2) investigate if the ability of LVEF to determine exercise ability is improved when combined with additional patient demographics.

Method: Anonymised data from the four REACH-HF study sites will be used investigate the ability of LVEF and patient demographics in determining exercise ability.

Conclusion: The findings will be published in a peer reviewed journal and will potentially improve decision, beyond that of just LVEF, in respect of making a referral to CR.

Introduction

Cardiac rehabilitation (CR) for patients with **coronary heart disease** (CHD) and those with heart failure is a clinically effective intervention that has yet to achieve optimal uptake in routine clinical practice (Anderson et al NACR 2015). The stated ambition of NHS England and that of NICE quality standard (QS99) is to improve uptake from 45% to > 65% in the next five years (CVD Outcomes, NICE CG172, NICE CG 108). Cardiologists play a fundamental role in treating and managing heart disease, especially following a heart attack, and represent, alongside cardiac nurse specialists, the primary source of referral to CR. National audit data (NACR 2015) shows that uptake to CR is at 47% for conventional CHD patients which is reasonable when compared to European rehab programmes where uptake is around 30%. The situation is very different for patients with heart failure where uptake is estimated to be less than 15% of all eligible patients. It makes sense that if most patients are not being referred then uptake will inevitably be poor. One of the reasons suggested for the lack of referral by cardiologists and GPs is that they somehow believe that patients with **low ejection fraction** are either at greater risk during exercise or are unlikely to cope with exercise.

There is a strong physiological link between cardiac output (i.e. stroke volume x heart rate) and exercise capacity in healthy populations with a similar, albeit modest relationship, found in patients with mild to moderate cardiovascular disease (CVD) (Vanhees et al 2013). The amount of blood ejected from the heart, at rest, known as left ventricular ejection fraction (LVEF), has in many respects become a clinical surrogate for cardiac function/output yet LVEF is, at best, moderately associated with exercise capacity in patients with cardiac disease. Despite the low level of evidence supporting this association LVEF is used as a fundamental part of clinical decision making when advising patients about exercise risks. Guidance from professional associations, for instance the British Association for Cardiac Rehabilitation (BACPR), has stressed the need to include a measure of exercise capacity and not just LVEF when deciding on patient risk during exercise training. The problem facing heart failure services and cardiac rehab programmes generally is that exercise capacity assessment, albeit recommended, is not routinely carried out (BACPR 2012, NACR data 2016). This study intends to investigate the relevant cardiovascular parameters including transthoracic echocardiogram (TTE) alongside the patient characteristics to better determine the ability of heart failure patients to exercise.

The relationship between LVEF and related patient characteristics in determining exercise capacity, as measured in clinical practice, has not been established in patients with heart failure. Due to the severe lack of uptake to cardiac rehab there is an urgent need to assess the ability of cardiovascular measures to determine exercise capacity. We believe our findings will improve clinical decision making, beyond that of just using LVEF, in respect of the appropriateness of referral to exercise based cardiac rehab.

1.1 Background to the study

The REACH-HF sub study forms part of an MD project that aims to capitalize on an existing NIHR funded project (REACH-HF) that has one of four arms of the trial running at York Hospital. The ***Re***habilitation En***A***blement in ***CH***ronic Heart Failure (REACH-HF) trial is part of a research programme designed to develop and evaluate a health professional facilitated, home-based, self-help rehabilitation intervention to improve self-care and health-related quality of life in people with heart failure and their caregivers. (Taylor et al. REACH: rationale and protocol for a multicentre randomized controlled trial. BMJ Open 2015).

York Hospital is one of four RCT sites running the REACH-HF trial which involves cardiology support from Dr Rashed Hossain (MD student). Key part of this role, working with Prof Doherty, is to screen heart failure patients for inclusion and collect data on cardiac metrics including LVEF, medications and heart failure status using the four NYHA categories where class I ~ breathlessness with moderate exertion to class IV ~ being breathless at rest.

This sub study aims to investigate and correlate relevant cardiovascular parameters that would enable us to better determine exercise ability of heart failure patients in contrary to the use of conventional transthoracic echocardiogram alone. Our findings will help to guide clinical decisions about the ability of patients with heart failure to take part in exercise interventions which may aid referral to cardiac rehabilitation.

1.2 Background to the disease (Heart Failure)

Heart failure (HF) is a syndrome that comprises symptoms of exertional shortness of breath, fatigue and fluid retention and becoming more prevalent worldwide. In the UK around 900,000 people have HF (BHF 2015).

Diagnosis of HF relies on clinical judgement based on a combination of history, physical examination and appropriate investigations. The symptoms and functional exercise capacity are used to classify the severity of HF, using the New York Heart Association (NYHA) classification (NYHA 1994), and to judge responsiveness to treatment. There is no single diagnostic test to identify HF but echocardiographic assessment of ejection fraction can be used as quantified objective measures for severity of the symptoms. People with HF experience marked reductions in their exercise capacity, which has detrimental effects on their activities of daily living, health-related quality of life (HRQoL), and ultimately their hospital admission rate and mortality (WGCR 2001). HF has a poor prognosis, as 30% to 40% of people diagnosed with HF die within one year but survival after HF diagnosis has improved (AHA 2014). People with HF may be categorized as having either systolic HF or diastolic HF. (NICE CG108). Systolic HF is due to impaired left ventricular contraction, which results in a reduced ejection fraction (usually <45%) and diastolic HF is due to stiffness of the ventricle wall delaying filling of the heart chamber. Although maximizing pharmacological therapies and recent advances in device implantation, mainly CRT-D or P (Cardiac resynchronization therapy with defibrillator or biventricular pacing options) have shown to improve physiological parameters and quality of life, reduce symptoms and decrease mortality and readmission rates but still HF continues to have significant negative impacts on the quality of life of patients and their families or care-givers. Despite significant advances HF remains a common cause of hospitalization, and accounts for a substantial personal and economic burden. Ongoing challenges of HF management include multiple hospital admissions causing financial costs, of up to £1 billion per year. Research has shown that the association between ejection fraction of the heart and fitness is poor (R^2 28%) meaning that other factors are influencing the relationship.

Cardiac rehabilitation (CR) is a process by which patients with heart disease, in partnership with health professionals, are encouraged and supported to achieve and maintain optimal physical health. Cardiac rehabilitation programmes have historically relied on ejection fraction as surrogate determinant of physical fitness and the assessment of risk of a cardiac event during exercise.

The Cochrane systematic review of exercise based cardiac rehabilitation in conventional CVD patients (Heran et al 2011) for HF patients (Taylor et al 2014) identified important quality of life benefits in participants, as well as reductions in HF admissions compared with usual care. 33 randomized trials in 4740 individuals with HF showed that participation in exercise-based CR was associated with a significant reduction in the risk of overall hospitalization (relative risk: 0.75; 0.62 to 0.92, p=0.005) and HF-specific hospitalization (relative risk: 0.61; 0.46 to0.80, p=0.0004) and improvements in patient health-related quality of life. Data from the NACR indicates that around 16% of those surveyed offer a specific CR programme for those with HF. (NACR 2014)

1.4 Initial literature review

The critical appraisal remains a fundamental process of evidence based practical review which aims to identify gaps in the literature in order to provide research evidence. Critical appraisal tools (CAT) are based on various types of study such as randomized controlled trials (RCT), qualitative research, systematic review, meta-analysis, nonrandomized controlled trials, case studies and outcome measures but the majority of the studies involve evaluation and investigation of intervention programs.

Rationale and methods of review

The review will focus on providing an overall review of heart failure (HF) and management. It will include a critical review of exercise tolerance testing (ETT) in patients with HF. The review will use several resources such as Pubmed, CIHANL, Medline, the Cochrane Library and Ovid databases, Science Direct and Wiley. The search period has yet to be confirmed as there is debate about only including studies in the modern era of cardiology.

A key part of my review was to take account of the most recent Cochrane review on exercise in patients with Heart failure (Taylor R et al. the Cochrane Library 2014, Issue 4). Their review involved several key search techniques such as systematic reviews (most notably the recent Cochrane review), prospective study, cross-sectional study and cohort study. Keywords are likely to include heart failure (HF), incidence, prevalence, LVEF, HF assessment (echocardiogram, electrocardiography, pharmacological, blood test), New York Heart Association (NYHA) classification, exercise testing and HADS. Their review focused on providing an overall review of exercise based rehabilitation in heart failure to determine the effectiveness of exercise-based rehabilitation on the mortality, hospitalisation admissions, morbidity and health-related quality of life for people with HF.

Key results from the Taylor et al Cochrane review of exercise in heart failure

The authors found 33 RCTs comprised of 4740 participants. Overall risk of bias was moderate in this review. Important benefits of exercise-based rehabilitation were shown on reduction in the risk of hospital admissions due to HF and improvements in health-related quality of life compared with no exercise. (RR 0.88; 95% CI 0.75 to 1.02, fixed-effect analysis) compared with control, exercise training reduced the rate of overall (RR 0.75; 95% CI 0.62 to 0.92, fixed-effect analysis) and HF specific hospitalisation (RR 0.61; 95% CI 0.46 to 0.80, fixed-effect analysis).

Sub-study method

York Hospital is one of four RCT sites running the REACH-HF trial which involves cardiology support from Dr Rashed Hossain (MD student). Key part of this role, working with Prof Doherty, is to screen heart failure patients for inclusion and collect data on cardiac function metrics including LVEF, medications and heart failure status using the four NYHA categories where class I ~ breathlessness with moderate exertion to class IV ~ being breathless at rest.

Demographics for patients from York Hospital

Mean age = 54, Male 43, Female 11

≤70 yrs (n=15), >70 yrs (n=39)

Table 1: Diagnostic origin of heart failure in York REACH-HF patients

Ischaemic in origin		27 patients			
Non-Ischaemic in origin		27 patients			
Total		54 patients			
Dilated Cardiomyopathy (DCM)	11 patients				
Atrial Fibrillation/Atrial Flutter	8 patients				
Valvular Heart Disease	2 patients				
Others	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
	CVA/PPM/AAA	AVBlock/PPM	High BM/Diastolic dysfunction	LBBB with normal coronaries	ESRF
Unknown	1 patient				

<u>Preparatory analysis:</u>

In order to gain an understanding of possible correlation trends the team at the University of York has allowed the MD student access to their NACR dataset which represents patient data at entry to conventional cardiac rehab. All data is anonymised and is only accessible from within the Department of Health Sciences using secure NACR computers and SPSS statistical software.

Table 2 shows the initial analyses based on National audit data from Coronary heart disease (CHD) patients showing how few conventional CR patients (<5%) actual perform a fitness test prior to starting CR. The table also highlights slight differences in age (~3 years) and large differences in the distanced achieved (~72 metres) using the ISWT between males and females.

Table 2. Patient characteristics and ISWT score derived from conventional CR patients (NACR 2016)

Baseline data from NACR for CHD

Gender		Age at Event	BMI.1	Waist.1	BP Systolic.1	SixMinuteWalkMetres.1
Male	Mean	64.26	28.1392	99.1932	128.90	356.24
	Std. Deviation	11.739	4.85809	12.25626	20.293	135.908
	N	100889	100889	47512	86784	4635
Female	Mean	67.80	28.0669	92.6367	130.69	283.34
	Std. Deviation	12.202	6.03318	14.47676	21.965	130.661
	N	37163	37163	13952	31723	1839
Total	Mean	65.21	28.1197	97.7049	129.37	335.44
	Std. Deviation	11.970	5.20082	13.08698	20.768	138.394
	N	138299	138299	61555	118703	6488

<u>Initial findings from the NACR data:</u>

An analysis using national audit data for patients with CHD has found that age predicts 20% of fitness as measured by ISWT scores.

Psychosocial measures (HADS) predict less than 1% of fitness

Large gender differences, independent of age differences, existed in ISWT scores at baseline.

Preliminary analysis from REACH-HF data

The following analysis used a small sample of REACH-HF data based on patients from York Hospital. Figure 1 shows that when considered in isolation LVEF failed to explain even 1% of exercise capacity as measured using the ISWT.

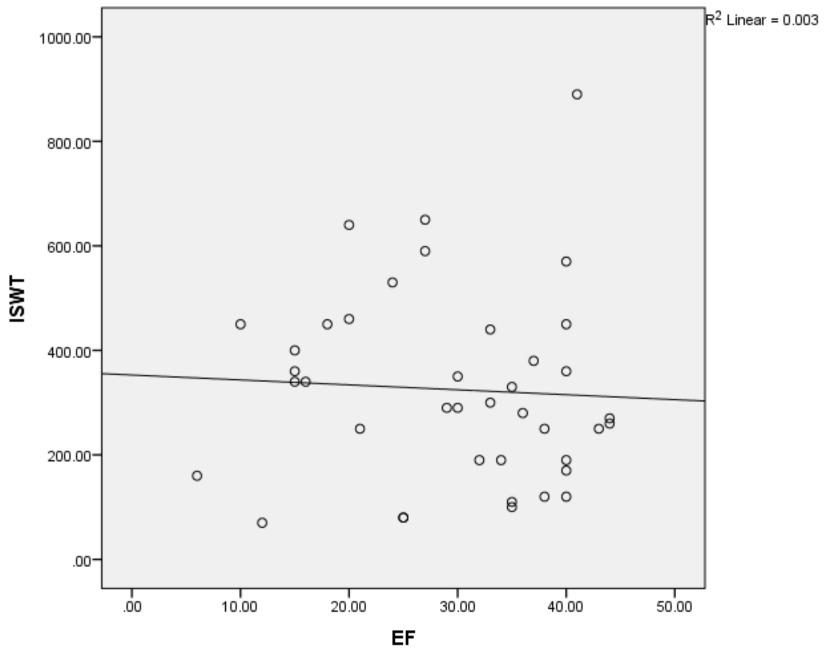

Figure 1. Relationship between LVEF (EF) and ISWT score in heart failure patients

The proposed sub study will use the full REACH-HF data to define the extent of this association in HF generally and then in non-IHD and non-IHD patients where this relationship has not been investigated. Our future analysis will also combine various baseline demographics with LVEF to investigate the ability to exercise capacity and help inform exercise prescription. To do this effectively the sample size will need to increase hence the request for additional REACH-HF patients. All data sought (table 3) will be anonymised by the REACH-HF trials unit before sending to Prof Doherty and Dr Hossain.

Table 3: Data requested to enable the analysis include:

	Baseline data
Demographics	Age, gender, BMI & smoking status
Medical history	NYHA class, Hypertension, diabetes, CAD, previous MI or angina, AF, valvular heart disease, cardiac devices
Co-morbidity	Charlson index score
HADS questionnaire (psychosocial)	Anxiety and depression scores
MLHFQ	
Pro-BNP level (biomarker)	
Incremental shuttle walk test (fitness)	Test 1 and 2: distance walked, peak HR, RPE
Accelerometry (physical activity status)	**Absolute values and categories**
Left ventricular Ejection fraction (LVEF)	
Pulse rate Blood pressure at baseline ISWT visit	
Current Medications	E.g. Beta-blocker, ACE, ARBs, loop diuretics, aldosterone receptor antagonists

<u>Next steps:</u>

- Await data from REACH-HF (1 month from approval of request) in either an excel or SPSS format
- Complete analysis by end of Sept 2016
- Draft initial paper and circulate to REACH-HF authors by end of Nov 2016
- Submit a peer reviewed paper Jan 2017 with relevant authors from the REACH HF team (journal to be decided between Heart, EJCP or IJC). These dates are subject to the main REACH-HF trial data publication date as no papers using REACH-HF data will be published before REACH-HF main paper is accepted.

REACH-HF sub-study proposal references:

1. Vanhees L, Rauch B, Piepoli M, Van Buuren F, Takken T, Börjesson M, Bjarnason-Wehrens B, **Doherty P**, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular disease (Part III). Eur J Prev Cardiol, 2012 Dec;19(6):1333-56.
2. Vanhees L, De Sutter J, Geladas N, Doyle F, Prescott E, Cornelissen V, Kouidi E, Dugmore D, Vanuzzo D, Börjesson M, **Doherty P**, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health within the general population: recommendations from the EACPR (Part I). Eur J Prev Cardiol. 2012; DOI: 10.1177/2047487312437059http://cpr.sagepub.com/content/early/2012/01/23/2047487312437059
3. British Association for Cardiovascular Prevention and Rehabilitation. BACPR standards and core components for cardiovascular disease prevention and rehabilitation 2012 . 2nd ed. UKBACPR, 2012. www.bacpr.com/resources/46C_BACPR_Standards_and_Core_Components_2012.pdf
4. Piepoli M, Corrà U, Adamopoulos S, Benzer W, Bjarnason B, Cupples M, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery. Eur J Prev Cardiol 2014; 21:664-81.
5. Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease. J Am Coll Cardiol 2016; 67(1): 1-12
6. The National Audit of Cardiac Rehabilitation: annual statistical report 2015. British Heart Foundation. http://www.cardiacrehabilitation.org.uk/docs/BHF_NACR_Report_2015.pdf
7. National Institute for Health and Care Excellence. Secondary prevention in primary and secondary care for patients following a myocardial infarction (clinical guidance 172). NICE, 2013. www.nice.org.uk/guidance/cg172
8. National Institute for Health and Care Excellence. Management of chronic heart failure in adults in primary and secondary care ((clinical guidance 108). NICE, 2010. www.nice.org.uk/guidance/cg108
9. Dalal H, Doherty P, Taylor R. Clinical Review: Cardiac Rehabilitation. BMJ 2015;351:h5000 doi: 10.1136/bmj.h5000
10. Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, et al. Exercise-based rehabilitation for heart failure. Cochrane Database Syst Rev 2014;4:CD003331
11. Taylor et al. REACH-HF: rationale and protocol for a multicentre randomized controlled trial. BMJ Open2015;5: e009994. Doi: 10.1136/bmjopen-2015-009994
12. Ponikowski P, Anker SD, Al Habib KF, et al. Heart failure: preventing disease and death worldwide.ESC Heart Fail2014;1:4–25.
13. Dickstein K, Cohen-Solal A, Filippatos G,et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008:the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail2008; 10:933–89
14. Bartholomew LK, Parcel GS, Kok G,et al. Planning health promotion programs: an intervention mapping approach. 3rd edn.USA: Jossey-Bass, 2011.
15. Rector T et al. Patients' self-assessment of their congestive heart failure. Part 2: content, reliability and validity of anew measure, the Minnesota Living with Heart Failure questionnaire. Heart Fail1987; 3:198–209
16. Pulz C, Diniz RV, Alves AN,et al. Incremental shuttle and six-minute walking tests in the assessment of functional capacity in chronic heart failure. Can J Cardiol2008; 24:131–5
17. Oldridge N, Hofer S, McGee H, et al. The HeartQoL: part II. Validation of a new core health-related quality of life questionnaire for patients with ischemic heart disease. Eur J Prev Cardiol2014; 21:98-106
18. McKelvie RS. Heart failure. BMJ Clin Evid 2011;2011:pii: 0204.
19. Davies EJ, Moxham T, Rees K, et al. Exercise based rehabilitation for heart failure. Cochrane Database Syst Rev 2010; 14:CD003331.
20. Van Hout B, Janssen MF, Feng YS,et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health2012;15:708–15.

End of REACH-HF sub-study proposal

Appendix 2: Search strategy one: Date of search: 22nd November 2016

Search strategies

MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

via Ovid http://ovidsp.ovid.com/

1946 to Present

Record retrieved: 3465

1 exp Heart Failure/ (108062)

2 exp myocardial ischemia/ (408815)

3 exp Ventricular Dysfunction/ (33207)

4 ((heart or cardiac or myocard$) adj2 failure).ti,ab. (151841)

5 HFNEF.ti,ab. (141)

6 (HFPEF or HF-PEF).ti,ab. (1123)

7 Diastolic HF.ti,ab. (154)

8 DHF.ti,ab. (1880)

9 ((myocard$ or cardiac or heart) adj2 infarct$).ti,ab. (179020)

10 heart attack$.ti,ab. (5310)

11 ((cardiac or heart or myocard$) adj2 arrest$).ti,ab. (28805)

12 ((myocard$ or cardiac or heart) adj2 isch?emi$).ti,ab. (77681)

13 ventricular dysfunction$.ti,ab. (15219)

14 or/1-13 (665781)

15 Physical Fitness/ (26751)

16 Exercise Test/ (59425)

17 Exercise Tolerance/ (10695)

18 exp Accelerometry/ (5488)

19 fitness.ti,ab. (59763)

20 physically fit.ti,ab. (521)

21 physical activity status.ti,ab. (278)

22 ((exercise or fitness) adj2 test$).ti,ab. (29807)

23 (exercise adj2 (capacit$ or capabilit$ or abilit$ or tolerance)).ti,ab. (18903)

24 ((step or treadmill or tread mill or bicycle) adj2 test$).ti,ab. (11727)

25 (acceleromet$ or actigraph$ or actimetry).ti,ab. (15455)

26 or/15-25 (170742)

27 14 and 26 (32109)

28 predict$.ti,ab. (1308794)

29 determinant$.ti,ab. (216929)

30 covariat$.ti,ab. (55718)

31 risk factor$.ti,ab. (484679)

32 exp Regression Analysis/ (391042)

33 multivariate analysis/ (114037)

34 regression.ti,ab. (580933)

35 28 or 29 or 30 or 31 or 32 or 33 or 34 (2419672)

36 27 and 35 (8422)

37 Stroke Volume/ (36070)

38 Cardiac Output/ (40923)

39 ((stroke or ventricular) adj2 volume$).ti,ab. (23680)

40 (ejection adj2 fraction$).ti,ab. (54910)

41 ((cardiac or heart) adj2 output$).ti,ab. (43655)

42 exp Echocardiography/ (120427)

43 (echocardiograph$ or echo cardiograph$).ti,ab. (121099)

44 37 or 38 or 39 or 40 or 41 or 42 or 43 (273948)

45 27 and 44 (10131)

46 36 or 45 (15350)

47 limit 46 to english language (13206)

48 limit 47 to yr="2010 -Current" (3465)

Embase

via Ovid http://ovidsp.ovid.com/

1974 to 2016 November 21

Date of search: 22nd November 2016

Records retrieved: 6922

1 exp *heart failure/ (189461)

2 exp *ischemic heart disease/ (316854)

3 ((heart or cardiac or myocard$) adj2 failure).ti,ab. (218848)

4 HFNEF.ti,ab. (320)

5 (HFPEF or HF-PEF).ti,ab. (2657)

6 Diastolic HF.ti,ab. (281)

7 DHF.ti,ab. (2684)

8 ((myocard$ or cardiac or heart) adj2 infarct$).ti,ab. (234801)

9 heart attack$.ti,ab. (6370)

10 ((cardiac or heart or myocard$) adj2 arrest$).ti,ab. (40028)

11 ((myocard$ or cardiac or heart) adj2 isch?emi$).ti,ab. (98534)

12 ventricular dysfunction$.ti,ab. (20988)

13 or/1-12 (718276)

14 fitness/ (44717)

15 exp exercise test/ (57793)

16 treadmill test/ (1344)

17 exercise tolerance/ (14555)

18 accelerometry/ (4456)

19 accelerometer/ (8619)

20 actimetry/ (6277)

21 fitness.ti,ab. (58956)

22 physically fit.ti,ab. (638)

23 physical activity status.ti,ab. (365)

24 ((exercise or fitness) adj2 test$).ti,ab. (38559)

25 (exercise adj2 (capacit$ or capabilit$ or abilit$ or tolerance)).ti,ab. (26694)

26 ((step or treadmill or tread mill or bicycle) adj2 test$).ti,ab. (14667)

27 (acceleromet$ or actigraph$ or actimetry).ti,ab. (18107)

28 or/14-27 (183323)

29 13 and 28 (30689)

30 predict$.ti,ab. (1534417)

31 determinant$.ti,ab. (227837)

32 covariat$.ti,ab. (66962)

33 risk factor$.ti,ab. (627487)

34 exp regression analysis/ (516315)

35 exp multivariate analysis/ (472704)

36 regression.ti,ab. (722324)

37 30 or 31 or 32 or 33 or 34 or 35 or 36 (2865807)

38 29 and 37 (8907)

39 heart stroke volume/ (22788)

40 heart output/ (58778)

41 heart ejection fraction/ (53801)

42 ((stroke or ventricular) adj2 volume$).ti,ab. (31004)

43 (ejection adj2 fraction$).ti,ab. (91587)

44 ((cardiac or heart) adj2 output$).ti,ab. (53185)

45 exp echocardiography/ (267584)

46 echocardiograph/ (1658)

47 (echocardiograph$ or echo cardiograph$).ti,ab. (179687)

48 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 (429732)

49 29 and 48 (11130)

50 38 or 49 (16251)

51 limit 50 to english language (14392)

52 limit 51 to yr="2010 -Current" (6922)

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Issue 10 of 12, Oct 2016

Date of search: 22nd November 2016

Records retrieved: 737

#1 MeSH descriptor: [Heart Failure] explode all trees 6613

#2 MeSH descriptor: [Myocardial Ischemia] explode all trees 23987

#3 MeSH descriptor: [Ventricular Dysfunction] explode all trees 2060

#4 ((heart or cardiac or myocard*) near/2 failure):ti,ab,kw 16002

#5 HFNEF:ti,ab,kw 13

#6 (HFPEF or HF-PEF):ti,ab,kw 166

#7 (diastolic next HF):ti,ab,kw 12

#8 DHF:ti,ab,kw 65

#9 ((myocard* or cardiac or heart) near/2 infarct*):ti,ab,kw 21286

#10 (heart next attack*):ti,ab,kw 548

#11 ((cardiac or heart or myocard*) near/2 arrest*):ti,ab,kw 2719

#12 ((myocard* or cardiac or heart) near/2 (ischemi* or ischaemi*)):ti,ab,kw 7748

#13 (ventricular next dysfunction*):ti,ab,kw 2771

#14 2-#13 51186

#15 MeSH descriptor: [Physical Fitness] this term only 2525

#16 MeSH descriptor: [Exercise Test] this term only 7264

#17 MeSH descriptor: [Exercise Tolerance] this term only 2026

#18 MeSH descriptor: [Accelerometry] explode all trees 413

#19 fitness:ti,ab,kw 5564

#20 physically next fit:ti,ab,kw 54

#21 physical next activity next status:ti,ab,kw 16

#22 ((exercise or fitness) near/2 test*):ti,ab,kw 11413

#23 (exercise near/2 (capacit* or capabilit* or abilit* or tolerance)):ti,ab,kw 6274

#24 ((step or treadmill or tread next mill or bicycle) near/2 test*):ti,ab,kw 2290

#25 (acceleromet* or actigraph* or actimetry):ti,ab,kw 2130

#26 3-#25 21590

#27 #14 and #26 5182

#28 predict*:ti,ab,kw 57489

#29 determinant*:ti,ab,kw 4835

#30 covariat*:ti,ab,kw 4804

#31 risk next factor*:ti,ab,kw 41830

#32 MeSH descriptor: [Regression Analysis] explode all trees 17818

#33 MeSH descriptor: [Multivariate Analysis] this term only 5147

#34 regression:ti,ab,kw 34553

#35 4-#34 127099

#36 #27 and #35 926

#37 MeSH descriptor: [Stroke Volume] this term only 3049

#38 MeSH descriptor: [Cardiac Output] this term only 1712

#39 ((stroke or ventricular) near/2 volume*):ti,ab,kw 4923

#40 (ejection near/2 fraction*):ti,ab,kw 8111

#41 ((cardiac or heart) near/2 output*):ti,ab,kw 4598

#42 MeSH descriptor: [Echocardiography] explode all trees 3876

#43 (echocardiograph* or echo next cardiograph*):ti,ab,kw 8305

#44 5-#43 18721

#45 #27 and #44 1797

#46 #36 or #45 2355

#47 #36 or #45 Publication Year from 2010 to 2016 762

Cochrane Database of Systematic Reviews (CDSR) via Wiley http://onlinelibrary.wiley.com/

Issue 11 of 12, November 2016

Date of search: 22nd November 2016

Records retrieved: 6

See above under CENTRAL for search strategy used.

Database of Abstracts of Reviews of Effects (DARE)

via Wiley http://onlinelibrary.wiley.com/

Issue 2 of 4, April 2015

Date of search: 22nd November 2016

Records retrieved: 13

See above under CENTRAL for search strategy used.

Health Technology Assessment database (HTA)

via Wiley http://onlinelibrary.wiley.com/

Issue 4 of 4, October 2016

Date of search: 22nd November 2016

Records retrieved: 1 See above under CENTRAL for search strategy used.

The search found 11,144 papers from all of the databases which reduced to 7,810 after taking out the duplicates.

Appendix 3: Search strategy two: Date of search: May 2019

MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

via Ovid http://ovidsp.ovid.com/

1946 to May 2019

Record retrieved: 1768

1 exp Heart Failure/ (106178)

2 (heart adj2 failure$).ti,ab. (141063)

3 1 or 2 (176432)

4 Physical Fitness/ (25319)

5 Exercise Test/ (58144)

6 Exercise Tolerance/ (10689)

7 exp Accelerometry/ (5992)

8 fitness.ti,ab. (59849)

9 physically fit.ti,ab. (514)

10 physical activity status.ti,ab. (287)

11 ((exercise or fitness) adj2 test$).ti,ab. (29876)

12 (exercise adj2 (capacit$ or capabilit$ or abilit$ or tolerance)).ti,ab. (19016)

13 ((step or treadmill or tread mill or bicycle) adj2 test$).ti,ab. (11566)

14 (acceleromet$ or actigraph$ or actimetry).ti,ab. (15767)

15 or/4-14 (169600)

16 3 and 15 (8269)

17 predict$.ti,ab. (1309282)

18 determinant$.ti,ab. (205575)

19 exp Regression Analysis/ (376429)

20 regression.ti,ab. (588635)

21 or/17-20 (2031103)

22 16 and 21 (2235)

23 (ejection adj2 fraction$).ti,ab. (56046)

24 exp Echocardiography/ (121385)

25 (echocardiograph$ or echo cardiograph$).ti,ab. (122739)

26 or/23-25 (205173)

27 16 and 26 (3575)

28 22 or 27 (4619)

29 limit 28 to english language (4207)

30 limit 29 to yr="2010 -Current" (1768)

Embase

via Ovid http://ovidsp.ovid.com/

1974 to 2019 May

Records retrieved: 5248

1 exp *heart failure/ (190448)

2 (heart adj2 failure).ti,ab. (226047)

3 1 or 2 (307222)

4 fitness/ (35846)

5 exp exercise test/ (74045)

6 treadmill test/ (1577)

7 exercise tolerance/ (14903)

8 accelerometry/ (5036)

9 accelerometer/ (8390)

10 actimetry/ (7053)

11 fitness.ti,ab. (66636)

12 physically fit.ti,ab. (702)

13 physical activity status.ti,ab. (416)

14 ((exercise or fitness) adj2 test$).ti,ab. (41532)

15 (exercise adj2 (capacit$ or capabilit$ or abilit$ or tolerance)).ti,ab. (29184)

16 ((step or treadmill or tread mill or bicycle) adj2 test$).ti,ab. (15671)

17 (acceleromet$ or actigraph$ or actimetry).ti,ab. (21702)

18 or/4-17 (211313)

19 3 and 18 (13816)

20 predict$.ti,ab. (1713695)

21 determinant$.ti,ab. (245871)

22 exp regression analysis/ (391124)

23 regression.ti,ab. (827276)

24 or/20-23 (2506117)

25 19 and 24 (3886)

26 heart ejection fraction/ (49837)

27 (ejection adj2 fraction$).ti,ab. (102013)

28 exp echocardiography/ (285366)

29 echocardiograph/ (1896)

30 (echocardiograph$ or echo cardiograph$).ti,ab. (195106)

31 or/26-30 (382896)

32 19 and 31 (6911)

33 25 or 32 (8544)

34 limit 33 to english language (8045)

35 limit 34 to yr="2010 -Current" (5248)

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Issue 2 of 12, May 2019

Records retrieved: 610

#1 MeSH descriptor: [Heart Failure] explode all trees 7188

#2 (heart near/2 failure*):ti,ab,kw 19197

#3 #1 or #2 19208

#4 MeSH descriptor: [Physical Fitness] this term only 2775

#5 MeSH descriptor: [Exercise Test] this term only 7844

#6 MeSH descriptor: [Exercise Tolerance] this term only 2304

#7 MeSH descriptor: [Accelerometry] explode all trees 621

#8 fitness:ti,ab,kw 6626

#9 physically next fit:ti,ab,kw 73

#10 physical next activity next status:ti,ab,kw 30

#11 ((exercise or fitness) near/2 test*):ti,ab,kw 12763

#12 (exercise near/2 (capacit* or capabilit* or abilit* or tolerance)):ti,ab,kw 7259

#13 ((step or treadmill or tread next mill or bicycle) near/2 test*):ti,ab,kw 2522

#14 (acceleromet* or actigraph* or actimetry):ti,ab,kw 2938

#15 6-#14 25169

#16 #3 and #15 2216

#17 predict*:ti,ab,kw 73207

#18 determinant*:ti,ab,kw 5858

#19 MeSH descriptor: [Regression Analysis] explode all trees 19278

#20 regression:ti,ab,kw 45955

#21 #17 or #18 or #19 or #20 117212

#22 #16 and #21 314

#23 (ejection near/2 fraction*):ti,ab,kw 9934

#24 MeSH descriptor: [Echocardiography] explode all trees 4189

#25 (echocardiograph* or echo next cardiograph*):ti,ab,kw 9894

#26 #23 or #24 or #25 16901

#27 #16 and #26 1241

#28 #22 or #27 1364

#29	#22 or #27 Publication Year from 2010 to 2016	618

Cochrane Database of Systematic Reviews (CDSR)

https://www.cochranelibrary.com/search

Issue 7, May 2019

Records retrieved: 4

See above under CENTRAL for search strategy used.

Database of Abstracts of Reviews of Effects (DARE)

via Wiley http://onlinelibrary.wiley.com/

The search of DARE was not updated as the database is now closed.

Health Technology Assessment database (HTA)

via CRD Databases https://www.crd.york.ac.uk/CRDWeb/

Date of search: May 2019

Records retrieved: 0

Line	Search	Hits
1	MeSH DESCRIPTOR heart failure EXPLODE ALL TREES IN HTA	148
2	(heart ADJ2 failure*) OR (failure* ADJ2 heart) IN HTA	290
3	#1 OR #2	290
4	MeSH DESCRIPTOR Physical Fitness IN HTA	9
5	MeSH DESCRIPTOR Exercise Test IN HTA	6
6	MeSH DESCRIPTOR Exercise Tolerance IN HTA	3
7	MeSH DESCRIPTOR Accelerometry EXPLODE ALL TREES IN HTA	2
8	(fitness) IN HTA	28
9	(physically fit) IN HTA	0

10 (physical activity status) IN HTA 0

11 ((exercise or fitness) ADJ2 test*) OR (test* ADJ2 (exercise or fitness)) IN HTA 16

12 (exercise ADJ2 (capacit* or capabilit* or abilit* or tolerance)) OR ((capacit* or capabilit* or abilit* or tolerance) ADJ2 exercise) IN HTA 38

13 ((step or treadmill or tread mill or bicycle) ADJ2 test*) OR (test* ADJ2 (step or treadmill or tread mill or bicycle)) IN HTA 4

14 (acceleromet* or actigraph* or actimetry) IN HTA 7

15 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 89

16 #3 AND #15 5

17 (predict*) IN HTA 718

18 (determinant*) IN HTA 62

19 MeSH DESCRIPTOR Regression Analysis EXPLODE ALL TREES IN HTA 10

20 (regression) IN HTA 53

21 #17 OR #18 OR #19 OR #20 821

22 #16 AND #21 1

23 (ejection ADJ2 fraction*) OR (fraction* ADJ2 ejection) IN HTA 41

24 MeSH DESCRIPTOR Echocardiography EXPLODE ALL TREES IN HTA 20

25 (echocardiograph* or echo cardiograph*) IN HTA 55

26 #23 OR #24 OR #25 94

27 #16 AND #26 1

28 #22 OR #27 2

29 (*) IN HTA FROM 2010 TO 2018 7402

30 #28 AND #29 0

Appendix 4. NACR dataset used in study one: determinants of fitness in HF

NACR DATASET - RECORD FORM

Gender:	☐Not Known	☐Male
☐Female	☐Not specified	
Marital Status:	☐Single	☐Married
☐Permanent Partnership	☐Divorced	☐Widowed
☐Separated	☐Unknown	
Ethnic Group:		
☐British	☐Irish	☐White (other)
☐White/Black Caribb	☐White/Black African	☐White/Asian
☐Any other mixed	☐Indian	☐Pakistani
☐Bangladeshi	☐Other Asian	☐Black Caribbean
☐African	☐Black Other	☐Chinese
☐Other Ethnic Group	☐Not Stated	☐Not Known
Did you measure Patient Satisfaction? ☐Yes ☐ No		

Initiating Event Record

Initiating Event (IE)	☐MI Unknown	☐MI Stemi
☐MI (NStemi)	☐MI with Heart Failure	☐Angina
☐Unstable Angina	☐Heart Failure	☐Valve Disease
☐CHD	☐Arrhythmia	☐Cardiac Arrest
☐Cardiomyopathy	☐Congenital Heart	☐High Risk
☐Prehab	☐Other	☐Use Treatment
☐Peripheral Arterial Disease	☐Unknown	**IE Date:**
Ankle Brachial Indice Ratio (assoc. with PAD)		
Treatment associated with IE	☐PCI	☐PPCI
☐CABG	☐Mitral Valve Repair/Replace	☐Aortic Valve Repair/Replace
☐Tricuspid Repair/Replace	☐Medical Management	☐Pacemaker
☐Transplant	☐LV Assist Device	☐ICD
☐Staged PCI	☐TAVI	☐Other Surgery
☐Other		

Treatment Date:	Discharge Date:	Invited to Join Date:

Source of Referral: ☐BMI Hospital ☐Private Hospital ☐GP ☐NHS Trust

Referring Trust (Initiating Event):

Referred by: ☐Consultant ☐Cardiac Nurse ☐GP ☐PC Nurse ☐Other

Risk Ass ☐Low	☐Medium	☐High
Acute Events During Rehab	☐ MI	☐ Bypass Surgery
☐ Angioplasty/PCI	☐ Cardiac Arrest	☐ Angina
☐ Other Surgery	☐ Heart Failure ☐ Congenital Heart	☐ Pacemaker
☐ ICD	☐ Other	☐ Transplant
☐LV Assist Device	☐ Period Acute Non Card Illness	☐ Readmission CHD
☐ Readmission other cause		☐ Unknown
Previous Events	☐MI	☐Cardiac Arrest
☐Pacemaker	☐LV Assist Device	☐ Angina
☐ ICD	☐ Bypass Surgery ☐ Angioplasty/PCI	☐ Other Surgery
☐ Congenital Heart	☐ Other	☐ Heart Failure
☐ Transplant	☐Unknown	☐No/None
☐ Arrhythmia		

Comorbidity	☐Angina	☐Arthritis (Osteo)
☐Cancer	☐Diabetes	☐Rheumatism
☐Stroke	☐Osteoporosis	☐Hypertension
☐Chronic Bronchitis (COPD)	☐Emphysema (COPD)	☐Asthma
☐Claudication	☐Chronic Back Problems	☐Anxiety
☐Depression	☐Family History	☐Erectile Dysfunction
☐Hypercholesterolaemia/Dislipidaemia	☐No/None	☐Other Comorbid

Rehabilitation Record

CARDIAC REHAB COMMISSIONING PACK or PHASES			
Phase 1	**Phase 2**	**Phase 3**	**Phase 4**
Referred Date	**Referred Date**	**Referred Date**	**Referred Date**
Date Started	**Date Started**	**Date Started**	**Date Started**
Date Complete	**Date Complete**	**Date Complete**	**Date Complete**
Reason Not Taking Part: phase one ☐Not Interest/Refused ☐Ongoing Investigation ☐Physical Incapacity ☐Returned to work ☐Local Exclus Criteria ☐Language Barrier ☐Holidaymaker ☐Mental Incapacity ☐No transport ☐Died ☐Not Referred ☐Too Ill ☐Rehab Not Needed ☐Rehab Not Appropriate ☐Staff Not Available ☐Rapid transfer/tertiary ☐DNA/No Contact ☐Patient Req transfer ☐No Service Available ☐Transfer for PCI Interv ☐Transfer to DGH/Trust ☐Other ☐Unknown	**Reason Not Taking Part: Phase two** ☐Not Interest/Refused ☐Ongoing Investigation ☐Physical Incapacity ☐Returned to work ☐Local Exclus Criteria ☐Language Barrier ☐Holidaymaker ☐Mental Incapacity ☐No transport ☐Died ☐Not Referred ☐Too Ill ☐Rehab Not Needed ☐Rehab Not Appropriate ☐Staff Not Available ☐Rapid transfer/tertiary ☐DNA/No Contact ☐Patient Req transfer ☐No Service Available ☐Transfer for PCI Interv ☐ Transfer to DGH/Trust ☐Other ☐Unknown	**Reason Not Taking Part: Phase three** ☐Not Interest/Refused ☐Ongoing Investigation ☐Physical Incapacity ☐Returned to work ☐Local Exclus Criteria ☐Language Barrier ☐Holidaymaker ☐Mental Incapacity ☐No transport ☐Died ☐Not Referred ☐Too Ill ☐Rehab Not Needed ☐Rehab Not Appropriate ☐Staff Not Available ☐Rapid transfer/tertiary ☐DNA/No Contact ☐Patient Req transfer ☐No Service Available ☐Transfer for PCI Interv ☐ Transfer to DGH/Trust ☐Other ☐Unknown	**Reason Not Taking Part: Phase four** ☐Not Interest/Refused ☐Ongoing Investigation ☐Physical Incapacity ☐Returned to work ☐Local Exclus Criteria ☐Language Barrier ☐Holidaymaker ☐Mental Incapacity ☐No transport ☐Died ☐Not Referred ☐Too Ill ☐Rehab Not Needed ☐Rehab Not Appropriate ☐Staff Not Available ☐Rapid transfer/tertiary ☐DNA/No Contact ☐Patient Req transfer ☐No Service Available
Reason Not Completing: ☐DNA/Unknown Reason ☐Returned to work ☐Left this area ☐Planned/Emergency Intervention ☐Too Ill	**Reason Not Completing:** ☐DNA/Unknown Reason ☐Returned to work ☐Left this area ☐Planned/Emergency Intervention ☐Too Ill	**Reason Not Completing:** ☐DNA/Unknown Reason ☐Returned to work ☐Left this area ☐Planned/Emergency Intervention ☐Too Ill	**Reason Not Completing:** ☐DNA/Unknown Reason ☐Returned to work ☐Left this area ☐ Planned/Emergency Intervention

☐Died ☐Other ☐Hospital Readmission ☐Unknown	☐Died ☐Other ☐Hospital Readmission ☐Unknown	☐Died ☐Other ☐Hospital Readmission ☐Unknown	☐Too Ill ☐Died ☐Other
Rehab Delivery: ☐Group Based ☐Home Based ☐Web Based ☐Home Visit ☐ Tel Call &/or Self Mgt ☐Ward ☐Clinical ☐Face to Face ☐Other	**Rehab Delivery:** ☐Group Based ☐Home Based ☐Web Based ☐Home Visit ☐ Tel Call &/or Self Mgt ☐Ward ☐Clinical ☐Face to Face ☐Other	**Rehab Delivery:** ☐Group Based ☐Home Based ☐Web Based ☐Home Visit ☐ Tel Call &/or Self Mgt ☐Ward ☐Clinical ☐Face to Face ☐Other	**Rehab Delivery:** ☐Group Based ☐Home Based ☐Web Based ☐Home Visit ☐ Tel Call &/or Self Mgt ☐Ward ☐Clinical ☐Face to Face ☐Other
Onward Referral: ☐Hospital Programme ☐Comm Based Prog ☐Ph 4 Exercise Prog ☐Patient Support Group ☐ Medical Spec/Treat ☐Sexual Health Clinic ☐ GP (Med Treatment) ☐ Prim Care CHD Clinic ☐Community Matron ☐Specialist Nurse ☐Clinical Psychology ☐Counselling Service ☐IAPT ☐Voc/Welf/Ben/CAB ☐Council Activity ☐Social Services ☐Voluntary Body ☐Smoking Cessation ☐Home Based ☐Dietitian	**Onward Referral:** ☐Hospital Programme ☐Comm Based Prog ☐Ph 4 Exercise Prog ☐Patient Support Group ☐ Medical Spec/Treat ☐Sexual Health Clinic ☐ GP (Med Treatment) ☐ Prim Care CHD Clinic ☐Community Matron ☐Specialist Nurse ☐Clinical Psychology ☐Counselling Service ☐IAPT ☐Voc/Welf/Ben/CAB ☐Council Activity ☐Social Services ☐Voluntary Body ☐Smoking Cessation ☐Home Based ☐Dietitian	**Onward Referral:** ☐Hospital Programme ☐Comm Based Prog ☐Ph 4 Exercise Prog ☐Patient Support Group ☐ Medical Spec/Treat ☐Sexual Health Clinic ☐ GP (Med Treatment) ☐ Prim Care CHD Clinic ☐Community Matron ☐Specialist Nurse ☐Clinical Psychology ☐Counselling Service ☐IAPT ☐Voc/Welf/Ben/CAB ☐Council Activity ☐Social Services ☐Voluntary Body ☐Smoking Cessation ☐Home Based ☐Dietitian	**Onward Referral:** ☐Hospital Programme ☐Comm Based Prog ☐Ph 4 Exercise Prog ☐Patient Support Group ☐ Medical Spec/Treat ☐Sexual Health Clinic ☐ GP (Med Treatment) ☐ Prim Care CHD Clinic ☐Community Matron ☐Specialist Nurse ☐Clinical Psychology ☐Counselling Service ☐IAPT ☐Voc/Welf/Ben ☐Council Activity ☐Social Services
Phase I CR Acute	**Phase II intermediate**	**Phase III core outpatients**	**Phase IV long term maintenance**

Rehab assessmen**t record**

Examinations and Tests	**Assessment Date:**	**Assessment No:**
Reason Not Sending Q'naire ☐Illiterate ☐No resources ☐Ass sent and not returned	☐Mental Incapacity ☐Language Barrier ☐Left the Area ☐Died	☐Too Ill ☐Not Interested/Refused ☐Other ☐Unable to Contact
Weight:	**Height:**	**BMI** *(auto-calc)*
Waist:	**Blood Pressure:**	
Smoked: ☐Never Smoked ☐Ex Smoker ☐Stopped since event ☐Currently Smoking	**Cholesterol:** Total HDL LDL Ratio Triglycerides	**HbA1c** Mmol/L Or %
Units of Alcohol/wk	**Canadian Angina Scale**	
TAM2: Strenuous: No.Sessions: Minutes:	**Moderate:** No.Sessions	Minutes:
Mild: No.Sessions: Minutes:		
METS **(other measures)**	**150 mins mod/wk**	**75 Mins Vigorous ex/wk**
Heart Failure (NYHA)	**Mediterranean Diet Score:**	
6 min walk:	Metres	Minutes
Shuttle Walk: Level	Sub Level	Total Metres
Quality of Life:		
Dartmouth Co-op:		
Physical Fitness	**Feelings**	**Daily Activities**
Social Activities	**Pain**	**Change in Health**
Overall Health	**Social Support**	**Quality of life**
HAD Anxiety Score	**HAD Depression Score**	
Current Employment Status	☐Employed Full Time	☐Employed Part Time
☒Self-Employed Full Time	☐Self-Employed Part Time	☐Unemploy/Looking for work
☐Govt Training Course	☐Looking after Family/Home	☐Retired

Cardiac rehab d**rugs record:**			
ACE Inhibitors ☐Captopril ☐Enalapril ☐Lisinopril ☐Perindopril ☐Ramipril ☐Trandolapril ☐Quinapril ☐Other/Not Spec	**Angiotensin receptor blockers (ARB)** ☐Candesartan ☐Losartan ☐Valsartan ☐Other/Not Specified	**Heart Rate Meds** ☐Bisoprolol ☐Carvedilol ☐Nebivolol ☐Atenolol ☐Propranolol ☐Metoprolol ☐Ivabradine ☐Other/Not Specified	**Diuretic: loop** ☐Bumetanide ☐Ethancrynic acid ☐Frusemide ☐Torasemide ☐Other/Not Spec
Diuretic: Thiazide ☐ Bendroflumethiazi ☐Metolazone ☐Other/Not Spec	**Selective aldosterone receptor antagonist (SARA) Diuretic/antihypertensive** ☐Eplerenone ☐Spironolactone ☐Other/Not Specified	**Anti-platelet** ☐Aspirin ☐Clopidogrel ☐Other/Not Specified	**Antiarrhythmics** ☐Digoxin ☐Other/Not Specified
Calcium channel blockers (CCB) ☐Amlodipine ☐Felodipine ☐Diltiazem ☐Verapamil ☐Other/Not Spec	**Therapy for Lipids (Statins)** ☐Atorvastatin ☐Pravastatin ☐Rosuvastatin ☐Simvastatin ☐Other/Not Specified	**Anticoagulant** ☐Warfarin ☐Other/Not Specified	**Vasodilators** ☐Nitrates (incl GTN Spray) ☐Other/Not Specified
Current Diabetes Therapy ☐Metformin ☐Sulphonylurea ☐Glitazone ☐Insulin ☐Other/Not Specified			

Cardiac Rehab Core Components	
Health Behaviour Change & Education	☒Individual assessment of health behaviour ☐Agreed & written treatment plan ☐Goal setting for health behaviour change for core components ☐Regular review of progress with goals
Lifestyle Risk Factor Management	☐Education about smoking ☐Individual counselling/motivational interviewing for smoking cessation ☐Individual assessment of diet needs ☐Education about healthy diet ☐Individual goal setting for dietary change ☐Referral to dietetics/weight management prog ☐Baseline assessment of activity level ☐Education about physical activity ☐Group based exercise programme ☐Individual Exercise
Psychosocial Health	☐Assessment of illness beliefs / misconceptions ☐Relaxation & stress management training ☐Referral to psychological care ☐Vocational advice ☐Financial Social Security / Benefits advice ☐ADL, aids or home adaption assessment
Medical Risk Factor Mgt	☐Regular monitoring & education of risk factors
Cardioprotective Therapies	☐Regular monitoring & education of cardioprotective therapies
Long Term Management	☐Long-term maintenance plan for goals
Audit & Evaluation	☐Final review of goals & progress
Other	☐Other