Optimising clinical and functional outcomes in older adults with chronic heart failure

A thesis submitted in fulfilment of the requirements for the degree of

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by

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Abstract

Globally, the age of patients with chronic heart failure (CHF) is increasing, which is presenting new challenges for providing exercise rehabilitation that is accessible, effective and well tolerated. This thesis explores factors affecting eligibility, referral and participation in exercise rehabilitation among older persons with CHF and investigates muscle-focused exercise modalities. This thesis consists of three exploratory studies, leading to a pilot randomised controlled trial.

The exploration of factors affecting referral to, and participation in, exercise rehabilitation among older adults was achieved by two independent studies: first, a multiple regression analysis of factors associated with referral in patients discharged from Victorian public hospitals with acute heart failure; and second, an observation of recruitment data from the PRIME-HF[1] randomised control trial, reporting eligibility, decline and recruitment rates. These two original studies found that while advancing age negatively influences participation, recruitment and engagement in exercise training among older adults is possible. Specifically, for every year of advancing age the likelihood of referral to outpatient exercise rehabilitation following an acute hospital admission with heart failure decreased by 2.5%. Furthermore, the presence of comorbidities—a common characteristics among older adults—was negatively associated with referral and participation. These studies are the first to describe factors that affect participation in outpatient exercise rehabilitation within the Australian context. In this way, they provide an understanding of current service utilisation, which will guide future service development.

The aim to investigate muscle-focused exercise modalities was based on the muscle hypothesis of CHF which theorises that changes in skeletal muscle and peripheral tissues are primarily responsible for exercise intolerance in CHF. The meta-analysis investigating the effects of resistance training in patients with CHF showed that resistance training, as a standalone intervention, can increase muscle strength (one repetition maximum standardised change score = 0.60; 95% confidence interval [CI] 0.43, 0.77), aerobic capacity (change score mean difference [CSMD]: 2.71ml/kg/min; 1.96, 3.45) and quality of life (CSMD: - 5.71; -9.85, -1.56).

[1] A full list of abbreviations is provided on page 3.

Furthermore, the PRIME-HF pilot randomised control trial showed that PRIME exercise training significantly increased VO_{2peak} after eight weeks of training (2.4 mL/kg/min; 95% CI .7-4.1; $p = .004$), which was significantly greater in comparison to the usual care (combined aerobic and resistance training) exercise control group (ES 0.6), which showed minimal change in VO_{2peak} after eight weeks of training (.2 mL/kg/min; 95% CI −1.5 to 1.8). Taken together, these findings support the hypothesis that PRIME may have potential advantages for older patients with HFrEF and could be a possible alternative exercise modality.

In conclusion, as an investigation of a real-world clinical challenge, this research has shown that age should not be a barrier to exercise training in patients with CHF. The research showed that with appropriate and routine assessment, older adults with CHF can be safely enrolled into exercise training programs and achieve important improvements in clinical and functional outcomes. This research provides high-quality, preliminary evidence supporting PRIME and resistance training as alternative exercise modalities for patients with HFrEF.

Declaration

I, Catherine Giuliano, declare that the PhD thesis entitled "Optimising clinical and functional outcomes in older adults with chronic heart failure" is no more than 80,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work.

I have conducted my research in alignment with the Australian Code for the Responsible Conduct of Research and Victoria University's Higher Degree by Research Policy and Procedures

Signature  Date: 18/05/2021

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Abbreviations

1RM	One repetition maximum
ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
ADHF	Acute decompensated heart failure
ADLs	Activities of daily living
AF	Atrial fibrillation
AHA	American Heart Association
AMI	Acute myocardial infarction
ATP	Adenosine triphosphate
ARB	Angiotensin receptor blocker
AVO_2	Arterial-venous oxygen content
CAD	Coronary artery disease
CHF	Chronic heart failure
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CVP	Central venous pressure
CR	Cardiac rehabilitation
EF	Ejection fraction
EOV	Exercise oscillatory ventilation
ESSA	Exercise and Sport Science Australia
ETC	Electron transport chain
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart Failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction

HIIT	High intensity interval training
HR	Heart rate
HTN	Hypertension
IHD	Ischaemic heart disease
LVEF	Left ventricular ejection fraction
LVEDV	Left ventricular end-diastolic volume
MCD	Muscle capillary density
MRA	Mineralocorticoid/aldosterone receptor antagonists
NTproBNP	N-terminal prohormone of brain natriuretic peptide
NYHA Class	New York Heart Association classification
O_2	Oxygen
PCWP	Pulmonary capillary wedge pressure
PRIME	Peripheral remodelling through intermittent muscular exercise
PRIME-HF	The peripheral remodelling through intermittent muscular exercise – Heart failure study
RAAS	Renin-angiotensin-aldosterone-system
RCT	Randomised controlled trial
SNS	Sympathetic nervous system
SD	Standard deviation
SV	Stroke volume
TCA	Tricarboxylic acid
VCOR	Victorian Cardiac Outcomes Registry
VE/VCO2	Minute ventilation/carbon dioxide production
VO_{2peak}	Peak aerobic capacity
VT	Ventilatory threshold
WH	Western Health

Publications, awards, grants and presentations

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Publications related to this thesis

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2. **Catherine Giuliano**, Itamar Levinger, Sara Vogrin, Christopher James Neil and Jason David Allen. PRIME-HF: Novel Exercise for Older Patients with Heart Failure. A Pilot Randomized Controlled Study. *Journal of the American Geriatrics Society* (2020) doi:10.1111/jgs.16428
3. **Catherine Giuliano,** Don Vicendese, Sara Vogrin, Rebecca Lane, Andrea Driscoll, Diem Dinh, Katie Palmer, Itamar Levinger, Christopher Alan Neil. Predictors of referral to cardiac rehabilitation in patients following hospitalisation with heart failure: A multivariate regression analysis *Under Review at Journal of Cardiopulmonary Rehabilitation and Prevention*
4. **Catherine Giuliano**, Catherine Giuliano, Christopher James Neil, Rebecca Louise Lane, Jason David Allen, Itamar Levinger. Challenges in recruiting elderly patients with heart failure to exercise rehabilitation: findings from a randomised controlled trial. *Under Review at Journal of Physiotherapy*

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6. **Catherine Giuliano,** Christopher Neil, Itamar Levinger. Letter to the editor: "The frailty syndrome is associated with adverse health outcomes in very old patients with

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Chapter 1: Introduction

1.1 Development of the problem

Chronic Heart Failure (CHF) is a complex syndrome affecting approximately 1-2% of the Western world (Mosterd and Hoes, 2007, Ohlmeier et al., 2015). Each year in Australia, there are approximately 70,000 new cases diagnosed and the annual economic burden is over $3 billion (Clark et al., 2004, Chen et al., 2017).

CHF is a dynamic, multisystem and progressive syndrome and most patients are characterised by exercise intolerance, shortness of breath and fatigue (Ponikowski et al., 2016b). The fundamental objectives of CHF therapy are to reduce symptoms, maintain or improve aerobic capacity, reduce the frequency of hospitalisations and ultimately, to prolong survival while maintaining or improving quality of life (Ponikowski et al., 2016a, Atherton et al., 2018, Yancy et al., 2017). These objectives are achieved by a multi targeted treatment approach involving pharmacotherapy, device therapy and exercise rehabilitation (Ponikowski et al., 2016a, Atherton et al., 2018, Yancy et al., 2017).

This thesis centres around two unresolved gaps in the literature: First, it is well established that older individuals are disproportionately affected by CHF and this shifting patient demographic presents a significant challenge to care provision (Ho et al., 1993b, Curtis et al., 2008, Cvetinovic et al., 2016). Despite the 'typical' age demographic of patients with CHF, older adults with CHF are underrepresented in clinical trials, often as a result of arbitrary upper age limits or other exclusion criteria unsupported by clinical guidelines (Crome et al., 2014). As a result, the external validity of current exercise guidelines for patients with CHF—which recommend combined aerobic and resistance training—is limited and it is difficult to ascertain the true eligibility and recruitment potential of older patients with CHF for exercise training, or whether they can gain benefits from exercise training.

Second, there is an accumulation of evidence supporting the "Muscle Hypothesis" of CHF, which suggests that pathological changes in peripheral tissues and in particular in skeletal muscle, contribute to exercise intolerance in CHF more so than central cardiac limitations (Piepoli and Coats, 2013). This hypothesis has provided the impetus to find treatments that mitigate these peripheral deficits. Two such treatments, resistance training and the "PRIME"

(Peripheral Remodelling through Intermittent Muscular Exercise) regime may offer potential advantages but are yet to be fully evaluated. Briefly, PRIME offers a hybrid aerobic-resistance program of low intensity and high repetitions and was designed to target the peripheral tissue dysfunctions responsible for reduced VO_{2peak} in older adults, without imposing excess cardiovascular or musculoskeletal strain (Allen et al., 2013). By focusing initially on individual muscle groups with low mass and high repetition resistance training, PRIME aims to provide a localized stimulus that is not restricted by compromised or competing perfusion.

1.2 Statement of the problem

Exercise training is an important treatment for patients with CHF, but there are limited clinical trials that involve patients with CHF who are over the age of 65 years. Anecdotal evidence suggests attendance at exercise rehabilitation among older adults is poor. Currently, little is known about factors that are associated with referral and participation in exercise rehabilitation. Furthermore, fatigue, dyspnoea and exercise intolerance in CHF are largely due to several pathological changes in skeletal muscle and peripheral tissues. While current exercise recommendations for CHF mostly centre on aerobic-based regimes, little is known about other exercise modalities which may be more effective in targeting the unique muscle pathology seen in patients with CHF.

1.3 Thesis and publication overview

This thesis with publications includes three main studies, from which two manuscripts were published and a further two are under review in peer reviewed journals.

Table 1.1: Thesis and publication overview

Thesis chapter	Publication title	Status	Publication Details
3	Predictors of referral to cardiac rehabilitation in patients following hospitalisation with heart failure: A multivariate regression analysis	Under review	Journal of Cardiopulmonary Rehabilitation and Prevention.
4	The effects of resistance training on muscle strength, quality of life and aerobic capacity in patients with chronic heart failure — A meta-analysis	Published	**Giuliano, C**., Karahalios, A., Neil, C., Allen, J., & Levinger, I. (2017). The effects of resistance training on muscle strength, quality of life and aerobic capacity in patients with chronic heart failure—A meta-analysis. *International journal of cardiology*, 227, 413-423. Scimago Rank Q1 Citations 78
5	PRIME-HF: Novel exercise for older patients with heart failure. A pilot randomized controlled study	Published	**Giuliano, C**., Levinger, I., Vogrin, S., Neil, C. J., & Allen, J. D. (2020). PRIME-HF: Novel Exercise for Older Patients with Heart Failure. A Pilot Randomized Controlled Study. *Journal of the American Geriatrics Society*, 68(9), 1954-1961 Scimago Rank Q1
6	Challenges in recruiting elderly patients with heart failure to exercise rehabilitation: findings from a randomised controlled trial	In preparation for submission	TBA

Appendix A	Cardiac rehabilitation for patients with coronary artery disease: A practical guide to enhance patient outcomes through continuity of care	Published	**Giuliano, C**, Parmenter, B.K, Baker, M.K, Mitchell, B.L, Williams, A.D, Lyndon, K, Mair, T, Maiorana, A, Smart, N.A and Levinger, I. (2017). Cardiac rehabilitation for patients with coronary artery disease: a practical guide to enhance patient outcomes through continuity of care. Clinical *Medicine Insights: Cardiology*, 11, 1179546817710028. Scimago Rank Q2 Citations 26
Appendix B	Barriers to exercise rehabilitation in the older adult with heart failure	Abstract	**Giuliano, C**., Cowie, K., Saliba, J., Scholes, E., Fisher, K., Cox, N., & Neil, C. (2015). Barriers to exercise rehabilitation in the older adult with heart failure. *Heart, Lung and Circulation*, 24, S450. Scimago Rank Q2
Appendix C	Letter to the editor: “The frailty syndrome is associated with adverse health outcomes in very old patients with stable heart failure: A prospective study in six Spanish hospitals”	Published	**Giuliano, C**., Neil, C., & Levinger, I. (2017). Letter to the Editor:" The Frailty Syndrome Is Associated With Adverse Health Outcomes in Very Old Patients With Stable Heart Failure: A Prospective Study in Six Spanish Hospitals". *International journal of cardiology*, 246, 56. Scimago Rank Q1 Citations 2

Chapter 2: Literature review

2.1 Heart failure

2.1.1 Definition

CHF is a clinical syndrome that centres on a structural or functional abnormality of the heart and results in significant clinical, functional and financial costs to individuals and the community (Cook et al., 2014, Chen et al., 2017) CHF is characterised by hallmark symptoms of fatigue, dyspnoea and exercise intolerance (Zambroski et al., 2005, Ponikowski et al., 2016b).

2.1.2 Prevalence and prognosis

Epidemiological studies and systematic reviews estimate that the prevalence of CHF is 1-2% of Western (Mosterd and Hoes, 2007, Mosterd et al., 1999) and Australian (Chen et al., 2017, Sahle et al., 2016) populations. In Australia, approximately 70,000 new cases of CHF are diagnosed each year (Clark et al., 2004, Chen et al., 2017) and it is the eighth and tenth leading cause of death in Australian females and males respectively, accounting for 2.8% and 1.9% of deaths each year (Welfare, 2014). Rates of CHF are higher among indigenous than non-indigenous Australians and in those living in rural and remote regions (Sahle et al., 2016, Clark et al., 2004). The CHF population is expected to grow, partly due to an ageing population and increasing prevalence of CHF risk factors, as well as improved post-myocardial infarction survival (Australian Institute of Health and Welfare, 2014). By 2025, the number of cases of CHF is expected to increase by 657,000 (Chen et al., 2017). In a large population-based study of 4 million people in the UK, the number of new diagnoses of CHF each year increased by 12% between 2002 and 2014; an increase which is higher than the yearly diagnosis rate of the four most common cancers combined (i.e. lung, breast, bowel and prostate) (Conrad et al., 2018).

CHF is associated with a high incidence of hospitalisations, with over 1 million bed-days occupied by patients with CHF annually (Ambrosy et al., 2014, Teng et al., 2012, Jhund et al., 2009, Welfare, 2003). In an epidemiological study of CHF in Germany, CHF-related

hospital admissions increased by 65.4% in 2000, and by 22.1% in 2013 (Christ et al., 2016). In Australian general practice, one in every 20-25 patients over the age of 45 years has CHF (Taylor et al., 2017).

The economic burden of CHF is considerable. Globally, an estimated $108 billion is spent on CHF-related health care costs each year (Cook et al., 2014), while in Australia, this amount reaches over $3.1 billion, of which over $2 million can be attributed to hospitalisations (Chen et al., 2017). Advances in CHF treatment have seen life expectancy in patients increasing, yet prognosis remains poor (Jhund et al., 2009). The Framingham Heart Study is the largest longitudinal cardiovascular cohort study in the world, which involved residents in Massachusetts, USA and found a survival rate between 57-64% at one year following diagnosis of CHF and between 25-37% at five years (Ho et al., 1993a, Levy et al., 2002). The survival rate was slightly higher in men than in women.

2.1.3 Aetiologies of CHF

CHF can develop from multiple aetiologies. In western high-income regions, the leading causes of CHF are coronary artery disease (CAD) (also known as ischaemic heart disease (IHD)), accounting for between 36-59% of CHF cases; and hypertension (HTN) (Mosterd and Hoes, 2007) (

Table **2.1**).

Table 2.1: Causes of heart failure in population-based studies

Adapted from Mosterd and Hoes (2007)

Cause of CHF	**Framingham heart study** (Levy et al., 1996)		**Hillingdon HF study** (Levy et al., 2006)	**Bromley HF study** (Fox et al., 2001)
	Men	Women		
Ischaemic, %	59	48	36	52
Hypertension, %	70	78	14	4
Valvular heart disease, %	22	31	7	10

CHF aetiologies can be categorised into three main precipitators which lead to cardiac remodelling and eventual cardiac failure: a diseased myocardium, abnormal pressure loading conditions and arrhythmias.

A ***diseased myocardium*** can result from an injury or disease to the myocardium. This is most commonly a result of CAD, which leads to acute myocardial infarction (AMI). Injury to the myocardium can also result from toxic damage caused by substance abuse, medications, or chemotherapy (Iacovelli et al., 2018, Li and Gu, 2018, Sliman et al., 2016, Markman and Markman, 2018). Auto-immune diseases or infection may also damage the myocardium (Comarmond and Cacoub, 2017) and, in the case of genetic abnormalities, the structure of the heart itself is altered from birth and cardiac function is impaired (Ponikowski et al., 2016a).

Abnormal pressure loading conditions are those which abnormally alter cardiac preload or afterload, either by pressure or volume overload (Dunlay et al., 2009, Khatibzadeh et al., 2013). Preload is defined by the end-diastolic volume at the beginning of systole and is measured by central venous pressure for the right side of the heart, and by pulmonary capillary wedge pressure for the left side (Rothe, 2003). Afterload on the other hand is defined by ventricular pressure at the end of systole (end systolic pressure) and therefore, the pressure against which the heart must pump to eject blood during systole (Rothe, 2003). Common conditions affecting preload and afterload are HTN and valvular heart disease.

Finally, ***Arrhythmias*** (i.e. tachycardias, bradycardias and loss of atrial-ventricular synchrony) can also cause CHF (Devkota et al., 2016, Ehrlich et al., 2002, Masarone et al., 2017). Tachycardiomyopathy is a type of dilated cardiomyopathy that develops in patients with prolonged tachycardia and is reversible if the underlying tachycardia can be resolved (Mohamed, 2007). Box 2.1 summarises the common aetiologies of CHF as described above.

Diseased Myocardium
Ischaemic heart disease Toxic damage (e.g. substance abuse, medications, radiation, chemotherapy) Immune-mediated inflammatory damage (e.g. infection, autoimmune diseases) Malignant and non-malignant infiltration (e.g. sarcoidosis, metastases Genetic abnormalities
Abnormal Loading Conditions
Hypertension Valve and myocardium defects Pericardial and endomyocardial pathologies High output states Volume overload
Arrhythmias
Tachyarrhythmias Bradyarrhythmias

Box 2.1 A summary of the common aetiologies of Heart Failure

Adapted from ACS Guidelines (Ponikowski et al., 2016a)

2.1.4 Diagnosis and classifications

2.1.4.1 Classification based on ejection fraction

Left ventricular ejection fraction (LVEF), also referred to as simply ejection fraction (EF), describes the ratio of SV to left ventricular end-diastolic volume that is ejected during systole. There are three main types of CHF based on EF (Ponikowski et al., 2016a):

- heart failure with *reduced* ejection fraction (HFrEF): EF less than or equal to 40%,
- heart failure with *mid-range* ejection fraction (HFmrEF): EF 41 to 49%

- heart failure with *preserved* ejection fraction (HFpEF): EF greater than or equal to 50%.

EF was historically viewed as the primary indicator of global ventricular performance and therefore reductions in EF were considered the primary indicator of the CHF severity. This is true in the case of HFrEF, where EF is reduced to less than or equal to 40%. However, studies have consistently reported that a substantial proportion of the CHF population (approximately 50%) are affected by HFpEF, where EF is maintained at or above 50% (Bhatia et al., 2006, Owan et al., 2006) (Desai, 2007, Paulus et al., 2007). In this instance, an increase in wall thickness or wall stiffness, or both, in the left ventricle impairs relaxation and ventricular filling during diastole. Subsequently, SV is reduced, and oxygen delivery is impaired, which leads to exercise intolerance (Borlaug and Paulus, 2011). This mismatch between oxygen demand and supply for the working muscles is exaggerated during conditions of increased demand, such as exercise. Importantly, the clinical symptoms of HFpEF and HFrEF are the same (i.e. breathlessness, fatigue and exercise intolerance) and patients suffer similar mortality rates and equivalent risks of hospitalisation (Santas et al., 2017).

In 2016, the European Society of Cardiology defined a third subgroup group of patients who have an EF in the range of 41 to 49% as HFmrEF (Ponikowski et al., 2016a). The subtypes of CHF and the diagnostic criteria for each are summarised in Table 2.3.

A universal diagnostic test for CHF does not exist (Zannad et al., 2008, Martindale et al., 2016). Rather, diagnosis relies on a differential diagnosis involving the clinical judgement of signs and symptoms and supported by cardiac imaging investigations. A diagnostic investigation for CHF is triggered when a patient presents with signs and symptoms of CHF. Diagnosis is challenging in practice, because there is a significant overlap between the signs and symptoms of CHF and other diseases, such as chronic obstructive lung disease (COPD) (Komajda et al., 2009, Barsheshet et al., 2010, Mogensen et al., 2011, Lainscak et al., 2009, Lien Christopher et al., 2002, Hawkins et al., 2009). The more typical signs and symptoms of CHF include orthopnoea, peripheral oedema and breathlessness, as well as elevated jugular veins, peripheral oedema and sudden increases in weight caused by fluid retention (Ponikowski et al., 2016a). There is also a high prevalence of comorbidities in CHF including HTN, diabetes and obesity which can further complicate diagnosis (Tsutsui et al., 2010, Lien Christopher et al., 2002).

Diagnostic criteria	**HFrEF**	**HFmrEF**	**HFpEF**
LVEF	≤40%	41 to 49%	≥50%
Other	-	Elevated levels of natriuretic peptides and At least one of: • structural heart disease • diastolic dysfunction	Elevated levels of natriuretic peptides and At least one of: • structural heart disease • diastolic dysfunction
Signs with or without symptoms	Signs Elevated jugular venous pressure Third heart sound (gallop rhythm) Laterally displaced apical impulse Weight gain (greater than2 kg/week) Weight loss (in advanced CHF) Tissue wasting (cachexia) Cardiac murmur Peripheral oedema (ankle, sacral, scrotal) Pulmonary crepitations Reduced air entry and dullness to percussion at lung bases (pleural effusion) Tachycardia Irregular pulse Tachypnoea Cheyne Stokes respiration		Symptoms Breathlessness Orthopnoea Paroxysmal nocturnal dyspnoea Reduced exercise tolerance Fatigue, tiredness, increased time to recover after exercise Ankle swelling

	Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure

Table 2.2: Diagnostic criteria for CHF types

Adapted from Ponikowski et al. (2016a)

Echocardiographic measures and EF, however, do not fully explain the reduction in aerobic capacity seen in patients with CHF (Baker et al., 1984, Franciosa et al., 1981, Higginbotham et al., 1983, Szlachcic et al., 1985, Carell et al., 1994, Cohen-Solal, 1996) (discussed further in section 2.2.3) and therefore an alternative classification system for CHF is based on the severity of the hallmark symptom: exercise intolerance.

2.1.4.2 Classifications based on symptoms

The New York Heart Association (NYHA) is one of the most commonly used systems to classify patients with CHF and is based on the severity of exercise intolerance (i.e. the degree of breathlessness at rest and during exercise). The NYHA classification stratifies patients on a scale of I to IV (Little, 1994), from least symptomatic (Class I) to most symptomatic (Class IV) (Table 2.3).

In 2009, the American College of Cardiology (ACC) and the American Heart Association (AHA) developed a new classification system to use in conjunction with the NYHA (Hunt et al., 2009), which provided the additive benefit of identifying individuals who are at risk of developing CHF based on structural heart disease and other treatable precurses of CHF, so that appropriate preventative treatment can be initiated. The so-called ACC/ASC system classes high-risk individuals who have precursors or structural changes in cardiac tissue into two early stages: A and B. These individuals, however, do not experience any symptoms of CHF and therefore they have not yet developed the syndrome. Individuals in stages C and D have developed symptoms and therefore meet the diagnostic criteria for CHF.

and patients who experience symptoms of CHF, and those with the end-stage disease into Stage C and D (Table 2.3).

	ACC/ASC system		NYHA system	
	Stage	**Description**	**Class**	**Description**
Asymptomatic	Stage A	High risk for HF but without structural heart disease or symptoms of HF		-
	Stage B	Structural heart disease but without signs or symptoms of HF		-
Symptomatic	Stage C	Structural heart disease with prior or current symptoms of HF	Class I	No symptoms at rest, symptoms only at levels of exertion that would limit healthy individual
			Class II	No symptoms at rest or mild exertion, symptoms on moderate exertion
	Stage D	Refractory HF requiring specialised interventions	Class III	No symptoms at rest, symptoms at mild exertion
			Class IV	Symptoms at rest

Table 2.3: A comparison of the NYHA classes and ACC/ASC stages

Adapted from Hunt et al. (2009)

A vast nomenclature also exists to describe the location of dysfunction (right-sided versus left-sided HF), structural alterations (dilated or hypertrophic cardiomyopathies) and other functional characteristics (diastolic and systolic dysfunction) observed in HF.

2.2 The pathophysiology of chronic heart failure

2.2.1 Cardiac remodelling and disease progression

Cardiac remodelling is a broad term used to describe alterations in the size, function or geometry of the heart. These alterations occur to compensate for tissue damage or excessive pressure demands which impair cardiac function (Azevedo et al., 2016, Bertero and Maack, 2018). Cardiac remodelling occurs following exposure to the conditions described in section 2.1.3 (aetiologies of CHF), either acutely (e.g. following AMI or toxic damage) or chronically (e.g. in the case of chronic HTN or valvular disease). The underlying mechanisms that lead from cardiac remodelling to CHF are not fully understood, but are believed to involve the complex interaction of cellular, metabolic, interstitial and molecular changes (Azevedo et al., 2016, Bertero and Maack, 2018).

The geometric changes that occur in CHF (e.g. ventricular dilation) are initially favourable in compensating for failing cardiac function. This can be understood in accordance with the Frank-Starling mechanism. Briefly, the Frank-Starling mechanism represents the relationship between left ventricular end-diastolic volume (LVEDV) and SV, where increasing LVEDV is followed by increases SV (Figure 2.1, curve A) (Kemp and Conte, 2012, Sequeira and van der Velden, 2015). The mechanism behind this relationship is driven by the length-tension relationship. In early CHF, when cardiac output is impaired, cardiac remodelling takes place to increase LVEDV in an attempt to increase the contractile force. However, this remodelling process is progressive and eventually detrimental: the curve becomes flat and, despite an increasing LVEDV, SV does not increase (Figure 2.1, curve B). In advanced CHF, as depicted by curve 3 (Figure 2.1) the pressure in the left ventricle can surpass the pressures of the pulmonary system and pulmonary congestion can occur.

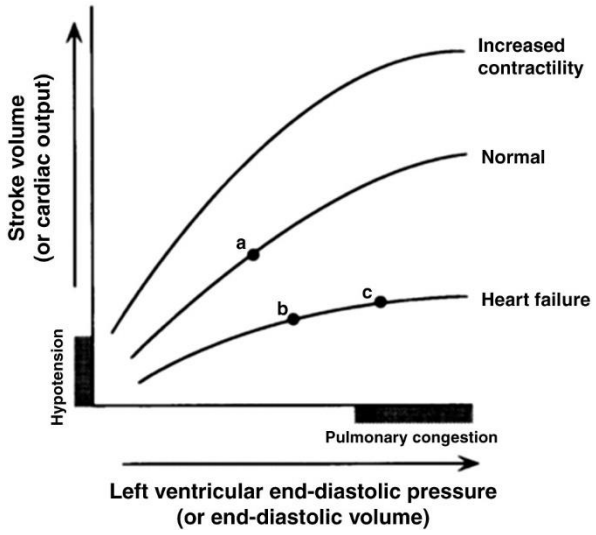

Figure 2.1: The Frank-Starling mechanism

Source: Kemp and Conte (2012)

Curves b and c illustrate the failure of the Frank-Starling mechanisms seen in CHF.

Other negative consequences of cardiac remodelling include an increase in cardiac oxygen demand, a reduction in the efficiency of myocardial contraction and malignant arrhythmias such as ventricular tachycardia and fibrillation (Cohn et al., 2000). In the clinical context of CHF, by the time a patient is symptomatic and can be diagnosed with CHF (i.e. ACC/ASC Stage C and D), significant pathological cardiac remodelling has already occurred (Hunt et al., 2009).

Figure 2.2 provides an example of the progression of CHF from risk factors through to worsening CHF and death. For example, when an individual with a history of HTN remains untreated, cardiac afterload is increased (abnormal loading) and subsequently cardiac work is also increased (ACC/ASC Stage A). Cardiac remodelling involving dilation of the ventricles may occur to maintain an adequate SV (i.e. via the Frank-Starling mechanism) (ACC/ASC Stage B). Over time, this mechanism fails and despite an increase in LVEDV cardiac output falls. The patient becomes symptomatic and can be diagnosed with CHF (ACC/ASC Stage C). Further compensatory mechanisms of the Renin-Angiotensin-Aldosterone-system (discussed further in section 2.2.2) are activated to maintain cardiac output (CO); however, these mechanisms are also eventually detrimental and lead to a vicious cycle of worsening LV function and ultimately to death (ACC/ASC Stage D).

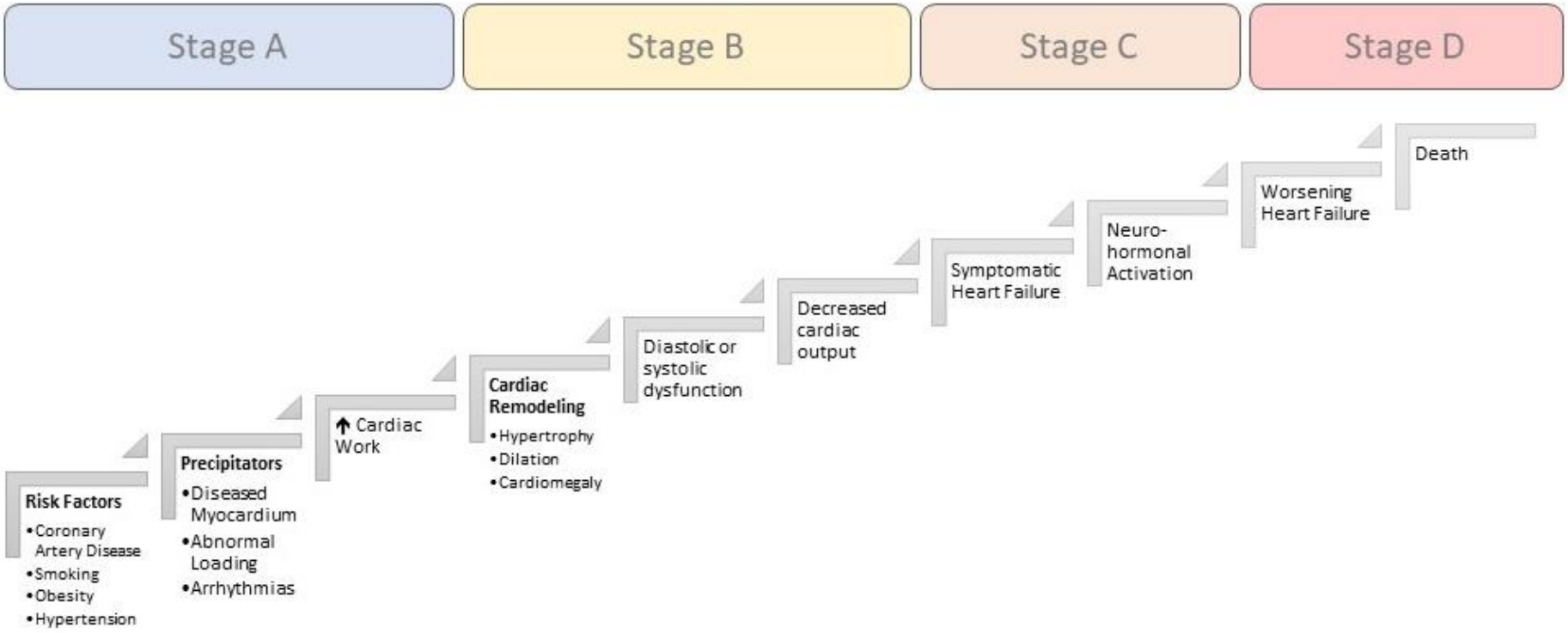

Figure 2.2 An example of the progression of CHF from risk factors through to worsening CHF and death

2.2.2 Compensatory mechanisms: The neurohormonal system

Although the underlying causes of CHF are heterogeneous, all aetiologies lead to a reduction in SV and CO and on to a common pathway involving activation of the neurohormonal system. The Renin-Angiotensin-Aldosterone-System (RAAS) (Figure 2.3) is responsible for regulating vascular tone and extracellular fluid (Brewster et al., 2003, Sayer and Bhat, 2014). The RAAS system is an effective short-term survival mechanism to maintain pressure and oxygen diffusion capacity when CO is reduced and there is a subsequent fall in blood pressure. The RAAS is upregulated via the sympathetic nervous system (SNS) (Adams, 2004), which sets in motion the following biological processes (Figure 2.3):

1. Renin (also known as angiotensinogenase) is released from the kidneys, which carries out the conversion of angiotensinogen to angiotensin I.
2. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE), in the lungs.
3. Angiotensin II acts as a potent vasoconstrictor, resulting in an increase in blood pressure and thus, oxygen perfusion can be maintained despite a reduction in cardiac output
4. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex. Aldosterone increases the volume of extracellular fluid in the body via sodium and fluid retention, thereby providing an additional mechanism to maintain blood pressure despite the failing heart.
5. Finally, angiotensin II stimulates the release of vasopressin, also known as antidiuretic hormone, which increases water reabsorption in the kidney.

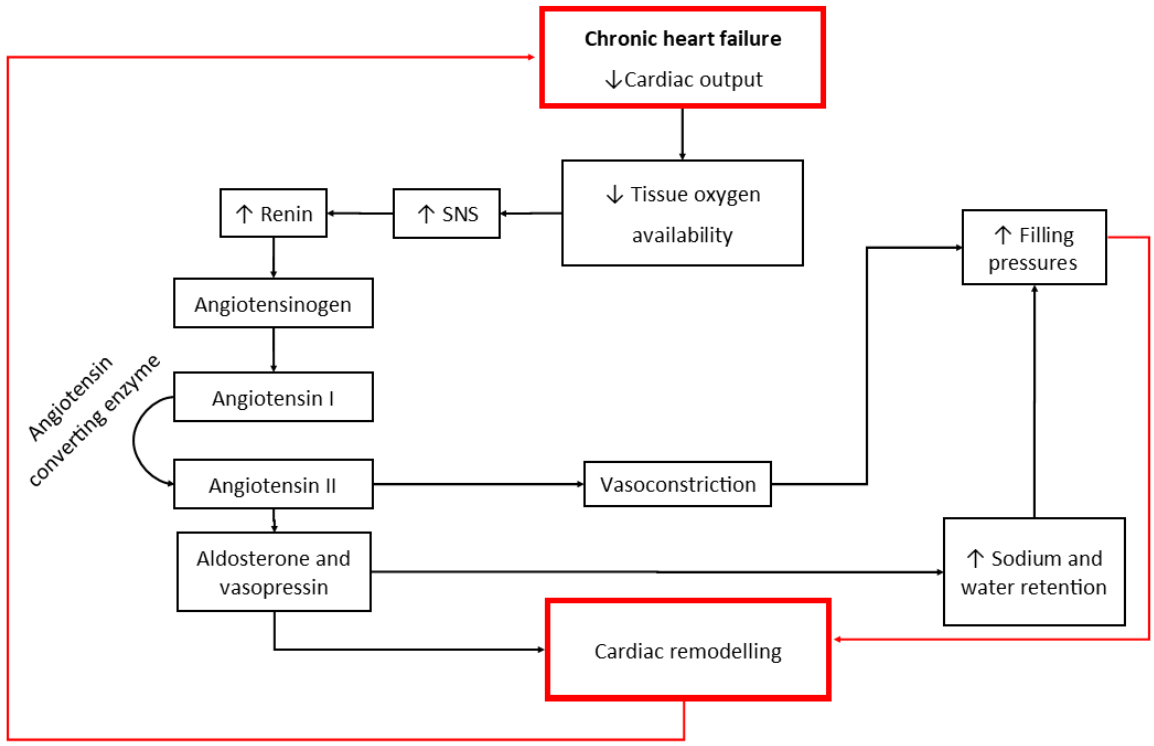

Figure 2.3: Renin-Angiotensin-Aldosterone System (RAAS)

Despite the short-term benefit of the RAAS, (i.e. maintenance of blood pressure and oxygen perfusion to tissues) the consequent increases in total peripheral resistance, cardiac afterload (i.e. filling pressures) and left ventricular stress further increase cardiac afterload and ultimately accelerate cardiac remodelling and worsening of CHF. The pharmacological approaches to the treatment of CHF are targeted at interrupting these physiological mechanisms (discussed in section 2.6) (Orsborne et al., 2017).

2.2.3 Exercise intolerance and the Fick principle

Exercise intolerance (i.e. a reduction in aerobic capacity), dyspnoea and fatigue are hallmark symptoms of CHF. The reductions in aerobic capacity, as measured by oxygen consumption (VO_2), is evident both at peak (i.e. VO_{2peak}) and submaximal exercise (Albouaini et al., 2007). VO_{2peak} is a strong predictor of mortality in patients with CHF, including those treated with beta-blockage therapy. A VO_{2peak} of less than 14 ml/kg/min is the established criterion for cardiac transplantation (Mancini et al., 1991, O'Connor et al., 2009, Peterson et al., 2003), while a 1 ml/kg/min reduction in VO_{2peak} results in an adjusted mortality hazard ratio of 1.13 over 3.5 years (95% CI 1.09 to 1.17) (O'Neill et al., 2005).

Submaximal aerobic capacity is also important in CHF due to its relevance to performance of activities of daily living (ADLs) (Mezzani et al., 2000, Spruit et al., 2011) and prognosis (Gitt Anselm et al., 2002). In a study including 223 patients with HFrEF, a ventilatory threshold (VT) of less than11 ml/kg/min was associated with a 5.4-fold increase in death over six months (Gitt Anselm et al., 2002).

The "Fick Principle" (Wasserman et al., 2012) offers an understanding of aerobic capacity by identifying that VO_2 is the product of central (i.e. CO) and peripheral (i.e. arterial-venous O_2 content difference) factors:

$$VO_2 = CO \times A\text{-}VO_2 \text{ difference},$$

where VO_2 is measured in mL/min, and A-VO_2 difference is the difference in oxygen content of the arterial and venous system (therefore a measure of the oxygen extraction capacity of the peripheral tissues), measured in mL of O_2 per 100ml of blood. Considering the components of CO as stroke volume (SV) and heart rate (HR) the equation can also be expressed as:

$$VO_2 = (SV \times HR) \times A\text{-}VO_2 \text{ difference}$$

A suitable increase in VO_2 peak during exercise relies on increases in both the central and peripheral components. In healthy individuals, the increase in VO_2 during maximal exercise results from an approximate 2-3-fold increase in HR, a 0.4-fold increase in SV and 3-fold increase in A-VO_2 difference (Higginbotham et al., 1986, Powers and Howley, 2017). In CHF, however, the contributions of each component are altered due to both central and peripheral pathologies.

2.2.3.1 Central limitations: cardiac output

It was first thought that exercise intolerance in CHF was a direct consequence of impaired CO during exercise (Weber et al., 1982), where the reduction in CO is due to reductions in both SV and HR reserves. Indeed, resting SV is up to 22% lower in patients with CHF compared to healthy controls (Fukuda et al., 2012) and several studies report that SV during exercise in patients with CHF rises to only 50-89mL during exercise compared to greater than 100 mL in healthy individuals (Piña et al., 2003, Dhakal et al., 2015, Fukuda et al., 2012). The failure to increase SV during exercise may be due to alterations in filling volume (preload), myocardial contractility and afterload and/or failure of the Frank-Starling

Mechanism (see section 2.2.1) (Piña et al., 2003, Kemp and Conte, 2012, Sullivan and Cobb, 1992).

In healthy individuals, a reduction in SV may activate compensatory mechanisms to maintain normal CO, including an increase in HR. In patients with CHF, however, HR responses are often impaired as a result of chronotropic incompetence (the failure of HR to increase during exercise) (Al-Najjar et al., 2012, Brubaker Peter and Kitzman Dalane, 2011), elevated resting HR (resting tachycardia) and reduced HR reserves (HRR) (Piña et al., 2003, Orso et al., 2009). Chronotropic incompetence and reduced HRR have been significantly correlated with lower VO_{2peak} and early fatigue in patients with CHF (Al-Najjar et al., 2012, Brubaker et al., 2006), which again is supported by the Fick Principle. A study by Brubaker et al. (2006) showed that increases in HR during exercise explained 15% of the observed increases in VO_{2peak} (Brubaker et al., 2006). There are conflicting findings, however, with several studies failing to find associations between chronotropic incompetence and VO_{2peak} (Clark and Coats, 1995, Roche et al., 2001) and inconclusive findings from interventional studies aiming to correct chronotropic incompetence with pacing strategies to increase aerobic capacity (Tse et al., 2005).

While there are indeed significant central limitations in CHF, there is strong evidence to suggest that they are not sufficient to entirely explain exercise intolerance in CHF. For instance, several studies have failed to find direct correlations between LV function, as measured by LVEF, and VO_{2peak} (Figure 2.4) (Baker et al., 1984, Franciosa et al., 1981, Higginbotham et al., 1983, Szlachcic et al., 1985, Carell et al., 1994, Cohen-Solal, 1996), suggesting that other, peripheral, factors may have a significant effect on exercise intolerance in these patients.

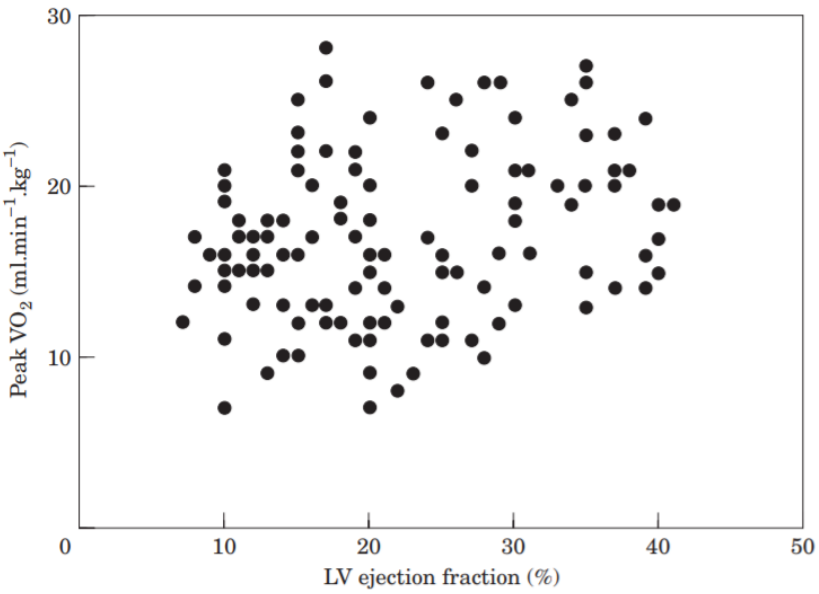

Figure 2.4: No relationship between LV ejection fraction and VO_{2peak} in 150 patients with HFrEF.

Source: Cohen-Solal (1996)

As further evidence of a peripheral cause of exercise intolerance in CHF, an early pivotal study enhanced CO and central haemodynamics in patients with CHF with dobutamine therapy, yet this treatment failed to evoke parallel improvements in exercise capacity (Wilson et al., 1984). A more recent study investigated the relative contributions of each component of VO_2 (i.e. SV, HR, A-VO_2difference) and reported that O_2 extraction in the peripheral tissues is more attributable to reductions in VO_2 than SV or HR (

Figure **2.5**) (Dhakal et al., 2015).

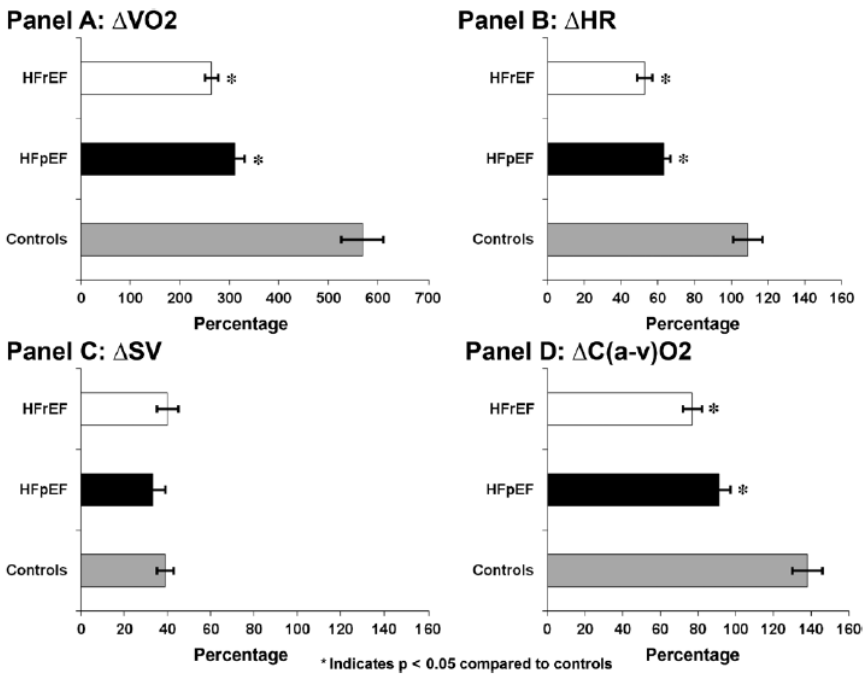

Figure 2.5: Percentage increase in VO_2 and each of its components, HR, SV and arterio-mixed venous saturation difference (C(a-v)O2) from rest to peak exercise

Source: Dhakal et al. (2015)

With the knowledge that pharmacologically induced improvements in CO do not translate directly into improvements in aerobic capacity, contemporary investigations are now focusing on the role of skeletal muscle as a critical limiter of exercise tolerance: a theory labelled the muscle hypothesis of CHF (Coats, 1996, Coats et al., 1994).

2.2.3.2 Peripheral limitations: The muscle hypothesis

It is now accepted that the main factors limiting exercise capacity in patients with CHF are peripheral maladaptations, particularly those occurring in the skeletal muscle. Professor Andrew Coats introduced the muscle hypothesis of CHF in 1994 (Coats et al., 1994). According to the hypothesis, the initial reductions in LV function and CO in CHF reduce blood flow to peripheral tissues and induce a catabolic state and subsequent skeletal muscle myopathy. The resulting muscle abnormalities lead to early fatigue and dyspnoea that, in turn, further reduces physical activity and sets in motion a deleterious feedback loop that drives disease progression (Figure 2.6). The most recognised muscle abnormalities include

ergoreflex dysfunction, mitochondrial dysfunction, changes to fibre type characteristics and muscle atrophy.

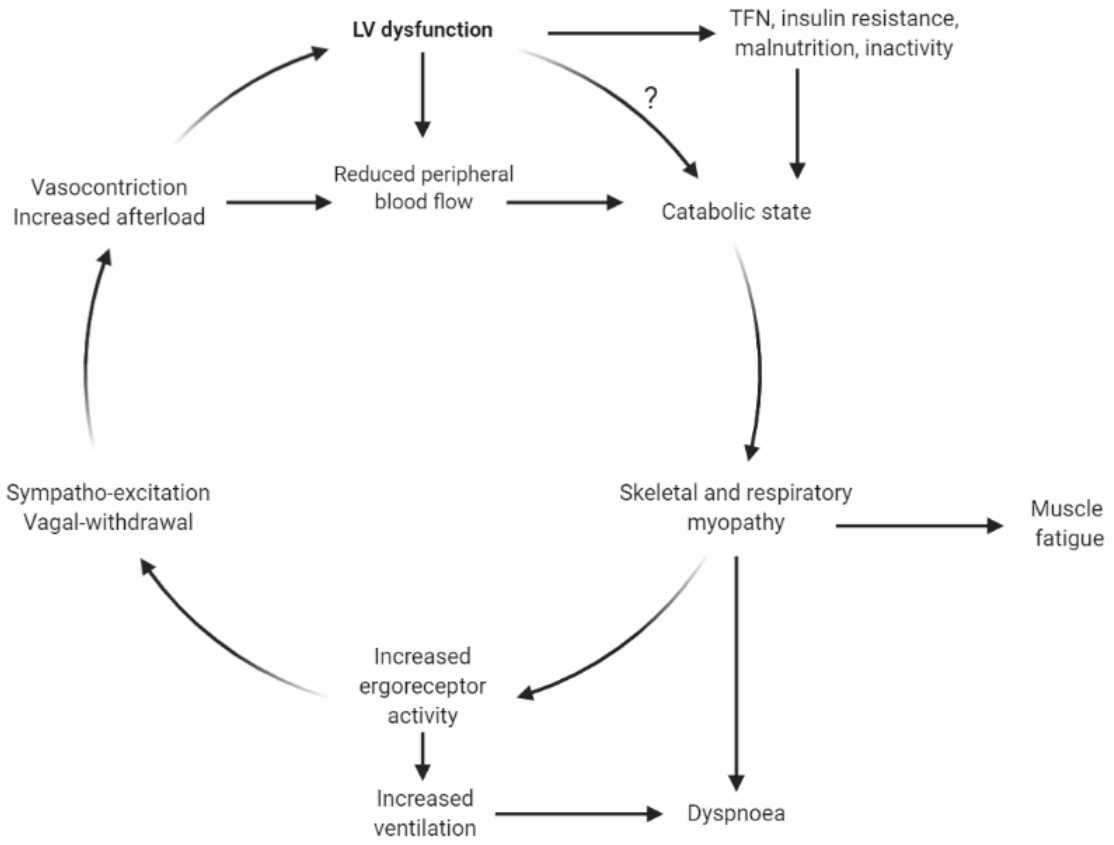

Figure 2.6: The muscle hypothesis of HF

Re-created from Coats et al. (1994)

2.2.3.2.1 Ergoreflex

In healthy individuals, exercise stimulates several neural signals originating in the brain (central command), the aorta and carotid arteries (chemo and baroreflex) and in skeletal muscle (ergoreflex) (Fadel, 2013). These signals modulate the central nervous system to upregulate cardiovascular response (i.e. heart rate and contractility) and respiration to meet the demands of physical activity (Fadel, 2013). In CHF, an overactivity of muscle ergoreceptors at rest and low-intensity activity causes abnormal coupling of ventilation and cardiovascular responses, thus causing early exercise fatigue and breathlessness (Belli et al., 2011, Piepoli et al., 1996b). In turn, this further stimulates sympathetic nervous system response via the RAAS (previously discussed in section 2.2.3), increases in afterload and left

ventricular strain which ultimately accelerates disease progression (Piepoli, 1998, Piepoli et al., 1996b, Piepoli et al., 1999, Piepoli and Crisafulli, 2014). Vasoconstriction also occurs simultaneously in tissues remote from the overactive ergoreceptors (as blood supply is redistributed to the *apparently* stimulated muscle) which can result in permanent damage and endothelial dysfunction to organs experiencing chronically reduced blood supply (Piepoli et al., 2008).

2.2.3.2.2 Mitochondria

The mitochondria are the powerhouses of oxidative metabolism and adenosine tri-phosphate (ATP) production via the tricarboxylic acid cycle and the electron transport chain (Bertram et al., 2006, Nazaret et al., 2009). These systems allow production of ATP for all cells within the body, at rest and during exercise. In CHF, oxidative metabolism within the skeletal muscle is impaired (Andrews et al., 1997, Abozguia et al., 2008, Okita et al., 1998). A significant contributor to this impairment is the decrease in mitochondrial efficiency (Rosca and Hoppel, 2013).

Studies investigating mitochondrial impairment in CHF have demonstrated a reduction in the total area of skeletal and cardiac muscle occupied by mitochondria (mitochondrial density) by up to 75% (Guzmán Mentesana et al., 2014, Drexler et al., 1992) and this reduction is strongly correlated with VO_{2peak} (Figure 2.7) (Drexler et al., 1992).

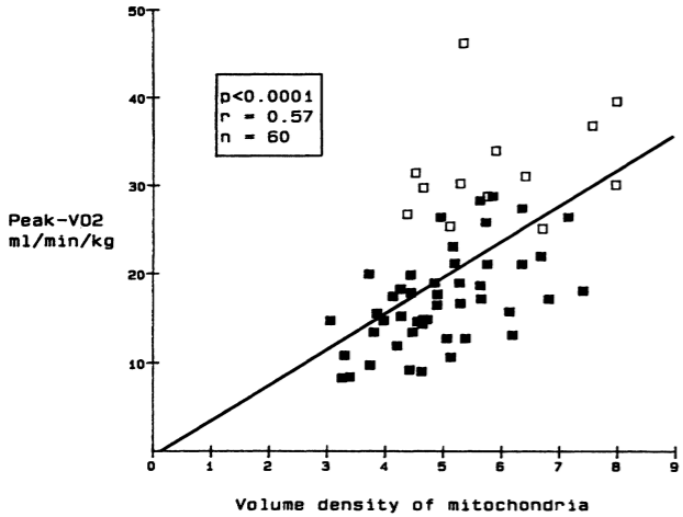

Figure 2.7: The relationship between volume density of mitochondria and peak VO_2 in 47 patients with CHF (patients with CHF are identified by solid squares)

Source: Drexler et al. (1992)

As a result of impaired mitochondrial function, individuals with CHF are inefficient at producing the energy required for physical activity, which leads to a reduction in $VO_{2peak,}$ early fatigue, and exercise intolerance (Drexler et al., 1992, Ning et al., 2000, Schaper et al., 1991).

2.2.3.2.3 Muscle fibre type

Human skeletal muscle is composed of two main fibre types which are differentiated by their metabolic capabilities and which allow for a broad range of functions and physical abilities (Bottinelli and Reggiani, 2000). Type I, or slow-twitch muscle fibres, contain a rich capillary supply, are dense with mitochondria and have a high expression of oxidative enzymes and therefore offer high aerobic potential and are resistant to fatigue (Picard et al., 2012). Indeed, Type I fibres are correlated with VO_{2peak} (Figure 2.8**)** (Schaufelberger et al., 1995, Mancini et al., 1989). These characteristics are ideal for performance of ADLs, which require long durations of aerobic energy transfer.

Conversely, Type II fibres, also known as fast-twitch fibres, have fewer mitochondria, oxidative enzymes and myoglobin and so have a lower resistance to fatigue (Picard et al., 2012). However, the ability of Type II fibres to create small amounts of ATP quickly via anaerobic metabolism enables the generation of short bursts of strength at high velocities, which is useful during activities involving power movements such rising from a chair, or 'catching' oneself from a near fall (Bottinelli and Reggiani, 2000). There are also subtypes within Type II muscle fibres, Type IIa and IIb: the former offering more aerobic energy production potential (Bottinelli and Reggiani, 2000).

In CHF, there is a relative loss of Type 1 oxidative muscle fibres (Sullivan et al., 1997, Vescovo et al., 2000, Drexler et al., 1992, Sullivan et al., 1990) and a fibre type shift from Type IIa to IIb fibres (Sullivan et al., 1997, Vescovo et al., 2000, Sullivan et al., 1990, Schaufelberger et al., 1995). The predominant fibre type shift from Type I to Type II observed in CHF creates a more glycolytic response to exercise, which increases fatigability and therefore contributes to exercise intolerance (Schaufelberger et al., 1995, Middlekauff, 2010).

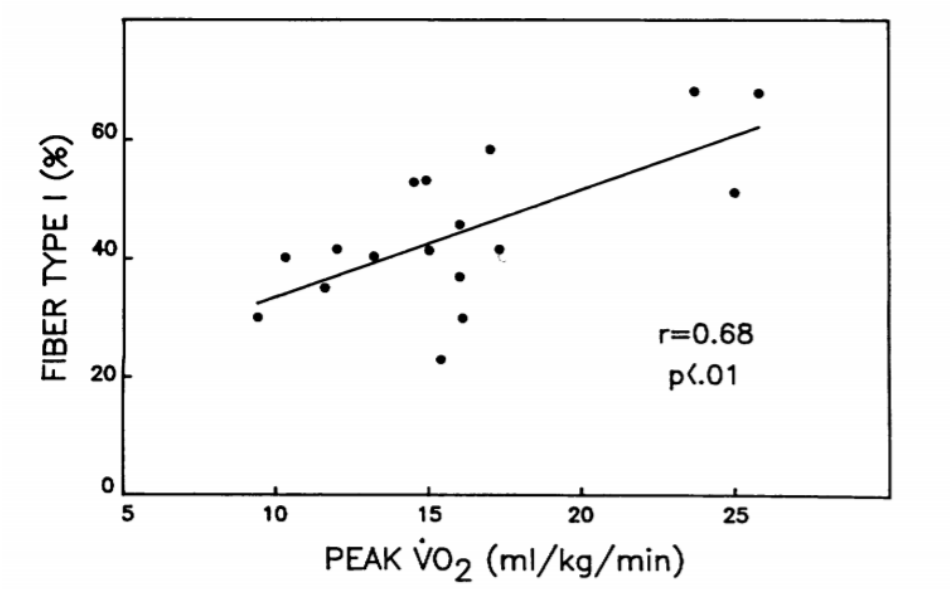

Figure 2.8: Correlations between the percentage of Type 1 muscle fibres and VO_{2peak}

Cited from Mancini et al. (1989)

2.2.3.2.4 Muscle mass

Skeletal muscle mass accounts for approximately 42% of fat-free mass in the human body (Kyle et al., 2001). During healthy ageing, there is a progressive loss of skeletal muscle mass and strength (known as Sarcopenia) that is most prominent in the lower limbs and is seen from the fourth decade of life (Janssen et al., 2000, Evans, 1995). Estimates of lifetime declines in leg muscle mass of 25-40% have been reported, (Janssen et al., 2000, Goodpaster et al., 2006, Hughes et al., 2001a), or 15-18% per decade (Hughes et al., 2001b). Muscle mass is an essential determinant of exercise capacity (Boo et al., 2019), and individuals with sarcopenia have a reduced aerobic capacity, slow gait speeds, a reduced capacity to perform ADL's and an increased risk of falls (Landi et al., 2012, Visser et al., 2002, Janssen et al., 2002, Boo et al., 2019).

Depending on the diagnostic criteria used, epidemiological studies have reported an incidence of sarcopenia between 8 to 24% between the ages of 60 to 70 years, rising to 18-50% in those older than 80 years (Baumgartner et al., 1998, Melton et al., 2000, Morley et al., 2014, Shafiee et al., 2017). In patients with CHF, the incidence of sarcopenia is greater than in healthy individuals of the same age (Fülster et al., 2012, Zamboni et al., 2013, Mancini et al.,

1992, von Haehling, 2015), with one study reporting an incidence of 47% in patients with CHF under 55 years (Vescovo et al., 1996).

The combination of age and CHF-related sarcopenia contributes to exercise intolerance, with skeletal muscle mass acting as a strong predictor of VO_{2peak} in patients with CHF, independent of NYHA class, age and gender and resting haemodynamics (Mancini et al., 1992, Cicoira et al., 2001).

2.2.3.2.5 Capillary muscle density

Muscle capillaries are blood vessels that connect arteries to veins and serve to supply muscle tissue with oxygenated blood and to feed deoxygenated blood and carbon dioxide back into the circulatory system. Capillaries, therefore, are one of many factors that determine the oxygen uptake capacity of the body and directly correlate with muscle oxidative capacity (Ingjer, 1979). The influence of muscle capillary density (MCD) on aerobic capacity in CHF was first investigated in the mid-1990s, where studies showed a 25% lower MCD per unit of the cross-sectional area of quadriceps femoris compared to healthy controls (Magnusson et al., 1996). Others have reported significant reductions in the number of capillaries per muscle fibre in patients with CHF, but the ratio of capillaries to cross-sectional fibres was not different from controls, suggesting the overall diffusion distances were unchanged (Sullivan et al., 1990). In direct contrast, Mancini et al. found no difference in capillaries per fibre but an overall increase in capillaries per cross-sectional area (Mancini et al., 1989), while Lipkin et al. (Lipkin et al., 1988) reported no difference in capillaries per fibre. Many of these studies assessed capillary density by indirect measures, which may explain the contrasting findings (Duscha et al., 1999). The direct influence of MCD on VO_{2peak} is also unclear (Duscha et al., 1999). Therefore, it is still unknown to what extent MCD contributes to exercise intolerance in CHF.

2.3 Chronic heart failure and the older adult

2.3.1 The ageing population

Over the past four decades, the number of people aged 60 years and over has more than doubled and by 2050 the worldwide number is expected to double again to almost 2.1 billion, by which time older people will outnumber youth and adolescents (Division;, 2017). This changing demographic structure is universally described as a 'widening' of the population pyramid, as shown in

Figure 2.9: the age distribution curves of 1950 produce a pyramid shape (shown in dark blue), whereas the population projections for 2100 widen the top of the pyramid (shown in yellow).

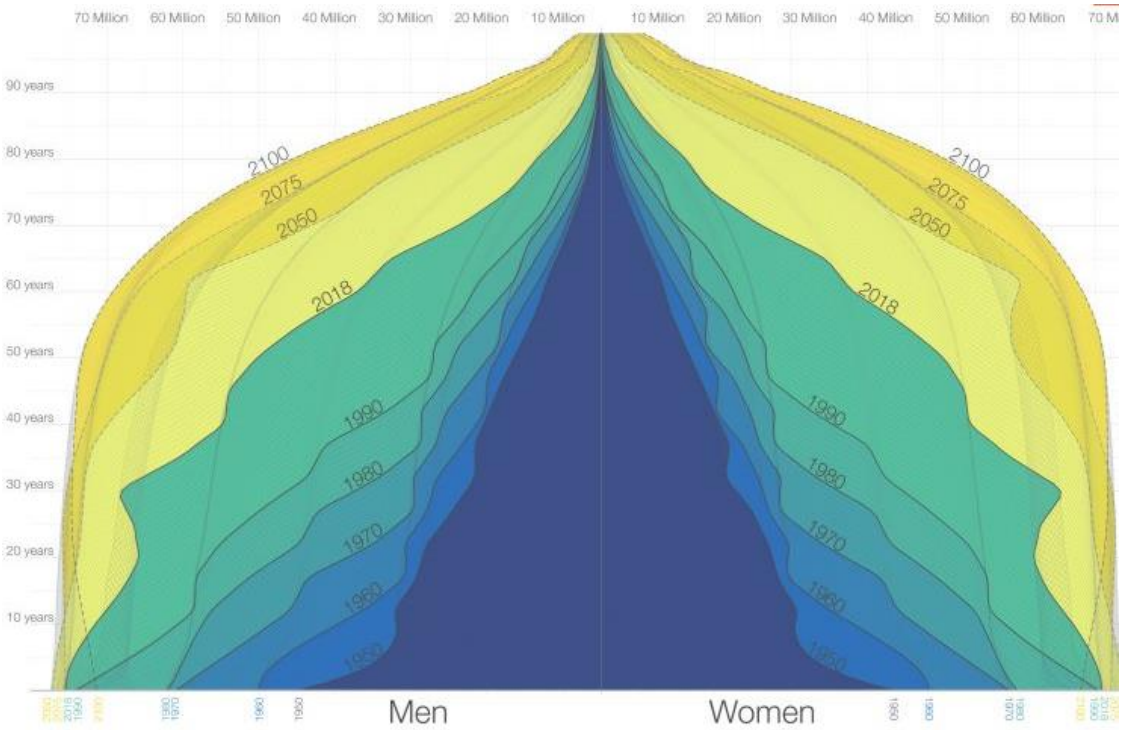

Figure 2.9: The demography of the world population from 1950 to 2100

A depiction of the age distributions of the world population for men (left side of figure) and women (right side of figure) from 1950 to 2018, as well as population projections for years 2018 to 2100.

Source: United Nations Population Division- World Population Prospects (2014)

This shifting demographic is a consequence of increased life expectancy achieved by advances in medicine, overall population growth, decreased birth rate as well as declines in fertility (Australian Government, 2018). This global trend is also mirrored in the Australian population, where the number of individuals aged 65 and over increased by 3.5% between 1998 and 2018 (Australian Government, 2018). This age group is expected to increase more rapidly over the next decade, as more "baby boomers"[2] turn 65. Australian population projections estimate an increase of 25% in people aged over 65 years between 2002 and 2042 (Figure 2.10). The most dramatic increases by age are seen in persons aged 85 and older, where the Australian population of this group increased by 125.1% in the past 2 decades, compared to the total population growth of 34.3% (Australian Government, 2018).

As a consequence of the ageing population, the prevalence of chronic illnesses is also increasing, placing increased burdens on the health care system (Nowossadeck, 2012, Tonelli and Riella, 2014, Perry, 2013, MacNee et al., 2014).

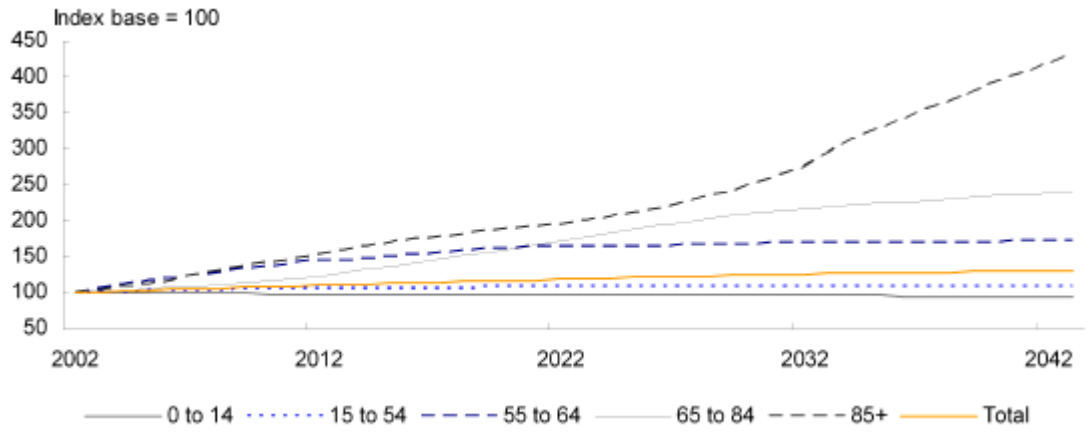

Figure 2.10: Australian forecasted population growth by age indices

Source: Commonwealth of Australia (2004)

[2] "Baby Boomers" is a term used to describe the 5.5million people born between the post-second world war years of 1946 to 1965. COMMISSION, P. 2005. Economic implications of an ageing Australia. *Productivity Commission, Government of Australia Research Reports*.

2.3.2 Age distributions in CHF

It is well established that older individuals are disproportionately affected by CHF (Ho et al., 1993b, Curtis et al., 2008). The Framingham Heart Study remains the largest longitudinal cohort study of cardiovascular disease and found the annual prevalence of CHF in men and women to be 8 per 1000 between 50-59 years, which increased to 66 per 1000 between 80-89 years for men and 79 per 1000 for women. (Ho et al., 1993b). Similarly, a cohort longitudinal study of 622,789 persons in the USA found a prevalence of CHF of 19.3 per 1000 in persons aged 65-69 and 48.4 per 1000 in persons aged 80-84 years (Curtis et al., 2008). The age of the first presentation of CHF has been reported between 75-76 years (Conrad et al., 2018, Ho et al., 1993a).

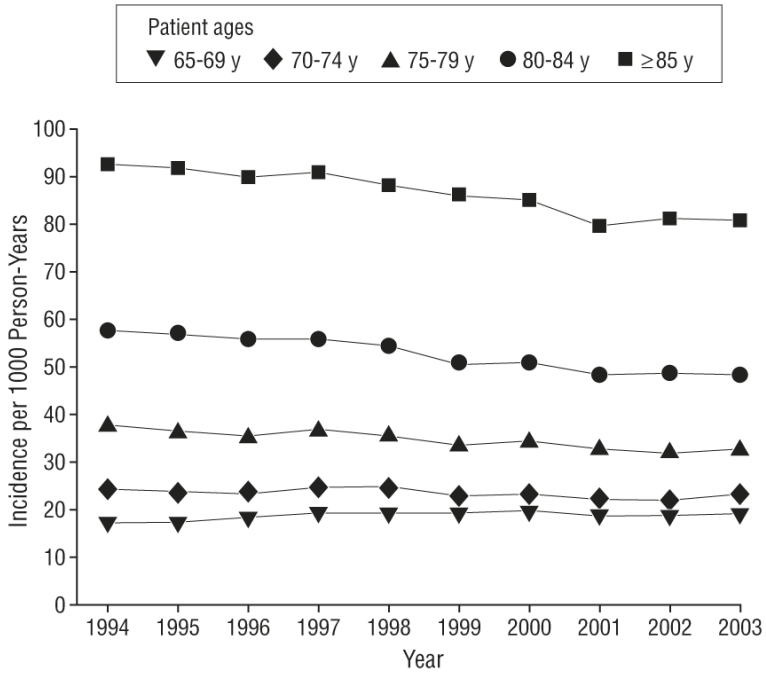

Figure 2.11: The incidence rates of CHF by age group

Source: Curtis et al. (2008)

Hospitalisation is a common burden for patients with CHF. Rates of CHF-related hospitalisations are higher amongst older patients with CHF compared with younger patients (Christ et al., 2016, Newton et al., 2016) (Corrao et al., 2014, Kozak et al., 2006). For

instance, CHF-related hospitalisations were greater in patients older than or equal to 75 years compared to those younger than 75 years (69% versus 31%) (Christ et al., 2016). Length of stay (LOS) is also known to increase with advancing age, with patients greater than 85 years staying 2–4 days longer than those under 65 years (Cowie et al., 2015).

The high rates of admissions in older patients with CHF is a local challenge, as well as a global one. The Victorian Cardiac Outcomes Registry Heart Failure study (VCOR-HF), reported on 289 patients admitted with acute decompensated HF from 16 regional and metropolitan hospitals between the years of 2014 and 2017. Age distribution was heavily skewed towards older individuals with a mean age of 80 years (IQR 71-87) (Figure 2.12) (Driscoll et al., 2020). At the Footscray and Sunshine Hospitals, part of the Western Health (WH) organisation in Melbourne Victoria, patients over 65 years accounted for 89% of all admissions with the primary diagnosis of acute heart failure (WH Performance Unit, 2013)

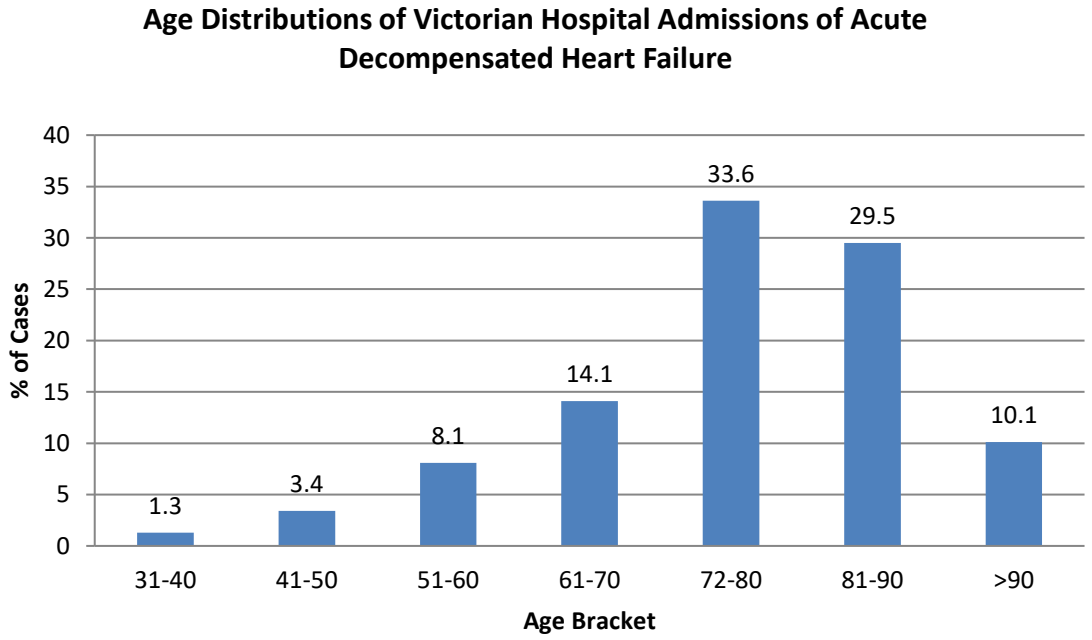

Figure 2.12: Age distributions of Victorian hospital admissions of acute decompensated HF

Source: Original graph created using data from VCOR-HF (Driscoll et al., 2020)

2.3.3 The older patient with CHF

2.3.3.1 Comorbidities

Older patients with CHF have distinctive clinical features and risks compared to younger patients with CHF, most notably the higher prevalence of co-morbidities that occur alongside CHF including atrial fibrillation (AF), HTN, COPD, anaemia, diabetes and chronic kidney disease (CKD) (Komajda et al., 2009, Barsheshet et al., 2010, Mogensen et al., 2011, Lainscak et al., 2009). Comorbidities frequently accompanying CHF lead to increased mortality and morbidity and decreased quality of life (Braunstein et al., 2003). In a cross-sectional survey of 122,650 older patients with CHF in the USA, approximately 40% of individuals had greater than or equal to five comorbidities, and these individuals accounted for 81% of the total days spent in hospital for the entire cohort (Braunstein et al., 2003). The five most common non-cardiac conditions are shown in Table 2.4. The presence of comorbidity results in a greater predisposition to develop CHF and is associated with further reduced functional capacity, higher rates of hospitalisations and early mortality in those with diagnosed CHF (Londono et al., 2018, Barsheshet et al., 2010).

Table 2.4: Five most common non-cardiac conditions for among 122,630 patients aged greater than 65 years with CHF

Adapted from Braunstein et al. 2003 (Braunstein et al., 2003)

Chronic Disease	**Percentage prevalence (n)**
Hypertension	55 (67,211)
Diabetes Mellitus	31 (38,175)
COPD and bronchiectasis	26 (32,275)
Ocular disorders (retinopathy, macular disease, cataract, glaucoma)	24 (29,548)
Hypercholesterolaemia	21 (25,219)

2.3.3.2 Sarcopenia, frailty and cachexia

Sarcopenia, frailty and cachexia are overlapping syndromes related to changes in body composition, strength and physical function (Gingrich et al., 2019). Several definitions are proposed for each of these overlapping conditions, currently without consensus (Fried et al., 2001, Evans et al., 2008, Cruz-Jentoft et al., 2010, Muscaritoli et al., 2010, Fielding et al., 2011). Common approaches to identifying frailty include the Fried frailty criterion (Fried et al., 2001) which is based on five key physical indicators of frailty: unintentional weight loss, exhaustion, low physical activity, slowness and weakness; and the Rockwood Clinical Frailty Index which identifies individuals at different stages of frailty based on the proportion of accumulated deficits (Rockwood et al., 2005). For sarcopenia, most definitions are based on three criteria: muscle strength, muscle mass and physical function (Levinger and Duque, 2021). Table 2.5 summarises the most commonly used definitions from key international societies and working groups.

Table 2.5 Most commonly used definitions for sarcopenia

Source: Levinger and Duque (2021)

Definition	Strength	Muscle mass	Function
EWGSOP2	Grip strength: M <27kg, W <16Kg Chair stand: >15 s for five rises	ASM: M <20 kg, W <15 kg ASM/height^2: M <7.0 kg/m^{2,} W <5.5 kg/m^2	Gait speed: ≤0.8 m/s SPPB: ≤8 point score TUG: ≥20 s 400 m walk test: Non-completion or ≥6 min for completion
AWGS	Grip strength: M <28 kg, W <18 kg	Height-adjusted muscle mass: DXA, M <7.0 kg/m^2 , W <5.4 kg/m^2 and bioimpedance, M <7.0 kg/m^2, W <5.7 kg/m^2	6-m walk <1.0 m/s, Short Physical Performance Battery score ≤9 5-time chair stand test ≥12 seconds.

SDOC	Grip strength: M <35.5 kg, W <20.0 kg Grip/BMI: M <1.05 kg/kg/m^2, W <.79 kg/kg/m^2 Grip/TBF: M <1.66 kg/kg, W <.65 kg/kg Grip/ALM: M <6.08 kg/kg, W <3.26 kg/kg Grip/Weight: M <.45 kg/kg, W <.34 kg/kg	-	
IWGS		Height-adjusted muscle mass: M< 7.23 kg/m^2, W< 5.67 kg/m^2	Gait speed: <1 m/s
FNIH	Grip strength: M <26 kg, W <16 kg	ASM/BMI: Men < 0.789, W< 0.512	Gait speed: ≤0.8 m/s
ASM, appendicular skeletal muscle mass; AWGS, Asian Working Group for Sarcopenia; BMI, Body Mass Index; EQGSOP2, European Working Group on Sarcopenia in Older Adults; FNIH, Foundation for the National Institutes of Health; IWGS, International Group on Sarcopenia; M, men; SDOC, Sarcopenia Definition and Outcomes Consortium; SPPB, Short Physical Activity Performance Battery; TUG, timed up and go; W, women			

Thus, depending on the definitions used, the reported prevalence for these conditions can vary. Among community-dwelling adults the prevalence of sarcopenia is reported between 2.3 and 29% (Cruz-Jentoft et al., 2014, Kim et al., 2016), with higher rates amongst long-term care or medical inpatients (Cruz-Jentoft et al., 2014, Gingrich et al., 2019). The prevalence for frailty is between 3.9-51% (pooled prevalence from meta-analyses 17.4%) (Siriwardhana et al., 2018, Xie et al., 2020).

Older patients with CHF are particularly affected by these tissue loss syndromes (Zamboni et al., 2013, Fulster et al., 2013, von Haehling, 2015). Frailty has been detected in up to 76% of patients with CHF greater than 70 years (Vidan et al., 2016). Furthermore, in a prospective study of 200 patients with CHF (mean age; 66.9 ± 10.4 years), muscle wasting was observed in 19.5% of patients, which correlated significantly with reduced exercise time during maximal exercise testing (Fulster et al., 2013).

Sarcopenia and frailty are associated with poorer outcomes. In a meta-analysis that included 2645 patients from 8 studies, the presence of frailty was associated with a significant increase risk of mortality over a mean follow-up period of 1.82 years and hospitalisation, over a mean follow-up period of 1.12 years (Yang et al., 2018).

2.3.3.3 Cognitive deficits

Several longitudinal studies have shown faster cognitive declines in patients with CHF compared to those without (Verhaegen et al., 2003, Hammond et al., 2018). In comparison to younger patients with CHF, older individuals with CHF demonstrate a higher incidence of cognitive deficits, as well as mental health and sleep disorders (Komajda et al., 2009). In a longitudinal study of 4864 men and women over the age of 65 years, the decline in cognitive function was faster after diagnosis with CHF and this association was stronger at older ages (Hammond et al., 2018).

Given the importance of self-care in CHF management, impairments in cognitive function have clinical implications for patients. Cognitive dysfunction and memory impairment are associated with poorer self-care (Lee et al., 2013, Hajduk et al., 2013) and inadequate health literacy (Hawkins et al., 2016, Morrow et al., 2006, Lee and Son, 2018). Furthermore, reduced health literacy has known associations with self-care (Son et al., 2018, Chen et al., 2011) and knowledge attainment in patients with CHF (Chen et al., 2014).

2.3.3.4 Representation in clinical trials

Although older patients suffer worse outcomes due to comorbidities, they are in fact, under-represented in clinical trials (Pressler et al., 2008). Data from the PREDICT (Increasing the PaRticipation of the ElDerly in Clinical Trials) study showed that among 251 trials for patients with CHF, 64 (25.5%) excluded older patients by an arbitrary upper age limit and 109 trials (43.4%) excluded older patients due to other exclusion criteria not justified by clinical guidelines, including comorbidities or concurrent treatment (Crome et al., 2014).

To our knowledge, there is no published description reporting the detailed reasons for the exclusion of older patients with CHF from exercise training studies and therefore it is difficult to ascertain the true eligibility and recruitment potential of older patients with CHF for exercise training. Furthermore, understanding the reasons leading to their exclusion may

guide the development of strategies to optimise recruitment and thus, improve the translation of research findings into clinical practice.

These limitations were considered in Study 4, Chapter 6 of this thesis.

2.4 Treatment overview

As discussed previously, CHF is a complex syndrome whereby a reduced cardiac output triggers a sequence of maladaptive processes which eventually lead to further cardiac remodelling (Ge et al., 2019, Tanai and Frantz, 2015, Sayer and Bhat, 2014). This chronic neurohormonal activation leads symptomatically to exercise intolerance, dyspnoea and fatigue (Zambroski et al., 2005). The fundamental objectives of CHF therapy are to reduce symptoms, maintain or improve exercise capacity, reduce the frequency of hospitalisations and ultimately to prolong survival while maintaining quality of life (Ponikowski et al., 2016a, Atherton et al., 2018, Yancy et al., 2017). These objectives are achieved by a multi-targeted treatment approach involving pharmacotherapy, device therapy and exercise rehabilitation (Ponikowski et al., 2016a, Atherton et al., 2018, Yancy et al., 2017). The following sections describe these treatments and explore newer approaches in the field of exercise rehabilitation.

2.5 Pharmacotherapy

The basic therapeutic principle for pharmacotherapies in CHF is to deregulate the maladaptive activation of the RAAS and SNS (Berliner and Bauersachs, 2017). The prolonged effects of angiotensin II and catecholamines contribute towards cardiac remodelling and deteriorating cardiac function and are the central target for pharmacological treatment. Optimal pharmacological treatment is proven to prolong life expectancy and reduce the frequency of hospitalisations (Brann et al., 2019). The first-line pharmacological agents for HFrEF are angiotensin-converting enzyme inhibitors (ACE-I), beta-adrenergic receptor blockers (β-blockers) and mineralocorticoid/aldosterone receptor antagonists (MRAs) and should be prescribed to the vast majority patients with HFrEF (Ponikowski et al., 2016a, Atherton et al., 2018, Yancy et al., 2017).

2.5.1 Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors (ACE-I) prevent the conversion of angiotensin I to angiotensin II, thereby inhibiting the vasoconstrictor effect of angiotensin II, increasing blood pressure, fluid retention and cardiac contractility (Opie and Gersh, 2012).

ACE-I reduce the risk of mortality by 11-31% in patients with CHF (up to 4.5 years follow-up) (Consensus Trial Study Group, 1987, Yusuf et al., 1992, Tai et al., 2017) and reduce rates

of hospitalisations by 6–26% over 24–37.4 months (Yusuf et al., 1992, Khan et al., 2017). Treatment with ACE-Is has also been shown to delay the development of cachexia (Anker et al., 2003, Rolfe et al., 2019) but the mechanisms of this benefit are not fully understood. One hypothesis suggests that ACE-I have an effect on catecholamines, endothelial function and other neurohormones, which all contribute to oxidative stress, ischemia, tissue damage and apoptosis (Hornig et al., 1998, Francis et al., 1993, Swedberg et al., 1990, Anker et al., 2003).

ACE-I may also influence exercise tolerance in patients with CHF. A meta-analysis reported a 5% increase in total exercise duration on an exercise tolerance test (bicycle ergometer, treadmill, 6-min walk) following ACE-I treatment (duration of treatment; 4-12 weeks) (Abdulla et al., 2004). However, this study had several limitations, including the exclusion of patients with NYHA Class IV (which increases the risk of attrition bias due to the potential of increased participant dropouts and death in those with NYHA IV) and the lack of gold standard exercise endpoints (VO_{2peak}). Considering this, the effect of ACE-I on exercise capacity is not fully understood.

The primary ACE-I prescribed for CHF are Captopril, Enalapril, Lisinopril and Ramipril. Side effects from ACE-I are common and include a chronic dry cough, hypotension and renal impairment. For patients who are sensitive to these side effects, Angiotensin Receptor Blockers (ARB) are an alternative agent (Ponikowski et al., 2016a).

2.5.2 Beta-adrenergic receptor blockers

Beta-adrenergic receptor blockers (β-blockers) block β_1-receptors (found in cardiac tissue) to reduce heart rate (HR), myocardial contractility and renin release, as well as β_2-receptors (mostly found in bronchial tissue and peripheral blood vessels), which increase bronchial resistance and inhibit catecholamine-induced glucose metabolism (MIMS Online, 2020). Due to their effect on HR, β-blockers are primarily anti-arrhythmic agents and are regarded as the central treatment for many cardiovascular diseases (Opie and Gersh, 2012).

Several trials and meta-analyses in CHF have shown an unequivocally beneficial effect of β-blockade on survival, with reports of a decrease in all-cause mortality between 12–34% over a mean follow-up of studies between 6–32 months (MERIT-HF Investigators, 1999, CIBIS-II Study Group, 1999, Flather et al., 2005, Kotecha et al., 2014, Chatterjee et al., 2013, Lee and Spencer, 2001, Bonet et al., 2000), a reduction in sudden death by 31-49% over 6-23 months (MERIT-HF Investigators, 1999, CIBIS-II Study Group, 1999, Al-Gobari et al., 2013, Lee

and Spencer, 2001) and reductions in hospitalisations and lengths of stay (Packer et al., 2002, Flather et al., 2005). Common β-blockers prescribed for CHF include Metoprolol, Carvedilol, Bisoprolol and Nebivolol (Chatterjee et al., 2013).

The primary mechanisms of β-blockers in the improved survival in CHF are; 1) the attenuation of the SNS, leading to the partial normalisation in resting HR, filling pressures and afterload, thereby slowing cardiac remodelling and; 2) due to the agent's anti-arrhythmic and anti-ischemic properties (Opie and Gersh, 2012, Rehsia and Dhalla, 2010).

Although the survival benefits of β-blockers are demonstrated, their effects on increasing functional capacity are not clear (MERIT-HF Investigators, 1999, CIBIS-II Study Group, 1999). Systematic reviews demonstrate only a preservative effect of β-blockers on VO_{2peak} (Montero and Flammer, 2018, Bolger and Al-Nasser, 2003, Dekleva et al., 2012, Ismail et al., 2013), suggesting that while β-blockers are the keystone pharmacotherapy for CHF, additional strategies such as exercise training are required to address the physical and functional impairments caused by the syndrome.

2.5.3 Mineralocorticoid/aldosterone receptor antagonists

Fluid retention and oedema are common signs of CHF (Clark and Cleland, 2013) and are effectively managed by mineralocorticoid/aldosterone receptor antagonists (MRA). MRA block the receptors for aldosterone, thereby reducing its effect on fluid retention (Opie and Gersh, 2012). When used in patients with CHF, MRA inhibit the sodium reabsorption and potassium secretion effects of aldosterone and in turn reduce fluid overload (Bauersachs et al., 2015). MRA are recommended for all patients with HFrEF who remain symptomatic despite treatment with both ACE-I and β-blockers (Ponikowski et al., 2016a). This recommendation is made on the basis that treatment with MRA reduces the severity of symptoms (Pitt et al., 1999), reduces the frequency of hospitalisations over 24 months by 35% (Pitt et al., 1999) and significantly reduces death from all causes and sudden death by 19–30% and 19–23%, respectively (Pitt et al., 1999, Rossello et al., 2019, Le et al., 2016, Wei et al., 2010, Bapoje et al., 2013).

Aldosterone antagonist treatment with spironolactone is also shown to significantly reduce the symptoms of CHF in patients with HFrEF, as measured by an improvement in NYHA Class (Pitt et al., 1999).

Several second-line agents are also available for select patients with CHF, to reduce signs and symptoms of fluid overload and over activation of the RAAS. These include angiotensin receptor blockers (ARB), vasodilators/nitrates, angiotensin receptor-neprilysin Inhibitor (ARNI), digoxin and diuretics (Ponikowski et al., 2016a, Atherton et al., 2018, Yancy et al., 2017). The point of effect for each of the pharmaceutical agents for CHF on the processes within the RAAS is depicted in Figure 2.13.

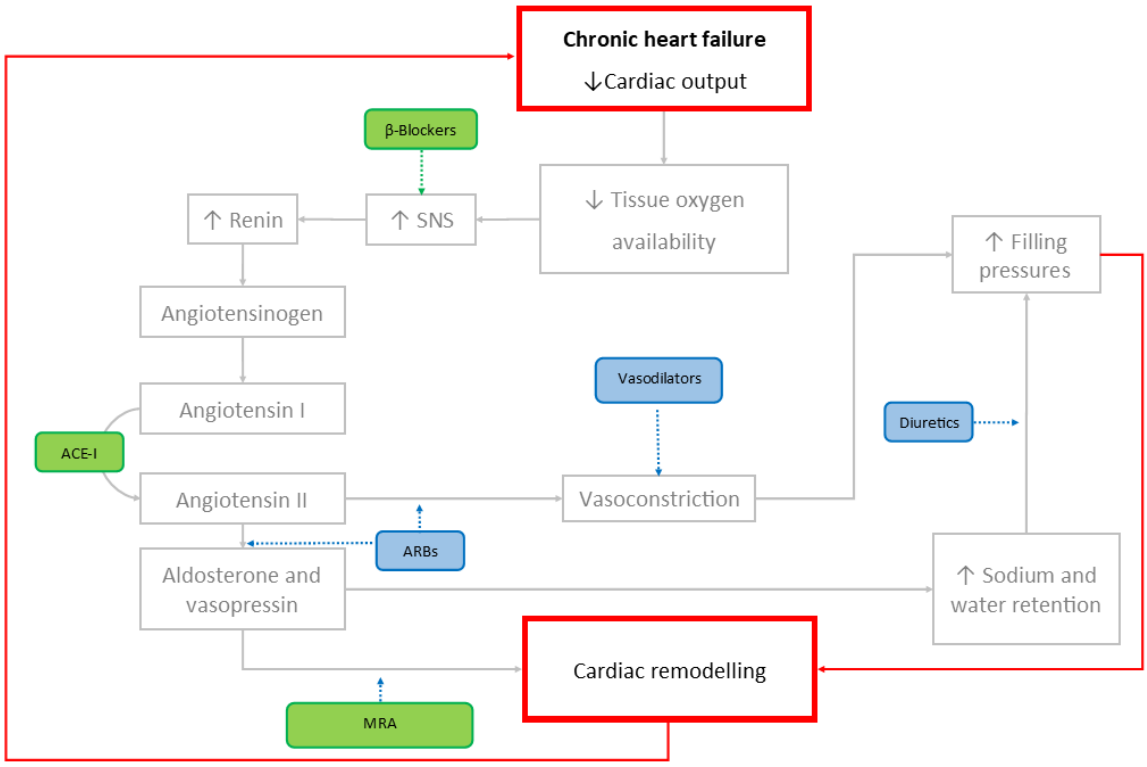

Figure 2.13: Pharmacotherapy agents and their effect on the RAAS

First-line pharmaceutical agents and their effect on the RAAS are shown in green and second-line pharmaceutical agents are shown in blue.

The evidence presented demonstrates a clear role for pharmacological treatment in the partial normalisation of the RAAS, which has follow-on benefits to mortality. However, despite the survival benefits, pharmacological treatment provides at best only partial benefits for aerobic capacity and other measures of physical fitness. Furthermore, the prevalence of polypharmacy (i.e. the prescription of ≥10 medications) is particularly common among older adults with CHF and carries a greater risk of excessive side effects, diminished effectiveness

and confusion (Unlu et al., 2020). For many patients the symptomatic burden remains significant despite optimal pharmacotherapy and many are unable to tolerate ADLs. Normalising physical impairments is equally important as improving survival and can be achieved by exercise training.

2.6 Clinical exercise rehabilitation

2.6.1 Exercise training: An overview

Exercise training is recommended for patients with CHF based on strong and consistent evidence that shows its beneficial effects on muscle function, aerobic fitness and quality of life (Atherton et al., 2018, Ponikowski et al., 2016a). Suitably designed exercise programs may also reduce the risk of hospitalisations and premature mortality (Long et al., 2019).

Broadly, exercise is characterised by two primary training modalities: aerobic and RT. The basic exercise prescription principle of *specificity* suggests that aerobic exercise primarily stimulates improvements in cardiorespiratory fitness, whereas resistance training stimulates improvements in muscle mass, strength and power (Swain and Brawner, 2014). Importantly, however, the unique skeletal muscle physiology pertinent to older adults with HFrEF (previously discussed in section 2.4.3) causes atypical adaptations achieved by each modality. This concept will be explored in the following review of the evidence for aerobic exercise and resistance training for patients with HFrEF.

2.6.1.1 Aerobic exercise

Aerobic exercise involves rhythmic activities that use a large muscle group and draw from aerobic metabolic systems to produce energy (Swain and Brawner, 2014). Examples of aerobic activities include running, walking and swimming. Due to the breadth of evidence investigating the benefits of aerobic exercise for people with HFrEF, the following section will summarise level 1 and level 2 evidence[3].

The importance of regular aerobic exercise for improving aerobic capacity in patients with HFrEF is clear. A meta-regression analysis by Vromen et al. (2016), including 17 studies and 2935 participants (median age of intervention group; 60 years [range 50 to 72], weighted mean EF; 26.8%) reported that aerobic training increased VO_{2peak} by 2.10 ml/kg/min in

[3] Refers to the National Health and Medical Research Council levels of research evidence that include data derived from randomised controlled trials and systematic reviews of randomised controlled trials (COUNCIL;, N. H. M. R. 2009. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. *NHMRC*.

comparison to the non-exercise control group (Figure 2.14, $p < 0.001$). The mean intensity of prescribed exercise of included studies ranged from 50–79% of $VO_{2peak,}$ while the mean program length was 12 weeks (range 4 to 39), of four sessions per week (range 3 to 20) and of 30 minutes in duration (range 18 to 57).

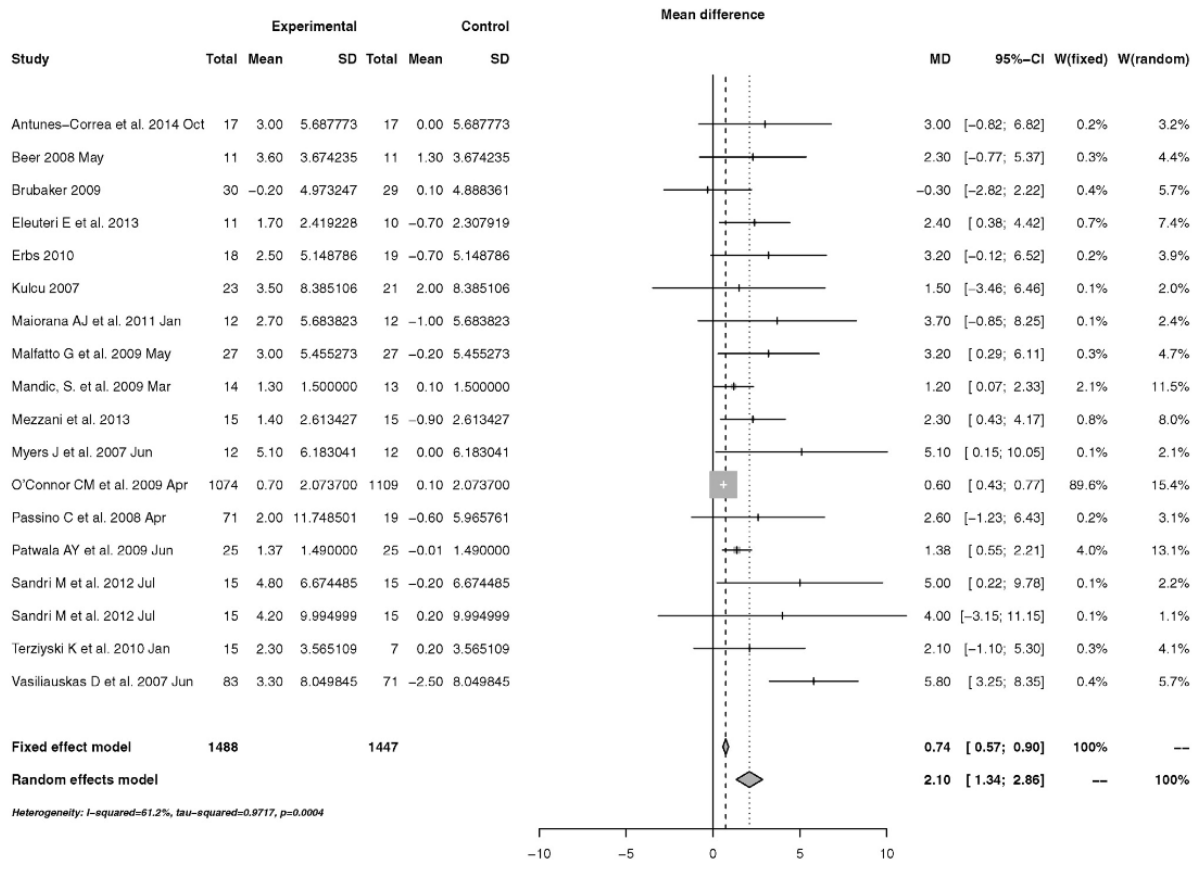

Figure 2.14: Forest plot of the effect of aerobic training on VO_{2peak} in patients with HFrEF

Aerobic training resulted in a group mean difference in VO_{2peak} of 2.10 $ml.min^{-1}.kg^{-1}$ ($p<0.001$)

Source: Vromen et al. (2016)

An abundance of randomised controlled trials (RCT) and meta-analyses also demonstrate the beneficial effect of aerobic exercise on quality of life and symptoms of depression (Tu et al., 2014) and on improving prognostic markers including VE/VCO_2 slope (Cipriano et al., 2014, Smart et al., 2012, Smart and Steele, 2010), N-terminal prohormone of brain natriuretic peptide (NTproBNP)(Smart et al., 2012, Smart and Steele, 2010) and vascular function as measured by flow-mediated dilation (Pearson and Smart, 2017).

Despite these proven benefits, a major limitation of this evidence is that most trials comprise a comparatively young participant cohort, compared to the typical patient with CHF. HF-ACTION, for instance, is the largest aerobic exercise study in CHF (n= 2331) and has a mean age of participants of only 59 years (O'Connor et al., 2009). Furthermore, among meta-analyses with outcomes for VO_{2peak} and VE/VCO_2 slope, the mean age of participants ranged from 51 to 60 years (Vromen et al., 2016, Gomes-Neto et al., 2019a). Remarkably, only four individual RCTs have investigated the effects of aerobic exercise in patients with HFrEF where the mean age of participants was greater than 70years (Brubaker et al., 2009, Nilsson et al., 2008, Antonicelli et al., 2016, Sandri et al., 2012b). The reported outcomes and exercise prescription among these studies vary considerably (Table 1).

Two of these measured aerobic capacity by VO_{2peak} (Brubaker et al., 2009, Sandri et al., 2012a). One study randomised 59 participants to a 16-week exercise program of walking and stationary cycling, 3 times per week for 30–40 minutes at moderate intensity (40–70% HRR) and found no changes in VO_{2peak} in comparison to a non-exercise control group (Brubaker et al., 2009). However, mean cycle ergometer distance per session and combined walking and cycle distance per session both increased significantly in the intervention group in comparison to baseline, suggesting improved functional capacity despite no change in VO_{2peak} (Brubaker et al., 2009). Sandri and Kozarez et al. (2012a) investigated the effect of a 4-week aerobic exercise training program in patients with HFrEF in two age categories (less than or equal to 55 years and greater or equal to 65 years) in comparison to age-matched non-exercise control groups, as well as in comparison to a cohort of healthy reference controls. Authors reported a 27% increases in VO_{2peak} in the older intervention group in comparison to baseline ($p=0.008$), whereas no changes in exercise capacity were reported among control groups (Sandri et al., 2012a). Interestingly, LVEF also increased in adults with HFrEF ≥65 years undertaking the exercise intervention, from 29±2% to 35±2% ($p < 0.05$ versus age-matched HFrEF control).

The remaining two studies among older adults with CHF (Table 1) measured functional capacity by 6MWD and reported significant increases in the intervention group compared to baseline (Antonicelli et al., 2016, Nilsson et al., 2008) and in comparison to the non-exercise controls (Nilsson et al., 2008). Regarding quality of life, Antonicelli and Spazzafumo et al. (2016) reported significant improvements in comparison to control (Antonicelli et al., 2016), whereas Brubaker and Moore et al. (2009) reported no difference between groups (Brubaker et al., 2009).

Table 2.6: A summary of aerobic exercise RCTs investigating where study participants had a mean age greater than 70 years (original table)

Author	Participants	Intervention	Outcomes (compared to baseline)	Outcomes (compared to control)
Antonicelli et al. (2016)	**n** = 343 **Age:** 76.9 ± 5.67 **EF:** 48.4±13.4 **Males:** 195 (56.9%)	**Mode:** Stationary bike **Frequency:** 3/week, 3 months (supervised) + 3 months (telemonitored) **Intensity:** 60 RPM, 60–70% predicted HR max **Duration:** General warm-up/cool down + (Bike) 5 min warm-up, 20 min efforts, 5 min cooldown **Progression**: Not specified **Control:** Non-exercise usual care	↑↑ 6MWD (3 months and 6 months)	↓↓ All-cause hospital admission ↑↑ HR QoL ↑↑ 6MWD (at 3 and 6 months)
Brubaker et al. (2009)	**n** = 59 **Age:** 70.2 ± 5.1 **EF:** 30.7% ± 9.0 **Male:** 39 (66%)	**Mode:** Track walking and stationary cycling **Frequency:** 3/week, 16 weeks **Intensity:** 40–50% HRR (first two weeks), 60–70% HRR **Duration:** 30–40 minutes + warm up/cool down **Control:** Non-exercise control	↑↑ Mean cycle ergometer distance per session ↑↑ Combined walking and cycle distance ↑ Walk distance per session	↑↑ Exercise time and workload ⇔ VO_{2peak} ⇔VE_{peak} ⇔ VE/VCO_2 slope ⇔ Ventilatory anaerobic threshold ⇔ LV volumes, EF, diastolic

				filling ⇔6MWD ⇔ QoL
Sandri et al. (2012a)	**n** = 30+ **EF:** 28+5% **Age:** 72 ± 5.0 **Male:**	**Mode:** Stationary Bike **Frequency:** 4/week, 4 weeks **Intensity:** 70% VO_{2peak} **Duration:** 20 minutes + warm up/cool down **Control:** Non-exercise, non-HF control	↑↑ VO_{2peak} □□ LVEF ↓↓ LV isovolumetric relaxation time ↑↑ E/A ratio ↓↓ DT ↑↑ septal E′ ↓↓ E/e′ ratio ↓↓ NT-proBNP	
Nilsson et al. (2008)	**n** = 80 **Age:** 70.1 ± 7.9 **EF:** 31% ± 8 (int) 31 ± 9 (con) **Male:** 63 (79%)	**Mode:** Aerobic dance (with music) **Frequency:** 2/week, 4 months **Intensity:** 15–18/20 Borg Scale **Duration:** 50 minutes including warm-up/cool down **Control:** Non-exercise control		↑↑ 6MWD (maintained at 12 months) ↑↑ Exercise time on exercise test (maintained at 12 months)

				↑↑ QoL (maintained at 12 months)

↓↓ Indicates significant reduction; ↓indicates non-significant reduction; ⇔ indicates no change; ↑↑ indicates a significant increase; ↑ indicates non-significant increase

QoL, quality of life; 6MWD, 6-minute walk distance; LV, left ventricle; E/e', ratio of early mitral inflow velocity and mitral annular early diastolic velocity; NT-proBNP, N-terminal pro B-type natriuretic peptide; HFNAQ, heart failure needs assessment questionnaire; HR, heart rate, VE, ventilatory equivalent; RPM, revolutions per minute.

+ Includes older age group only (i.e. ≥ 65 years)

Taken together, these findings suggest a potential benefit of aerobic training among older patients with HFrEF but the evidence is limited by the small number of studies and study limitations. Of note, Antonicelli et al. (2016) did not specify their method of progressing exercise intensity and the initial starting intensity was prescribed by a percentage of age-predicted HR max—a method which was reported to be unsuitable for patients on beta-blocker medications (Keteyian et al., 2012, Brawner et al., 2004).

Despite these limitations, current guidelines recommend aerobic exercise for all patients with HFrEF without specific mention of the evidence limitations for older adults and without special considerations for this patient group.

2.6.1.1.1 Interval aerobic training and high intensity interval training

Interval training involves aerobic training with alternating periods of work and rest (Cress et al., 2015). Prescription of exercise intensity for the rest period can include complete rest, or exercise prescribed at a lower relative intensity to the work phase (Cress et al., 2015). This method of alternating exercise intensity is particularly useful for individuals with limited aerobic capacity, as it allows for periods of recovery so that a greater net volume of exercise can be achieved in one exercise session. Interval training is shown to produce superior effects on VO_{2peak} and LVEF in comparison to continuous aerobic training (Pattyn et al., 2018, Smart et al., 2013, Haykowsky et al., 2013). Improvements in quality of life (Pattyn et al., 2018) and VT (Pattyn et al., 2018), however, appear similar when compared with continuous aerobic training.

High intensity interval training (HIIT) is a form of interval training that involves high intensity aerobic exercise (greater than 90% HRmax) for the work phase and is an effective exercise modality to increase VO_{2peak} in healthy populations (Milanovic et al., 2015, Ferguson, 2014). The knowledge that greater increases in VO_{2peak} can be achieved with higher intensity exercise has generated interest for the potential of HIIT for patients with CHF (Ismail et al., 2014). A systematic review and meta-analysis including 13 studies and 411 patients with HFrEF (mean age range; 58–65 years) found that HIIT was superior to continuous aerobic exercise in regard to increases in VO_{2peak}. However, no differences have been observed between groups for quality of life outcomes (Gomes Neto et al., 2018) or VE/VCO_2 slope (Xie et al., 2017) between the two modalities.

There are two primary issues which have prevented the routine use of HIIT for patients with CHF. First, exercising at higher intensity exercise is associated with a greater risk of

myocardial infarction or sudden death (Siscovick et al., 1984, Levinger et al., 2015), particularly in individuals who are habitually inactive or who have cardiac risk factors (Giri et al., 1999). Second, meta-analyses on HIIT generally recruit younger patients (mean range 57.0 to 65) (Pattyn et al., 2018, Haykowsky et al., 2013, Gomes Neto et al., 2018). Taken together, HIIT is not routinely recommended for patients with CHF.

2.6.1.2 Resistance training

Resistance training is designed to increase muscle mass, strength, power and size by exercising a muscle group against an external resistance (Swain and Brawner, 2014). Muscle strength is a key component of physical fitness and is important for weight management and overall cardiovascular health (Boo et al., 2019). In older individuals, muscular strength, power and endurance are particularly important for mobility, the performance of ADLs, quality of life and for reducing the risk of falls and fractures (Landi et al., 2012, Visser et al., 2002, Janssen et al., 2002, Boo et al., 2019, Williams et al., 2007, Torres et al., 2017, Scott et al., 2015).

Before the 1990s, there was a reluctance to implement resistance training for patients with CHF due to safety concerns that a high cardiac afterload observed during resistance training may adversely affect blood pressure responses and lead to further left ventricular remodelling (Mitchell and Wildenthal, 1974). These concerns have mostly been alleviated, with several studies confirming the integrity of the left ventricle during resistance training (Pu et al., 2001, Levinger et al., 2005, Karlsdottir et al., 2002, Meyer et al., 1999) and with consideration of general precautions for resistance training, such as avoidance of the Valsalva manoeuvre and proper basic resistance training techniques (Swain and Brawner, 2014) (Niewiadomski et al., 2012).

2.6.1.2.1 Resistance training as a standalone therapy

At the time of writing, few studies have investigated resistance training *as a standalone therapy* in patients with CHF. A meta-analysis by Hwang et al. (2010) that included 8 trials and 241 patients with HFrEF (EF range; 23 to 36%) found that resistance training significantly increased 6MWD versus usual care (weighted mean difference; 52m, 95% CI; 19 to 85) and also found a non-significant favourable trend on VO_{2peak} (weighted mean difference 1.4ml/kg/min) (Hwang et al., 2010). Data for the outcome of VO_{2peak}, however, was limited to only four included studies (Figure 2.15) and the age range among seven of the

eight included studies was 55 to 60 years, while one study (Pu et al., 2001) had a mean age of 77 years.

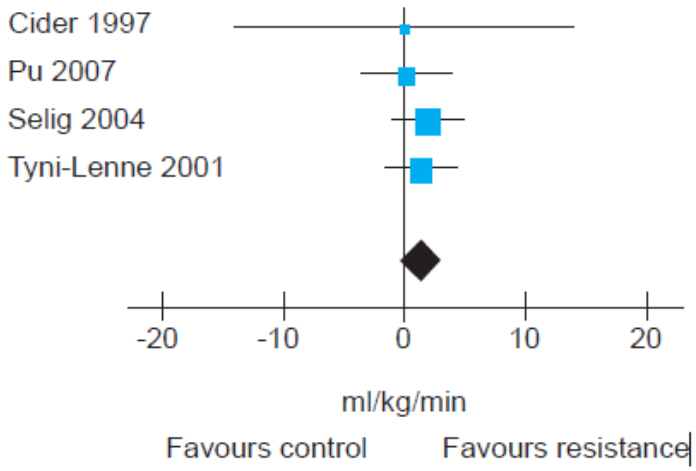

Figure 2.15: The weighted mean difference (1.4ml.kg^{-1}.min^{-1}) of effect of resistance training on VO_{2peak} compared with non-exercise control.

Source: (Hwang et al., 2010)

The limited attention to resistance training within exercise training research for patients with CHF may be due to its lesser effect on aerobic capacity in comparison to other exercise modalities. For instance, a review by Smart (2013) ranked training modalities according to improvement in VO_{2peak} in patients with CHF and found that resistance training performed the lowest according to peak VO_2 response (Smart, 2013) (**Box 2.1**).

Hierarchy of training modality arranged from highest to lowest according to reported Peak VO_2 response
High-intensity interval exercise
Moderate-intensity continuous aerobic exercise (outpatient and home-based)
Functional electrical stimulation inspiratory muscle training
Aerobic exercise (home-based only)
Combined aerobic and resistance training
Resistance training

Box 2.1: A Hierarchy of training modality arranged from highest to lowest according to reported Peak VO_2 response.

Source: Smart (2013)

This hierarchy of training modalities, however, may not apply to older patients with CHF, who are underrepresented across the existing exercise literature and in whom the potential benefits of resistance training may go beyond general health and strength outcomes. As previously discussed (section 2.4.3) the combination of age and CHF-related sarcopenia contributes to exercise intolerance, with skeletal muscle mass and strength acting as strong predictors of VO_{2peak} in patients with CHF (Mancini et al., 1992, Cicoira et al., 2001, Anker et al., 1997). Furthermore, muscle strength is a strong predictor of mortality in patients with CHF (Hülsmann et al., 2004) and skeletal muscle mass and strength are associated with a greater distance achieved during the 6-minute walk test among older adults with CHF (Koshikawa et al., 2020)

As described previously (section 2.3.3) the muscle hypothesis of CHF suggests that exercise intolerance in CHF is largely due to impairments in peripheral tissues. This knowledge has led to the hypothesis that targeting muscle dysfunction may interrupt these maladaptive feedback loops and improve exercise tolerance (Piepoli et al., 1996a). Resistance training has also been suggested as a possible alternative for patients who have insufficient capacity to tolerate aerobic exercise, such as those who are elderly or have more advanced disease (Jankowska et al., 2008, Koch et al., 1992, Smart, 2013).

Several additional RCTs investigating the effect of resistance training on aerobic capacity have been undertaken since the meta-analysis of Hwang et al. (2010). Study 2, Chapter 4 of this thesis further analyses the effects of resistance training as a standalone therapy on muscle strength, aerobic capacity and quality of life in patients with CHF.

2.6.1.2.1 Resistance training as an adjunct therapy

It is well documented that resistance training *as an adjunct* to aerobic training has many benefits for patients with CHF. This evidence base includes specifically designed RCTs, as well as comprehensive reviews of cardiac rehabilitation (CR) programs. Meta-analyses report superior increases in quality of life with combined aerobic and resistance training compared to continuous aerobic exercise (Cornelis et al., 2016) but little difference is reported for change in VO_{2peak} (Hwang et al., 2010, Cornelis et al., 2016, Mandic et al., 2009) or in VE/VCO_2 slope (Cornelis et al., 2016).

In an RCT including 58 patients with HFrEF (mean age range; 58 to 59 years, mean EF; 23 to 26%) comparing the effect of combined training versus aerobic training, combined training produced superior improvements to steady-state workload, upper limb one repetition maximum (1RM) muscle strength and health-related quality of life ($p < 0.001$). However, there was no difference between groups for outcomes of VO_{2peak}, lower leg strength, maximal workload and work-economy ($Wattmax/VO_{2peak}$) (Beckers et al., 2008). Similarly, in an RCT investigating combined versus aerobic training in 52 patients with CHF (mean age; 62 ± 12 years, NYHA ranges I to III), leg press strength significantly improved from baseline in the combined group but not the aerobic group and chest press strength increased significantly more in the combined exercise group versus aerobic only. Neither intervention improved VO_{2peak} (Mandic et al., 2009).

Several reviews have also investigated the effect of combined aerobic and resistance training on the risk of mortality and hospitalisations. The most comprehensive and recent review by the Cochrane group included 44 trials and 5783 participants (mean age range 51 to 81 years) receiving exercise-based CR (in which all trials involved an aerobic intervention and 14 trials also included resistance training). This study reported that exercise training made little or no difference to short term all-cause mortality at less than 1-year follow-up but may improve all-cause mortality with greater than 12-month follow-up (Long et al., 2019). Low-moderate quality evidence (as assessed by the GRADE method (Schünemann et al., 2019)) supported

CR for reducing the risk of all-cause and HF-related hospital admissions and improved quality of life within 12-months of follow-up (Long et al., 2019).

The limited benefit for mortality and hospitalisations was also demonstrated in an individual patient data meta-analysis, EXTRAMATCH II, which included 18 trials (in which all trials included aerobic exercise and six additionally included resistance training) and 3912 patients (mean age 61±13 years, mean EF 26.7%) (Taylor et al., 2018). Results showed that CR did not have a significant effect on mortality or hospitalisation (median follow up 11.2 to 18.6months) (Taylor et al., 2018). Bjarnason-Wehrens et al. (2019) also found no difference in 6 to 12 month mortality or hospitalisation in a systematic review and meta-analysis of exercise-based CR (25 studies; n=4481, LVEF less than or equal to40%)(Bjarnason-Wehrens et al., 2019).

Taken together, these findings suggest that resistance training provides an additive benefit for improving quality of life and measures of muscular strength when combined with aerobic training in patients with HFrEF.

The evidence for combined aerobic and resistance training, however, is also limited by a large age-recruitment bias. Figure 2.16 is a graphical illustration of the mean age of participants among studies included in the 2019 Cochrane Review, in comparison to the mean age at diagnosis of CHF (76.4 ± 12 years [35]). Only 15 of the 44 included studies (29%) had a mean age of participants within the mean and standard deviation (SD) range of age at diagnosis of CHF. Consequently, it is unclear whether combined aerobic and resistance training is an effective exercise modality for improving aerobic capacity and muscular strength in older adults with CHF. These limitations were considered in Study 3, Chapter 5 of this thesis, which will determine whether older patients with HFrEF can benefit from combined moderate-intensity aerobic and resistance training.

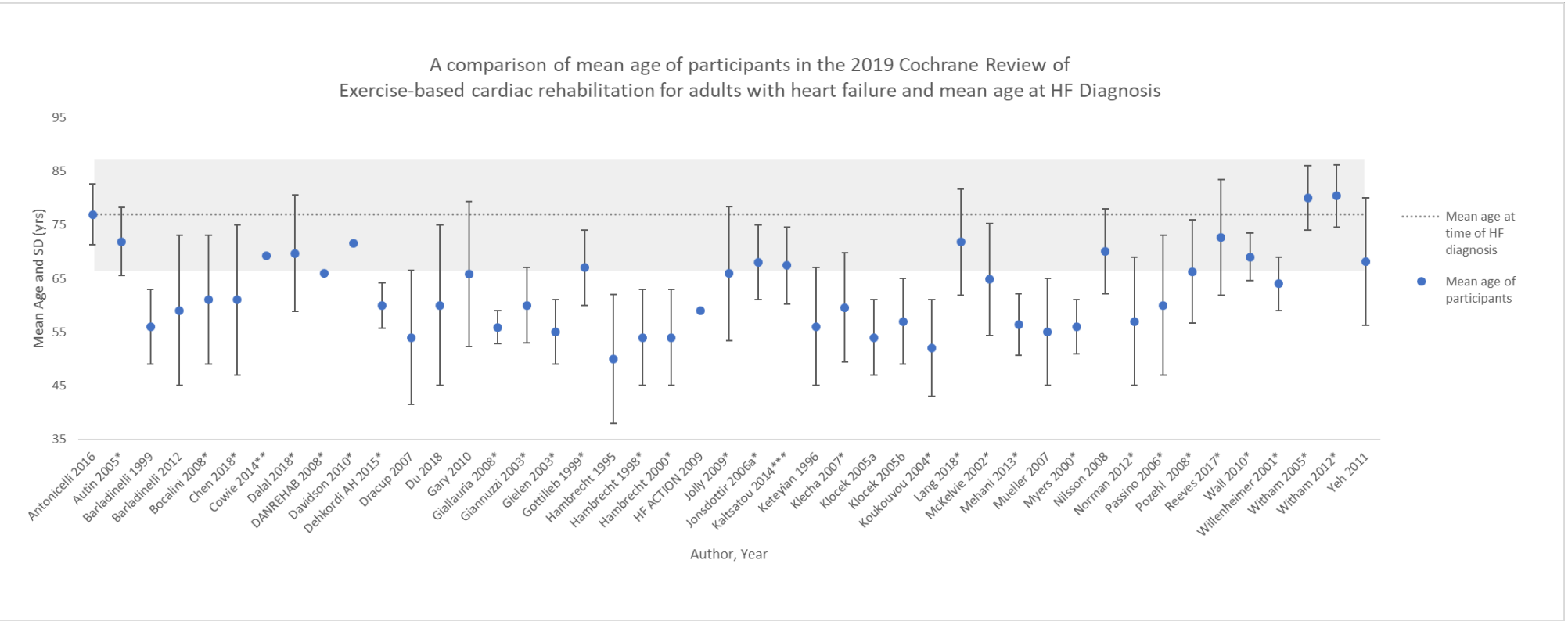

Figure 2.16: A graphical illustration of the mean age of participants (y-axis) among studies included in the 2019 Cochrane review of exercise-based cardiac rehabilitation for adults with heart failure (y-axis), in comparison to the mean age and SD at diagnosis of CHF (mean indicated by the grey dotted line and SD by shaded area) (Original Figure).

Authors with an * indicate the mean age reported was for the intervention group only

2.6.1.3 PRIME: A novel exercise for older adults

It was recently demonstrated that healthy older individuals (mean age 76.0 ± 4.9 years) with reduced aerobic capacity (VO_{2peak} less than 20 ml/kg/min) can benefit from a novel exercise regime known as Peripheral Remodelling through Intermittent Muscular Exercise, PRIME (Allen et al., 2018, Allen et al., 2013). PRIME offers a hybrid aerobic-resistance program and was designed to address the peripheral tissue dysfunctions responsible for reduced VO_{2peak} in older adults without imposing excess cardiovascular or musculoskeletal strain (Allen et al., 2013). By focusing initially on individual muscle groups with low weights and a high number of repetitions, PRIME aims to provide a localized stimulus not restricted by compromised or competing perfusion. As shown in Figure 2.17, when PRIME is applied as a bridging therapy to a traditional approach of combined aerobic and resistance training, participants experience greater increases in aerobic capacity, muscle strength and physical function compared to combined training alone.

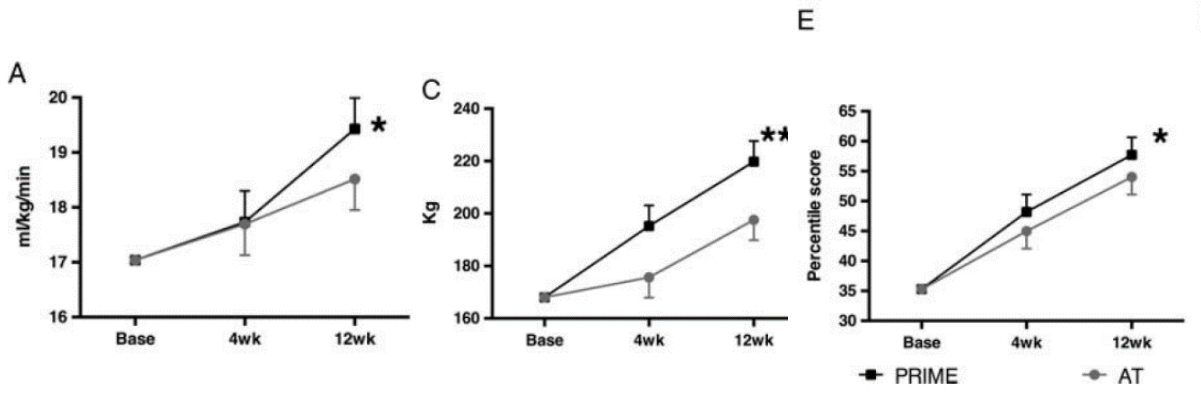

Figure 2.17: Group mean data of training response to PRIME and aerobic exercise treatment

The left panel represents VO_{2peak}; middle panel represents the combined maximal voluntary contraction and right panel represents the percentile ranking for the senior fitness assessment. Statistical significance is denoted as *p = 0.05, †p = 0.01

Source: Allen et al. (2018).

These results suggest that early improvement in the peripheral tissue resulting from the PRIME regimen allowed for greater potential functional gains once the individual progressed into a well-rounded training program that also included larger muscle volume and therefore

cardiac stimulation. This makes PRIME an ideal initial regimen for people with central aerobic limitations and low levels of initial physical function, such as CHF but this approach is yet to be tested in clinical populations.

Study 3, Chapter 5 of this thesis will test for the first time the hypothesis that four weeks of PRIME training before 4 weeks of combined moderate-intensity aerobic and resistance training (COMBO) will improve aerobic capacity and muscle strength to a greater extent than 8 weeks of COMBO.

2.6.2 Current exercise guidelines

Based on the high-quality evidence summarized earlier, exercise training is considered an integral part of the rehabilitation process for patients with HFrEF and is recommended by leading cardiac institutions around the world (Ponikowski et al., 2016a, Atherton et al., 2018, Piepoli et al., 2011, Selig et al., 2010a) (Table 2.7). However, there is no universal agreement on exercise prescription (i.e. frequency, intensity, modality, duration)(Price et al., 2016).

To date, aerobic exercise is the foundation of all exercise guidelines for patients with CHF (Price et al., 2016). The two most recent guidelines from Europe and Australia and New Zealand recommend moderate-intensity aerobic exercise for patients with HFrEF (Ponikowski et al., 2016a, Atherton et al., 2018). These documents cite evidence established by the 2014 Cochrane review (Anderson and Taylor, 2014) (updated in 2019 (Long et al., 2019) and by the HF-ACTION trial (O'Connor et al., 2009).

Guidelines from Europe and North America support the progression of aerobic exercise to high-intensity (80–90 % of VO_2 peak) as tolerated (Price et al., 2016, Achttien et al., 2015) and suggest interval training as a useful approach for select patients, such as those who are frail (Price et al., 2016, Pavy et al., 2012, Herdy et al., 2014).

The additive benefit of resistance training to general health and fitness is well recognised and an exercise program of combined aerobic and resistance training is the mainstay approach for patients with CHF (Atherton et al., 2018, Piepoli et al., 2011, Balady Gary et al., 2007, Selig et al., 2010a). Some institutions still take caution by recommending periods of 2–6 weeks of aerobic training before introducing resistance training (Price et al., 2016). Resistance training is not currently recommended *as a standalone therapy* for patients with CHF, due to the minimal benefit for improvement in aerobic capacity in comparison to other modalities.

Table 2.7: Recommendations for exercise testing, prescriptions and monitoring in outpatient cardiac rehabilitation programs for independent regions and nations, including leading cardiac rehabilitation n organisations. Source: Price et al. (2016)

Country	Type of exercise	Intensity of exercise	Duration and frequency of sessions	Programme length	Exercise testing and monitoring	Expectations for additional activity
Leading cardiology and cardiac rehabilitation organizations						
Europe (European Association of Cardiovascular Prevention and Rehabilitation)[21,27]	**Aerobic endurance training** (e.g. walking, jogging, cycling, swimming, rowing, stair climbing, elliptical trainer, aerobics)	50–80% VO_{2max} (close to anaerobic threshold) 50–80% HR_{peak} or 40–60% HRR RPE 10–14	≥20–30 minutes per session ≥3 sessions per week (preferably 6–7)	2–16 weeks	**Exercise testing** Symptom-limited exercise test **Monitoring** Observation of symptoms HR monitoring BP monitoring ECG monitoring during initial stages or for patients with new symptoms	Equivalent of 30 minutes of moderate-intensity walking per day
	Resistance training	To moderate fatigue	10–15 reps per set 2 sessions per week			
Canada (Canadian Association of Cardiac Rehabilitation)[20]	**Aerobic endurance training**	40–85% HRR	20–40 minutes per session 3–5 sessions per week	≥12 weeks	**Exercise testing** Graded exercise test (Bruce protocol) with ECG monitoring **Monitoring** HR monitoring BP monitoring RPE ECG monitoring at discretion of medical director (progress from continuous monitoring to intermittent as appropriate for risk level of patient) Respiratory rate if indicated Arterial oxygen saturation	Encouraged to engage in lighter forms of physical activity on days when not attending a formal exercise session in order to accumulate 30–60 minutes of moderate- to vigorous-intensity on most days of the week
	Aerobic interval training	Not specified				
	Resistance training	30–40% 1RM for upper body 50–60% 1RM for lower body	1–3 sets of 12–15 reps for 6–10 different exercise for both upper and lower body 2–3 sessions per week			
	Flexibility training	Not specified	Static stretching: ≥4 reps per exercise, 15–60 seconds per stretch PNF stretching: 6-second contraction followed by 10–30 second assisted stretch			

Table 2.6 (continued)

Country	Type of exercise	Intensity of exercise	Duration and frequency of sessions	Programme length	Exercise testing and monitoring	Expectations for additional activity
United States (American Heart Association, American Association of Cardiovascular and Pulmonary Rehabilitation)[18,19,70]	**Aerobic endurance training** (e.g. walking, treadmill, cycling, steps, rowing)	40–80% VO_{2peak} or HR_{max} based on maximal exercise test RPE 11–16	20–60 minutes per session 3–5 sessions per week	≤36 sessions	**Exercise testing** Symptom-limited exercise test strongly recommended **Monitoring** Observation of symptoms HR monitoring BP monitoring RPE ECG (progress from continuous monitoring to intermittent as appropriate for risk level of patient)	Home-based physical activity to achieve 30–60 minutes per day of moderate-intensity activity on at least 5 days of the week
	Resistance training (e.g. calisthenics, hand weights, pulleys, dumbbells, free weights, machine weights)	To moderate fatigue (RPE 11–13) 50% 1RM progressing to 60–70% 1RM	1–3 sets of 10–15 reps for 8–10 different exercises 2–3 sessions per week (non-consecutive days)			
	Flexibility training (static stretching with emphasis on lower back and thigh)	To point of mild discomfort	3–5 reps per exercise, 30–90 seconds for each stretch as tolerable 2–3 sessions per week (non-consecutive days)			
Independent nations and regions						
Japan (Japanese Circulation Society)[29]	**Aerobic endurance training** (e.g. aerobics, cycling)	At anaerobic threshold (40–60% VO_{2peak}, 40–60% HRR, RPE 12–13)	15–60 minutes per sessions 1–3 sessions per week	5 months (first 5 months following treatment)	**Exercise testing** Exercise stress test **Monitoring** HR monitoring BP monitoring RPE ECG monitoring recommended if chest pain is experienced	3–4 days per week of home-based training prescribed through the programme

(continued)

Table 2.6 (continued)

Country	Type of exercise	Intensity of exercise	Duration and frequency of sessions	Programme length	Exercise testing and monitoring	Expectations for additional activity
Australia (National Heart Foundation of Australia, Australian Cardiovascular Health and Rehabilitation Association)[6,22,23,42]	**Aerobic endurance training** (e.g. walking, cycling, treadmill, dancing) **Resistance training**	Low- to moderate-intensity physical activity As appropriate	30–60 minutes per session (NSW) 1–2 sessions per week Not specified	3–12 weeks	**Exercise testing** 6-minute walk test (NSW) Symptom-limited maximal exercise stress test recommended prior to high-intensity programme or for high-risk patients **Monitoring** Observation of symptoms HR monitoring BP monitoring RPE ECG monitoring for high-intensity programmes or high-risk patients (VIC) Respiratory rate if indicated	At least 30 minutes of light- to moderate-intensity physical activity on most days of the week through home-based activities
New Zealand (New Zealand Guidelines Group, National Heart Foundation of New Zealand)[24]	**Aerobic endurance training** **Resistance training**	40–75% VO_{2max} Low intensity and high reps	30–45 minutes per session 3–5 sessions per week Not specified	6–12 weeks	**Exercise testing** Exercise stress test (not necessary for low-risk patients undertaking supervised low- to moderate-intensity exercise training) **Monitoring** Observation of symptoms HR monitoring	At least 30 minutes of moderate physical activity on most days of the week

(continued)

Table 2.6 (continued)

Country	Type of exercise	Intensity of exercise	Duration and frequency of sessions	Programme length	Exercise testing and monitoring	Expectations for additional activity
South America (South American Society of Cardiology, Inter-American Committee of Cardiovascular Prevention and Rehabilitation)[25]	**Aerobic endurance training**	60–80% HR_{max} or 50–70% HRR (beginning at lower limit of range) At anaerobic threshold	30–60 minutes per session 2–5 sessions per week	1–5 months	**Exercise testing** Exercise stress test with ECG monitoring (or 6–minute walk test) **Monitoring** ECG (progress from continuous monitoring to intermittent as appropriate for risk level of patient)	Not specified
	Aerobic interval training	Not specified				
	Resistance training	Load sufficient to cause fatigue for final 3 reps	6–15 reps per muscle group at an interval of 20–60 seconds 2–3 sessions per week			
	Flexibility training	Not specified	At end of each session			
World Health Organization (emphasis on developing countries)[4]	**Aerobic endurance training** (e.g. stationary cycle, rowing, stepping as part of a circuit) **Resistance training** (e.g. light weights and pulley exercises for upper body as part of a circuit) **Flexibility training** (calisthenics)	High intensity (60–75% peak work capacity or 70–85% HR_{peak}) Low/moderate intensity HR <20 bpm above resting HR (symptom and observation limited)	20–30 minutes per session ≥3 sessions per week 30–60 minutes including 15 minutes of calisthenics at beginning of session ≥2 sessions per week	≥6–8 weeks	**Exercise testing** Treadmill exercise test **Monitoring** For basic and intermediate facilities: HR monitoring RPE For advanced facilities: as above, plus ECG (progress from continuous monitoring to intermittent as appropriate for risk level of patient)	Home-based, moderate-intensity activity or walking for 30 minutes per day plus twice-daily calisthenics

VO_{2max}: maximal oxygen uptake; HR_{peak}: peak heart rate; HRR: heart rate reserve; RPE: rating of perceived exertion (based on Borg 6–20 scale); reps: repetitions; HR: heart rate; BP: blood pressure; ECG: electrocardiograph; 1RM: one-repetition maximum; PNF: proprioceptive neuromuscular facilitation; VO_{2peak}: peak oxygen uptake; HR_{max}: maximum heart rate; NSW: New South Wales (Australian state); VIC: Victoria (Australian state).

Table 2.6 (continued)

Country	Type of exercise	Intensity of exercise	Duration and frequency of sessions	Programme length	Exercise testing and monitoring	Expectations for additional activity
Europe (European Association of Cardiovascular Prevention and Rehabilitation)[21,27]	**Aerobic endurance training** (e.g. walking, jogging, cycling, swimming, rowing, stair climbing, elliptical trainer, aerobics)	50–80% VO_{2max} (close to anaerobic threshold) 50–80% HR_{peak} or 40–60% HRR RPE 10–14	≥20–30 minutes per session ≥3 sessions per week (preferably 6–7)	2–16 weeks	**Exercise testing** Symptom-limited exercise test **Monitoring** Observation of symptoms HR monitoring BP monitoring ECG monitoring during initial stages or for patients with new symptoms	Equivalent of 30 minutes of moderate-intensity walking per day
	Resistance training	To moderate fatigue	10–15 reps per set 2 sessions per week			
Austria (Austrian Cardiac Society)[26]	**Aerobic endurance training**	50–70% symptom-limited HR 80–90% of HR at anaerobic threshold	Phase II: 10–30 minutes per session 3 sessions per week Phase III: 20–50 minutes per session 2 sessions per week	Phase II: 4–6 weeks Phase III: 6–12 month (depending on the status of the patient)	**Exercise testing** Maximal ergometry including exercise ECG **Monitoring** Not specified	Phase III: minimum of 20–40 minutes per week (1 session) progressing to minimum of 3 sessions by second half of this phase, exercising at same intensity as during supervised sessions
	Resistance training	<50% 1RM progressing to 60–80% 1RM	1–2 sets of 8–15 reps for 6–8 muscle groups 2 sessions per week			
	Flexibility training	Not specified	Not specified			
Belgium (Belgian Society of Cardiology)[38]	**Aerobic endurance training**	45–85% VO_{2peak} 60–90% HR_{max}	40–60 minutes per session 3–5 sessions per week	12 weeks (but may continue for up to 38 weeks if required)	**Exercise testing** Maximal exercise test Submaximal test (if maximal test is contraindicated) **Monitoring** ECG monitoring advised for high-risk patients	Not specified
	Aerobic interval training	Not specified				
	Resistance training (dynamic with machine weights)	50–60% 1RM Weight that can be lifted for 8–10 reps	1–3 sets for 8–10 exercises			

(continued)

Table 2.6 (continued)

Country	Type of exercise	Intensity of exercise	Duration and frequency of sessions	Programme length	Exercise testing and monitoring	Expectations for additional activity
England (Department of Health, National Institute for Health and Care Excellence, National Health Service)[30]	Not specified	Moderate intensity	For sufficient time to result in a safe and appropriate physiological challenge within the session At least 2 sessions per week	6–12 weeks	**Exercise testing** Functional capacity testing (ergometer test or walking/step tests) **Monitoring** HR monitoring BP monitoring RPE Rate-pressure product	30 minutes of exercise on 5 days of the week
France (French Society of Cardiology)[28]	**Aerobic endurance training** **Aerobic interval training**	60% HRR (constant intensity) Up to 2 minutes at 80–95% VO_{2max}, 1–4 minutes of active recovery (20–30% VO_{2max})	20–60 minutes per session 3–6 sessions per week	≥20 sessions	**Exercise testing** Exercise stress test (maximal or symptom limited) 6–minute walk test **Monitoring** HR monitoring BP monitoring Telemetry monitoring (for initial training sessions)	Equivalent of 30 minutes of moderate-intensity walking per day
	Resistance training (dynamic)	30–50% 1RM	10–15 reps, 8–10 different exercises (20–30 minutes) 2–3 sessions per week			
	Flexibility training (gymnastics exercises)	Not specified	Not specified			
Germany[a] (German Federation for Cardiovascular Prevention & Rehabilitation)[17,31]	**Resistance training** (dynamic)	Pre-training: <30% MVC Muscular endurance training: 30–50% MVC (RPE 12–13) Hypertrophy/strength training: 40–60% MVC (RPE ≤15)	Pre-training: 1–3 sets of 5–10 reps Muscular endurance training: 1 set of 12–25 reps Hypertrophy/strength training: 1 set of 8–15 reps 2–3 sessions per week	3 weeks (with extensions only in exceptional circumstances)	**Exercise testing** Exercise stress test (symptom limited) **Monitoring** HR monitoring RPE BP monitoring (before and after session) Observation of symptoms ECG (during early stages of programme)	Not specified

(continued)

Table 2.6 (continued)

Country	Type of exercise	Intensity of exercise	Duration and frequency of sessions	Programme length	Exercise testing and monitoring	Expectations for additional activity
Ireland (Irish Association of Cardiac Rehabilitation)[5]	**Aerobic endurance training**	40–80% VO_{2peak} 50–85% HR_{max} 40–70% HRR RPE 13–16	30 minutes per session ≥2 sessions per week	≥6 weeks	**Exercise testing** Functional capacity testing using Bruce protocol, 6–minute walk test, shuttle walk test or Chester step test **Monitoring** ECG (progress from continuous monitoring to intermittent as appropriate for risk level of patient)	Not specified
	Resistance training (dynamic)	Pre-training: <30% MVC Muscular endurance training: 30–50% MVC (RPE 12–13) Hypertrophy/strength training: 40–60% MVC (RPE ≤15)	Pre-training: 1–3 sets of 5–10 reps Muscular endurance training: 1 set of 12–25 reps Hypertrophy/strength training: 1 set of 8–15 reps 2–3 sessions per week			
The Netherlands (Royal Dutch Society for Physical Therapy)[34,41]	**Aerobic endurance training**	Increase from 50–80% VO_{2max}/HRR (determined by maximal or symptom-limited test)	20–30 minutes per session 3–5 sessions per week	Not specified	**Exercise testing** Maximal or symptom-limited exercise test with ECG monitoring Functional exercise capacity test (shuttle walk test or 6–minute walk test) **Monitoring** HR monitoring BP monitoring RPE ECG monitoring for complex conditions	Moderate-intensity endurance training (RPE 11–13) for 45–60 minutes preferably on every day for reduction of cardiovascular risk factors
	Aerobic interval training	4–minute blocks, 80–90% VO_{2peak}/HRR, 3 minutes of active recovery (40–50% VO_{2peak}/HRR)				
	Resistance training (circuit training and functional exercises)	Increase from 50 to 70–80% 1RM	1–3 sets of 10–15 reps for 8–10 exercises 2–3 sessions per week			
Northern Ireland (Clinical Resource Efficiency Support Team)[33]	**Aerobic endurance training** (e.g. cycling, walking)	Low to moderate intensity	20–30 minutes per session 2 sessions per week	≥8 weeks	**Exercise testing** Functional exercise capacity test (e.g. shuttle walk test) Exercise stress test with ECG recommended for high-risk patients or high-intensity exercise programmes **Monitoring** HR monitoring RPE	Additional home exercise programme
	Resistance training	Not specified	Not specified			

(continued)

Table 2.6 (continued)

Country	Type of exercise	Intensity of exercise	Duration and frequency of sessions	Programme length	Exercise testing and monitoring	Expectations for additional activity
Scotland (Scottish Intercollegiate Guidelines Network)[32]	**Aerobic endurance training** **Resistance training**	Low to moderate intensity Not specified	Long-duration sessions ≥2 sessions per week Single set of 10–15 reps per exercise 2–3 sessions per week	≥8 weeks	**Exercise testing** Functional exercise capacity test (shuttle walk test or 6–minute walk test) Maximal exercise test with exercise ECG only recommended for high-risk patients or high-intensity activity **Monitoring** HR monitoring RPE	Not specified
United Kingdom (Association of Chartered Physiotherapists in Cardiac Rehabilitation, British Association for Cardiovascular Prevention and Rehabilitation)[35,39]	**Aerobic endurance training** **Resistance training** **Flexibility training** (static, ballistic or PNF stretches)	Moderate intensity 40–70% HRR RPE 11–14 30–40% 1RM for upper body 50–60% 1RM for lower body Progress to 50–80% 1RM for both To point of tightness	20–60 minutes per session 2–3 sessions per week 2–4 sets of 8–12 reps for 8–10 muscle groups 2–4 sessions per week 2–4 reps, accumulating 60 seconds per stretch 2–3 sessions per week	4–24 weeks (depending on the status of the patient)	**Exercise testing** Functional capacity test (6–minute walk test/shuttle walk test/Chester step test or submaximal or symptom-limited ergometer test – no ECG monitoring) **Monitoring** Observation of symptoms HR monitoring BP monitoring RPE Oxygen saturation by pulse oximetry if indicated by condition	Not specified

(continued)

Table 2.6 (continued)

Country	Type of exercise	Intensity of exercise	Duration and frequency of sessions	Programme length	Exercise testing and monitoring	Expectations for additional activity
Wales[b] (Welsh Assembly Government, Aneurin Bevan Health Board)[36]	Not specified	Not specified	Session duration not specified 2 sessions per week	≥8 weeks	**Exercise testing** Functional capacity test (6–minute walk test/shuttle walk test/Chester step test/ergometer test) Exercise tolerance test **Monitoring** Not specified	Not specified

VO_{2max}: maximal oxygen uptake; HR_{peak}: peak heart rate; HRR: heart rate reserve; RPE: rating of perceived exertion (based on Borg 6–20 scale); reps: repetitions; HR: heart rate; BP: blood pressure; ECG: electrocardiograph; 1RM: one-repetition maximum; VO_{2peak}: peak oxygen uptake; HR_{max}: maximum heart rate; MVC: maximum voluntary contraction; PNF: proprioceptive neuromuscular facilitation.
[a]Only resistance training recommendations for cardiac rehabilitation have been published in English for Germany. Recommendations for aerobic endurance training were not located in English for inclusion in this review.
[b]The policy document for cardiac rehabilitation in Wales contains limited exercise prescription recommendations and does not refer to other guidelines for this information.

2.6.3 Cardiac rehabilitation: program content and uptake

Cardiac Rehabilitation (CR) was first offered in an outpatient setting in the early 1990s as a means to deliver exercise training and to provide education and secondary prevention to patients with cardiovascular disease (American Heart Association, 1994). In Australia, CR caters for patients with a range of heart diseases including, but not limited to, CAD, heart transplant recipients, patient with cardiac arrhythmias and CHF. Provision of CR is guided by key documents from the National Heart Foundation of Australia and the Australian Cardiac Rehabilitation Association (National Heart Foundation of Australia and Australian Cardiac Rehabilitation Association, 2004, Woodruffe et al., 2014). These documents describe CR as an integrated pathway spanning the continuum of care across 3 phases: commencing during the inpatient period after an acute episode (Phase I), continuing through the post-discharge period, often in an outpatient setting (Phase II) and subsequently to a community-based maintenance program for ongoing adherence to exercise and healthy lifestyle (Phase III) (Giuliano et al., 2017) (see Appendix A).

Despite the disparity between guidelines regarding the optimal exercise modality there appears to be little variation in program content among Australian CR providers (Palmer et al., 2019, Abell et al., 2016). In a cross-sectional survey of 251 Australian centres offering exercise-based cardiac rehabilitation, 235 centres (96%) included a resistance component in addition to aerobic exercise, 74% of which were in a circuit-based format (Abell et al., 2016). Only 1% of Australian programs report using HIIT—a lack of resources and staff knowledge being perceived as the biggest barrier amid concerns about the required pre-screening and safety requirements (Hannan et al., 2018).

Even with the unequivocal benefits of CR, programs are currently underutilised. A study from the US investigated the rates of referral to CR among patients with CHF and found that only 6–10% of patients were referred to CR following an acute admission with acute decompensated heart failure (ADHF) (Golwala et al., 2015). Multivariable analysis showed that younger age and fewer comorbid conditions were associated with referral.

A preliminary explorative study, “Barriers to Exercise Rehabilitation in older adults with heart failure” was completed before the commencement of this thesis by Giuliano et al. (2015) (Appendix B) and found that only 4% of older adults with CHF attended CR following admission with acute decompensated heart failure. This study was small and limited to a single hospital site. Currently, no data are available from an Australian

perspective regarding referral rates to CR among older patients with CHF and little is known about the root causes of variable rates of referral to and participation in CR. This provided the impetus for developing Chapter 3, Study 1 of this thesis, which investigates rates of referral to CR following hospitalisation with acute HF and identifies factors associated with referral and participation, as well as Study 4, Chapter 6, which describes the factors associated with enrolment and non-enrolment among patients screened for exercise in the context of a randomised controlled trial of exercise training in older patients with CHF.

2.7 Summary of Chapter 2

CHF is a prevalent and progressive syndrome that causes significant economic and personal burdens. Whereas the underlying pathophysiology of CHF involves central abnormalities (i.e. a reduction in SV and CO), reductions in exercise tolerance are primarily due to peripheral pathologies. Older adults with CHF, who constitute the majority of the CHF population, are uniquely characterised by comorbidities including sarcopenia and frailty.

Treatment by pharmacological agents can reduce mortality but they have little effect on quality of life or functional capacity. Exercise training delivers a range of unique benefits for patients with CHF including increases in aerobic power, muscle strength and quality of life. However, a key limitation of the current exercise literature and exercise clinical guidelines is that older adults are under-represented across clinical trials. Consequently, the transferability of study findings and the applicability of guideline-based recommendations for exercise have limited application to many patients with CHF who are older.

Furthermore, there is little information about the referral rates to cardiac rehabilitation amongst patients discharged from hospital with CHF and it is unclear what factors lead to enrolment or non-enrolment.

Finally, despite the influence of skeletal muscle limitations on reduced exercise capacity, the effects of resistance training and PRIME exercise training on increasing aerobic capacity in patients with CHF is unknown.

These gaps in the knowledge will be addressed in this thesis.

2.8 Aims

The overarching aims of this thesis were to explore factors affecting eligibility, referral and participation in cardiac rehabilitation among older persons with CHF and to investigate novel, muscle-focused rehabilitation techniques in this patient group. To achieve these aims, four studies were undertaken, with the following objectives:

Study 1 (Chapter 3)

- to investigate the rates of referral to cardiac rehabilitation in patients recently discharged from Victorian hospitals with acute decompensated heart failure
- to investigate factors associated with referral

Study 2 (Chapter 4)

- to analyse the effects of resistance training as a standalone therapy in patients with CHF on muscle strength, aerobic capacity and quality of life in patients with CHF.

Study 3 (Chapter 5)

- to investigate whether older patients with HFrEF can tolerate current exercise recommendations involving COMBined Moderate-Intensity Aerobic and Resistance Training (COMBO)
- to analyse the effects of a novel muscle-focused exercise regime called PRIME on aerobic capacity and muscle strength in older adults with HFrEF

Study 4 (Chapter 6)

- to determine eligibility, recruitment and dropout rates among older adults with HFrEF screened for enrolment in exercise training
- to identify the leading clinical reasons for exclusion

Findings from these investigations, alongside the literature review presented in Chapter 2, guided the development of the concluding chapter:

- to provide updated guidelines for exercise training for older adults with CHF.

Chapter 3: Predictors of referral to exercise rehabilitation in patients following hospitalisation with heart failure: A multivariate regression analysis

3.1 Background and context

The literature review presented in Chapter 2 highlighted the benefits of exercise training for patients with CHF. It also acknowledged that outpatient exercise rehabilitation programs may be underutilised in Australia with only 30% – 50% of eligible patients engaging in cardiac rehabilitation (Sundararajan et al., 2004, Scott et al., 2003b, Worcester et al., 2004). These data, however, mostly represent patients with acute coronary syndrome or patients undergoing coronary revascularisation procedures (Sundararajan et al., 2004, Scott et al., 2003b, Worcester et al., 2004). Current utilisation of outpatient exercise rehabilitation among patients with CHF in Australia remains largely unknown, as do the factors that influence referral and participation in this patient group.

3.2 Research aims

This chapter addresses the first two objectives of this thesis (see section 2.9); To investigate the rates of referral to outpatient exercise rehabilitation in patients recently discharged from Victorian hospitals with acute decompensated heart failure and; to investigate factors which affect referral.

3.3 Manuscript

The following paper, "Predictors of referral to cardiac rehabilitation in patients following hospitalisation with heart failure: A multivariate regression analysis" is currently under review at *Heart, Lungs and Circulation*.

Full Title: Predictors of referral to exercise rehabilitation in patients following hospitalisation with heart failure: A multivariate regression analysis

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Abstract

Aims

This study investigated the rates of referral to outpatient exercise rehabilitation (ER) among patients following hospitalization with heart failure (HF) and identified factors associated with referral.

Methods

This prospective observational case control study involved patients hospitalized with HF as identified by the Victorian Cardiac Outcomes Registry Heart Failure study. The unadjusted effect of factors of interest on referral was evaluated using univariate logistic regression. Factors found to be univariately associated with referral were selected for multivariate logistic regression. This process was also completed for subgroups of patients with HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).

Results

Among 1281 patients, (mean age; 76.9 years, 32.8% with HFrEF and 33.9% with HFpEF) 125 (9.8%) were referred to ER. Patients referred were younger (73.6 [62.7, 81.5] vs. 80.2 [71.1, 86.5] $p < 0.001$) and were more likely to be men (72%, $p<0.001$). Factors associated with referral included inpatient percutaneous coronary intervention procedure (OR, 3.31; 95% CI, 1.04-10.48; $p=0.04$), an aetiology of ischaemic or rhythm-related cardiomyopathy and anticoagulants prescribed on discharge. Factors that lowered the likelihood of referral included older age, female, receiving inpatient oxygen therapy and the presence of COPD or anaemia.

Conclusions

Despite established evidence supporting ER, referral to ER following hospital admission with HF is low. Referral shortfalls are particularly evident among females, older patients and in those with COPD or anaemia. Future studies should focus on improving referral processes during hospitalisation and translating proven strategies that increase referrals to ER, into practice.

Keywords: heart failure, referral, exercise rehabilitation, exercise training

Introduction

Heart failure (HF) is a complex syndrome that affects more than 30 million people worldwide (Cook et al., 2014, Vos et al., 2012) and results in significant clinical, functional and financial costs to individuals and the community (Cook et al., 2014, Chen et al., 2017). The prevalence of HF is expected to grow due to the global aging population, increasing prevalence of HF risk factors and improved post-myocardial infarction survival (Australian Institute of Health and Welfare, 2014). Symptomatically, patients with HF experience a significant burden, including exercise intolerance, dyspnoea and fatigue (Zambroski et al., 2005).

Exercise rehabilitation (ER) is an integral component in the treatment paradigm for HF, with evidence consistently demonstrating the reversal of muscle dysfunction and increased aerobic capacity following ER (Atherton et al., 2018, Yancy et al., 2017, Ponikowski et al., 2016a). Suitably designed exercise programs may also reduce premature mortality and the risk of hospitalisations, as well as improve quality of life, regardless of disease severity (Long et al., 2019, Palmer et al., 2018). Despite these benefits, ER programs may be underutilised in Australia, with only 30% - 50% of eligible patients engaging in ER (Sundararajan et al., 2004, Scott et al., 2003b, Worcester et al., 2004). These data, however, mostly represent patients with acute coronary syndrome or patients undergoing coronary revascularisation procedures (Sundararajan et al., 2004, Scott et al., 2003b, Worcester et al., 2004). Importantly, patients with HF are clinically distinct from individuals with other cardiovascular conditions: they are uniquely characterised by comorbidity and older age, while the progressive and deteriorating nature of the syndrome is underpinned by recurrent exacerbations and a gradual decline in functional capacity. As such, patients with HF should be uniquely considered in investigations of ER engagement.

Only one previous study from the USA has investigated the rates of referral to ER among patients hospitalised with HF (Golwala et al., 2015), however, due to the possible influence of patient insurance and program eligibility criteria, these findings may not be transferrable to the other nations, including Australia. Current utilisation of ER among patients with HF in Australia remains largely unknown, as do the factors that influence referral and participation in this patient group. This study investigated the rates of referral to ER among patients following hospitalization with HF in Victoria and identified factors associated with referral and participation.

Methods

This prospective observational case control study is nested within the Victorian Cardiac Outcomes Registry Heart Failure study (VCOR-HF) (Driscoll et al., 2020)—a prospective longitudinal cohort studying involving patients admitted to Victorian Hospitals with an acute episode of heart failure. The VCOR-HF study (described in detail elsewhere (Driscoll et al., 2020)) was rolled out across 16 hospital sites and enrolled all adults hospitalised with a primary diagnosis of HF, over a one month period annually, between the years of 2014 and 2017. Data collected included patient demographics, medical history, cardiac risk factors, HF aetiology, clinical measures, cardiac investigations (i.e. echocardiogram and angiogram), inpatient procedures received, discharge medications, discharge clinical status and referral information. The primary outcome, referral to ER, included patients who were referred to either outpatient cardiac rehabilitation, or a specific HF exercise program.

The research protocol was approved by Ethics Committees from Melbourne Health and Victoria University as well as the VCOR Data Research & Publications (DRP) Committee.

Patients included in this study were identified from the VCOR-HF study dataset based on eligibility for referral to ER, as determined by discharge destination; patients were excluded if they were discharged to palliative care or died in hospital. The study population was then grouped according to the status of referral to ER on discharge.

Statistical analysis

Descriptive statistics are presented as median and interquartile range ([IQR] 25th percentile, 75th percentile) for continuous variables (none of the data was normally distributed) and frequency and percentage for categorical variables. Baseline patient characteristics were compared between ER referral groups using Man-Whitney non-parametric tests for continuous variables and Pearson's chi-square or Fisher's exact test for categorical values. The unadjusted effect of each factor of interest on referral to ER was evaluated using univariate logistic regression and presented as odds ratios (OR) and 95% confidence intervals (CI). This process was completed for the entire study population and repeated for subgroups of patients with HF with reduced ejection fraction (HFrEF [EF≤ 40%]) and HF with preserved ejection fraction (HFpEF [EF≥50%]) (Ponikowski et al., 2016a). Factors found to be univariately associated with ER referral for each group were selected for multivariate logistic regression to assess the independent effect of each factor on the outcome, while adjusting for all other factors of interest. The covariates of age and gender were included in

the multivariate logistic regression, regardless of univariate associations. Backward and forward elimination was carried out with an SPSS (Inc, 2010) automatic algorithm based on the backward Likelihood Ratio and forward Likelihood Ratio methods respectively (Pereira et al., 2016). Final resultant models were compared using likelihood ratio tests (LRT), Akaike information criterion (AIC) and calculating the area under the receiver operator curve (AUC).

The influence on model selection from several variables that either had a high proportion of missing observations or categories defined as unknown was assessed by separately building models that included and then excluded them. The high proportion of missing data may have biased model selection due to the exclusion of a higher number of non-complete cases. All statistical analyses were performed using SPSS software, version 23.

Results

Patient Identification and Referral to ER

Patient identification and referral outcome are shown in Figure 3.1. A total of 1357 patients were identified in the index dataset. Of these, 76 patients were excluded due to hospital discharge to palliative care (n = 15), in-hospital mortality (n = 60) or missing ER referral data (n = 1), leaving 1281 patients who were potentially eligible for referral to ER at time of discharge (median age; 76.9 years [70.3,86.3], 32.8% with HFrEF and 33.9% with HFpEF). At the time of discharge, 125 (9.8%) patients were referred to ER (median age; 73.6 years [62.7, 81.5], 28% females). This included 92/1087 (8.5%) adults ≥ 65 years, 62/420 (14.8%) patients with HFrEF and 26/434 (6%) patients with HFpEF.

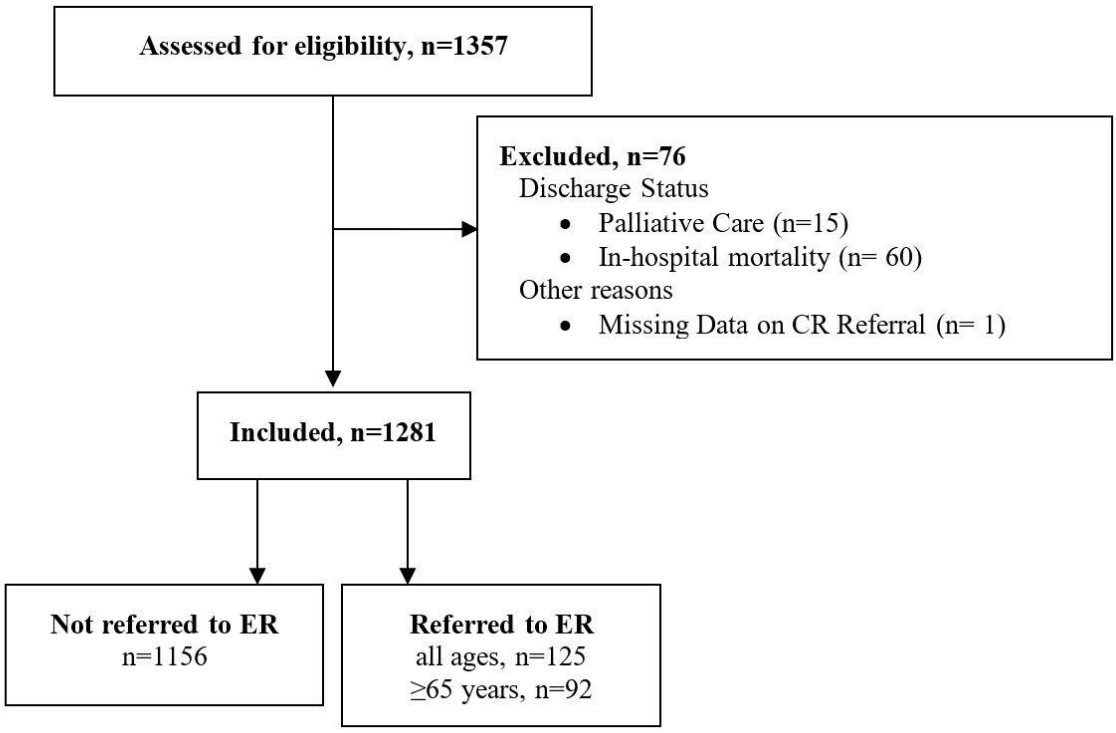

Figure 3.1 Patient identification and referral to exercise rehabilitation

Baseline Characteristics of the Population

Select baseline characteristics of the population are presented in Table 3.1. A complete baseline characteristics table is reported in Appendix D. Patients referred to ER were younger (73.6 [62.7, 81.5] vs. 80.2 [71.1, 86.5] $p < 0.001$) and were more likely to be men (72% vs 28%, $p < 0.001$). In patients where the HF Subtype was known, there was a statistically significant difference for level of HF Subtype ($p < 0.001$), with the main difference being that referred patients were more likely to have HFrEF than HFpEF (49.6% vs 20.8%) compared to non-referred patients (30.1% vs 35.3%). The presence of hypertension, dementia, COPD/asthma, chronic kidney disease, iron deficiency and anaemia were significantly more frequent in the Non-Referred group compared to the Referred group, whereas the proportion of patients with ischaemic or arrhythmia related HF aetiology was significantly greater in the Referred group compared to the Non-Referred group ($p = 0.001$ and 0.04, respectively). Patients not referred to ER had a significantly greater number of medications prescribed on discharge (9 [8,11] vs 10 [8,13], $p = 0.047$).

Table 3.1: Select baseline patient characteristics among all patients and those referred and not referred to exercise rehabilitation

Characteristics	All (%) (n = 1281)	ER Referral (%) (n = 125)	No ER Referral (%) (n=1156)	*p*-value
Age, y	79.7 (70.3, 86.3)	73.6 (62.7, 81.5)	80.2 (71.1, 86.5)	<0.001
Male, n (%)	723 (56.4)	90 (72.0)	633 (54.8)	<0.001
ǂ BMI, kg/m^2	29.1 (35.8, 34.5)	29.7 (25.8, 34.9)	29.0 (24.8, 34.5)	
HF Subtype, n (%)				
HFrEF	420 (32.8)	62 (49.6)	358 (31.0)	<0.001ǂ
HFmrEF	169 (13.2)	11 (8.8)	158 (13.7)	
HFpEF	434 (33.9)	26 (20.8)	408 (35.3)	
Unknown	258 (20.1)	26 (20.8)	232 (20.1)	
ǂ LVEF (%)	38.0 (25.6, 50.3)	30.0 (22.3, 39.8)	40 (26.0, 53.0)	0.004
NYHA on discharge, n (%)				
Class I / II	20 (4.5) / 236 (53.5)	2 (0.5) /37 (68.8)	18 (4.7) / 198 (51.4)	
Class III/ IV	162 (36.7) / 23 (5.2)	14 (25.9) / 1 (1.9)	148 (38.2) / 22 (5.7)	
Unknown	840 (65.6)	71 (56.8)	770 (66.7)	
Admission Speciality, n (%)				0.001ǂ
HF Unit	126 (9.8)	18 (14.5)	108 (9.3)	
Cardiology	434 (33.9)	58 (46.8)	376 (32.5)	
Gerontology	36 (2.8)	5 (4.0)	31 (2.7)	
General Medicine	622 (48.6)	39 (31.5)	583 (50.4)	
Other	62 (4.8)	4 (3.2)	58 (5.0)	
Cardiovascular History, n (%)				
History of heart failure	968 (75.5)	93 (74)	874 (75.6)	
Previous hospitalisation for HF	774 (60.4)	75 (60.0)	698 (60.4)	
Cerebrovascular disease	242 (18.9)	27 (21.6)	215 (18.6)	
Hypertension	977 (76.2)	85 (68.0)	891 (77.1)	0.02
History of angina	481 (37.5)	43 (34.4)	437 (37.8)	
History of PCI or CABG	393 (30.7)	37 (29.6)	356 (30.8)	
History of MI	394 (30.7)	40 (32)	353 (30.5)	
Arrythmia	695 (54.2)	66 (52.8)	628 (54.3)	
CIED therapy	284 (22.2)	29 (23.2)	255 (22.1)	0.004
ǂ Smoking Status				
Current smoker	133 (12.4)	18 (16.5)	115 (11.9)	
Ex-smoker	504 (46.8)	51 (46.8)	451 (46.8)	
Heart Failure Aetiology, n (%)				
Ischaemic	458 (35.8)	62 (49.6)	396 (34.3)	0.001
Hypertension	223 (17.4)	16 (12.8)	207 (17.9)	
Valvular	179 (14.0)	12 (9.6)	137 (14.4)	
Arrhythmia	187 (14.6)	26 (20.8)	161 (13.9)	0.04
Other Medical History, n (%)				
Diabetes	552 (43.1)	56 (44.8)	496 (42.9)	
Dementia	100 (7.8)	4 (3.2)	96 (8.3)	0.04
Depression	251 (19.6)	20 (16.0)	231 (20.0)	
COPD / Asthma	394 (30.8)	23 (18.4)	371 (32.1)	0.002
Obstructive Sleep Apnoea	187 (14.6)	17 (13.6)	170 (14.7)	
Chronic kidney disease				0.002
Mild	241 (18.8)	22 (17.6)	217 (19.0)	

Moderate	408 (31.9)	28 (22.4)	380 (32.9)	
Severe	159 (12.4)	10 (8.0)	149 (12.9)	
Iron Deficiency	253 (20)	16 (12.9)	237 (20.8)	0.04
Anaemia	394 (30.8)	23 (18.4)	371 (32.1)	0.002
Treatments during admission, n (%)				
IV diuretics	1096 (85.8)	102 (82.9)	994 (86.1)	
Oral Diuretics	1161 (90.9)	108 (88.5)	1053 (91.2)	
Oxygen therapy	837 (65.6)	65 (53.3)	772 (66.9)	0.003
CPAP / BiPAP	174 (13.6)	13 (10.6)	161 (14.0)	
Angiography	112 (8.8)	19 (15.3)	93 (8.1)	0.01
PCI	15 (1.2)	5 (4.0)	10 (0.9)	0.002
CIED Therapy				
Pacemaker	28 (2.2)	3 (2.4)	25 (2.2)	
CRT-P	2 (0.2)	0 (0.0)	2 (0.2)	0.002
ICD	15 (1.2)	5 (4.1)	10 (0.9)	
CRT-D	18 (1.4)	13 (1.1)	5 (4.1)	
Resting Haemodynamics on discharge				
Systolic BP (mmHg)	120 (110.0, 135)	118 (110, 130)	120 (110, 135)	
Diastolic BP (mmHg)	68 (60, 75)	68 (60, 75)	68 (60, 75)	
HR (bpm)	74.0 (65, 83)	75.0 (65, 85)	74.0 (65, 82)	
HF Pharmacotherapy, n (%)				
ACE Inhibitor	534 (41.8)	54 (43.2)	480 (41.6)	
ARB	219 (17.1)	24 (19.4)	195 (16.9)	
Beta Blocker	910 (71.2)	98 (79.0)	812 (70.4)	0.04
Aldosterone Antagonist	474 (37.1)	48 (38.7)	426 (36.9)	
Digitalis	210 (16.4)	15 (12.1)	195 (16.9)	
Loop Diuretic	1207 (94.2)	118 (94.4)	1089 (94.2)	
Antiplatelet	674 (52.7)	60 (48.0)	614 (53.2)	
Anticoagulant	586 (45.8)	69 (55.6)	517 (44.8)	0.02
Calcium channel antagonist	209 (16.4)	21 (16.9)	188 (16.3)	
Total Number of Meds	10.0 (8.0-13)	9 (8,11)	10 (8,13)	0.047

Data expressed as median and percentiles (75%, 25%) for continuous variables and count and proportions (%) for categorical variables.

ǂ Variables where missing data >15%.
ǂwhere factor has more than one level, *p*-value applies to the overall association of this factor with the outcome. .

BMI, body mass index; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HF, heart failure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; MI, myocardial infarction; CIED, Cardiac Implantable Electronic Device; CRT-p, cardiac resynchronisation therapy – pacemaker; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronisation therapy – defibrillator;

IV, intravenous; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure; BP, blood pressure; HR, heart rate; ACE, angiotensin converting enzyme; ARB, aldosterone receptor blocker

Factors associated with referral to ER

Factors associated with referral to ER at the time of discharge are presented in

Table **3.2** and include; inpatient percutaneous coronary intervention (PCI) procedure (OR, 3.31; 95% CI, 1.04 - 10.48; $p = 0.04$), an aetiology of ischaemic-related or rhythm-related cardiomyopathy and anticoagulants prescribed on discharge. Factors that lowered the chance of referral included older age, female, receiving inpatient oxygen therapy and the presence of COPD or anaemia. Due to missing data, the variables of smoking history, HF Subtype and estimated ejection fraction were excluded from the model; the sensitivity analysis resulted in identical final variables found to be independently associated with the outcome.

Table 3.2: Factors associated with referral to exercise rehabilitation at time of discharge among all patients with HF

Factor	Odds Ratio	95% CI	*p*-value
Age (years)	0.98	0.96, 0.99	0.001
Gender (female)	0.65	0.42, 1.02	0.06
COPD	0.52	0.31, 0.87	0.01
Anaemia	0.59	0.36, 0.99	0.04
Ischaemic Aetiology	1.91	1.27, 2.90	0.01
Rhythm Related Aetiology	1.90	1.13, 3.18	0.02
Inpatient Oxygen Therapy	0.63	0.42, 0.94	0.02
Inpatient PCI	3.31	1.04, 10.48	0.04
Discharge Medication: Anticoagulant	1.55	1.03, 2.33	0.04
COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention			

Subgroup analysis

Factors associated with referral to ER by multivariate analysis by HF subgroup type are shown in

Table **3.3**. For patients with HFrEF, factors significantly associated with increased referral to ER included; inpatient PCI (OR, 4.91; 95% CI, 1.27 - 18.92; $p = 0.02$), discharge heart rate and implantable cardiac defibrillator inserted during hospital admission (refer to

Table 3.3 for OR, CI and *p*-values), while antiplatelets prescribed on discharge was significantly associated with decreased odds of referral. No association was found for age

among patients with HFrEF. For patients with HFpEF, factors that significantly increased the odds of referral included; ischaemic or rhythm-related aetiology, while receiving inpatient oxygen therapy significantly decreased odds of referral. No associations were found for age and gender among patients with HFpEF.

For patients with HFrEF, forward elimination compared to backward elimination resulted in a better model based on LRT, AIC and AUC, whereas, for patients with HFpEF, backward elimination was the preferred model.

Table 3.3: Factors associated with referral to exercise rehabilitation at time of discharge, in patients with HFrEF and HFpEF

Factor	Odds Ratio	95% CI	*p*-value
HFrEF			
Age (years)	0.99	0.97, 1.00	0.13
Gender (female)	0.47	0.21, 1.04	0.06
Discharge HR	1.03	1.01, 1.05	0.01
Inpatient PCI	4.91	1.27, 18.92	0.02
Inpatient ICD	3.89	1.15, 13.14	0.03
Inpatient CRT-D	3.03	0.92, 9.95	0.07
Discharge Medication: Antiplatelets	0.46	0.25, 0.85	0.01
HFpEF			
Age (years)	1.02	0.97, 1.07	0.52
Gender (female)	0.58	0.25, 1.36	0.21
Ischaemic Aetiology	3.01	1.29, 7.02	0.01
Rhythm Related Aetiology	3.08	1.26, 7.53	0.01
Inpatient Oxygen Therapy	0.39	0.17, 0.88	0.02

HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; PCI, percutaneous coronary intervention; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronisation therapy-defibrillator

Discussion

In this study, we observed several key findings that are summarized in Figure 2. First, less than 10% of patients following hospitalisation with HF are referred to ER. Second, factors independently associated with increased referral included younger age, male, receiving an inpatient PCI and an aetiology of ischaemic or rhythm-related cardiomyopathy, as well as receiving anticoagulants on discharge. Finally, factors independently associated with decreased referral included; older age, female, receiving oxygen therapy, and the presence of COPD or anaemia.

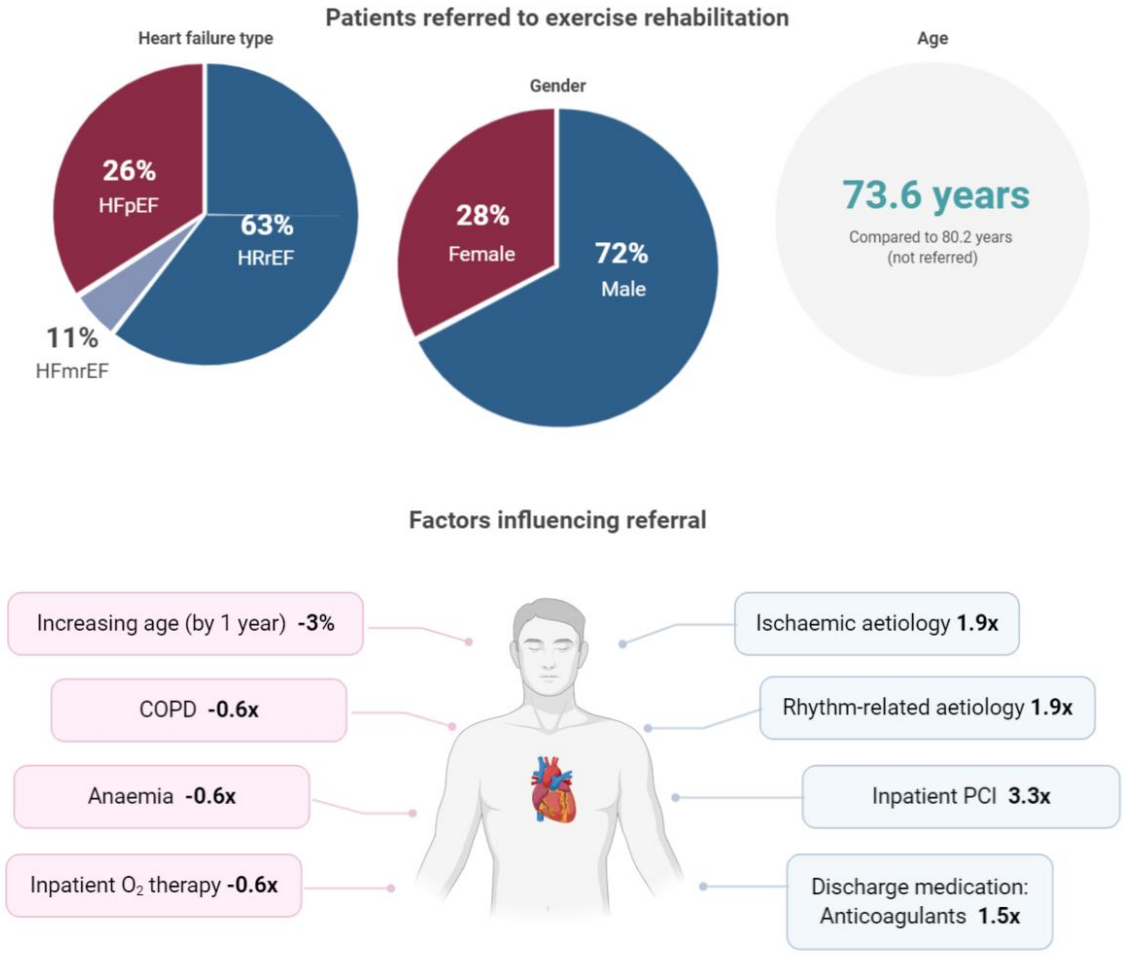

Figure 3.2: Central illustration of key findings

ER is recommended by leading cardiological societies around the world (Ponikowski et al., 2016a, Atherton et al., 2018, Piepoli et al., 2011, Selig et al., 2010b). While this study involved patients admitted to hospital with acute decompensated HF, these patients fall within the chronic heart failure (CHF) spectrum and the findings of this research extend well

to the general population with CHF. The issue of poor engagement in ER in Australia was identified as early as 2003 (Scott et al., 2003a), however, this is the first study to report referrals to ER in patients hospitalised with HF. Referral to ER is the essential first step to program engagement, yet this study found a referral rate of less than 10%. Several strategies have been suggested to improve the ER referral process such as; electronic referral systems (Pirruccello et al., 2017), integrating referral to ER into the quality assessment of HF management (Fernandez et al., 2010, Piepoli et al., 2011) and pre-printed hospital discharge orders (Fernandez et al., 2010), as well as several opportunities to facilitate continuity of care, including a dedicated and consistent team of health professions and established pathways of communication between inpatient and outpatient ER facilitators (Giuliano et al., 2017). Despite these strategies, our data suggests low referral rates remains a key issue that affects engagement in ER among patients with HF and further work is required to translate previously proven effective strategies into practice.

This study identified several factors that significantly influenced the odds of referral. Notably, patients who received an inpatient PCI were 3.3 times more likely to receive a referral and the odds of referral were almost doubled in patients or with an ischaemic of rhythm related aetiology. Other studies have found a greater proportion of referrals to cardiac rehabilitation – by two-thirds – in patients with cardiovascular conditions other than chronic HF (Scott et al., 2003a). This is perhaps not surprising, given the evidence supporting ER for patients with chronic HF lagged that for other cardiovascular conditions by as much as 14 years (Pashkow, 1993, McKelvie et al., 1995). It is plausible that there are cultural differences in the considered importance of ER for patients with acute ischemic conditions, compared to those with HF exists, that may influence clinicians referring practices. Suitably designed future studies should consider investigating this hypothesis.

This study also found that for every year increase in age, the odds of referral decreased by 2%, 95%CI (1%, 4%), while the presence of COPD or anaemia reduced the likelihood of referral by 41%, 95%CI (1%, 64%) and 48%, 95%CI (13%, 69%), respectively. It is well established that older individuals are disproportionately affected by HF (Curtis et al., 2008). Older patients with HF are characterized by a higher incidence of comorbidities such as COPD, anaemia, sarcopenia and frailty (Barsheshet et al., 2010, Mogensen et al., 2011, von Haehling, 2015, Fulster et al., 2013), and they experience higher rates of hospitalisation and clinically adverse events in comparison to younger individuals with HF (Londono et al., 2018, Barsheshet et al., 2010). Hence, older individuals represent a group of patients that may

benefit the most from engagement with ER and referring these individuals should be considered a priority. Furthermore, gender is an important clinical consideration across all specialities. Although not found to be statistically significant in this study, females had half the odds of referral to ER among all patients, and in subgroups of HFpEF and HFrEF. Our results indicate that specific strategies for increasing referrals for older individuals, those with comorbidities and females need to be further evaluated.

Patients with HFrEF were more likely to be referred compared to patients with HFpEF (63% vs. 26%). It is known that individuals with HFpEF are generally older than patients with HFrEF, and are more likely to be female. Although not statistically significant, only gender appeared to be a driving factor for referral to ER in patients with HFpEF. It is also possible that the difference in referrals between HF Subtype may be due to a relatively smaller evidence base supporting exercise training for patients with HFpEF (Gomes-Neto et al., 2019b), and there may be a lag in translation to practice for this patient group, which also needs to be addressed by future studies.

This study has some potential limitations. First, this analysis determined eligibility for ER based on discharge destination following hospital admission. In reality, not all patients discharged home may be eligible for ER due to contraindications to exercise training, for instance, due to severe aortic stenosis or uncontrolled diabetes (Selig et al., 2010b). Second, this study assessed referral status based on a single hospital admission and we were unable to ascertain whether patients had already attended ER following an earlier/previous hospital discharge. Likewise, the VCOR-HF data did not capture referrals that may have been initiated in the outpatient or primary care setting following hospital discharge. Third, this study only assessed the influence of a select number of factors on ER referral. It did not consider possible individual patient, clinician or system-related influences on referral and participation, including the proportion of patients who were offered referral to ER but declined. Further research investigating a possible cultural influence among referring practitioners is important. Despite these limitations, this is the first study to evaluate factors influencing referral to ER in an Australian context and as such, provides a valuable insight into the current issues facing rehabilitation engagement in the HF population.

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Conflict of Interest

None to declare

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Chapter 4: The effects of resistance training on muscle strength, quality of life and aerobic capacity in patients with chronic heart failure—A meta-analysis

4.1 Background and context

Up until the 1990's, resistance training was not advised for patients with CHF. This was due to concerns about the integrity of the left ventricle under high afterloads, thought to be raised during this form of exercise. However, modern studies indicate that resistance training provides an additive benefit for improving quality of life and measures of muscular strength when combined with aerobic training in patients with HFrEF, thus, resistance training is recommended as a complementary exercise mode to aerobic training within clinical practice guidelines.

Considering the muscle hypothesis of CHF (discussed in section 2.2.3.2), this chapter explores the greater utility of resistance training, with interest to its effectiveness as a standalone therapy to increase aerobic capacity. The study hypothesis – that resistance training as a standalone therapy can increase aerobic capacity in patients with CHF – if proven, could broaden the exercise therapy options to patients who are unable or unwilling to participate in aerobic based exercise training. The study presented in Chapter 4 explores this narrative.

4.2 Research aims

Chapter 4 presents a meta-analysis which addresses the third objective of this thesis (see section 2.9); To analyse the effects of resistance training as a standalone therapy in patients with CHF on muscle strength, aerobic capacity and quality of life in patients with CHF.

4.3 Manuscript

The following paper, "The effects of resistance training on muscle strength, quality of life and aerobic capacity in patients with chronic heart failure - A meta-analysis" was published

in the *International Journal of Cardiology* in 2017. It was also presented at the following conferences:

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I declare that the publication above meets the requirements to be included in the thesis as outlined in the HDR Policy and related Procedures – policy.vu.edu.au.

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In the case of the above publication, the following authors contributed to the work as follows:

The undersigned certify that:

1. They meet criteria for authorship in that they have participated in the conception, execution or interpretation of at least that part of the publication in their field of expertise;
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Review

The effects of resistance training on muscle strength, quality of life and aerobic capacity in patients with chronic heart failure — A meta-analysis

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ABSTRACT

Background: Resistance training (RT) has been utilised to target muscle dysfunction associated with Chronic Heart Failure (CHF). However, there is limited meta-analysis evidence to support its use as a standalone therapy. This meta-analysis examined the effects of RT on muscle strength (one repetition maximum, 1RM and Peak Torque), aerobic capacity (VO_{2peak} and 6 min walk distance) and quality of life (QoL) in patients with CHF.
Methods: We searched Medline, EMBASE, Cochrane and CINAHL for studies published up to July 2016, combining terms related to the population (eg, *heart failure, CHF*) with terms for the intervention (eg, *resistance, strength training*) and the outcomes (eg, *QoL, VO_2 peak, strength, aerobic capacity*).
Results: Ten studies including 240 participants were included in our meta-analysis (aged 48–76 years, Ejection Fraction 18–37%). Training duration ranged from 8 to 24 weeks and intensity up to 80% of 1RM. RT increased 1RM (standardised change score = 0.60; 95% Confidence Interval: 0.43, 0.77) but not strength measured via peak torque at $60°/s^{-1}$ and $180°/s^{-1}$. RT increased VO_{2peak} (CSMD: 2.71 ml/kg/min; 1.96, 3.45) and QoL (CSMD: −5.71; −9.85, −1.56).
Conclusion: RT as a single intervention can increase muscle strength, aerobic capacity and QoL in patients with CHF and may offer an alternative approach, particularly for those unable to participate in aerobic training. The effect of RT on muscle strength is mainly during slow controlled movements and not during rapid movements. Older adults and patients with advanced CHF are underrepresented in RT trials and future studies should seek to optimise their inclusion.

1. Introduction

Chronic Heart Failure (CHF) is a dynamic and progressive syndrome, which develops secondary to structural or functional abnormalities of cardiac tissue. It leads to the inability of the heart to supply enough blood to meet the body's metabolic needs and causes breathlessness, fatigue and reduced exercise tolerance [1]. Life expectancy in patients with CHF is increasing however, many of these recovered years are spent with debilitating burden of symptoms [2], high incidence of hospitalisations [3,4] and a poor ultimate prognosis [4].

Treatment for patients with CHF is alike other terminal illnesses and is primarily focussed on managing symptoms and maintaining quality of life (QoL). Exercise training is an integral component of this paradigm [5–7] due to its capacity to ameliorate symptoms [8], reduce hospital admissions [9] and improve functional capacity, which translate into improved QoL [8,10–12]. Traditional approaches to exercise rehabilitation have largely focussed on aerobic-based training given its ability to increase aerobic capacity (VO_{2peak}) [13–15]. However, it is now accepted that exercise intolerance in CHF is not exclusively due to central cardiovascular factors and consequently, clinicians are moving beyond a centrally focussed treatment approach. Specifically, the "muscle hypothesis" argues that abnormalities in peripheral muscle tissue initiate deleterious feedback loops and become drivers for disease progression [16]. Adding to the fact that muscle mass is strongly correlated with VO_{2peak} [17,18] it has been argued that targeting muscle dysfunction may interrupt these maladaptive feedback loops and improve exercise tolerance [19].

Resistance training (RT) is normally employed for conditioning skeletal muscle tissue however, it was largely overlooked for patients with CHF prior to 1990's due to concerns that high cardiac afterload

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may adversely affect left ventricular remodelling [8,20]. More recently, modern methods of hemodynamic measurement have allayed these concerns by confirming the integrity of the left ventricle during RT [12,21]. With confirmation of safety and acknowledgment of the wider health and fitness benefits, RT is now supported in clinical practice guidelines for people with cardiovascular disease [22]. There are however, several unresolved limitations to these guidelines, which continue to impact on clinical decision making.

Firstly is the question of applicability of current best practice guidelines to patients with CHF. The joint council Scientific Statement from the American Heart Association recommends RT for individuals with and without cardiovascular disease [22]. The guideline presents a consensus of evidence supporting the safety and efficacy of RT through large randomised controlled trials and meta-analyses. However, these data are largely derived from patients with cardiovascular diseases other than CHF, or in patients with few comorbidities or risk factors. In specific reference to CHF, the guidelines are based on only a small number of individual studies [23,24]. The precision of estimates of effects derived from such studies is limited and authors acknowledged the need for further evidence. The consequences of overly generalised guidelines for cardiovascular disease is particularly problematic in CHF, since it is the end stage of other cardiovascular conditions and as such, patients often suffer from multi-organ and co-morbid disease which can further challenge management. For instance, Havranek et al. [25]. reported an incidence of diabetes and chronic obstructive pulmonary disease of 40% and 33%, respectively, in elderly patients with CHF.

Secondly, patients with CHF are generally older than those with other cardiovascular conditions, yet this age discrepancy is largely unaddressed in these guidelines. The Framingham Heart study reported a mean age of diagnosis of 76.4 years for CHF [26], compared to 56 or 65 years for the median age of first myocardial infarction, for men and women respectively [27]. Patients with CHF, particularly those who are elderly, are a heterogeneous group and differ significantly from patients with other cardiovascular diseases. The complexity of the illness merits exclusive exercise recommendations for treatment. It is for this reason, that explicit medical guidelines exist for patients with CHF which pay specific attention to the management of co-morbidities, as well as issues related to older age [28].

Finally, the focus for cardiac rehabilitation remains heavily on aerobic or centrally focussed training and limited evidence exists to support RT as an effective standalone therapy. It was previously reported that RT has a smaller effect compared to aerobic training in increasing peak VO_2 in patients with CHF [29], however RT produces greater improvements in skeletal muscle strength and endurance [30]. The American Heart Association acknowledges the potential benefits of RT for cardiovascular health, weight management and prevention of disability and falls, however, given the extensive benefits of aerobic training, RT was not recommended to be used as its substitute [22]. Some clinicians and researchers have argued that many patients have insufficient capacity to tolerate aerobic exercise, such as those who are elderly or have more advanced CHF and that RT may be a suitable alternative for these patients [31–33].

Systematic reviews and meta-analysis are the reference standard for developing clinical practice guidelines because of their methodological rigour and assessment of potential bias. To our knowledge only one meta-analysis has analysed the effects of RT versus usual care in patients with CHF [34], however this study did not analyse muscular strength. Therefore, the purpose of this meta-analysis was to systematically review randomised controlled trials (including quasi-randomised designs) and meta-analyse the effects of RT, as a single intervention, on muscle strength, aerobic capacity and QoL in patients with CHF.

2. Methods

2.1. Search strategy

With the support from a clinical librarian, we developed search strategies to identify controlled trials of RT in patients with CHF. Specifically, we focussed on the effect of RT on muscle strength (1 repetition maximum, 1RM, and/or peak isokinetic torque), aerobic capacity (measured by $VO_{2\ peak}$ and/or 6 min walk distance [6MWD]), and QoL measured using the Minnesota Living with Heart Failure questionnaire. We searched CINAHL, Medline, EMBASE, and Cochrane databases up to 10th July, 2016. In brief, the search strategy combined terms related to the population (eg, *heart failure, cardiomyopathy, CHF*) with terms for the intervention (eg, *resistance training, strength training, circuit training*) and the outcomes (eg, *QoL, $VO_{2peak,}$ muscle strength, aerobic capacity*). The full electronic search strategy for Medline is presented in Appendix 1. Next, we hand searched the reference lists of retrieved papers to identify additional relevant studies. Unpublished studies or eligible abstracts (i.e. from conferences and research meetings) that did not have full text available were not included.

2.2. Eligibility criteria

The inclusion criteria for studies were: (i) controlled trials (including quasi-randomised design); (ii) adult participants >18 years with CHF, where a diagnosis was based on clinical signs or left ventricular ejection fraction less than 40%; (iii) intervention of interest was progressive RT, and included regimes designed for targeted muscle training, or those in which high central cardiovascular strain or aerobic stimulus was specifically avoided; (iv) the comparison group was a non-exercise control group (i.e. studies comparing RT to another mode of exercise were excluded); and (v) the outcome of interest was aerobic capacity measured using the 6 min walk distance (6MWD), and/or VO_{2peak}, QoL measured using the Minnesota Living with Heart Failure Questionnaire; and/or muscle strength measured using 1RM and/or peak isokinetic torque measurements (Fig. 1). In the case of suspected duplication of data across publications, authors were contacted for confirmation and only the largest study was included.

2.3. Data extraction

CG and AK extracted the data from the included studies and IL resolved discrepancies. The following data were extracted: (i) the characteristics of the participants in the control and intervention group i.e. sample size, mean (standard deviation) age, sex, New York Heart Association Class (NYHA), ejection fraction (%), mean height (meters) and mean

Participants

- Adults with Chronic Heart Failure
- Diagnosis based on clinical signs or left ventricular ejection fraction <40%

Intervention

- Progressive resistance exercise training, including circuit, or other modified strength training regimes

Comparison

- Control group (i.e. not another mode of exercise)

Outcome measures

- Aerobic capacity
  - 6 Minute Walk Distance
  - $VO_{2\ peak}$
- Quality of Life
  - Minnesota Living with Heart Failure Questionnaire
- Muscle Strength
  - 1 Repetition Maximum (RM)
  - Peak Isokinetic Torque measurements

Study Design

- Controlled trials (including quasi-randomised)

Fig. 1. Eligibility criteria for study inclusion.

weight (kilograms); (ii) details of the methodology used for the resistance training group (i.e. the treatment group): type of training, frequency and duration, session time, intensity, sets and repetitions, and method of progression; and (iii) details of the outcomes of interest measured at baseline and follow-up for the treatment and control groups, i.e. aerobic capacity measured using the 6 Minute Walk Distance (metres), VO_{2peak} ($mL/kg^{-1}/min^{-1}$), QoL measured using the Minnesota Living with Heart Failure Questionnaire, Muscle Strength measured using 1RM, or Peak Isokinetic Torque measurements ($180°/s^{-1}$ and/or $60°/s^{-1}$).

2.4. Data analysis

We estimated using meta-analysis with random effects the pooled mean difference of the change scores for each outcome. We used the restricted maximum likelihood estimator to estimate the between study heterogeneity [35]. For outcomes that were measured with different equipment/scales (i.e. 1RM), we estimated a pooled standardised mean difference of the final values.

We visually inspected funnel plots of the study size versus standard error and performed Egger's regression asymmetry test to assess bias due to small study effects [36]. There was no indication of small-study effects (available on request) from the funnel plots or Egger's test.

Statistical heterogeneity between studies was tested with the Q statistic and quantified with the I^2 statistic [37].

2.5. Assessment of study quality

We used the Cochrane Risk of Bias tool to assess the quality of the studies [38]. The tool consists of the following seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'. Each domain was considered for each of the included studies and assigned either a low, high or unclear risk of bias. For each of the included studies an overall risk was displayed visually utilising RevMan5 software.

2.6. Sensitivity analyses

We estimated the pooled mean difference of the change score between baselines and follow-up for each outcome between the two groups (i.e. resistance training and control) using meta-analysis with fixed effect. The standard deviation of the change score was calculated from the baseline and follow-up standard deviations by assuming that the correlation between baseline and follow-up scores was 0.8 [39,40].

We assessed the balance of the outcomes measurements at baseline for each study by undertaking a meta-analysis of the primary outcome at baseline [41];baseline imbalance was not detected.

This systematic review was planned, conducted and reported based on the guidelines set out by the Preferred Reporting Items for Systematic reviews and Meta-Analyses Guidelines [42] (Appendix 2). Statistical analyses were carried out using Stata version 13.1[43].

3. Results

3.1. Study selection

The search strategy identified 10,424 citations. After removal of duplicates, 7650 were broadly screened by title and abstract and 7596 articles were excluded. Fifty-five articles were included for full text review. Of these, a further 45 were excluded leaving 10 articles for inclusion in the meta-analysis. The reasons for excluding articles are shown in Fig. 2; 19 papers did not report on the outcome(s) of interest. One additional study was identified incidentally while confirming inclusion criteria for another identified paper, via direct contact with the author.

3.2. Study characteristics

Table 1 summarises the characteristics of the included studies. A total of 240 patients (59 females; 25%) took part in the ten studies, of which 112 were in the control groups. Studies were published between 1997 and 2011 of which three were conducted in Australia [44–46], three in the USA [24,47,48], two in Sweden [49,50] and one each in Germany [51] and Luxembourg [52]. Sample sizes were generally small and ranged from 15 to 39 participants. Two studies recruited only male participants [44,48], one study recruited women only [24] and the remaining studies recruited both males and females [45–47, 49–52].

Age of participants across studies ranged from 48 to 76 years. Eight of the studies included patients with a mean age of less than 65 years [44–47,49–52]. One study [24] specifically recruited older women, and had a mean age of 76 years.

Eight of the studies reported NYHA class [24,45,46,48–52]. Seven studies [44,45,47–50,52] reported the number of participants per class group; NYHA Class I: 19 (17%), Class II: 48 (42%) , Class III: 46 (41%), and none of the studies involved patients with NYHA class IV. Three studies [24,46,51]. Reported the mean class as a continuous variable of which the mean across studies was 2.6. Left Ventricular Ejection Fraction (LVEF) ranged from 18 to 37%.

Study protocols for RT interventions varied and included the use of free weights, cuff weights, machine resisted exercise, multi-system gym systems and Theraband resisted exercise (Table 2). Two studies [46,47] utilised cycle ergometers for their training intervention. Although this is traditionally viewed as aerobic training, authors commented on the rationale for their exercise prescription, which was to avoid intensities in the aerobic training zone in order to limit central strain and specifically target muscle tissue. Specifically, Selig et al. stated that "Arm and leg cycling were each of short duration (0.5 to 2 min) and relatively moderate intensities (by heart rate monitoring)—the objective being to provide additional strength exercise while minimizing aerobic training effects" [46]. Beniaminoitz et al. ultised "selective exercise of leg muscles at a low level that does not condition the respiratory muscles. To do this, patients were carefully trained at a work load that did not increase the minute ventilation beyond 25 l/min". Therefore, these studies were included in the analysis.

3.3. Lower body muscle strength

Four studies [24,44,45,48] with a total of 35 participants in the intervention group and 36 participants in the control group were included in the analysis of 1RM of leg press. Pu et al. [24]used pneumatic resistance equipment for the measurement of 1RM, whilst the other studies used weight stacked machines, so we estimated a pooled standardised mean difference using a fixed effect. Lower body muscle strength was increased in the RT group compared to the control group (standardised change score = 0.60, 0.43, 0.77) (Fig. 3).

Four studies [46,47,49,52] evaluated changes to lower body muscle strength via isokinetic peak torque at $60°/s^{-1}$ with 63 participants in the intervention group, and 55 in the control group. These studies reported no change in muscle strength (6.84 $60°/s^{-1}$ Nm, −0.75, 14.43). Two studies [49,52] analysed lower body muscle strength via peak isokinetic torque at 180 $°/s^{-1}$ with 27 participants in the control and the intervention groups. These studies reported no change in muscle strength (5.02180$°/s^{-1}$ Nm; −7.07, 17.12) (Fig. 4).

3.4. Aerobic capacity

Nine studies [24,44–47,49–52] reported VO_{2peak} data, with 122 participants in the intervention group and 102 participants in the control group. Four studies [24,47,48,50] used the 6MWD and they included 32 participants in the intervention group and 25 participants in the control groups. Both VO_{2peak} and 6MWD improved in the RT group compared to the control group (VO_{2peak}, 2.71 ml/kg/min, 1.96, 3.45; 6MWD, 59.26 m; 36.75, 18.78) (Figs. 5 and 6).

3.5. Quality of Life

Three studies included QoL assessment [44,47,52]. The studies included a total of 40 participants in the RT group and 30 participants in the control groups. A reduction in QoL scores (indicating an improvement in QoL) was seen following RT, compared to the control (−5.71 points, −9.85, −1.56) (Fig. 7).

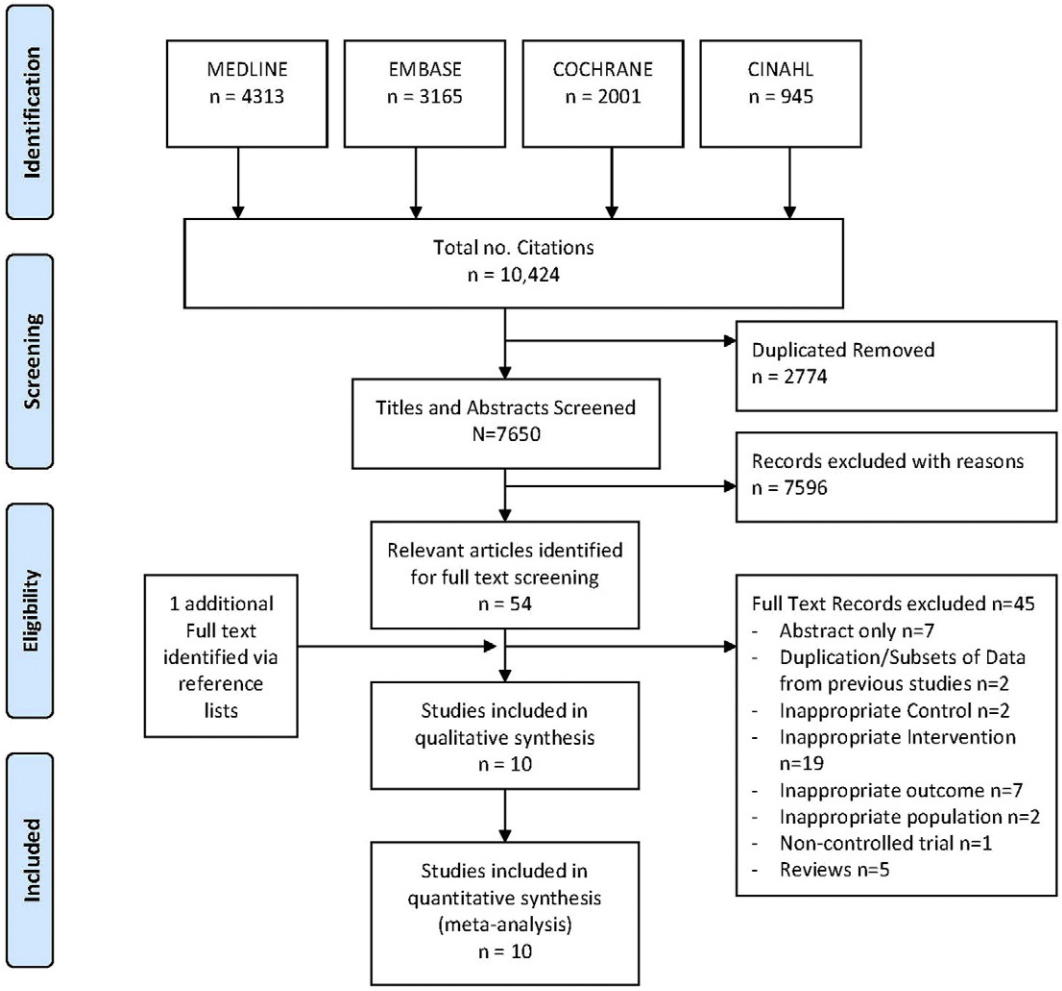

Fig. 2. Identification, screening, and selection of studies. (PRISMA Flow Diagram).

3.6. Sensitivity analyses

We conducted a sensitivity analysis where we used the final values instead of the change scores; the effect estimates did not materially change.

3.7. Study quality

Fig. 8 shows the risk of bias for each study according to the seven domains in the Cochrane Risk of Bias Tool. Our attempts to assess risk of bias were limited in many cases by incomplete reporting by authors.

Table 1
Participant characteristics.

Author, year	Height (m) and weight (m) or BMI (kg/m2) (mean ± SD)		Age (mean ± SD)		NYHA class (I/II/III/IV or mean ± SD)		LVEF (%) (Mean ± SD)	
Cider, 1997 [48]	· Height: 171.6 ± 32.9 · Weight: 76.1 ± 44.7	· Height: 172.2 ± 23.2 · Weight: 75.8 ± 42.3	61.8 ± 33.9	64.7 ± 18.35	7/3/2/0	5/2/3/2	Not stated	Not stated
Feiereisen, 2007 [51]	· Height: 174 ± 7 · Weight: 86.7 ± 15.5	· Height: 173 ± 6 · Weight: 84.2 ± 15.3	57.9 ± 5.8	55.5 ± 7.5	0/3/12/0	0/8/7/0	24 ± 7	25 ± 6
Grosse, 2001 [50]	· Height: 175.5 ± 7.4 · Weight: 65.0 ± 22.1	· Height: 174.8 ± 8.8 · Weight: 77.1 ± 15.0	56.5 ± 9.5	58.4 ± 5.8	3 ± 0.4	3 ± 0.5	28.3 ± 10.1	26.2 ± 11.2
Levinger, 2005 [43]	· Height: 178.6 ± 4.7 · Weight: 91.4 ± 14.0	· Height: 177.7 ± 10.5 · Weight: 91.1 ± 10.7	57.3 ± 11.1	56.7 ± 10.0	Not stated	Not stated	35.4 ± 6.3	34.0 ± 8.8
Palevo, 2009 [47]	· Height: 175 ± 0.08 · Weight: 77 ± 19	· Height: 1.78 ± 0.08 · Weight: 91 ± 24	70 ± 12	65 ± 13	0/3/7/0	0/4/3/0	32 ± 0.12	40 ± 0.8
Pu, 2001 [24]	· BMI: 24.7 ± 3.6	· BMI: 28.0 ± 5.0	76.6 ± 6	76.6 ± 6.4	2.2 ± 0.3	2.3 ± 0.5	36.3 ± 8.1	36.0 ± 7.7
Selig, 2004 [45]	· Height: 171 ± 9 · Weight: 84 ± 19	· Height: 171 ± 7 · Weight: 79 ± 12	65 ± 13	64 ± 9	2.4 ± 0.5	2.3 ± 0.4	27 ± 7	28 ± 6
Tyni-LennÈ, 2001 [49]	· BMI: 28 ± 4	· BMI: 27 ± 7	63 ± 9	62 ± 11	0/11/5/0	0/6/2/0	30 ± 9	30 ± 10
Beniaminovitz, 2002 [46]	· Height: 172.7 ± 7 · Weight: 84.6 ± 11.1	· Height: 172.7 ± 7 · Weight: 76.5 ± 3.9	50 ± 12.3	48 ± 11.3	Not stated	Not stated	20 ± 4.1	18 ± 2.8
Maioriana, 2011 [44]	· BMI: 28.4 ± 2.7	· BMI: 30.1 ± 4.5	58.8 ± 12.1	64.4 ± 8.3	3/6/3/0	4/6/2/0	26 ± 3	37 ± 3
Cider, 1997 [48]	· Height: 171.6 ± 32.9 · Weight: 76.1 ± 44.7	· Height: 172.2 ± 23.2 · Weight: 75.8 ± 42.3	61.8 ± 33.9	64.7 ± 18.35	7/3/2/0	5/2/3/2	Not stated	Not stated

Table 2
Intervention characteristics.

Author	Type of resistance training	Frequency & duration	Duration of session	Intensity (% of 1RM) and method of progression	Tempo	Sets × reps	Rest between sets
Cider, 1997 [49]	Circuit weight training	· 2 per week · 5 months	60 min	· 60% of 1RM · 1RM tested once a month and weights progressed accordingly	2 s concentric 2 seccentric Ŧ	2 × 30 ł	15 s
Feiereisen, 2007 [52]	Machine weights · latissimus pulldown, reverse butterfly, row, shoulder abduction, knee extension, knee flexion, leg press, calf raises, trunk flexion, trunk extension	· 3 per week · 14.33 weeks ¥	45 min	· 60% of 1RM for first 20 sessions · increased to 70% final 20 sessions	3 s concentric 3 s eccentric	4 × 10	120 s
Grosse, 2001 [51]	Cuff weights · Four muscle groups; biceps, triceps, quadricepts, ischiocrurale	· 2 per week · 12 weeks	Not stated	· 65% 1RM ≠ · Progression individually based on using RPE	Not stated	2 × 15	120 s
Levinger, 2005 [44]	Multi-station machine · 8 different exercises for the major muscle groups	· 3 per week · 8 weeks	60 min	· 40–60% of 1RM · Increased 4.54 kg as upper desired number of repetitions was reached	Not Stated	1 × 15–20 Progressing to 3 × 8–12	Not Stated
Palevo, 2009 [48]	Free weights & machine weights · Bench press, seated knee extension, lateral raise, leg curl, back extension, incline leg press, abdominal curl, latissimus pulldown, elbow flexion, calf raise, elbow extension and toe raise	· 3 per week · 8 weeks	Not stated	· 60% 1RM initially · Progression individually based on using RPE, no more than 10% per week	Not stated	2 × 12–15	120 s
Pu, 2001 [24]	Pneumatic-resistance training equipment · Seated leg press, chest press, knee ext., triceps and knee flex	· 3 per week · 10 weeks	60 min	· 80%1RM · Not stated	Each rep 6–9 s 2–3 s rest between reps	3 × 8	60–90 s
Selig, 2004 [46]	Multi-station machine and leg ergometers	· 3 per week · 12 weeks	Not stated	· Cycling/climbing (0.5–2 min) and 2 × 30 s of strength training at moderate intensity · Progression by increasing resistance or sets	Not stated	Cycling/climbing (0.5–2 min) and 2 x 30s of strength training at moderate intensity? how this was measured	Determined by heart rate to within 10 beats of resting
Tyni-LennÈ, 2001 [50]	Therabands	· 3 per week · 8 weeks	60 min	· Theraband increased when RPE scored <13/20	70 beats per minute	2 × 25	Not Stated
Beniaminovitz, 2002 [47]	Therabands and cuff weights · Bicycle and treadmill at <50% of peak VO2 and minute ventilation <25 l/min and heart rate < 120 beats/min	· 3 per week · 3 months	Not stated	· 2 lb./leg increasing by 2 lb./leg per month and additional set · Theraband also progressed each month	Not Stated	Not Stated	Not Stated
Maioriana, 2011 [45]	Not specified	· 3 per week · 12 weeks	46.5 min	· 50–60%1RM for first 6 weeks · increasing to 60–70%1RM for weeks 7 to 12	Not Stated	· First few sessions: 45 s work:45 s rest · Thereafter, 3 × 9	· First few sessions: 45 s · Thereafter, 3 min rest

ł = reported by authors as 2 sets, performed for 1 min of time; at 1 rep every 2 s = 30 reps, Ŧ = reported by authors as 1 activation every other second, ≠ = 1RM estimated from 15RM by calculations.

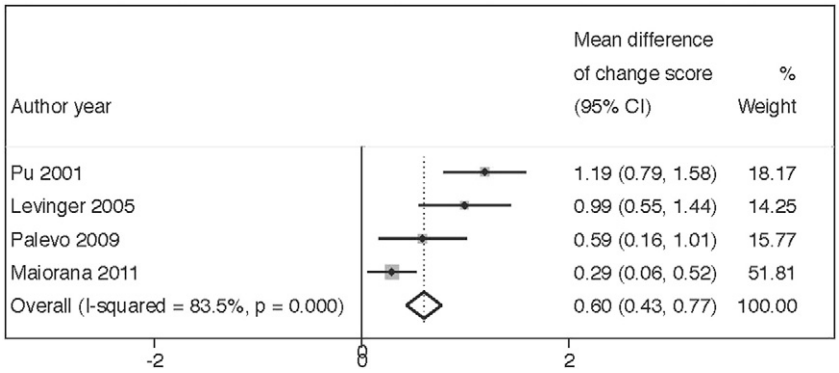

Fig. 3. Mean difference between resistance training group and control group for the change in 1 repetition maximum between baseline and follow-up; dashed line, overall estimate; bars, 95% confidence interval (CI).

Where reporting detail made assessment possible, bias was most commonly seen due to a lack of blinding of participants and personnel, which is difficult to manage in an exercise intervention study whereby exercise must be supervised. Two of the included studies [44,47] were controlled trials, but not randomised.

4. Discussion

The main findings of the current meta-analysis are that RT as a single intervention can increase muscle strength, aerobic capacity, and QoL in patients with CHF. However the effect of RT on muscle strength is mainly during slow controlled movements (1RM) and not during rapid movements. Older adults, who are the vast majority of patients with CHF, are underrepresented across studies and there are no RT studies in patients with severe CHF (NYHA IV).

To our knowledge, only one previous meta-analysis [34] has reported on the isolated effects of RT and included only four studies comparing RT alone to a control group. In this review, two studies with 40 participants [24,50] were pooled using a fixed effect model and found an increased weighted mean difference of 52 m (95% CI: 19 to 85 m) for the 6MWD which is similar to our own findings. On the other hand, data from four studies with 96 participants [24,46,49,50] were pooled for VO_{2peak}, resulting in a weighted mean difference of 1.4 ml/kg/min (95% CI: −0.3 to 3.1 ml/kg/min). The authors did not assess whether or not the baseline values of the outcomes for the individual studies were balanced and using an analysis of final values could lead to biased estimates [53].

Contrary to this finding, our systematic review and meta-analysis pooled estimates from nine studies and revealed for the first time that RT increased VO_{2peak} compared to a control group. VO_{2peak} is an

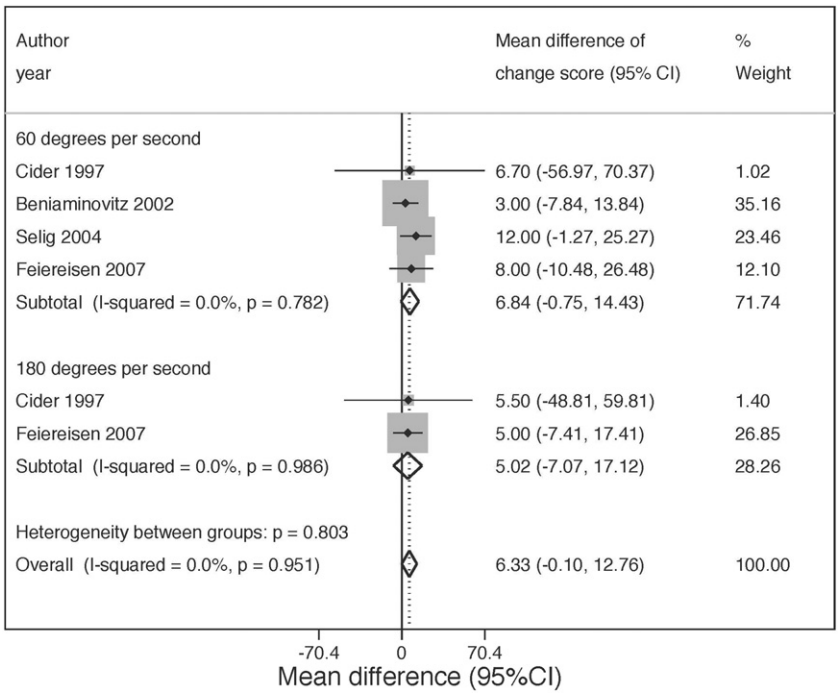

Fig. 4. Mean difference between resistance training group and control group for the change in isokinetic torque at 60 and 180 degrees per second between baseline and follow-up; dashed line, overall estimate; bars, 95% confidence interval (CI).

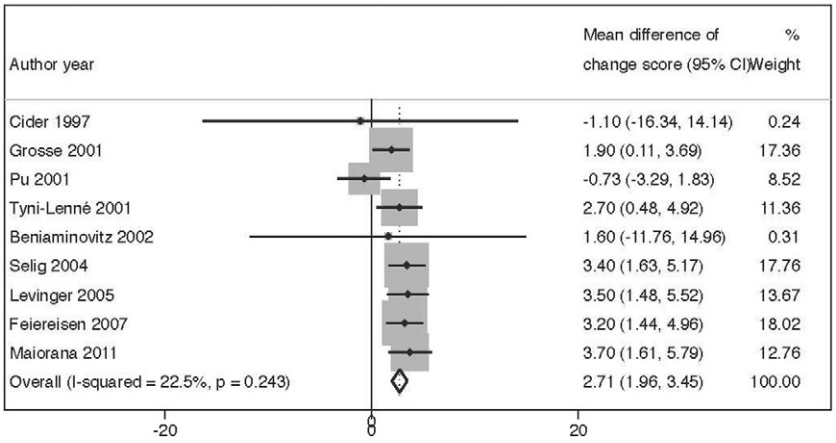

Fig. 5. Mean difference between resistance training group and control group for the change in VO_2 Peak between baseline and follow-up; dashed line, overall estimate; bars, 95% confidence interval (CI).

important clinical measure in patients with CHF as it is closely linked to cardiovascular mortality [54,55] . Therefore, increasing VO_{2peak} is a key objective of cardiac rehabilitation. Current guidelines favour aerobic training when the primary objective is to increase aerobic capacity, as this mode has been shown to have greater benefits than RT for this outcome [30,33]. However, clinicians and researchers have suggested that aerobic training may be unsuited to some patients, especially the elderly [33,56]. RT has an effect on skeletal muscle, but elicits less strain on the cardio-respiratory system compared to aerobic exercises. It may therefore be a suitable alternative for patients with CHF. Indeed, the current meta-analysis indicates that RT has the capacity to increase aerobic capacity in this population.

As expected, this meta-analysis revealed that RT improves muscle strength in the lower extremity in patients with CHF. This is clinically and functionally important for patients with CHF. Loss of muscle mass and strength, known as sarcopenia [57] is prevalent in the community-dwelling populations and is a determinant of independence, prolonged hospital admissions and reduced QoL [58]. In CHF, the changes in skeletal muscle may be even more pronounced, with further disease-mediated reductions in muscle mass and strength [59]. In CHF, skeletal muscle strength is strongly correlated with both morbidity and mortality [60,61] and is an independent predictor of VO_2peak [17]. The impact of muscle mass and muscle strength may be overlapping to some degree. Indeed, patients with reduced muscle mass have been shown to have poorer muscle strength and VO_2peak [59].

Muscle strength also has a profound impact on independent living and functional capacity. In patients with CHF, the capacity to perform activities of daily living (ADLs) is 30% lower than healthy controls and this can be attributed to both reduced muscle strength and aerobic capacity [62]. Furthermore, Seo et al., demonstrated that patients with CHF with poorer quadriceps muscle strength had greater dyspnea and exercise intolerance compared to individuals with greater muscle strength [63]. Improvement or at least preservation of muscle strength is an important clinical objective for patients with CHF. Our results confirm that RT is an important method to achieve this outcome.

Interestingly, this meta-analysis revealed that improvements in muscle strength were seen only during relatively slow 1RM movements and not during relatively rapid movements of 60 and 180°/s^{-1}. The implication of this finding is not entirely clear, but it may be hold clinical and functional importance. For instance, it was previously reported that the inability of skeletal muscle to generate rapid movements is related to a higher risk of falls in the elderly [64]. Moreover, it may be more important than muscle strength per se in preventing slip related falls [65]. Falls in patients with CHF, are common; 7–15% higher compared to other disease states [66] although the factors associated with falls in CHF are not clear [67]. It is plausible that standard RT programs that target muscle power will increase the capacity to perform ADLs and QoL, but will have a limited effect on falls risk. Future studies should test the hypothesis that power training is superior to standard RT in reducing falls risk in patients with CHF.

This meta-analysis highlights an under-representation of elderly patients, as well as those with advanced CHF (NYHA Class IV) in RT trials. This creates concerns regarding the interpretation and application

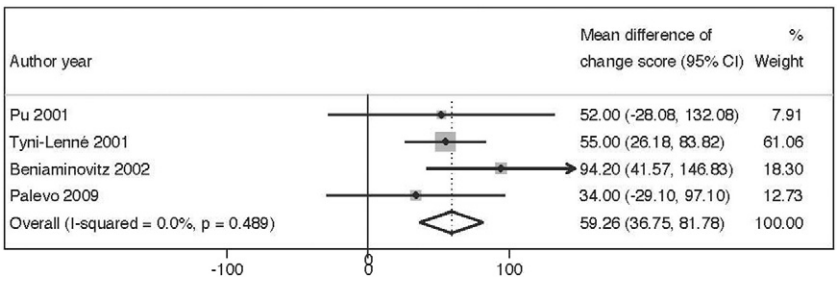

Fig. 6. Mean difference between resistance training group and control group for the change in 6MWD between baseline and follow-up; dashed line, overall estimate; bars, 95% confidence interval (CI).

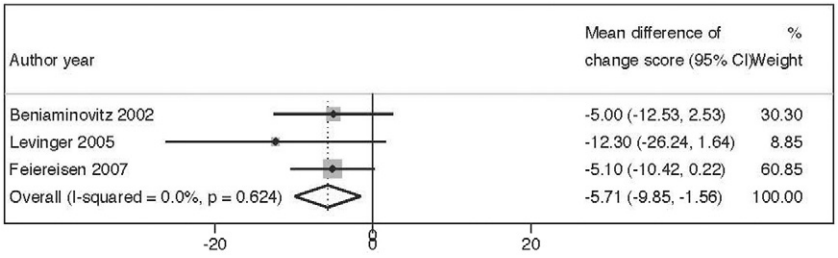

Fig. 7. Mean difference between resistance training group and control group for the change in QOL between baseline and follow-up; dashed line, overall estimate; bars, 95% confidence interval (CI).

of guidelines to the wider CHF population. For instance, the incidence of CHF was shown to increase 9% with each year of age over 65 [68]. Furthermore, the Framingham Heart Study reported a mean age of diagnosis of 76.4 years [26] yet only one of the included RT studies included patients above 65 years, the remaining were 6–28 years younger. Adding the fact that there is a growing population of elderly patients with CHF; a consequence of both an ageing population and improved survival from other cardiovascular conditions that are precipitators for CHF, the evidence base is limited and further studies are needed with a more representative group of patients.

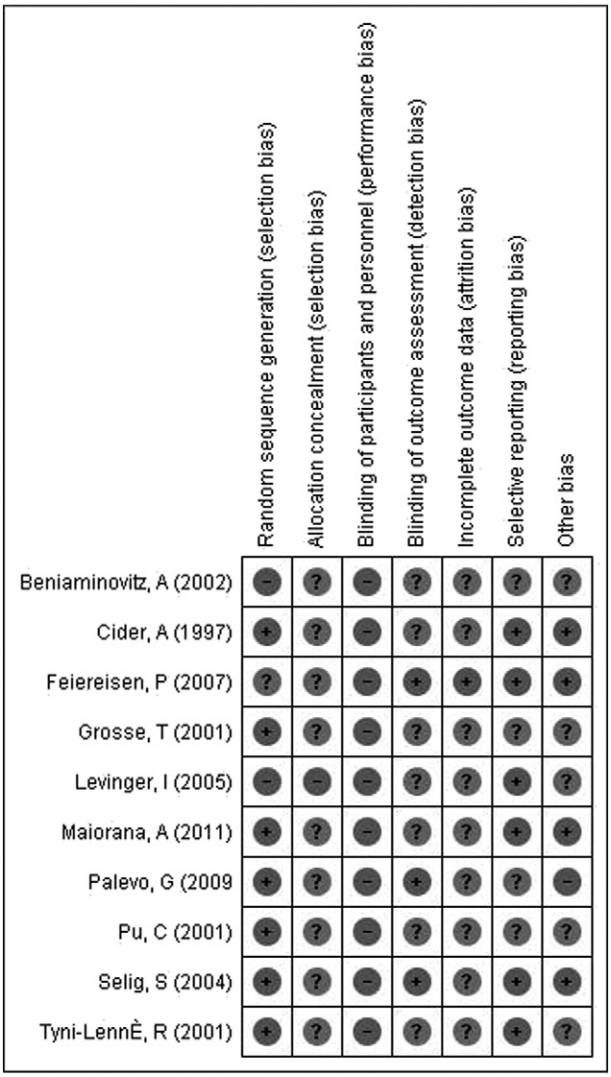

Fig. 8. Risk of Bias. Note: ? indicates unclear, + indicates low risk, − indicates high risk.

The strengths of this meta-analysis are that we employed a comprehensive search strategy, with the help of a clinical librarian, which resulted in a comprehensive list of citations. We used the Cochrane Risk of Bias tool to assess the risk of bias from individual studies. Our assessment of bias was limited by the information presented by the individual papers and we strongly encourage future studies to report in accordance with the CONSORT statement [69].

The current meta-analysis has some potential limitations. First, there are a relatively small number of studies, generally with a small number of participants. Second, meta-analyses are also limited by the potential of small study effects, where smaller studies that do not find an association do not publish their results. We used visual inspection of funnel plots and Egger's regression asymmetry test to ascertain bias due to small-study effects [36]. With the small number of studies included in our meta-analyses, it was difficult to ascertain whether there was any bias present from small-study effects and Egger's test is known to have low power when less than 20 studies are included in a meta-analysis [70]. Current recommendations for meta-analysis of continuous outcomes suggest the use of ANCOVA estimates when available [39]. However, ANCOVA estimates were poorly reported, we used the change scores and conducted a sensitivity analysis of the final values. Future studies should report the actual ANCOVA estimates when such analyses are conducted so they can be properly used in evidence synthesis [39].

In conclusion, RT as a single intervention can increase muscle strength, aerobic capacity, and QoL in patients with CHF. The effect of RT on muscle strength is mainly during slow controlled movements and not during rapid movements which may have clinical implications for falls related risks. In addition, this study identified that older adults and patients with advanced heart failure are underrepresented in resistance training controlled trials and further research should seek to optimise inclusion of these patients.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgements

Associate Professor Levinger is supported by Future Leader Fellowship (ID: 100040) from the National Heart Foundation of Australia. We would like to thank Evelyn Hutcheon and Steven Chang from Western Health library service for their help with the literature search.

Appendix 1. Search Stategy for Medline

#	Searches	Results
1	Exercise/	74,066
2	exercis*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	284,520
3	Circuit-based exercise/	11
4	Physical conditioning, human/	504
5	Plyometric exercise/	146
6	Resistance training/	4321
7	Walking/	23,153
8	Swimming/	14,362
9	Exercise therapy/	29,095
10	Hydrotherapy/	2300
11	hydrotherapy.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2611
12	"physical therap*".mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	41,725
13	((resistance or aerobic or strength* or interval or circuit) adj2 (training or program*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	16,295
14	calisthenic*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	170
15	callisthenic*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	29
16	rehab*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	140,613
17	kinesiotherap*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	139
18	strengthen*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	53,209
19	exp Running/	15,010
20	running.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	50,911
21	walk*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	89,560
22	exp Walking/	23,241
23	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	603,308
24	heart failure.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	154,113
25	exp Heart Failure/	95,125
26	Ventricular dysfunction, Left/	22,541
27	cardiomyopathy.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	60,012
28	exp Cardiomyopathies/	78,146
29	Left Ventricular Ejection Fraction.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	18,484
30	Cardiac resynchronization.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	5648
31	LV dysfunction.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	3134
32	Left ventricular systolic dysfunction.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2290
33	Left ventricular diastolic dysfunction.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1118
34	Cardiac failure.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	10,660
35	(HFNEF or HFPEF or HFREF or "HF NEF" or "HF PEF" or "HF REF").mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	983
36	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	261,972
37	Randomized controlled trial.pt.	418,427
38	Controlled clinical trial.pt.	92,318
39	Randomized.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	644,093
40	Placebo.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	176,469
41	Clinical trials as topic.sh.	180,293
42	Randomly.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	246,690
43	Trial.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	957,056
44	37 or 38 or 39 or 40 or 41 or 42 or 43	1,357,098
45	exp animals/	18,760,612
46	Humans/	14,599,060
47	45 not 46	4,161,552
48	44 not 47	1,259,412
49	*23 and 36 and 48*	*4207*

Appendix 2. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3–4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,14
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, 25 (appendix)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	26–29 (appendix)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5–6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6–7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5, 14 (Fig. 1)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6–7, 10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9–10, 15–18
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6,7,10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11 (available on request)
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10–13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12,13
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

References

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Chapter 5: PRIME-HF: Novel exercise for older patients with heart failure. A pilot randomised controlled study.

5.1 Background and context

The meta-analysis in Chapter 4 found that resistance training can be an alternative training modality for patients with CHF. However, older adults were underrepresented across all included studies in the meta-analysis. This finding became the foundation for conceptualising the pilot study of Chapter 5.

It was originally intended that Chapter 5 would be an RCT of resistance training in older adults with CHF. This followed the argument that resistance training can increase aerobic capacity, but may be a more tolerable form of exercise for older patients in comparison to whole-body aerobic training. However, during the planning process, Professor Jason Allen joined the Institute for Health and Sport at Victoria University and presented his work on the "PRIME" exercise intervention.

As described in the literature review, PRIME offers a 'hybrid' aerobic-resistance solution for individuals with peripheral or central limitations using a low-mass, high-repetition training regime, that induces low central cardiovascular strain (Allen et al., 2013). PRIME is applied as a bridging therapy to traditional exercise prescription involving whole body training. Hence, PRIME offered great potential to the focus patient group of this thesis.

5.2 Research aims

Chapter 4 presents a RCT which addresses the 4th and 5th objectives of this thesis (see section 2.9); To investigate whether older patients with HFrEF can tolerate current exercise recommendations involving COMBined Moderate-Intensity Aerobic and Resistance Training (COMBO) and, To analyse the effects of a novel muscle focused exercise regime called "PRIME", aerobic capacity and muscle strength in older adults with HFrEF.

5.3 Manuscript

The following paper, “PRIME HF: Novel exercise for older patients with heart failure: a pilot randomized controlled trial” was published in the *Journal of the American Geriatrics Society* in 2020.

It was also presented at the following conferences:

- Australian Cardiac Rehabilitation Association 2020 Annual Scientific Meeting
- Oral Presentation, nominated in the Best Exercise Prize Session
- Poster: ESSA Research to Practice 2020 (postponed due to COVID-19)

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This declaration is to be completed for each conjointly authored publication and placed at the beginning of the thesis chapter in which the publication appears.

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2. CANDIDATE DECLARATION

I declare that the publication above meets the requirements to be included in the thesis as outlined in the HDR Policy and related Procedures – policy.vu.edu.au.

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Signature **Date**

3. CO-AUTHOR(S) DECLARATION

In the case of the above publication, the following authors contributed to the work as follows:

The undersigned certify that:

1. They meet criteria for authorship in that they have participated in the conception, execution or interpretation of at least that part of the publication in their field of expertise;
2. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

3. There are no other authors of the publication according to these criteria;
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Western Health and Victoria University

Name(s) of Co-Author(s)	**Contribution (%)**	**Nature of Contribution**	**Signature**	**Date**
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Jason David Allen	10	Project planning, clinical support and appraisal of manuscript		5/01/21

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CLINICAL INVESTIGATION

PRIME-HF: Novel Exercise for Older Patients with Heart Failure. A Pilot Randomized Controlled Study

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OBJECTIVES: To test the hypothesis that (1) older patients with heart failure (HF) can tolerate COMBined moderate-intensity aerobic and resistance training (COMBO), and (2) 4 weeks of Peripheral Remodeling through Intermittent Muscular Exercise (PRIME) before 4 weeks of COMBO will improve aerobic capacity and muscle strength to a greater extent than 8 weeks of COMBO.

DESIGN: Prospective randomized parallel open-label blinded end point.

SETTING: Single-site Australian metropolitan hospital.

PARTICIPANTS: Nineteen adults (72.8 ± 8.4 years of age) with heart failure with reduced ejection fraction (HFrEF).

INTERVENTION: Participants were randomized to 4 weeks of PRIME or COMBO (phase 1). All participants subsequently completed 4 weeks of COMBO (phase 2). Sessions were twice a week for 60 minutes. PRIME is a low-mass, high-repetition regime (40% one-repetition maximum [1RM], eight strength exercises, 5 minutes each). COMBO training involved combined aerobic (40%-60% of peak aerobic capacity [VO_{2peak}], up to 20 minutes) and resistance training (50-70% 1RM, eight exercises, two sets of 10 repetitions).

MEASUREMENTS: We measured VO_{2peak}, VO_2 at anaerobic threshold (AT), and muscle voluntary contraction (MVC).

RESULTS: The PRIME group significantly increased VO_{2peak} after 8 weeks (2.4 mL/kg/min; 95% confidence interval [CI] = .7-4.1; P = .004), whereas the COMBO group showed minimal change (.2; 95% CI −1.5 to 1.8). This produced a large between-group effect size of 1.0. VO_2 at AT increased in the PRIME group (1.6 mL/kg/min; 95% CI .0-3.2) but not in the COMBO group (−1.2; 95% CI −2.9 to .4), producing a large between-group effect size. Total MVC increased significantly in both groups in comparison with baseline; however, the change was larger in the COMBO group (effect size = .6).

CONCLUSION: Traditional exercise approaches (COMBO) and PRIME improved strength. Only PRIME training produced statistically and clinically significant improvements to aerobic capacity. Taken together, these findings support the hypothesis that PRIME may have potential advantages for older patients with HFrEF and could be a possible alternative exercise modality. **J Am Geriatr Soc 00:1-8, 2020.**

Keywords: heart failure; exercise; strength; aerobic; resistance

Chronic heart failure (CHF) is a complex syndrome affecting 1% to 2% of Western populations,[1] and approximately 80% of patients are older than 60 years.[2] Patients with CHF are characterized by shortness of breath, fatigue, and exercise intolerance.[3] Exercise rehabilitation is considered a cornerstone intervention for people with CHF, with guidelines recommending moderate-intensity aerobic modalities,[3,4] often in conjunction with resistance training.[4-6] However, a key limitation of these guidelines is that they arise largely from data involving a patient cohort sometimes 2 decades younger (range = 51-81 years)[7] than the median age at diagnosis of CHF (77 years).[7,8] Considering that older adults with CHF experience a high prevalence of comorbidities, impaired functional capacity, reduced muscle mass and strength, and a 5-year survival of

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25%,[9-14] it is unclear whether they can actually tolerate current exercise guidelines or gain functional benefits.

It was recently demonstrated that older individuals with reduced peak aerobic capacity (VO_{2peak} 15-20 mL/kg/min) can benefit from a novel exercise regime known as Peripheral Remodeling through Intermittent Muscular Exercise (PRIME).[15,16] In brief, PRIME offers a hybrid aerobic-resistance program and was designed to address the peripheral tissue dysfunctions responsible for reduced VO_{2peak} in older adults, without imposing excess cardiovascular or musculoskeletal strain.[16] When PRIME is applied as a bridging therapy to combined aerobic and resistance training, participants experience greater increases in aerobic capacity, muscle strength, and physical function compared with combined training alone. This approach may offer potential advantages to older patients with central cardiovascular limitations; however, it is yet to be tested in clinical populations.

The aim of the current study was to test the hypothesis that (1) older patients with CHF can tolerate current exercise recommendations involving COMBbined moderate-intensity aerobic and resistance training (COMBO), and (2) 4 weeks of PRIME training followed by 4 weeks of COMBO will improve aerobic capacity and muscle strength to a greater extent than 8 weeks of the current recommended COMBO approach.

METHODS

Participants

Participants were recruited from the Western Health Heart Failure Clinic in Melbourne, Australia, following patient file review and an in-person interview. Inclusion criteria were (1) a diagnosis of HF with reduced ejection fraction (HFrEF) as defined by European Society of Cardiology Guidelines 2016,[3] (2) age 65 years and older, and (3) mild to moderate symptomatology (New York Heart Association [NYHA] class II-III). Exclusion criteria included any absolute contraindications to exercise for people with HFrEF, and relative contraindications were adjudicated by the study cardiologist. The algorithm for inclusion and exclusion criteria is supplied in Supplementary Figure S1. Patients meeting eligibility criteria were provided with information and invited to participate in the trial. Those who gave informed consent were scheduled for baseline testing and screening. The research protocol was approved by ethics committees from Melbourne Health and Victoria University.

Experimental Design

We used a prospective randomized open-label blinded endpoint parallel-group design. Participants were randomized to PRIME or COMBO training for an initial 4 weeks (phase 1). Following this, all participants completed 4 weeks of COMBO training (phase 2). Participants were randomized in a 1:1 ratio by an independent researcher (permuted block randomization with block size of 4, stratified by sex, with sequence saved in sequentially numbered opaque sealed envelopes), with treatment allocation revealed after baseline exercise testing. Outcomes were assessed at baseline, 4 weeks, and 8 weeks by a blinded assessor.

Outcome Measures

Aerobic Capacity

Peak aerobic capacity (VO_{2peak}) was assessed using a symptom-limited graded exercise test on a Lode Corival cycle ergometer, with simultaneous 12-lead electrocardiogram. Heart rate (HR), blood pressure (BP), and rating of perceived exertion (RPE) were recorded throughout. The protocol began at 20 W and increased by 10 W in 2-minute stages, and it was terminated when the patient achieved more than 17 on the RPE scale and was unable to continue cycling within 10 rpm of target cadence or exhibited clinical signs and symptoms. The volume of oxygen uptake (VO_2) for each 10-second interval was calculated utilizing MedGraphics (Breezesuite CPX Ultim system) that was calibrated before each test.

Muscle Strength

Muscle strength was assessed using the three-repetition maximum (3RM) test, and then predicated 1RM was calculated using standardized equations.[17] Total muscle voluntary contraction (total MVC) was considered as the sum of the calculated 1RM for seven movements tested including chest press, leg press, seated row, triceps pushdown, latissimus pulldown, upright row, and hack squat.

Exercise Training Protocols

Training sessions were conducted twice per week for 8 weeks and lasted approximately 60 minutes including warmup and cooldown. Sessions were conducted at Victoria University and Sunshine Hospital and supervised by an accredited exercise physiologist. In the case of missed exercise sessions, catch-up sessions were offered.

Phase I (PRIME)

The PRIME regime followed the protocol previously described[15,16] and was adjusted minimally for this study group. The protocol included eight exercises of chest press, leg press, seated row, triceps pushdown, latissimus dorsi pulldown, upright row, hack squat, and calf raises, starting at 40% of predicted 1RM and at a 2:1:2 movement tempo (concentric: rest: eccentric). During each exercise, participants were allowed breaks as needed, with each for a minimum of 30 seconds. Progression was made first by decreasing the number of rest periods during each exercise. When the patient could complete the whole duration of the exercise (5 minutes) without rest, the load was increased by approximately 10%.

Phase I (COMBO)

The COMBO protocol was based on exercise recommendations for patients with HFrEF and included both aerobic and resistance exercises.[5] The aerobic component began at 10 to 15 minutes at a target exercise intensity of 40% to 50% of VO_{2peak}, corresponding to an RPE of 11 to 13, progressing gradually according to patient's tolerance to 20 minutes. Intensity was adjusted so the RPE remained in the target

zones. The resistance component involved eight exercises, two sets of 10 repetitions, initially prescribed at 50% to 60% 1RM. Thereafter, the load was increased by approximately 10% when the participant fell below an RPE target range of 11 to 13.

Phase II

In phase II, all participants completed 4 weeks of identical COMBO training as described earlier, with the starting intensity for the aerobic and resistance components recalculated from

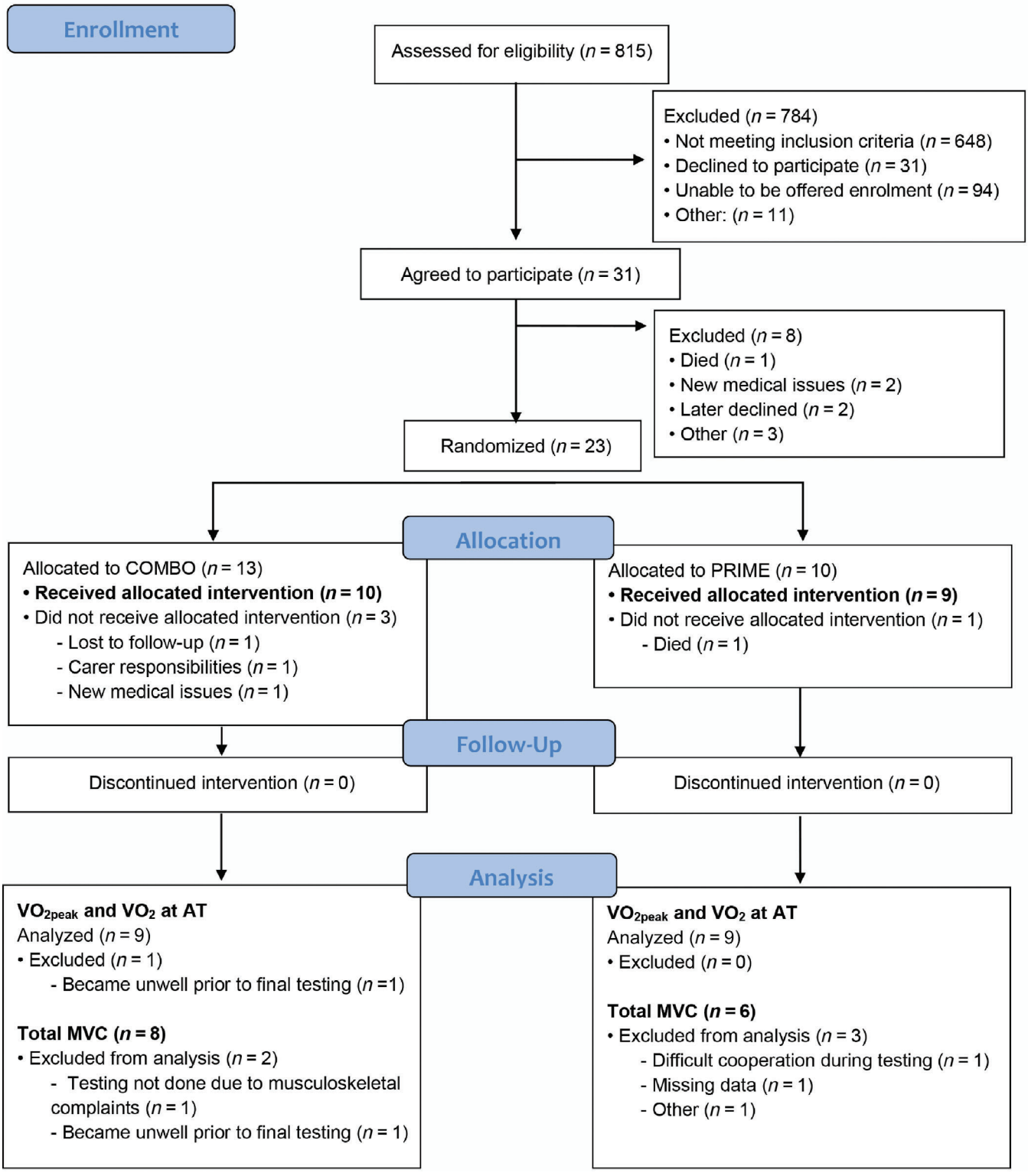

Figure 1. CONSORT flow diagram. AT, anaerobic threshold. COMBO, COMBined moderate-intensity aerobic and resistance training; MVC, muscle voluntary contraction; PRIME, Peripheral Remodeling through Intermittent Muscular Exercise. [Color figure can be viewed at wileyonlinelibrary.com]

Table 1. Baseline Participant Characteristics- Descriptive Statistics of Baseline Characteristics of Participants Who Completed the Entire Intervention

Characteristics	All (19)	PRIME (9)	COMBO (10)
Age, y	72.8 (8.4)	68.1 (6.4)	77.0 (8.0)
Male, n (%)	15 (79)	7 (78)	8 (80)
BMI, kg/m^2	31.0 (4.8)	31.0 (5.5)	31.1 (4.3)
NYHA class II/III (number)	13/6	6/3	7/3
LVEF (%)	31.6 (7.0)	31.1 (6.3)	32 (2.5)
Comorbidities, n (%)			
CAD	17 (89)	8 (89)	9 (90)
HTN	14 (74)	6 (67)	8 (80)
DM Type 2	10 (53)	4 (44)	6 (60)
CKD	10 (53)	5 (56)	5 (50)
AF	9 (47)	4 (44)	5 (50)
PPM	5 (26)	2 (22)	3 (30)
AICD	3 (16)	1 (11)	2 (20)
COPD	2 (11)	0 (0)	2 (20)
Frailty criterion, n (%)			
Karnofsky performance ≥60, n (%)	17 (89)	8 (89)	9 (90)
Rockwood scale ≥5, n (%)	4 (21)	2 (22)	2 (20)
Resting hemodynamics			
Systolic BP, mm Hg	119.6 (15.2)	117.3 (13.4)	121.7 (17.0)
Diastolic BP, mm Hg	67.5 (11.5)	64.2 (9.0)	70.5 (13.1)
HR, bpm	74.7 (10.3)	80.9 (8.2)	69.1 (9.0)
Heart failure pharmacotherapy, n (%)			
β-Adrenergic receptor blocker	16 (84)	7 (78)	9 (90)
Diuretics	12 (63)	6 (67)	7 (70)
Aldosterone antagonist	9 (47)	8 (89)	1 (10)
ACE inhibitor/ARB	11 (58)	7 (78)	4 (40)
Digoxin	2 (11)	2 (11)	0 (0)
>10 medications	3 (16)	3 (33)	0 (0)
Performance indicators			
Peak VO_2, mL/kg/min	13.5 (3.2)	13.1 (3.3)	13.3 (3.2)
Total exercise time, sec	481 (211)	454.4 (197)	508 (233)
Total MVC	315 (25.3)	323.3 (50.8)	307.8 (31.4)
Functional performance			
TUG test	8.7 (2.9)	8.1 (2.7)	9.5 (3.0)
10MWT	7.0 (1.7)	6.8 (1.9)	7.3 (1.6)
FSST	10.0 (2.7)	9.1 (2.3)	11.1 (2.9)

[a]Abbreviations: 10MWT, 10-Meter Walk Test; ACE, angiotensin converting enzyme; AF, atrial fibrillation; AICD, automated internal cardiac defibrillator; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COMBO, Combined Moderate-Intensity Aerobic and Resistance Training; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; FSST, Four Square Step Test; HR, heart rate; HTN, hypertension; LVEF, left ventricular ejection fraction; MVC, maximum voluntary contraction; NYHA, New York Heart Association; PPM, permanent pacemaker; PRIME, Peripheral Remodeling through Intermittent Muscular Exercise; TMVC, total maximum voluntary contraction; TUG, Time Up and Go; VO_2, volume of oxygen uptake during exercise.

[a]Data are expressed as mean (SD) unless otherwise stated.

repeat exercise testing, prescribed at 50% to 60% of VO_{2peak} for the aerobic component and 60% to 70% 1RM for the resistance component. Intensity was progressed according to RPE zones.

RPE, HR, and BP were monitored before, during, and after each training session. Individual HR and BP responses were monitored by the supervising exercise physiologist for signs of adverse responses or changing clinical status.

Volume load was calculated by repetitions [no.] × external load [kg], and aerobic exercise dose was estimated using published metabolic equations.[18]

Statistics

Given the novel nature of this study, a convenience sample size of 30 patients was used to estimate SD and effect sizes to inform power for a future definitive trial. Descriptive baseline characteristics data were presented as mean ± SD or frequency (percentage). Within-group comparisons between baseline and 8 weeks for all outcomes were analyzed with paired sample *t* tests and reported as mean with 95% confidence intervals (CIs). Between-group comparisons of improvement over 8 weeks were analyzed by Cohen's d effect sizes (due to the pilot nature of the trial). All statistical analyses were performed using GraphPad Prism v.7.04 for Windows (GraphPad Software, La Jolla, CA, USA; www.graphpad.com).

RESULTS

Participant Characteristics

Figure 1 presents the CONSORT flow diagram. Baseline characteristics are presented in Table 1. For the entire cohort, the mean age was 72.8 ± 8.4 years and approximately 80% of the participants were male. Baseline VO_{2peak} was 13.5 ± 3.2 mL/kg/min, body mass index was 31 ± 4.8 kg/m^2, and mean ejection fraction was 31.6 ± 7.0%. Common comorbidities were coronary artery disease (89%), hypertension (74%), and type 2 diabetes mellitus (53%). During the trial, all participants continued standard medical therapy as prescribed by their physician.

Training

Adherence and Side Effects

During phase I, all participants achieved more than 75% adherence (mean adherence = 97.3% ± 6.5). For phase II, 17 of 19 (89.5%) participants achieved more than 75% adherence (mean adherence = 96.1% ± 12.2). In total, 292 of the 304 target exercise sessions (96%) were completed by the 19 participants, with an average weekly session attendance of 1.6 sessions per week. None of the 19 participants who began the exercise interventions withdrew from the study. Mean total time to program completion (including testing visits) was 11.4 ± 1.4 weeks.

No major adverse events occurred during this study. Minor events included one unrelated exacerbation of HF and one unrelated chest infection. New musculoskeletal complaints occurred in four of the PRIME participants (on five occasions) and four of the COMBO participants

Table 2. Effects of PRIME and COMBO Interventions on Aerobic Capacity and Muscle Strength

	Baseline (0 wk)	Time point 1 (4 wk)	Time point 2 (8 wk)	Mean difference (0-8 wk)	Cohen's d between-group improvements (0-8 wk)
VO_{2peak}, mL/kg/min					
COMBO	13.4 (10.9 to 16.0)	13.2 (10.7 to 15.8)	13.6 (10.3 to 17.0)	.2 (−1.5 to 1.8)	1.0
PRIME	13.1 (10.6 to 15.5)	14.9 (12.3 to 17.5)	15.5 (12.6 to 18.3)	2.4 (.7 to 4.1)*	
VO_2 at AT, mL/kg/min					
COMBO	8.9 (6.9 to 10.9)	7.5 (6.4 to 8.6)	7.6 (5.7 to 9.6)	−1.2 (−2.9 to .4)	1.5
PRIME	7.7 (6.7 to 8.6)	8.6 (7.5 to 9.8)	9.2 (8.0 to 10.5)	1.6 (.0 to 3.2)	
Total MVC, kg					
COMBO	307.8 (257.3 to 358.3)	325.2 (266.4 to 384.0)	382.4 (326.8 to 438.0)	74.6 (39.4 to 110.0)*	.6
PRIME	323.3 (199 to 447.6)	359.6 (136.1 to 483.2)	374.9 (251.3 to 498.6)	48.6 (7.8 to 89.3)*	

Abbreviations: AT, anaerobic threshold; COMBO, COMBined moderate-intensity aerobic and resistance training; MVC, muscle voluntary contraction; PRIME, Peripheral Remodeling through Intermittent Muscular Exercise; VO_2, volume of oxygen uptake; VO_{2peak}, peak aerobic capacity.
*$P < .05$.

(on seven occasions). Complaints related to existing musculoskeletal injuries occurred in seven PRIME participants (27 occasions) and six from the COMBO group (11 occasions).

Training Loads

Details of the weekly training loads are presented in Table 2. By the final training week (week 8 of COMBO training), the participants initially allocated to PRIME and COMBO interventions were training at a weekly energy expenditure for the aerobic component of 169.7 ± 18.7 MET-min-wk^{-1} and 143.2 ± 9.2 MET-min-wk^{-1}, respectively ($P = .2$), and at a volume load for the resistive component of $9{,}075.7 \pm 1{,}015.4$ kg/wk and $8{,}067.0 \pm 527$ kg/wk, respectively ($P = .4$). RPEs were balanced between groups.

Effects of PRIME and COMBO

After 8 weeks of training, the PRIME group increased VO_{2peak} significantly, by 2.4 mL/kg/min (95% CI = .7-4.1; $P < .05$), whereas the COMBO group showed a minimal change of .2 mL/kg/min (95% CI = −1.5 to 1.8) (Table 2). This produced a large between-group response effect size (Cohen's d) of 1.0. A clinically important improvement in VO_{2peak} (defined as a >6% increase[19]) was observed in 60% of the PRIME group and 33% of the COMBO group after 8 weeks of training (Figure 2B).

The VO_2 at AT increased by 1.6 mL/kg/min (95% CI = .0-3.2) in the PRIME group, whereas a negative change (indicating a worsening of the clinical outcome) of −1.2 mL/kg/min (95% CI = −2.9 to .4) was observed in the COMBO group. This produced a large between-group effect size (Cohen's d = 1.5; Figure 2).

Total MVC increased significantly in both the PRIME (48.6 k; 95% CI = 7.8-89.3; $P = .01$) and COMBO groups (74.6 k; 95% CI = 39.3-110.0; $P < .001$) in comparison with baseline. The difference between groups produced a moderate between-group effect size of .6 (Figure 2).

DISCUSSION

We report that (1) older patients with HFrEF can safely perform current recommended exercise guidelines, despite these guidelines being formulated by data from younger cohorts, and (2) 4 weeks of PRIME before COMBO produced benefits for both aerobic power and strength, whereas 8 weeks of COMBO training provided no increase in aerobic power but superior strength gains. PRIME may provide a more beneficial exercise option for older patients with HFrEF, particularly those with both significant aerobic capacity and strength impairments.

The widely adopted exercise recommendations for patients with HFrEF involve moderate-intensity aerobic exercise in combination with resistance training.[3,4] These endorsements follow the consistent demonstration of improved functional capacity, reduced rates of hospitalization, and improved quality of life with exercise training.[3,4,7,20] As highlighted in the updated Cochrane review of 2019, the problem remains that older patients with HFrEF, who are often more functionally limited, are unrepresented in clinical trials. The current study successfully recruited a population reflective of the real-world patient, achieving a mean age of participants of 73 years and baseline VO_{2peak} of 13.5 mL/kg/min.

As hypothesized, COMBO and PRIME training was safe and well tolerated by participants, with no major adverse events reported and an acceptable frequency of minor events related mainly to existing musculoskeletal injuries. The lack of improvement in VO_{2peak} observed in the COMBO group is not unprecedented and was also reported in a meta-analysis of exercise training in older patients with HF.[21] Of note, the 2009 prospective trial by Brubaker et al involving 59 patients with HFrEF (mean age = 70.2 ± 5.1) demonstrated that after 16 weeks the exercise training group had 12% longer exercise time on the bike and 13% greater exercise workload than the control group, although there was no increase in VO_{2peak}.[22] Similarly, the HF-ACTION trial (mean age = 59 years) used a comparable exercise intervention and demonstrated a median increase in VO_{2peak} of just 4% in the exercise group compared with the control after 3 months of training.[23] Combined, these findings may indicate a nonoxidative

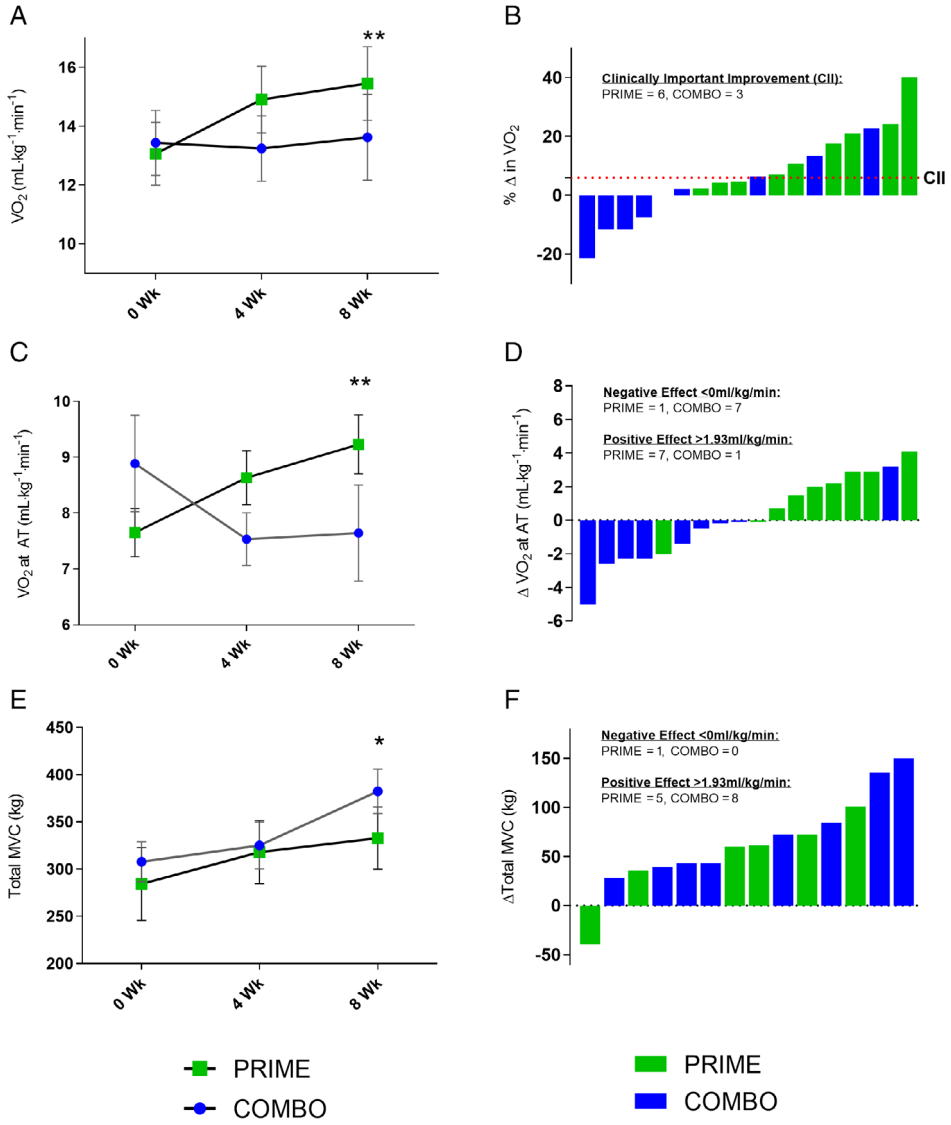

Figure 2. Group mean data at baseline, 4 weeks, and 8 weeks (left column) and waterfall graphs of individual training responses from baseline to 8 weeks to Peripheral Remodeling through Intermittent Muscular Exercise (PRIME) or COMBined moderate-intensity aerobic and resistance training (COMBO) treatment (right column), regarding peak aerobic capacity (VO_{2peak} mL/kg/min) (A and B); VO_2 at Anaerobic Threshold (AT) (VO_2 mL/kg/min) (C and D); and total weight lifted (total kg) (E and F). Dotted line f (tile b) indicates a clinically important improvement of 6%. Values are given as mean ± standard error of the mean. *Indicates moderate effect size (Cohen's d >.6 for between-group improvement 0-8 weeks). **Indicates large effect size (Cohen's d >1.0 between-group improvement 0-8 weeks).

muscle adaptation that may not be reflected in VO_{2peak} measurement.

In comparison, patients initially allocated to PRIME training exhibited a significant improvement in VO_{2peak} compared with baseline. The resultant difference between interventions (large effect size) suggests a potential superiority of PRIME for measures of aerobic capacity. According to the HF-ACTION trial, every 6% increase in VO_{2peak} is associated with a 5% lower risk of all-cause mortality and all-cause hospitalization[19] In this respect, initial allocation to PRIME training was also more frequently associated with improvements above this clinically important threshold, in comparison with participants in the COMBO group (Figure 2B; 66% vs 33% of participants). These increases in aerobic fitness are noteworthy given that PRIME does not include a traditional aerobic training component such as walking or cycle training, whereas COMBO does.

For the outcome of maximal muscular strength, both PRIME and COMBO produced statistically significant increases from baseline; however, COMBO appeared superior to PRIME with a moderate effect size of .6. This finding is logical, given strength was trained with heavier weights and lower repetitions during COMBO. Upon reflection, a measure of muscular endurance may have been a useful additional outcome measure.

This pilot study was not powered to delineate mechanisms of change with PRIME training, but we speculate that the increases in aerobic capacity may be owing to a mitigation

of peripheral tissue maladaptations that are primarily responsible for exercise intolerance in HF according to the "muscle hypothesis" of HF.[24] By focusing initially on relatively small peripheral muscle masses, the PRIME regime aims to provide a *localized stimulus, not restricted by compromised or competing perfusion*. This approach is based on earlier work that showed increases in arm vasoreactivity and strength in both healthy young subjects and those with CHF following handgrip exercise.[25,26] Conceptually, this type of stimulus would allow a higher intensity exercise in the exercising tissue bed for longer periods than what could be achieved with whole-body or large muscle group exercise. This may allow for greater peripheral training adaptations that increase oxygen extraction and metabolic efficiency, therefore partially reversing exercise intolerance.

This study represents an important step in closing the age bias seen across clinical exercise studies and has provided the impetus for the development of a larger, definitively powered study. If indeed PRIME exercise is shown to benefit older patients with HF, cardiac rehabilitation providers and policy developers need to consider how exercise guidelines can be modified to include older patients with HF more effectively, so that the benefits of exercise can be offered, safely and effectively, to the full spectrum of HF patients including older persons. It may also be useful in other disease states where central impairments limit exercise capacity, such as pulmonary disease.

The study has some potential limitations. First, women represented only 20% of our study population. The misrepresentation of older women is encountered in clinical trials and in cardiac rehabilitation programs, and it represents both a failure of clinicians to refer such patients, as well as logistic difficulties encountered by older women in attending these programs.[20,27] Furthermore, we did not include patients with HF with preserved ejection fraction (HFpEF), who represent approximately 50% of the HF population.[28] Patients with HFpEF are usually older than those with HFrEF and may have more peripheral limitations to exercise tolerance.[29] Future studies should include patients with both HF subtypes and consider strategies to improve the representation of women. In addition, although Cohen's d strongly suggested positive effects to aerobic capacity outcomes in favor of the PRIME group, the pilot sample size is relatively small, and a larger powered study is required to assess accurately the effects of PRIME vs COMBO exercise training.

In conclusion, among a sample of older patients with HFrEF, we found that although traditional exercise and PRIME exercise approaches were well tolerated, only PRIME training produced positive changes to aerobic capacity in conjunction with increases in muscular strength. Taken together, these findings support the hypothesis that PRIME may have potential advantages for older patients with HFrEF and could be a possible alternative exercise modality.

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Author Contributions: Jason David Allen and Christopher James Neil are shared senior authors. Jason David Allen is the original developer of the PRIME exercise intervention and contributed to the protocol development, contributed to the interpretation of study findings, and provided critical appraisal of the manuscript. Christopher James Neil is the study cardiologist and shared senior author. He contributed to the protocol development and interpretation of findings and provided critical appraisal of the manuscript. He provided expert clinical advice related to the care of the participants. Catherine Giuliano undertook this study as part of her PhD. She coordinated the overall project conduct and ethics requirements, contributed to the protocol development, managed data collection, and conducted the analysis and drafting of the manuscript. She carried out the study assessments and supervised the exercise physiologists delivering the training interventions. Itamar Levinger contributed to the study design, provided clinical exercise physiology support for the participants, and provided critical appraisal for manuscript. Sara Vogrin provided statistics oversight and critically reviewed all manuscripts with attention to the reporting and presentation of data.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Figure S1: Algorithm of inclusion and exclusion criteria. Adapted from the Exercise and Sports Science Australia Position Statement on exercise training and chronic heart failure.[5]

Chapter 6: Challenges in recruiting elderly patients with heart failure to exercise rehabilitation: Findings from a randomised controlled trial

6.1 Background and context

The PRIME-HF study presented in Chapter 5 successfully recruited a population reflective of the real-world patient, achieving a mean age of participants of 73 years and baseline VO_2peak of 13.5 mL/kg/min. This is important, as older patients are frequently excluded from clinical trials due to arbitrary upper age limits, or due to other exclusion criteria unsupported by clinical guidelines, including comorbidities or concurrent treatment (Crome et al., 2014). To our knowledge, there is no published description reporting the detailed reasons for the exclusion of older patients with CHF from exercise training studies and therefore it is difficult to ascertain the true eligibility and recruitment potential of older patients with CHF for exercise training.

6.2 Research aims

To determine eligibility, recruitment and dropout rates among older adults with HFrEF screened for enrolment in an exercise training study, and identify the leading clinical reasons for exclusion.

6.3 Manuscript

The following paper is being prepared for submission to a peer reviewed journal.

It was also presented at the following conference:

Poster: ESSA Research to Practice 2020 (postponed due to COVID-19)

Chapter 7: General discussion

7.1 Thesis overview

Exercise training is considered an integral part of the rehabilitation process for patients with CHF and is recommended by leading cardiac institutions around the world (Ponikowski et al., 2016a, Atherton et al., 2018, Piepoli et al., 2011, Selig et al., 2010a). The overarching aims of this thesis were to explore factors affecting eligibility, referral and participation in exercise rehabilitation among older patients with CHF and to investigate novel, muscle-focused exercise modalities.

These investigations are important for several reasons. As outlined in the literature review, evidence suggests that participation in exercise rehabilitation among older adults is low and until now, factors related to participation have been relatively unknown. In this regard, the detailed investigations of referral and participation in exercise rehabilitation undertaken within this thesis make a significant contribution to our understanding of current service utilisation and highlight several challenges to program engagement.

The subsequent investigations of two exercise modalities (i.e. resistance training and PRIME training) build on our understanding that exercise intolerance in CHF is largely caused by pathological changes in the muscles and peripheral tissues. Prior to this research, it was unknown whether resistance training and PRIME exercise—regimes that target the skeletal muscle and peripheral tissues—were effective at increasing aerobic capacity in older patients with CHF.

7.2 Key findings

The results presented in this thesis offer important evidence for enhancing the delivery of exercise rehabilitation for patients with CHF. The key findings of this thesis are:

- rates of referral to outpatient exercise rehabilitation among patients hospitalised with heart failure are suboptimal and older patients, females and those with multiple comorbidities are the most disadvantaged **(Studies 1 and 4)**

- current guideline-recommended exercise involving combined aerobic and resistance training increases muscular strength in older adults with HFrEF but has minimal effect on aerobic capacity **(Study 3)**
- resistance training as a standalone therapy increases aerobic capacity, maximal strength and quality of life in patients with CHF **(Study 2)** while, in older adults, PRIME training has the additive benefit of increasing aerobic capacity and thus, may offer an alternative exercise training option **(Study 2)**

7.2.1 Referral and engagement in exercise rehabilitation among older patients with CHF is low

Despite the well-established benefits of exercise training for patients with CHF, data from this thesis demonstrates that referral to outpatient exercise rehabilitation programs following hospitalisation with acute heart failure in Victoria is suboptimal (Study 1 of Chapter 3). The referral shortfalls were particularly evident among females, older patients and in those with comorbidities, and having ischemic or rhythm-related CHF dramatically increased the odds of referral. Moreover, we have shown that even when offered the opportunity to participate in an exercise program almost 60% of older adults with HFrEF will decline participation (Study 4 of Chapter 6). These findings present a challenging paradox, as patients with more complex presentations, or patients who are older, may have the greatest need for exercise training. The low rates of referral and engagement in exercise rehabilitation are concerning and requires urgent attention.

7.2.2 Combined aerobic and resistance training for older adults with HFrEF

The RCT presented in Study 3 of Chapter 5 aimed to investigate whether older patients with HFrEF could tolerate current guideline-recommended exercise of combined moderate-intensity aerobic and resistance training (COMBO) (Aim 1 of Study 3). As discussed in the literature review (section 2.7) the existing evidence for COMBO training for patients with CHF is strongly biased towards younger patients. A major strength of Study 3 was the successful recruitment of the typical patient with HFrEF, whereby the mean age of participants was 73 years and baseline VO_{2peak} was 13.5 mL/kg/min. Thus, this study represents an important step in closing the age-bias seen across clinical exercise studies.

Interestingly, the group randomised to COMBO training did not increase maximal or submaximal aerobic capacity (compared to baseline) after eight weeks of training. Patients in the COMBO group did, however, improve muscle strength significantly from baseline and this effect was significantly greater than the PRIME group.

The lack of improvement in VO_{2peak} following COMBO training is not unprecedented and was also reported in a meta-analysis of exercise training in older patients with CHF (Chen and Li, 2013). Of note, the 2009 prospective trial by Brubaker et al. involving 59 patients with HFrEF (mean age = 70.2 ± 5.1) demonstrated that there was no increase in VO_{2peak} after 16 weeks of combined exercise training (Brubaker Peter and Kitzman Dalane, 2011). However, participants had 12% longer exercise time on the bike and 13% greater exercise workload than the control group, which may suggest a nonoxidative muscle adaptation that is not reflected in VO_{2peak} measurement. Thus, Study 3 of Chapter 5 provides supporting evidence that COMBO training may not be an effective modality to increase VO_{2peak} in older patients with HFrEF.

The clinical implications of this finding must be taken with caution. Exercise professionals should not be discouraged from prescribing COMBO training for older patients with CHF because the benefits are likely to expand beyond the single, although important, measurement of VO_{2peak}. For individuals where improvement in VO_{2peak} is a priority, however, clinicians should consider PRIME (discussed in section 7.2.3 below).

7.2.3 Exercise modalities with a focus on skeletal muscle improve aerobic capacity in patients with CHF

Study 2 of Chapter 4 and Study 3 of Chapter 5 hypothesised that resistance training and PRIME exercise will increase aerobic capacity in patients with CHF.

Study 2 of Chapter 4 presented a meta-analysis of pooled estimates from nine studies and reported, for the first time, that resistance training increased VO_{2peak} among patients with HFrEF. Resistance training also increased muscle strength in the lower extremities. Furthermore, the PRIME-HF study presented in Study 3 of Chapter 5 showed that patients initially allocated to PRIME training exhibited a significant improvement in VO_{2peak} and VO_2 at anaerobic threshold compared with baseline. VO_{2peak} is an important clinical measure for patients with CHF as it is closely linked to cardiovascular mortality and risk of hospitalisation (Corrà et al., 2004, Swank et al., 2012). In this regard, 66% of participants who were initially

allocated to PRIME training experienced clinically important improvements in $VO_{2peak.}$ These findings are noteworthy, given that neither resistance training nor PRIME involves a traditional aerobic training component such as walking or cycle training.

Studies 2 and 3 were not designed to delineate the mechanisms of change following resistance training and PRIME exercise. However, we speculate that the increases in aerobic capacity may be owing to the mitigation of peripheral tissue maladaptation's that are primarily responsible for exercise intolerance in CHF according to the muscle hypothesis of CHF. By focusing initially on individual muscle groups, both resistance training and PRIME provide a localised stimulus that is *not restricted by compromised or competing perfusion*. Conceptually, this would allow greater aerobic stimulation in the exercising tissue bed for longer periods than could be achieved with whole-body or large muscle group exercise.

Both PRIME and resistance training influence skeletal muscle and aerobic capacity but elicit less strain on the cardiorespiratory system compared to aerobic exercises. They may, therefore, be suitable alternatives for patients with CHF who experience marked central limitations or who may be unable to participate in whole-body exercise.

7.3 Potential limitations

The research conducted within this thesis has some potential limitations that were described in detail for each study in the relevant chapters. The findings of this thesis should be viewed with acknowledgement of the following general limitations:

1. Studies 1, 3 and 4 were conducted in the Australian state of Victoria within the western metropolitan region. This region comprises a low sociodemographic profile and as such, the findings may not apply to all regions and socioeconomic levels
2. Study 3 (PRIME-HF) had a relatively small sample size and the findings are not conclusive. Furthermore, Study 2 (meta-analysis) included only a small number of studies with a small number of participants
3. This thesis focused mostly on patients with HFrEF who represent around half of the population with CHF. Findings may not apply to patients with HFpEF

7.4 Recommendations arising from this research

7.4.1 Clinical recommendations

7.4.1.1 Referring older adults with CHF to cardiac rehabilitation

Engaging older adults with CHF in exercise training is challenging but possible, as demonstrated by this thesis.

We have shown that older adults with CHF have a fluctuating clinical status that is often related to the presence of comorbidities. Consequently, their suitability to participate in exercise also fluctuates. Clinicians must not be deterred from referring medically complex individuals or those with comorbidities to exercise rehabilitation but instead should be especially encouraging of referring these patients. We suggest clinicians adopt routine screening practices for the assessment of exercise rehabilitation eligibility. Doing so will help identify periods of clinically stability where patients may be most appropriate for referral. This thesis also showed that engagement may be enhanced by the removal of transportation barriers and we recommend service providers offer transportation assistance to older individuals, for whom transportation is likely to be a barrier.

The paper titled “Cardiac Rehabilitation for Patients with Coronary Artery Disease: A Practical Guide to Enhance Patient Outcomes Through Continuity of Care” (see appendix A) was written during the tenure of this PhD program and highlights opportunities to enhance continuity of care across three domains: informational, management and relational continuity. While not directly related to the target population of this thesis, this paper provides several recommendations to enhance patient engagement with exercise rehabilitation and these recommendations can be generalised to patients with CHF. For instance, it is suggested that regular clinical team meetings can encourage informational continuity for complex case patients, while a dedicated, connected and consistent team of professionals can optimise relational continuity and enhance engagement. These simple, yet important, strategies may help overcome some of the barriers faced by older adults with CHF.

7.4.1.2 Exercise prescription for patients with CHF

Although published RCTs on resistance training remain scarce, this thesis has provided promising evidence supporting resistance training as a standalone therapy to increase aerobic

capacity and muscular strength in patients with CHF. Additional meta-analyses suggest that cardiac function does not deteriorate following resistance training in patients with CHF.

Study 2 of Chapter 4 from this thesis was published and has been cited by the following noteworthy societies:

- Heart Failure Society of America: A consensus statement (Vest et al., 2019)
- European Association of Preventive Cardiology: A position paper (Ambrosetti et al., 2020)
- Korean Society of Heart Failure: Guidelines for the management of chronic heart failure (Kim et al., 2019)
- American Physical Therapy Association: Clinical Practice Guideline (Shoemaker et al., 2020)

Whereas any physical activity in patients with CHF is likely to be beneficial, resistance training should now be considered as an effective exercise modality for patients with CHF, as a standalone therapy or in conjunction with aerobic training.

Due to the age-bias among combined exercise training studies for patients with CHF, the efficacy of combined exercise training on VO_{2peak} in older adults with CHF requires further investigation. However, the wider benefits of combined exercise training on physical health and wellbeing must be acknowledged and exercise professionals should continue to ensure an individualised and patient-centred approach. For older adults with CHF where improvement in VO_{2peak} is a priority, PRIME exercise may offer advantages and could be considered as a possible alternative.

7.4.2 Future research recommendations

7.4.2.1 Patient-reported barriers to engagement in exercise rehabilitation

This thesis presents clinical and demographic factors associated with referral to exercise rehabilitation but does not report individual patient reasons for refusing enrolment. Acknowledging the refusal rate of 60% reported in this thesis, future studies should seek to explore patient-reported barriers to engagement with an appropriately designed methodology.

7.4.2.2 Future research must seek to represent the typical patient with CHF

The age-bias among exercise RCTs is evident across all training modalities. Future studies should seek to optimise the inclusion of older patients with both CHF subtypes and consider strategies to improve the representation of women and older adults.

7.4.2.3 Larger statistically powered investigations are required to assess the effectiveness of resistance training and PRIME definitively among older adults with CHF

Although analysis by Cohen's d strongly suggested a positive effect on aerobic capacity outcomes in favour of PRIME training, the pilot sample size was relatively small and a larger statistically powered study is required to assess the effects of PRIME versus COMBO exercise accurately. Furthermore, the meta-analysis of resistance training in patients with HFrEF included only a relatively small number of studies, generally with a small number of participants. Further RCTs are required to increase the pool of evidence for resistance training.

7.5 Concluding remarks

As an investigation of a real-world clinical challenge, this research has shown that age should not be a barrier to exercise training in patients with CHF. The research showed that with appropriate and routine assessment, older adults with CHF can be safely enrolled into exercise training programs and achieve important improvements in clinical and functional outcomes. This research provides high-quality, preliminary evidence supporting PRIME and resistance training as alternative exercise modalities for patients with HFrEF.

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Appendices

Cardiac Rehabilitation for Patients With Coronary Artery Disease: A Practical Guide to Enhance Patient Outcomes Through Continuity of Care

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ABSTRACT: Coronary artery disease (CAD) is a leading cause of disease burden worldwide. Referral to cardiac rehabilitation (CR) is a class I recommendation for all patients with CAD based on findings that participation can reduce cardiovascular and all-cause mortality, as well as improve functional capacity and quality of life. However, programme uptake remains low, systematic progression through the traditional CR phases is often lacking, and communication between health care providers is frequently suboptimal, resulting in fragmented care. Only 30% to 50% of eligible patients are typically referred to outpatient CR and fewer still complete the programme. In contemporary models of CR, patients are no longer treated by a single practitioner, but rather by an array of health professionals, across multiples specialities and health care settings. The risk of fragmented care in CR may be great, and a concerted approach is required to achieve continuity and optimise patient outcomes. 'Continuity of care' has been described as the delivery of services in a coherent, logical, and timely fashion and which entails 3 specific domains: informational, management, and relational continuity. This is examined in the context of CR.

KEYWORDS: Continuity of care, cardiac rehabilitation, models of care, coronary artery disease

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Introduction

Coronary artery disease (CAD) remains the leading cause of disease burden in Australia and continues to cost the health care system more than 1.3 billion dollars annually.[1] Cardiac rehabilitation (CR) provides a cost-effective therapy[2] that aims to accelerate recovery following an acute event and reduce the risk of recurrent events through structured exercise prescription, education, and risk factor modification.[3] Referral to CR is a class I recommendation for all patients with CAD[4–7] based on a growing body of evidence that participation can reduce hospital bed usage, cardiovascular mortality, as well as improve functional capacity and quality of life.[8] In Australia, the provision of CR is guided by key documents[9,3] which describe an integrated pathway spanning the continuum of care, commencing during the inpatient period after an acute coronary event (phase I), continuing through the post-discharge period, often in an outpatient setting (phase II) and subsequently to a community-based maintenance programme for ongoing adherence to exercise and healthy lifestyle (phase III). However, CR is commonly underused throughout this process: only 30% to 50% of eligible patients are typically referred to outpatient CR, with fewer still completing programmes.[10–13] Consequently, many patients do not achieve long-term risk factor targets.[14] The aims of this document are to (1) apply a framework to CR, (2) identify where continuity of care is at risk, and (3) provide recommendations for improvement in the delivery of CR.

Continuity of Care in Contemporary Medicine

With increasing specialisations in clinical care, patients are no longer treated by a single practitioner, but rather by an array of health professionals, across multiple specialities and health

Table 1. The continuity of care framework.

INFORMATIONAL CONTINUITY	MANAGEMENT CONTINUITY	RELATIONAL CONTINUITY
Information transfer	Consistency of care	Consistency of personnel
Accumulated knowledge	Flexibility and accessibility	Ongoing patient-provider relationship

Adapted from Reid et al.[17]

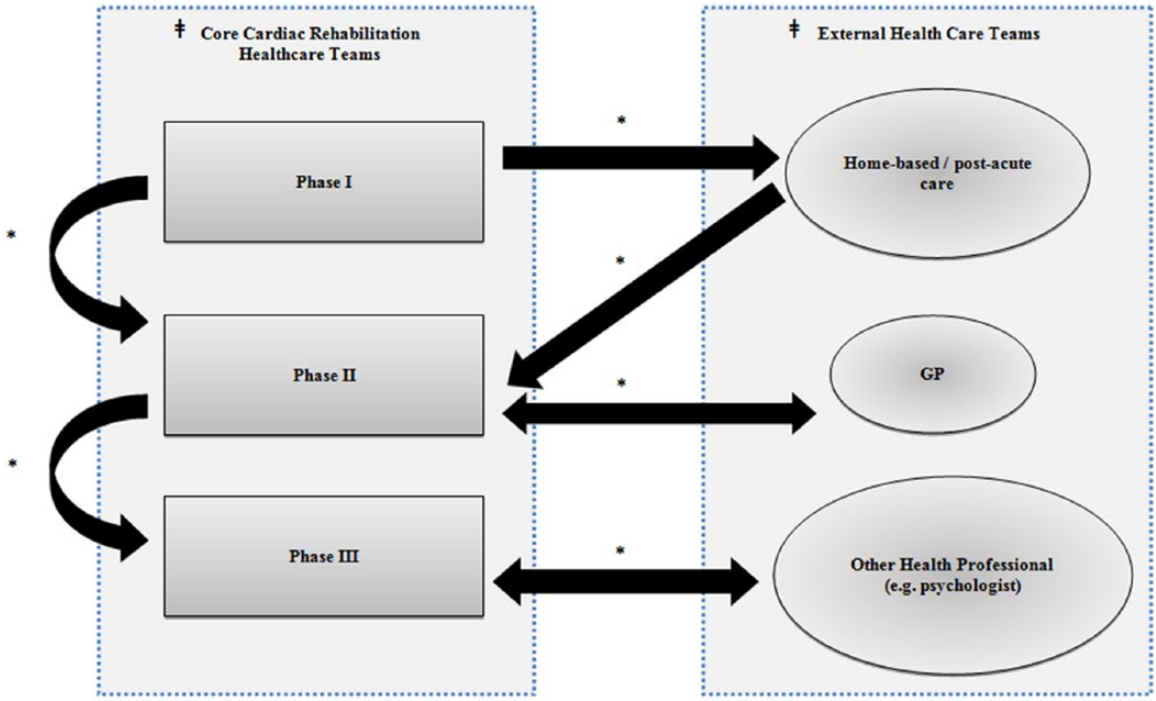

Figure 1. Current 3-phase model of cardiac rehabilitation. *Communications to ensure continuity of care including referral and clinical handover. For specific recommendations for management and informational continuity, refer to Table 2 summary. ‡Opportunities for improved relational continuity between health care professionals. For recommendations for relational continuity, refer to Table 2 summary.

care settings. This paradigm shift has increased the risk of fragmentation of care. Accordingly, a concerted approach is required to achieve continuity in contemporary models of health care, to eliminate division and maintain positive patient outcomes. Several approaches have been employed to achieve this, including organised discharge planning, integrated care, and case management. The unified term 'continuity of care' has been defined,[15] described as the delivery of services in a coherent, logical, and timely fashion which entails 3 specific domains: informational, management and relational continuity. Reid et al[16] further delineated the domains into sub-categories, as shown in Table 1. We will apply this framework to CR, identify instances where continuity of care is at risk, and provide recommendations on how it can be enhanced to improve patient outcomes.

Informational Continuity

Informational continuity refers to the availability and transferability of patient information between and across health care providers and settings which, over time, lead to the accumulation of knowledge about a patient. Information transfer is often the first element connecting services and linking health professionals and medical events and is fundamental to coordinating patient-centred care. Failure of informational continuity can pose risks to patient safety, lead to repetition or unnecessary testing, cause delays in treatment, and can ultimately lead to poor patient-centred practice.

Information transfer

Effective handover requires transfer of patient information between health care providers. Both basic and detailed information is required with each new referral, on progression to each successive CR phase and between health care professionals external to the CR team (eg, health psychologist or general practitioner). Figure 1 displays these likely time points that require referral. A key objective of CR handover is for the receiving clinician to be able to easily determine patient progress to date and plan ongoing care accordingly.

The rate of progression through each CR phase can be highly variable between patients and is determined by individual circumstances such as disease severity, complications, hospital length of stay, and sociodemographic and sociocultural factors. To account for this variability, a thorough

Table 2. Summary of opportunities to facilitate continuity of care within CR.

CONTINUITY OF CARE DOMAIN	SUB-CATEGORY	STRATEGIES TO FACILITATE CONTINUITY OF CARE WITHIN CARDIAC REHABILITATION
Information continuity	Information transfer	• Referrals to CR should be accompanied by a discharge summary which include the following minimum data sets: ○ Patient contact details ○ Assessments conducted and results ○ Short-term, medium-term, and long-term goals and progress towards achieving these ○ Barriers and enablers ○ Special considerations and circumstances • CR staff should maintain organised patient files with clear and consistent reordering
	Accumulated knowledge	• There should be clear pathways of communication between phase I, II, and III staff using a range of communication methods including case conferences or verbal handover • Regular clinical team meetings can also encourage informational continuity for complex case patients
Management continuity	Consistency of care	• There are numerous, evidence-based clinical practice guidelines detailing care pathways for cardiac rehabilitation • Organisational collaboration is required for future development of CR guidelines • Participation in phase I CR is highly influential on participation in phase II, and therefore, enrolment in phase I should be a priority
	Flexibility and accessibility	• A collaborative approach to CR referral is required • Administrative or scheduling delays may be overcome by early automated referrals while the patient is still in hospital • Patients should be involved in decision making and be made aware of referral to CR • Referrals should be physician endorsed and involve the cardiologist • CR staff should be knowledgeable about the range of flexible CR models offered including home-based, telephone-based, and centre-based programmes • Practices need a responsive system for enrolling patients
Relational continuity	Consistency of personnel	• CR requires a dedicated, connected, and consistent team of professionals • Programme directors should seek to establish an affiliation with the nearest CR programme • A co-ordinated effort is needed to achieve referral and enrolment in CR
	Ongoing patient-provider relationship	- Staffing structures require flexibility to extending patient-clinician relationships across the phases - Affiliation between members of the CR team extends beyond the 3 phases and should also include home-based bridging programmes or similar linking care pathways

Abbreviation: CR, cardiac rehabilitation.

clinical handover is required to ensure that care provision remains individualised.

An effective handover requires detailed summaries on discharge and referral. However, there has been a lack of standardisation in reporting practices to document a patient journey through inpatient, outpatient, and community settings. The development of national health database such as the *My Health Record* in Australia[17] will provide an opportunity for patient information to be accessed by multiple health services. However, these systems are relatively new in many sectors and are not fully used by all patients or providers where they are available. Informational continuity, therefore, continues to lack automation and remains highly dependent on local practices. When there is a failure of informational continuity, there is likely to be unnecessary repetition of assessments, and care provision may be generalised. Cardiac rehabilitation phases may operate as independent programmes, despite sharing common overall objectives. This is an inefficient and costly practice, and may also create a poor experience for the patient, ultimately restricting the capacity to individualise treatment and achieve the best clinical outcomes. Furthermore, missed or inadequate medical information can pose serious risks, particularly in the setting of exercise training.

Accumulated knowledge

Accumulated knowledge refers to information that gradually accrues over extended patient-provider relationships, usually of a personal or non-medical nature such as likes, dislikes, social supports, personality, and other personal characteristics or preferences.[16] Such information is important for behaviour change interventions and can assist in identifying barriers to attendance.[18] In the primary care setting, relationships have been found between longitudinal care and the doctors' sense of responsibility towards their patients[19] and likewise on patient satisfaction.[20,21] Accumulated knowledge is heavily influenced by a sustained patient-provider relationship and is often challenging in instances involving multiple care providers, such as in CR.

Recommendations: Informational continuity. In view of these risks to informational continuity, the following recommendations are proposed:

- Clinical handover should include a comprehensive medical history with specific details about the patient's presenting conditions and prior management, as well as

individual preferences, sociocultural, and sociodemographic contexts, which play an influential role in chronic disease management.[22] Importantly, clinicians should be mindful of the overarching goals of CR and provide sufficient information regarding progress. All referrals should be accompanied by a discharge summary and the following minimal data set is proposed:
  - Patient contact details;
  - Assessments conducted and results;
  - Short-term, medium-term, and long-term goals and progress towards achieving these;
  - Barriers and enablers to participation;
  - Personal preferences, special considerations, and circumstances;
- Staff should maintain organised patient files with clear and consistent recording of patient information and follow clinical documentation protocols.
- There should be clear, established pathways of communication between phase I, II, and III staff using a range of communication methods including case conferences, written, and/or verbal handover.
- For patients with complex needs, case conferences should be considered for clinical handover.

Management Continuity

Management continuity is a largely unifying dimension for each of the continuity domains and relates to organisational and logistical practices that enable timely and organised care. Management continuity includes 'consistency of care' which describes planned care pathways to ensure continuity in treatment and 'flexibility' to adapting care to suit individual patient needs and circumstances.[16] Elements of management continuity in CR include flexibility of the CR model, referral processes, handling of appointments, and programme availability.

Consistency of care

Integrated care pathways provide secure and predictable processes for the management of CAD, enabling multiple professionals to provide a unified and evidence-based approach over the duration of the illness.[23] The CR pathway commonly consists of 3 phases connecting acute care to chronic disease self-management.

Phase I. Phase I takes place while the patient is still an inpatient and occurs over a variable time frame (usually 1-14 days) that depends on the severity of the cardiac event and the length of time that the patient remains an inpatient. Phase I programmes should be based on recommendations contained within the National Heart Foundation of Australia framework document for CR[9] and practice guidelines developed by the Department of Human Service Victoria.[24] Phase I incorporates a combination of supportive counselling and reassurance for risk factor modification, medication adherence and education on when and how to resume daily living activities. This is complemented by early mobilisation to prevent the deleterious effects of bed rest and to initiate a progressive increase in activity to allow for, at the minimum, basic self-care at discharge from the hospital. Evidence suggests that active engagement in CR at an inpatient stage may improve uptake of phase II programmes by as much as 93%.[25,26]

Phase II. Phase II usually involves patients attending a hospital-based programme as an outpatient, weekly or twice weekly over a 6- to 12-week period,[9,27] although flexible modes of service delivery have been used to cater for the requirements of a broader range of patients (see Such modes have included centre or home-based services, as well as telephone, mobile and internet-based services.[3] Phase II programmes provide initial physical, psychological, and social assessments to facilitate return to everyday function, and education regarding cardiovascular disease risk factors, and exercise and lifestyle changes that may have long-term cardioprotective effects.[3]

Phase III. Phase III is community-based and aims to maintain activity beyond the period of subacute care to provide long-term benefits of exercise and minimise the risk for secondary events (secondary prevention). Current evidence suggests that participation in phase III is highly beneficial in reducing major adverse cardiac events.[28] Although the improvements in cardiorespiratory fitness, haemodynamic, and muscle functions during early rehabilitation are clear, it is essential to continue with lifelong exercise training as these benefits are all but lost within 3 months of training cessation.[29]

Alongside this triphasic model, there is a wealth of additional recommendations by National and International Guidelines for patients with CAD.[4,9–13,30,31] However, this has created a challenging paradox; the number of guidelines and variation in the information they offer can make interpretation and application challenging for clinicians. For example, the Australian Cardiovascular Health and Rehabilitation Association core components[3] provide a thorough review of referral and recruitment strategies, models of service delivery, and a detailed summary of key performance indicators for CR; however, information regarding programme content, such as exercise programming and lifestyle management, although mentioned, is only brief, whereas the National Heart Foundation of Australia and Australian Cardiac Rehabilitation Association–recommended framework provides more details on exercise prescription, testing, and patient monitoring.[9] The differences between documents may increase the risk of missed information and may ultimately reduce the likelihood of achieving evidence-based practice. Astley et al[32] highlighted a lack of inter-organisational collaboration in the preparation of CR publications, including 3 recent documents[3,33,34] which focus on varying features of CR but without reference to one another. Greater collaboration between organisations in future CR publications will help provide a more unified and consistent message for clinicians and enhance management continuity.

Flexibility and accessibility

Easy access, timely response to processing referral, and mode of programme delivery are important elements of flexibility and accessibility. Poor referral practices, such as inadequate referral procedures, and poor programme organisation contribute to the lack of attendance at CR.[35,36] There are at least 3 referrals required across the continuum of triphasic CR, and the responsibility for making and managing these referrals may fall on a variety of health professionals, including inpatient nursing staff, coordinators, allied health professionals, or physicians.

Barriers to CR referrals have been studied previously, and several strategies have been successfully employed. Research has shown that automatic referrals,[37,38] combined with a patient discussion[39] and physician-endorsed programmes, achieve higher attendance. Furthermore, the lack of standardised administrative processes is perceived as a barrier to referral by primary care physicians.[37,40]

Waiting lists for phases II and III are also common with few CR providers achieving targets for time to enrolment following discharge from acute care. This delay in proceeding to phase II has been shown to impact on clinical outcomes[41] and may depend on a range of factors including administrative processes involved in informing and enrolling patients, high demand and, in some patients, the need to schedule symptom-limited exercise testing prior to commencing exercise training.[9] However, these delays may be easily overcome. An uncomplicated hospital admission is quite predictable in terms of length of stay; similarly, the date of discharge from phase II outpatient programmes is foreseeable at 8 to 12 weeks after the initial commencement date. As such, referrals could be automated for uncomplicated admissions, which has been shown to result in greater attendance than physician referral.[15,16] Similarly, facilities which do not have a systematic approach to referrals, but rather adopt an ad hoc approach, tend to have lower enrolment than those that use formal referral systems,[25] especially when this occurs while the patient is still in hospital.[42] Patients admitted to large-volume hospitals,[43] or to hospitals offering CR,[44] are also more likely to be referred. For example, experience from a tertiary hospital identified that patients referred to their own organisation's CR programme were more than 4 times as likely to attend compared with those referred to an external programme.[31,25,42]

Recommendations: Management continuity. To optimise management continuity, the following recommendations are proposed:

- Participation in phase I influences participation in phase II, so phase I should be considered for all patients with CAD.
- Providers of CR should be familiar with evidence-based guidelines and use these in practice to ensure consistency of care. Collaboration across professional organisations in the future updates of CR guidelines should be undertaken to avoid a saturation of detached documents.
- To overcome administrative or scheduling delays, referrals should be made early while the patient is still in hospital, and where possible, should be automated. Patients should also be involved in the decision making related to CR and be made aware of referral to CR.
- There should be general endorsement of the referral process by a senior cardiologist; however, referrals need not be reliant on physician 'sign-off', except in cases where relative contraindications to exercise require a medical opinion. However, verbal endorsement of CR by a physician improves uptake. Providers of CR need a responsive system for enrolling patients.
- Staff should be well informed about available modes of service delivery including home-based, telephone-based, and centre-based programmes, both within and outside of their own organisation and be well connected to these services to offer alternative referrals to patients. It is important for staff to understand factors that influence patient's choices; the simple act of offering an alternative delivery mode may improve uptake.[45]

Relational Continuity

Relational continuity refers to the relationship between a health care professional and the patient, where the rapport is strengthened with time and over multiple illnesses or episodes.[16] Relational continuity is most clearly exemplified by the role of family physicians, who often have longstanding relationships with their patients. Continuity in patient-provider relationships can bridge past care to current care and involves both consistencies of personnel, as well as ongoing patient-provider relationships.

Consistency of personnel

Cardiac rehabilitation is a specialised field that requires a dedicated, connected, and consistent team of professionals. The team may comprise a range of health care professionals, including nurses, exercise physiologists, dieticians, physiotherapists, and physicians.[46] Although this provides a breadth of expertise, clinicians must ensure that they achieve connectedness and coherency in the care they provide. Inconsistent staffing is a common issue affecting continuity. Although it is mostly unavoidable, most professionals have other clinical responsibilities which sometimes take precedence over CR, such as general nursing duties, patient loads on other wards, and non-cardiac–related caseloads. Staff changes and bed changes are also frequent in the inpatient setting and can greatly disrupt continuity of care. Nursing staff, who are often primarily responsible for education in the immediate time after a cardiac event, are particularly affected by these elements. A Science Advisory from the American Heart Association urges all personnel to implement a co-ordinated effort to achieve referral and enrolment in

CR[47] and stresses that every member of the health care team plays a valuable role in promoting CR.

Ongoing patient–provider relationship

Cardiac rehabilitation presents a number of challenges to maintain ongoing relational continuity due to the multiphase model. In many cases, staffing structures are determined by systems which separate teams into inpatient and outpatient, and a patient might encounter entirely different teams for each of the CR phases which may not be conducive to effective chronic disease management and/or lifestyle behaviour change. Networking between phases is therefore critical in maintaining relational continuity. In a qualitative review of system-level factors that influence CR attendance in the United States, Gurewich et al[25] found that the relationship of CR facilities to a hospital and to hospital personnel had higher rates of attendance. Several advantages are gained when there are close working relationships between phases; the inpatient health care team holds great power to increase participation in outpatient rehabilitation, and the outpatient team has responsibility with the affiliated inpatient programme enabling rapport building early in a patients inpatient stay, even before their first outpatient appointment.

Recommendations: Relational continuity. In the light of these risks to relational continuity, the following recommendations are proposed:

- Cardiac rehabilitation requires a dedicated, connected, and consistent team of professionals who hold *primary responsibilities* for referral and implementation of the programme.
- Programme directors should seek to establish a strong affiliation with other nearby CR programmes, as well as with home-based therapy programmes or similar linking care pathways.
- Staffing structures require flexibility to maximise the duration of patient-clinician relationships across the phases. Where possible, managers should consider staffing structures that allow the same staff to work across both phases I and II.

Summary and Conclusions

The 3-phased CR model relies on continuity of care to increase the potential for long-term benefits and reduce the risk for a secondary event (secondary prevention). We hypothesise that applying the recommendations for informational continuity will reduce repetition or unnecessary testing which may delay treatment and/or increase the potential for patients dropping out from the exercise programmes. Improving clinical handover practices will ensure that critical information is not lost and that care remains patient centred across the care continuum. Optimising management continuity practice will help overcome scheduling delays, optimise enrolment, and improve service access to all patients with CAD. It will provide a uniform treatment approach using easy-to-access, collaborative, and inter-organisational evidence-based guidelines. Finally, enhancing relational continuity will make a difference to patient engagement by providing a dedicated and familiar health care team, with a devoted attention to patients' long-term cardiac health.

Author Contributions

CG wrote the first draft of the manuscript. BJP and MKB contributed to the writing of the manuscript. CG and IL jointly developed the structure and arguments for the paper. IL and AM made critical revisions and approved final version. All the authors agree with manuscript and reviewed and approved the final manuscript.

Disclosures and Ethics

As a requirement of publication, author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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Association between adequacy of long chain omega-3 intake and N-terminal pro brain natriuretic peptide (NT-proBNP) in those at risk of heart failure

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Background: Higher habitual long chain omega-3 polyunsaturated fatty acid (omega-3) intake may be associated with lower risk of developing heart failure (HF), and a limited number of smaller, short-term trials have suggested that omega-3 supplementation reduces BNP in those with HF. This study examined the relationships between habitual omega-3 intake and cardiovascular risk markers in a cohort at risk of developing HF.

Methods: In a cohort (n=446) at risk of HF (having at least one of: cardiovascular disease, hypertension, diabetes, renal impairment), dietary intake was assessed by 4-day food records. Associations between omega-3 intake, cardiovascular risk markers (including plasma NT-pro-BNP) and ventricular function assessed by echocardiography were examined using multivariate regression.

Results: In this cohort of men and women (mean age±SD: 71.8±6.0y), 31% were meeting recommended omega-3 intake through diet + supplements. There were significant differences in plasma NT-proBNP between those meeting (median (IQR):12(6-38) pmol/l) and not meeting adequate omega-3 intake (24(8-47) pmol/l), p<0.001. Adjusted for age and sex, adequacy of omega-3 intake was significantly associated with log NT-proBNP (B=-0.150 [95%CI: -0.268 to -0.074], p=0.001) and the association remained significant following further adjustment (for diabetes, BMI, smoking, systolic blood pressure, eGFR, dietary energy and physical activity) (B=-0.143 [95%CI: -0.260 to -0.063], p=0.001). No associations were seen between adequacy of omega-3 intake and echocardiographic parameters.

Conclusions: This study shows that in a cohort at risk of HF, circulating NT-proBNP is inversely related to adequacy of intake of very long chain omega-3 fatty acids, however the implications of this remain unclear.

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Barriers to exercise rehabilitation in the older adult with heart failure

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Introduction: Exercise training is an important component of best-care for chronic heart failure (CHF), following demonstrated reductions in morbidity and mortality. However, benefits are clearly confined to those who participate. At Western Health, patients over 65 years account for 89% of CHF admissions. Hence, optimising delivery to the elderly is a priority.

Methods: In the context of a prospective single-centre study of CHF management in the elderly, we monitored attendance to CHF rehabilitation over a 9-month period. Reasons for non-attendance were identified in order to develop and implement strategies to optimise delivery of exercise therapy to frail, elderly CHF patients.

Results: Only 10(4%) of 247 patients in this elderly group participated in CHF rehabilitation. Approximately 36% did not participate due to advanced disease, or living in residential-care. A predominantly aerobic-based program excluded participation in 20% of patients, who were severely deconditioned and unable to ambulate 100m to meet program referral criteria. A further 18% declined, often due to transportation difficulties. Accordingly, we developed an integrated program featuring: (1) inclusive referral criteria, without specifying mobility; (2) individualised exercise prescription, including an initial resistance-training phase, allowing tailoring to severely deconditioned patients; (3) smaller group size, enabling closer supervision of frailer individuals and; (4) access to community transportation assistance. This novel approach involving Nursing, Exercise Physiology and Cardiology has seen early changes to qualification and attendance rates in the elderly patient with CHF.

Conclusion: Specifically tailored rehabilitation programs appear necessary to deliver the benefits of exercise to the heterogeneous group of elderly CHF patients.

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Can a smartphone-based secondary prevention program facilitate early mobilisation in patients with acute coronary syndromes?

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Background: Secondary prevention strategies such as optimal pharmacotherapy, cardiovascular risk factor optimisation, cardiac rehabilitation and adherence to diet and lifestyle recommendations reduce mortality and morbidity. There is however poor translation of scientific evidence into

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Letter to the Editor

Letter to the editor: "The frailty syndrome is associated with adverse health outcomes in very old patients with stable heart failure: A prospective study in six Spanish hospitals"

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As allied health professionals, we read with great interest the recent work by Rodriguez-Pascual and colleagues on the frailty syndrome in very old patients with Heart Failure (HF) [1]. The findings of increased 1-year mortality, hospital readmission and functional decline is clinically important and supports our insights as clinicians that frailty should be used for risk stratification and treatment selection. From an applied viewpoint, we would like to add to the discussions regarding the practical implications of these findings.

Frailty and pre-frailty syndromes are potentially reversible with physical activity/exercise. Whilst there is an agreement that supports this statement in patients without HF [2,3], the evidence for those with HF is scarce and caution should be taken when generalising these recommendations. Sarcopenia, frailty and cardiac cachexia affect the capacity to perfom exercise. In contrast, resistance training can improve strength and functional capacity in patients with HF [4]. However, to date, there is a clear under-representation of older adults across trials (mean age 62 years compared to mean age of diagnosis of 76 years [5]) and no studies that specifically target the frail [4]. When examined closely, trials have extensive exclusion criteria which, probably inadvertently, exclude patients who may be elderly or frail.

The authors are commended for clearly identifying the consequences of frailty in chronic HF. In this important disease context, these observations should re-focus the attention of researchers and health professionals upon frail elderly, who now constitute the majority. This extends to exercise trials, where current evidence arguably has limited application to this cohort.

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Appendix D: Baseline patient characteristics among all patients and those referred and not referred to exercise rehabilitation (all data reported)

Characteristics	**All (%) (n = 1281)**	**ER Referral (%) (n = 125)**	**No ER Referral (%) (n=1156)**	***p*-value**
Age, y	79.7 (70.3-86.3)	73.6 (62.7-81.5)	80.2 (71.1-86.5)	<0.001
Male, n (%)	723 (56.4)	90 (72.0)	633 (54.8)	< 0.001
BMI, kg/m^2	29.1 (35.8-34.5)	29.7 (25.8-34.9)	29.0 (24.8-34.5)	
HF Subtype				
HFrEF	420 (32.8)	62 (49.6)	358 (31.0)	<0.001
HFmrEF	169 (13.2)	11 (8.8)	158 (13.7)	
HFpEF	434 (33.9)	26 (20.8)	408 (35.3)	
Unknown	258 (20.1)	26 (20.8)	232 (20.1)	
LVEF (%)	38.0 (25.6-50.3)	30.0 (22.3-39.8)	40 (26.0-53.0)	0.004
NYHA				
Class I / II	20 (4.5) / 236 (53.5)	2 (0.5) /37 (68.8)	18 (4.7) / 198 (51.4)	
Class III/ IV	162 (36.7) / 23 (5.2)	14 (25.9) / 1 (1.9)	148 (38.2) / 22 (5.7)	
Unknown	840 (65.6)	71 (56.8)	770 (66.7)	
Admission Speciality, n (%)				0.001
HF Unit	126 (9.8)	18 (14.5)	108 (9.3)	
Cardiology	434 (33.9)	58 (46.8)	376 (32.5)	
Gerontology	36 (2.8)	5 (4.0)	31 (2.7)	
General Medicine	622 (48.6)	39 (31.5)	583 (50.4)	
Other	62 (4.8)	4 (3.2)	58 (5.0)	
Cardiovascular History, n (%)				
History of HF	968 (75.5)	93 (74)	874 (75.6)	
Previous hospitalisation for HF	774 (60.4)	75 (60.0)	698 (60.4)	
Cerebrovascular disease	242 (18.9)	27 (21.6)	215 (18.6)	
Hypertension	977 (76.2)	85 (68.0)	891 (77.1)	0.02
History of angina	481 (37.5)	43 (34.4)	437 (37.8)	
History of PCI or CABG	393 (30.7)	37 (29.6)	356 (30.8)	
History of MI	394 (30.7)	40 (32)	353 (30.5)	
Arrythmia	695 (54.2)	66 (52.8)	628 (54.3)	
CIED therapy	284 (22.2)	29 (23.2)	255 (22.1)	0.004
Smoking Status				
Current smoker	133 (12.4)	18 (16.5)	115 (11.9)	
Ex-smoker	504 (46.8)	51 (46.8)	451 (46.8)	
Heart failure aetiology				
Ischaemic related cardiomyopathy	458 (35.8)	62 (49.6)	396 (34.3)	0.001
Idiopathic Cardiomyopathy	140 (10.9)	20 (16)	120 (10.4)	
Hypertension	223 (17.4)	16 (12.8)	207 (17.9)	
Infiltrative Cardiomyopathy	10 (0.8)	1 (0.8)	9 (0.8)	
Hypertrophic Cardiomyopathy	43 (3.4)	3 (2.4)	40 (3.5)	

Valvular	179 (14.0)	12 (9.6)	137 (14.4)	
Arrhythmia related	187 (14.6)	26 (20.8)	161 (13.9)	0.04
Non-Cardiovascular Medical History, n (%)				
Diabetes	552 (43.1)	56 (44.8)	496 (42.9)	
Dementia	100 (7.8)	4 (3.2)	96 (8.3)	0.04
Depression	251 (19.6)	20 (16.0)	231 (20.0)	
Current malignancy	88 (6.9)	7 (5.6)	81 (7.0)	
COPD / Asthma	394 (30.8)	23 (18.4)	371 (32.1)	0.002
Obstructive sleep apnoea	187 (14.6)	17 (13.6)	170 (14.7)	
Chronic kidney disease				0.002
Mild	241 (18.8)	22 (17.6)	217 (19.0)	
Moderate	408 (31.9)	28 (22.4)	380 (32.9)	
Severe	159 (12.4)	10 (8.0)	149 (12.9)	
Liver disease				
Mild	52 (4.1)	4 (3.2)	48 (4.2)	
Moderate or Severe	30 (2.3)	4 (3.2)	26 (2.3)	
Iron deficiency	253 (20)	16 (12.9)	237 (20.8)	0.04
Anaemia	394 (30.8)	23 (18.4)	371 (32.1)	0.002
Treatments received during admission, n (%)				
IV diuretics	1096 (85.8)	102 (82.9)	994 (86.1)	
IV GTN infusion	48 (3.8)	7 (5.7)	41 (3.5)	
IV inotrope infusion	62 (4.8)	10 (8.1)	52 (4.5)	
Oral Diuretics	1161 (90.9)	108 (88.5)	1053 (91.2)	
Oxygen therapy	837 (65.6)	65 (53.3)	772 (66.9)	0.003
CPAP / BiPAP	174 (13.6)	13 (10.6)	161 (14.0)	
IABP/ ECMO	6 (0.5)	1 (0.8)	5 (0.4)	
Invasive mechanical ventilation	25 (2.0)	5 (4.0)	20 (1.7)	
Angiography	112 (8.8)	19 (15.3)	93 (8.1)	0.01
PCI	15 (1.2)	5 (4.0)	10 (0.9)	0.002
CABG	9 (0.7)	1 (0.8)	8 (0.7)	
Dialysis	12 (0.9)	1 (0.8)	11 (1.0)	
LVAD	1 (0.1)	1 (0.8)	00 (0.0)	
Valve procedure	7 (0.5)	1 (0.8)	6 (0.5)	
CIED Therapy				0.002
Pacemaker	28 (2.2)	3 (2.4)	25 (2.2)	
CRT-P	2 (0.2)	0 (0.0)	2 (0.2)	
ICD	15 (1.2)	5 (4.1)	10 (0.9)	
CRT-D	18 (1.4)	13 (1.1)	5 (4.1)	
Resting Haemodynamics on d/c				
Systolic BP (mmHg)	120 (110.0-135)	118 (110-130)	120 (110-135)	0.02
Diastolic BP (mmHg)	68 (60-75)	68 (60-75)	68 (60-75)	
HR (bpm)	74.0 (65-83)	75.0 (65-85)	74 (65-82)	
Heart Failure pharmacotherapy, n (%)				
ACE Inhibitor	534 (41.8)	54 (43.2)	480 (41.6)	

ARB	219 (17.1)	24 (19.4)	195 (16.9)	
Beta blocker	910 (71.2)	98 (79.0)	812 (70.4)	0.04
Aldosterone antagonist	474 (37.1)	48 (38.7)	426 (36.9)	
Digitalis	210 (16.4)	15 (12.1)	195 (16.9)	
Antiarrhythmic	141 (11.0)	18 (14.5)	123 (10.7)	
Nitrate	217 (17.0)	17 (13.7)	200 (17.3)	
Loop diuretic	1207 (94.2)	118 (94.4)	1089 (94.2)	
Other vasodilator	62 (4.9)	3 (2.4)	59 (5.1)	
Ivabradine	45 (3.5)	6 (4.8)	39 (3.4)	
Lipid lowering agent	715 (55.9)	73 (58.4)	642 (55.6)	
Antiplatelet	674 (52.7)	60 (48.0)	614 (53.2)	
Anticoagulant	586 (45.8)	69 (55.6)	517 (44.8)	0.02
Thiazide diuretic	140 (11.0)	11 (8.9)	129 (11.2)	
Calcium channel antagonist	209 (16.4)	21 (16.9)	188 (16.3)	
Total Meds on d/c (SEM)	10.0 (8.0-13)	9 (8-11)	10 (8-13)	0.047

Data expressed as median and percentiles (25-75%) for continuous variables and count and proportions (%) for categorical variables.

ǂ Variables where missing data >15%.
+where factor has more than one level, p-value applies to the overall association of this factor with the outcome.

BMI, body mass index; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; HF, heart failure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; MI, myocardial infarction; CIED, Cardiac Implantable Electronic Device; COPD, chronic obstructive pulmonary disease; IV, intravenous; GTN, Glyceryl trinitrate; Cardiac Implantable Electronic Device; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure, IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; CRT-p, cardiac resynchronisation therapy – pacemaker; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronisation therapy – defibrillator; BP, blood pressure; HR, heart rate; ACE, angiotensin converting enzyme; ARB, aldosterone receptor blocker