Title: Effects of intentional weight loss in patients with obesity and heart failure: A systematic review

Author: Kirsty McDowell, Mark Petrie, Nahian Abdur Raihan, Jennifer Logue,

Institute of Cardiovascular and Medical Sciences, University of Glasgow

Key Words: Weight loss, Obesity, Heart Failure.

Running Title: Weight loss in obesity and heart failure

Acknowledgements:

Corresponding Author: Institute of cardiovascular and medical sciences, University of Glasgow. Email: kmcdowell@doctors.org.uk Tel: 07738085947

Conflicts of Interest: None declared.

Abstract

Objective: Obesity and heart failure commonly coexist.. Some have reported an obesity paradox in heart failure suggesting that intentional weight loss may not necessarily be beneficial and guidance on this is lacking. The aim of this study was to systematically review the outcomes following intentional weight loss in patients with heart failure and obesity.

Method: A systematic review was undertaken using databases PUBMED, EMBASE, CENTRAL. Randomised control trials and observational studies were included.

Results: 4 randomised controlled trials and 7 observational studies were identified. Randomised trials were small (n=<25), with the exception of one (n=100).Interventions included diet and exercise in 2, diet alone in 1 and use of orlistat in 1. All but 1 reported significant weight loss. 2 reported improvement in exercise capacity and quality of life. 1 reported improvement in NYHA class. Observational studies, 5 of which reported outcomes following bariatric surgery, despite being small, heterogenous and high risk of bias, suggested a trend in improvement of left ventricular function, quality of life and exercise capacity following weight loss.

Conclusion: Weight loss is achievable with lifestyle intervention in those with heart failure and obesity and may result in improvements in NYHA classification, quality of life and exercise capacity.

Abbreviations:

HF: Heart Failure

HF-Pef: Heart failure with preserved ejection fraction

HF-Ref:Heart failure with reduced ejection fraction

BMI: Body mass index

ESC:European society of Cardiology

LV:Left ventricle

NYHA:New york heart association

RCT:Randomised control trials

BNP:Brain natriuretic peptide

QOL:Quality of life

MHLF:Minnesota living with heart failure questionnaire

KCCQ:kansas city cardiomyopathy questionnaire

LVSD:Left ventricular systolic dysfunction

LVEF:Left ventricular ejection fraction

Introduction

Obesity and heart failure (HF) commonly coexist. The prevalence of obesity in heart failure with reduced ejection fraction (HF-rEF) is between 30%[1] and 40%[2], and in heart failure with preserved ejection fraction preserved ejection fraction (HF-pEF) is between 41%[3] and 55%[4]. A body mass index (BMI) of greater than 30 is an independent risk factor for the development of heart failure.[5] The risk increases by 5% in men and 7% in women for every 1kg/m^2 increase in BMI[5], with an increased probability of developing heart failure with increasing duration of morbid obesity[6].

A specific "obesity" cardiomyopathy has been proposed[7]. To what extent the development of HF in patients with obesity is due to specific pathophysiological processes of "obesity cardiomyopathy" or to concomitant conditions such as coronary artery disease, diabetes and hypertension is unclear. Some have described an obesity paradox where patients with HF and obesity live longer than those with HF with normal or underweight[8]. Whether or not weight loss is beneficial in heart failure is therefore uncertain. Current European Society of Cardiology (ESC) guidelines reflect this uncertainty by stating "for patients with moderate degrees of obesity (<31kg/m^2) weight loss cannot be recommended as intentional reduction in BMI has not been shown to be beneficial or safe in heart failure with reduced ejection fraction. In more advanced obesity, weight loss can be considered for symptomatic benefit."[9] Observational studies of intentional weight loss by bariatric surgery in patients and lifestyle interventions with obesity but without heart failure have reported reduction in left ventricle (LV) cavity size, LV mass, improved diastolic function, improved myocardial energetics and reduced myocardial triglyceride content.[10-12] A large prospective nonrandomised study of bariatric surgery vs lifestyle intervention in individuals without heart failure showed significant improvements in diabetes, hypertension and lipid abnormalities in the surgical group at 10 year follow up[13]. It can be hypothesised that these metabolic improvements may improve cardiac function and work alongside weight loss to metabolically and haemodynamically unload the failing heart in obesity.[14] If improvements in cardiac morphology are seen in a

non-heart failure population with intentional weight loss should this translate into a heart failure population?

We have performed a systematic review of the literature of intentional weight loss in heart failure with reduced and preserved ejection fraction. How successful are different methods of weight loss in achieving weight loss? What evidence is there for weight loss interventions improving measures of cardiac structure or function, cardiac biomarkers, symptoms, exercise capacity or quality of life?

Methods

Search Strategy

Electronic databases (Embase, Medline and the Cochrane Central Register of Controlled Trials) were searched for key search terms occurring in the title, keyword or abstract. The search was carried out in November 2017 and included articles published between 1946 and 2017. Studies were limited to those published in English language, involving humans and patients aged over 18 years. Search terms were used to identify articles which included patients with a primary diagnosis of heart failure (either reduced or preserved ejection fraction) and obesity who underwent an intervention designed with the intention to reduce weight and reported on outcomes related to cardiac morphology, exercise capacity, New York heart association (NYHA) classification, cardiac biomarkers and quality of life.

("heart failure" OR "cardiac failure" OR "congestive heart failure" OR "congestive cardiac failure" OR "chronic heart failure" OR "NYHA" OR "HFREF" OR "HFPEF") AND ("bariatric surgery" OR "gastric bypass" OR "Roux-en-Y Gastric Bypass" OR "sleeve gastrectomy" OR "gastric banding" OR "laparoscopic adjustable gastric band" OR "bilio-pancreatic diversion" OR "lifestyle" OR "weight management" OR "weight loss" OR "orlistat" OR "low energy" OR "low calorie" OR "diet" OR "dietician" OR "nutrition expert) AND ("cardiac geometry" OR "VO2max" OR "LVEF" OR "LV ejection fraction" OR "ejection fraction" OR "exercise

tolerance" OR "natriuretic peptide" OR "BNP" OR "nT-proBNP" OR "quality of life" OR "hospitalization" OR "medication use" OR "echocardiogram" OR "wall thickness")

Bibliographies, review articles and manuscripts identified through the search criteria were hand-searched for additional studies. Due to low numbers of randomised control trials (RCT) we have included both RCTs and observational studies. Two reviewers (KM and JL) firstly reviewed all titles and abstracts independently with discrepancies being resolved at subsequent meeting and discussion. The systematic search process resulted in a total of 3631 articles. After exclusions 11 articles were selected for review. (Figure 1)

(Figure 1 here)

Data Extraction and Synthesis

KM abstracted and tabulated each study that met the inclusion criteria. An assessment of the risk of bias (Low/High) was made for each RCT using the Cochrane Collaboration tool[15] (Supplemetary Table 1). For observational studies, risk of bias was assessed using the National Institute of Health quality assessment tool for observational cohort and cross sectional studies[16] (Supplementary Table 2). This systematic review was conducted and reported in accordance with the Cochrane handbook for systematic reviews.[17]

Results

Randomised Trials

4 randomised control trials were identified[18-21].(Figure 1) 3 of the trials included 21 patients or less [19-21]. One included 100 [18]. Two trials were conducted in HF-rEF[19-20] and one in HF-pEF[18]. The other did not report baseline ejection fraction[21].

Baseline Characteristics

The baseline characteristics from the trials are shown in table 1a. The mean age of participants in the trials was in the 50s (except for the largest trial of 100 patients where the mean age was 67[18]. The mean BMI in all trials was high (39 to 42.4 kg/m^2) despite inclusion

criteria of those who had a BMI in the range of overweight or obesity. All RCTs reported the number of patients on evidence based heart failure medications including ace inhibitors/angiotensin receptor blockers and beta blockers but only one reported number of patients on mineralocorticoid receptor antagonists. Two[19-20] of the four trials required stable doses of medical therapy for HF, one specified a duration of 3 months[19]. None of the trials described optimisation of HF therapies. After randomisation one trial showed a significantly lower BMI in lifestyle ve control group[20].

Trial Design and Reporting (table 2a)

One of the RCTs used a pharmacological intervention, orlistat[19]. In two[18,20] the intervention was diet and exercise, and the other diet alone[21]. One supplied the meals from the research centre[18] and one made use of a meal replacement drink[20]. All three[18,20-21] non-pharmacological interventions involved advice from dieticians. Three[19-21] of the RCT interventions lasted 12 weeks, one[18] lasted 20 weeks. 1 trial used a Consolidated Standards of Reporting Trials (CONSORT) flow diagram[18]. All but one study[18] was thought to have a high risk of bias. (Supplementary table 1)

Outcome Measures and Endpoints

One trial[18] provided a formal power calculation for primary outcomes. The other three[19-21] did not.

Weight loss and interventions

In three[18-19,21] of the four RCTs, greater weight loss was achieved in the intervention group compared to the control group (table 3a). In one trial of only 20 patients there was no weight loss difference between groups[20].

Left ventricular systolic function.

The two[18-19] RCTs that reported on the effect of weight loss on left ventricular function did not report a significant effect (Table 3a). The trial of 100 patients[18] did report a reduction in

mean LV mass (-04[95% CI -7,0g) p=0.005), a reduction in left ventricular relative wall thickness (-0.03[95%CI, -0.05 to -0.01] p=0.05), and an increase in E/A ratio (0.1[95%CI, 0.02-0.17]p=0.01) ,representing an improvement in diastolic function, with reduced calorie diet.

BNP

Neither of the two trials[19,20] that reported brain natriuretic peptide (BNP) found a change with weight loss (table 3a).

Exercise capacity

All four RCTs[18-21] reported on changes in exercise capacity associated with weight loss (Table 3a). This was based on 6 minute walk test in all and included maximal oxygen consumption at peak exercise (VO_2max) measured by cardiopulmonary exercise test in two[18,21]. Of the two trials[19-20] which did not demonstrate a significant improvement in exercise capacity, one was unable to demonstrate significant weight loss following a 12 week lifestyle intervention[20]. Of the two[18,21]which demonstrated an improvement in exercise capacity, one was the larger trial of 100 patients[18] which reported a significant increase in exercise capacity as assessed by VO_2max and 6 min walk distance. The effects were additive if both interventions were used together.

NYHA Classification

Two of the RCTs[18,19] reported change in NYHA classification (table 3a). One[18] included a HFpEF population only and reported a significant improvement in NYHA class as a result of diet and exercise induced weight change in this population. There was no demonstrable improvement in NYHA classification reported in a HFrEF population.

QOL

All four RCTs[18-21] reported on health-related quality of life (HRQoL) (table 3a). Three[18-19,21] used Minnesota living with heart failure questionnaire (MLHF) with one additionally using

Kansas City cardiomyopathy questionnaire (KCCQ)[18]. 1 used KCCQ only[20]. One trial reported a significant improvement in MLHF score in n=5 patients randomised to a high protein diet[21]. The larger trial[18] reported a significant improvement in HRQoL by diet, but not exercise based on KCCQ as an exploratory outcome.

Observational Studies

Seven[6,22-27] observational studies were identified. The studies are small (n<50). Five studies[6,22,24-25,27] measured results against control group however two control groups were non heart failure patients undergoing same intervention[6,27] while three were heart failure patients undergoing no weight loss intervention[22,24-25]. Five studies were conducted on HFREF patients[22-25,27]. Two studies did not clarify EF[6,26].

Baseline Characteristics

The baseline characteristics are shown in Table 1b, The mean BMI of participants ranged from 29.2-55kg/m ^{2} The mean age ranged from 38-68.2years. Three studies[22,25,27] reported number of patients on heart failure therapies and patients were poorly optimised.

Study Design and Reporting

Five studies[6,22-25] reported on outcome following bariatric surgery and included variety of laparoscopic and open procedures, including Roux-en-Y Gastric bypass, sleeve gastrectomy and gastric band. Both lifestyle interventions[26-27] included diet, exercise and self management. All studies were found to have a high risk of bias.

Outcome Measure and Endpoints

Weight loss and Interventions

Substantial weight loss was achieved in all the bariatric surgery studies[6,22-26]. Significant weight loss from baseline to final weight was also seen in the studies involving lifestyle intervention[26,27].

Left ventricular systolic function

One observational reported a significant improvement in ejection fraction following bariatric surgery compared to non surgical age, sex matched controls[22]. A trend towards improvement was also reported in two bariatric surgery studies[23-24] and one lifestyle intervention study[26].

Exercise Capacity

One study[27] reported a significant improvement in exercise capacity measured by exercise tolerance test from baseline to end of study period. (12 months)

QOL

3 studies[25-27] reported improvement in quality of life following weight loss intervention (two surgical, one lifestyle) Each used a different method to quantify quality of life and included KCCQ[26], MOS-SF[27] and a linear analogue self assessment questionnaire[25].

NYHA classification

3 surgical studies[6,22-23] and 1 lifestyle study[26] reported improvement in NYHA following weight loss intervention.

Discussion

Heart failure is a major cause of morbidity and mortality and poses a significant economic burden due to frequent readmission rates.[28] Despite the very high prevalence of obesity in patients with heart failure, our systematic review found little definitive evidence regarding the impact of intentional weight loss on cardiac morphology and, perhaps more importantly, quality of life and exercise capacity in heart failure patients. However, trends towards improvements suggest significant results may be expected if flaws in trial designs were addressed. Importantly, there was no evidence of harm from intentional weight loss in this population. If a benefit to weight loss exists for patients with heart failure and co-existing obesity, then clear evidence and guidance on the most effective means of weight loss is required.

Of the four trials[18-21] included, only one included more than 21 patients[18]. The three smaller trials[19-21] were feasibility studies and are too small to be adequately powered to demonstrate change. They did not include formal power calculations.This is a major limitation of this review. Although the mean BMI of participants across the trials ranged from 39-42.4kg/m ^{2} (class 3 obesity) the BMI inclusion criteria were much lower and varied across all trials, two trials included patients with “overweight “ range BMI. (25kg/m^2 in one[20] trial and 27kg/m^2 in another[21]) . The heart failure cohorts were variably optimised in terms of best heart failure therapies with changes in therapy throughout the interventions making it difficult to interpret outcomes as these therapies also reduce morbidy and mortality and improve quality of life. The interventions offered differed in terms of components (diet/exercise/pharmacotherapy/behavioural therapy) and frequency and duration of intervention. There was such a degree of heterogeneity of the intervention components and populations that meta-analysis would have had little meaning.

Mortality analysis of heart failure populations suggest there may be a survival benefit for individuals with obesity compared to their lean counterparts. A meta-analysis of 20000[29] patients with HFREF and HFPEF followed up for 3 years showed that overweight patients had lower total and cardiovascular mortality risk compared to normal weight patients. Underweight

patients carried the worse prognosis. Those with more significant obesity had more hospitalisations when compared to normal weight patients but still carried lower mortality risk. A similar “protective effect” is seen across other chronic conditions[30]. Arguments against the existence of the obesity paradox include evidence based on many retrospective studies with failure to match cohorts adequately, the existence of a “time-lag bias” whereby those with obesity develop heart failure symptoms much sooner, a “selection bias” whereby only the healthiest patients with obesity live to develop heart failure. BMI has been the regularly used metric for obesity across these studies. Body composition may be more important, lean muscle mass is a major determinant of cardiorespiratory fitness in heart failure which has been shown to modify the obesity paradox[31]. A recent study reported loss of lean mass or sarcopenia was associated with lower muscle strength, exercise capacity and quality of life in patients with HFPEF[32]. These trials address the important question of whether intentional weight loss aimed at fat reduction is beneficial. Although the inclusion criteria for 2 of the trials included overweight range BMI patients[20,21], the mean BMI in each trial included patients with class 3 obesity making it difficult to draw firm conclusions if weight loss would have similar benefits across all classes of obesity. Only one trial[18] used MRI to determine differences in body composition using MRI helping to separate intentional fat loss from the cachexia of heart failure.

It has not been possible to determine if similar improvements in cardiac morphology to those without heart failure are seen following weight loss in patients with heart failure. An improvement in left ventricular systolic dysfunction (LVSD) was not seen across the two trials[18-19] which included this as an outcome. One trial[19] included 21 patients and is therefore inconclusive. The other[18] which assessed cardiac function using MRI included a HFpEF population only where no improvement in ejection fraction would be expected. The mechanism by which weight loss allows improvement of left ventricular morphology in a non-heart failure population remains unclear and it is difficult to identify factors which would allow prediction of improvement or would identify when cardiomyopathy has progressed beyond

reversibility. Three observational studies[22-24] suggested an improvement in left ventricular ejection fraction following bariatric surgery and one following lifestyle intervention[26]. The largest study[24] compared 42 patients with documented LVSD to 2588 with no known pre-operative heart failure but no definite exclusion of this. 38 of the 42 patients had a postoperative echo and were matched against non-surgical controls. The surgical group increased their ejection fraction significantly and linear regression analysis indicated those who improved their ejection fraction by more than 10% were less likely to have history of myocardial infarction. This is an important observation and suggests there is a cohort of patients who are more likely to respond than others, particularly after scar formation in ischaemic cardiomyopathy. However, this study is poorly designed and not conclusive. 4 patients had cardiac resynchronisation therapy, 3 had valve intervention and 1 had coronary revascularisation between echocardiographs which could account for the reported benefit. None of the current studies[6,22-27] or trials[18-21,] provided comparison of different aetiologies or types of heart failure on outcomes. Furthermore, the rise in left ventricular ejection fraction (LVEF) seen across the studies was minimal. The approximate range of error for measurement of LVEF is 5%[23] and this may be amplified in this population with increasing body habitus decreasing the quality of imaging. Further studies using MRI as a more reliable imaging technique may help to understand the heterogeneity in LVEF response.

Weight loss may improve many of the negative effects of obesity on the cardiovascular system not necessarily reflected by ejection fraction[33] Diastolic dysfunction occurs more frequently than systolic dysfunction measured by ejection fraction although subclinical markers of LV contractile dysfunction using strain patterns have been reported.[34] Increased adiposity promotes inflammation, hypertension, insulin resistance and dyslipidaemia and impairs cardiac, arterial and skeletal muscle and physical function[35,36] all of which are common in heart failure with preserved ejection fraction and contribute to its pathophysiology[18]. These patients are difficult to treat, with very few evidence-based therapies available[9]. It has been shown that the severity of exercise intolerance, the main

determinant of quality of life in this patient group, correlates with increased adiposity[18]. It is important to be able to demonstrate if interventions which promote weight loss would be beneficial to their symptom load and quality of life.

Following the improvement in medical care and mortality rates associated with heart failure there has been a shift in attention towards improvement in quality of life in those affected by heart failure. Quality of life assessment is emerging as an important tool to determine the clinical efficacy of medical treatments and evaluate the impact of specific treatments on the daily life of a patient[18]. Kitzman[18] reported an improvement in KCCQ with diet but not exercise as an intervention. Diet did however lead to a greater weight loss than exercise overall. Quality of life is as important as survival to most patients living with chronic, progressive illness[37].

NYHA classification is used to assess symptom burden in patients with heart failure. Over 80% of patients with heart failure have physical symptoms[38]. Worsening symptoms are the main antecedents of hospitalisations[39]. Non-cardiac issues such as musculoskeletal and pulmonary limitations may also impair function. Observational studies suggest an improvement in NYHA following bariatric surgery and lifestyle-induced weight loss[22,26]. A significant improvement in NYHA was demonstrated in 100 patients with HFPEF following weight loss induced by diet or exercise[18]. Any improvement in NYHA from weight loss may not specifically be related to improvement in heart failure and may be multifactorial. For example, it may be related to a previously observed clinical improvement in the sleep apnoea/obesity hypoventilation syndrome with weight loss[40]. While any process leading to improvements in functional capacity is welcomed, objective functional testing may be useful to provide insight into the mechanism of improvement in exercise capacity. In addition to improvement in NYHA, Kitzman[18] reported that for obese HEFpEF patients, diet and exercise significantly increased exercise capacity as assessed by VO2max and 6 min walk distance, and that the effects were additive if both interventions were used together. An improvement in VO2max can be driven entirely by a reduction in weight however Kitzman[18]

also reported an improvement in other supporting factors which are independent of weight, including VO2 reserve, exercise time to exhaustion, workload and 6 minute walk test, suggesting a true improvement in exercise capacity. Leg power was also found to increase."

BNP is a useful biomarker to aid diagnosis of heart failure, assist with prognostication and quantify severity. None of the trials reported an improvement in BNP with weight loss. The reported values of BNP were low. The observational studies did not use natriuretic peptide however the study dates may mean that the commercial use of BNP was not widely available These modest BNP results could result from well-compensated, non-hospitalised participants. However, an inverse relationship between obesity and BNP levels has been shown to exist.[41] Increasing levels of BNP seem to retain prognostic capacities although increased risk may be seen at lower BNP values in an obese compared to lean heart failure population.[42] This makes any change with weight loss difficult to interpret.

Bariatric surgery has been acknowledged as the obesity treatment with the most durable success[43] and in a heart failure free population has demonstrated that the resultant weight loss leads to reduction in LV mass and diastolic dysfunction[44]. Safety concerns have limited the use of bariatric surgery in patients with heart failure and there have been no trials of such performed. One observational study[22] reported bariatric surgery to be safe, effective and durable in this patient population. 12 patients with HFrEF underwent bariatric surgery leading to a median length of hospital stay of 3+/-1.5 days. Post-operative complications included pulmonary oedema in 1 patient and transient acute kidney injury in another. These results were achieved with management by an experienced multidisciplinary team of cardiologists, bariatric surgeons and intensivists in specialist centres, with optimisation of haemodynamics and pharmacotherapy prior to surgery which may not be routinely available. This inadequately controlled, retrospective, small study makes it impossible to draw firm conclusions about the safety of this procedure in the general heart-failure population. A larger observational study[45] (n=524) reported a significant reduction in postoperative heart failure hospitalisation for

patients with heart failure who had undergone bariatric surgery in a self-controlled case-series but did not report on overall weight loss or changes in cardiac morphology on imaging.

One of the biggest challenges in assessing the impact of weight loss in heart failure patients is establishing which weight loss intervention is best and could be broadly implemented. Although successful weight loss can be challenging, all but one trial[20] demonstrated significant weight loss via non-surgical interventions. A modest 5-10% weight loss via lifestyle change has been shown to improve the cardiovascular risk profile by decreasing hypertension, dyslipidaemias and type 2 diabetes[46]. Of the successful interventions used, one achieved weight loss with orlistat and one with diet alone. Only one successful intervention included a combination of diet, focussing on achieving calorie deficit, exercise and individualised behavioural counselling; Lifestyle interventions designed to modify behaviours and physical activities are the first-line recommended option for weight management[47]. Due to the level of input required from the research centre to implement the interventions described (providing meals), this would not be easily repeatable for use in a routine care setting. However the principles used, of diet and exercise in addition to group interaction, are important. Extensive evidence has shown that in order to achieve and maintain weight loss behavioural counselling is essential[48]. Recommendations on diet alone results in minimal weight loss[47]. Successful weight loss has been achieved through lifestyle modification programmes with frequent interactive encounters, goal setting, self-monitoring, stimulus control and problem solving[49]. These open-group behavioural weight loss programmes are both clinically and cost-effective and commercial programmes are now recommended by NICE[50] and are available across the UK and internationally. In addition to any benefit of weight loss the “self-care” behaviours required when adhering to these programmes may impact positively on patients quality of life. Patients perceive that self-care behaviours and better social support improve quality of life[51]. In order for weight loss to be effective it must be able to be maintained. All the trials[18-21] included in this review involved interventions lasting less than 20 weeks. Pharmacotherapy with orlistat has been shown to improve weight loss only after one year of therapy[44]. Patients

are often disappointed with a moderate degree of weight loss and weight regain is common after termination of drug treatment[44]. The improvements in cardiac morphology seen after bariatric surgery (non-heart failure population) in the UTAH study were reported at 2 years[10]. Longer interventions and longer follow-up of outcomes maybe required.

The results of this review are promising as they may indicate that improvements in heart failure symptoms, quality of life and exercise capacity may be possible for patients with obesity and heart failure as a result of a weight-loss intervention. However, the results are preliminary rather than definitive due to significant design and methodological limitations. The use of prolonged, multicomponent, evidence-based intentional weight loss regimes may provide firmer evidence to allow for future clinical guidance.

Conclusion

Obesity is highly prevalent amongst patients with heart failure. Advice regarding weight management is difficult due to the lack of evidence-based guidelines. Other than restricting sodium intake to <2g per day there are no specific dietary heart failure guidelines[52]. Intentional weight loss in a patient with co-existent obesity and heart failure may improve exercise capacity, NYHA classification and quality of life. These advantages could be achieved with small, sustained changes to body weight. To date, trials have been small with considerable heterogeneity, using weight loss interventions that do not match best-practice, but trends suggest weight loss is achievable. Bariatric surgery may be safe in heart failure patients through intensive optimisation of pre-operative state and a multidisciplinary approach. Prospective randomised clinical trials using evidence-based weight management interventions, sufficiently powered to assess clinical outcomes, are required to aid management of this complex, comorbid population.

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Table and Figure Legends

Figure 1: Flow chart of the Literature search process.

Table 1A: Trial design and outcome measures: randomised controlled trials

ACS: acute coronary syndrome, BNP: brain natriuretic peptide, BMI: body mass index, CPET: cardiopulmonary exercise test, EF: ejection fraction, ETT: exercise treadmill test. HF: heart failure, KCCQ: Kansas City cardiomyopathy questionaire. LTFU: lost to follow up, MI: myocardial infarction, MLHF: Minnesota living with heart failure questionaire, NCEP III: National cholesterol education program III, ND: not defined, NHANES: National health and nutrition examination survey, NYHA: New York heart association classification, PAP: pulmonary artery pressure. QOL: quality of life, 6MWT: 6-minute walk test,

*Duration was predefined

Table 2A: Baseline characteristics: randomised control trials

Acei/ARB: angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker, BB: beta blocker, BMI: body mass index, CRT: cardiac resynchronisation therapy, EF: ejection fraction, HF: heart failure, ICD: implantable cardiac defibrillator, IHD: ischaemic heart disease, MRA: mineralocorticoid receptor antagonist. ND: not defined.

Table 3A: Results: randomised controlled trials

BNP: brain natriuretic peptide, EF: ejection fraction, NS: non-significant, KCCQ: Kansas City cardiomyopathy questionnaire, MLHF: Minnesota living with heart failure questionnaire, NYHA: New York heart association classification, SD: standard deviation

Table 1B Trial design and outcome measures: observational studies

BMI: body mass index, CABG: coronary artery bypass graft, EF: ejection fraction, ETT: exercise tolerance test, HF: heart failure, KCCQ: Kansas city cardiomyopathy questionnaire, LMS: left main stem, LTFU: lost to follow up, MLDP: multicentre lifestyle demonstration project, MOS-SF: medical outcomes study-short form survey, ND: not defined, NYHA: New York heart association, QOL: quality of life,

Table 2B: Baseline Characteristic of intervention group: Observational Studies

Acei/ARB: angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker, BB: beta blocker, BMI:body mass index,CRT: cardiac resynchronisation therapy, EF: ejection fraction, HF:heart failure, ICD: implantable cardiac defibrillator, IHD: ischaemic heart disease, MRA: mineralocorticoid receptor antagonist. ND: not defined

Table 3b results: observational studies

EF: ejection fraction, ETT: exercise tolerance test, FS: fractional shortening, KCCQ: kansas city cardiomyopathy questionnaire, LSAQ: linear analogue self assessment questionnaire, MOS-SF: medical outcomes study-short form survey ND: non described, NS: Non significant, NYHA: new york heart association,

*% weight mean weight loss,

‡median and range values

•control group used patients without heart failure undergoing same intervention

×Weights not defined therefore weight in kg calculated from body mass index figures given using a standard height of 1.7m

Table 1A: Trial design and outcome measures: randomised controlled trials

Study/ Year/ Country	Key heart failure inclusion criteria	Key obesity inclusion criteria	Key exclusion criteria	Recruitment dates	Multi-center	CONSORT diagram	Duration* weeks	LTFU %	Intervention	Outcome measure(s) of interest
HEFPEF										
Kitzman 2016 USA	-EF >50% -Signs and symptoms HF (NHANES >3 or Rich et al criteria[45] -Biomarkers not included	-BMI >30	-Wall motion abnormality -significant ischemic or valvular disease -pulmonary disease -anaemia -undergoing regular diet/exercise	2009-14	No	Yes	20	8	**Lifestyle Modification** **Randomised to 4 groups:** 1: Exercise alone: 1 hour supervised session 3x per week. Personalised intensity 2. Diet alone: hypocaloric diet. Meals prepared by research centre. Aim 400kcal deficit. 30% fat. 1.2g/kg protein 3. Diet and Exercise. Aim 350kcal deficit 4. Control-no diet or exercise for duration of study. Received 2 weekly phone calls to match interaction of other group	Primary Outcome 1) Exercise capacity by V02max 2) QOL by MLHF Exploratory outcomes 1) Exercise capacity by ETT and 6MWT 2) QOL by KCCQ 3) NYHA class 4) Left ventricular function by EF measured on cardiac MRI 5) BNP
HEREF										
Beck de Silva, 2005, USA	-EF < 40% (measured by radionuclide angiography) -NYHA II-IV -stable doses of conventional HF medical therapy for 3 months -Biomarkers not included	-BMI>30 -weight stability for 3 months	-Eating disorder -Previous weight reduction surgery	ND	No	No	12	10	**Pharmacotherapy** **Randomised to 2 groups:** orlistat three times daily plus multivitamin plus standard care vs standard care alone (dietician referral, prescription of low calorie diet, restricted 2g Na per day)	Primary and secondary endpoints ND 1) Exercise capacity by 6MWT 2) Left Ventricular function by radionuclide ventriculography 3) NYHA class 4) BNP 5) QOL by MHLF3
Pritchett 2012 *USA*	-EF <50% Framingham criteria -NYHA II-III -Stable doses of conventional HF medical therapy (duration ND) -Biomarkers not included	-BMI>25 -With Metabolic syndrome (NCEP III definition)	-NYHA IV -Weight loss>10lbs previous 3 months	2005-8	No	No	12	5	**Lifestyle Modification** **Randomised to 2 groups:** 1) Standard HF care plus diet and exercise program Initial 1 hour education session on self care, salt and fluid restriction. -Diet-Portion control diet including 2 meal	Primary and secondary endpoints ND 1) Exercise capacity by 6MWT 2) BNP 3) QOL by KCCQ

									replacement products (Slimfast), one portion controlled snack and self-selected meal, given kilocalorie goal based on weight. <30% fats, <10% saturated fats -Exercise-unsupervised walking. Advised to achieve moderate exertion. provided with pedometer -Behavioural adaptation-weekly scheduled group meetings with dietician with education on diet, exercise and personalised tailoring of the program to achieve goal 2) Standard medical heart failure care only	
EF Uncertain										
Evangelista 2009 USA	-NYHA II-III -EF not included -Biomarkers not included	-BMI>27 -type 2 diabetes mellitus (non insulin treated)	-Weight loss >10% in last 6 months -already involved in weight loss programme	ND	No	No	12	0	**Lifestyle Modification Randomised to 3 groups-** 1.HP: High protein, hypoenergetic diet (40% carbohydrates, 30% protein, 30% fat) 2.SP: Standard protein, hypoenergetic diet (55% carbohydrate, 15% protein, 30% fat) 3. conventional diet with no energy restrictions-high carbohydrates, high fibre, low fat.	Primary and secondary endpoints ND 1) Exercise capacity by 6MWT and CPET: VO2max 2) QOL by MHLF

ACS: acute coronary syndrome, BNP: brain natriuretic peptide, BMI: body mass index, CPET: cardiopulmonary exercise test, EF: ejection fraction, ETT: exercise treadmill test. HF: heart failure, KCCQ: Kansas City cardiomyopathy questionaire. LTFU: lost to follow up, MI: myocardial infarction, MLHF: Minnesota living with heart failure questionaire, NCEP III: National cholesterol education program III, ND: not defined, NHANES: National health and nutrition examination survey, NYHA: New York heart association classification, PAP: pulmonary artery pressure. QOL: quality of life, 6MWT: 6-minute walk test,

*Duration was predefined

Table 1b: Trial design and outcome measures: observational studies

Study/ Year/ Country	Key HF Inclusion criteria	Key Obesity inclusion criteria	Key Exclusion criteria	Control Group	Recruitment dates	Multi-center	LTFU	Follow up	Intervention	Outcome measure(s)
HFREF										
McCloskey 2006 USA	EF <35% Biomarkers not included Symptoms ND	BMI >40 Undergone bariatric surgery	ND	No Control	1998-06	No	15	3-89	**Surgical** -10 Laparoscopic Roux en Y Gastric bypass -1 open Roux en Y Gastric bypass -2 sleeve gastrectomy -1 laparoscopic adjustable gastric band	1) Left ventricular function by EF-echo or catheterization 2) NYHA
Miranda 2013 USA	1 of EF <50% Documentation of clinical diagnosis Echo evidence of diastolic dysfunction Biomarkers not included	BMI>35 referred for evaluation of bariatric surgery	ND	Non surgical patients with obesity and heart failure. Managed at nutrition clinic by cardiology, endocrinology and nutritionist	1990-05	No	23	ND	**Surgical** Roux-en-Y Gastric Bypass	1)Left ventricular function by EF 2) HF Symptoms by likert scale 3) QOL by linear analogue self assessment questionnaire
Ramani 2008 USA	"advanced systolic heart failure" EF not included Biomarkers not included Symptoms ND	"Morbid Obesity"	ND	Non surgical age, sex, BMI matched.	2001-06	No	0	12	**Surgical** 8 laparoscopic Roux-en-Y Gastric Bypass 2 laparoscopic sleeve gastroplasty 1 laparoscopic gastric band 1 opne Roux-En-y Gastric Bypass	1) Left ventricular function by EF (echo) 2) NYHA
Vest 2015 USA	EF <50% Biomarker not included Symptoms ND	Undergone bariatric surgery	ND	Subgroup of patients with pre and post procedure echo matched to non surgical heart failur patients with obesity	2004-13	No	0	23	**Surgical** Roux-en-Y gastric bypass, Adjustable gastric banding Sleeve gastrectomy	1) Left ventricular function by EF (echo)

Pischke 2007 USA	EF <40% NYHA I-II Biomarkers not included		LMS >50% CABG 6 weeks Angioplasty 6 months	Ejection fraction >40%	1993-97	Yes	24	12	**Lifestyle (52 weeks)** Initial 12 week 3 group sessions on diet/exercise/ stress management / Remaining 40 weeks 1 group session per week Goal-10% calories from fat based on 3 day food diary, 3h exercise per week, 1 hour yoga/meditation, attendednce at sessions	1)QOL by MOS SF 34 2) Exercise capacity by ETT
EF uncertain										
Alpert 1997 USA	HF((Framingham study) EF not included Biomarkers not included	Body weight >twice ideal body weight	Hypertension Evidence of coronary artery diease Uninterpretable echo	Patients without heart failure undergoing surgery	ND	No	42	4.5+/-1.2	**Surgical** Vertical band gastroplasty	1) Left ventricular function by FS 2)NYHA
Marriotti 2008 Italy	EF not included Biomakers not included Symptoms ND	-BMI >27.8	ND	No control	ND	No	15	6	**Lifestyle (6 months)** Personalised Hypocaloric diet Encouraged exercise Diaries to identify and adjust eating habits	1)Left ventricular function by -EF measured by echo 2) NYHA 3) QOL by KCCQ

BMI: body mass index, CABG: coronary artery bypass graft, EF: ejection fraction, ETT: exercise tolerance test, HF: heart failure, KCCQ: Kansas city cardiomyopathy questionnaire, LMS: left main stem, LTFU: lost to follow up, MLDP: multicentre lifestyle demonstration project, MOS-SF: medical outcomes study-short form survey, ND: not defined, NYHA: New York heart association, QOL: quality of life,

Table 2A: Baseline characteristics: randomised control trials

Study/ (Year)/ *Country*	Setting	Number of participants (n)	Age, years, (mean)	Female (%)	Weight,kg (mean)	BMI, kg/m² (Mean)	Mean EF (%)	HF Therapy (%)	Comorbidites (%)
Beck de Silva 2005 USA	Outpatients	21	50	19	126	42	27	ACEi/ARB (100) BB (90) MRA-ND CRT/ICD ND	Diabetes Mellitus (29) Hypertension ND IHD ND
Evangelista 2009 USA	Outpatients	14	59	22	106	38	26	ACEi/ARB (93) BB (93) MRA-ND CRT/ICD ND	Diabetes Mellitus (100) Hypertension (71) IHD (50)
Kitzman 2016 USA	Outpatients	100	67	81	106	39	61	ACEi/ARB (72) BB (40) MRA-ND CRT/ICD ND	Diabetes Mellitus (35) Hypertension (95) IHD-ND
Pritchett 2012 USA	Outpatients	20	52	30	ND	39	26	ACEi/ARB (90) BB (100) MRA (50) CRT/ICD (5/35)	Diabetes Mellitus (70) Hypertension (90) IHD (35)

Acei/ARB: angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker, BB: beta blocker, BMI: body mass index, CRT: cardiac resynchronisation therapy, EF: ejection fraction, HF: heart failure, ICD: implantable cardiac defibrillator, IHD: ischaemic heart disease, MRA: mineralocorticoid receptor antagonist. ND: not defined.

Table 2B: Baseline Characteristic of intervention group: Observational Studies.

Study/ Year/ Country	Setting	Number of participants Intervention (n)	Number of participants in control	Age, years, (mean)	Female (%)	Weight,kg (mean)	BMI, kg/m^2 (Mean)	Mean EF (%)	HF Therapy (%)	Comorbidites described(%)
Lifestyle Intervention										
Marriotti 2008 Italy	Outpatients	40	No control	68.2	35	92.9	31.8	33.5	ND	Diabetes Mellitus (29.4) Hypertension (79.4) IHD (45)
Pischke 2007 USA	Outpatients	50	186	57	18	89	29.2	ND	AceI/ARB (58) BB (66) MRA (ND)	Diabetes Mellitus (20) Hypertension (56) IHD (100)
Surgical Intervention										
Alpert 1997 USA	Outpatient	24	50	38	79	128	ND	ND	ND	ND
McCloskey 2006 USA	Database	14	No control	46	29	ND	50.8	23	ND	Diabetes Mellitus (58) Hypertension (64) IHD (29)
Miranda‡ 2013 USA	Database	13	6	62	62	146	55	57	AceI/ARB(54) BB (46) MRA (ND)	Diabetes Mellitus (77) Hypertension (92) IHD (ND)
Ramani 2008 USA	Database	12	10	41	75	ND	53	22	AceI/ARB (92) BB (67) MRA (36)	Diabetes Mellitus (50) Hypertension (75) IHD (17)
Vest 2015 USA	Database	38	38	50	47	ND	47.2	38	ND	Diabetes Mellitus (61) Hypertension (71) IHD (50)

Acei/ARB: angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker, BB: beta blocker, BMI:body mass index,CRT: cardiac resynchronisation therapy, EF: ejection fraction, HF:heart failure, ICD: implantable cardiac defibrillator, IHD: ischaemic heart disease, MRA: mineralocorticoid receptor antagonist. ND: not defined

Table 3A: Results: randomised controlled trials

Study	Measure	Mean change Intervention group/ Main change effect in Intervention factorial groups‡	Mean change control group/	p value
Weight loss				
Beck de Silva	kg	-4.65+/-9.8	+4.39+/-7.4	<0.001
Evangelista (High Protein)	Kg	-9.9+/-2	-1.5+/-0.6	<0.05
Evangelista (Standard Protein)	kg	-5.6+/-0.8	-1.5+/-0.6	<0.05
Pritchett	kg	-1.2+/-4.1	-0.56+/-3.71	0.71
Kitzman (Exercise)	kg	-3(-5,-1)‡	NA	<0.001
Kitzman (Diet)	kg	-7(-9,-5)‡	NA	<0.001
Exercise Capacity				
Beck de Silva	6 minute walk test (m)	+45.8 (No SD)	+14.9(No SD)	0.17
Evalgelista (High Protein)	6 minute walk test (m) $V0_2$max(ml/kg/min)	+287.3+/-69 +3.1+/-1	-138.4+/-77.1 -0.3+/-1/1	<0.05
Evangelista (Standard Protein)	6minute walk test (m) VO_2max(ml/kg/min)	-12.3+/-69 -0.3+/-1.0	-138.4+/-77.1	<0.05
Pritchett	6 minute walk test(m)	+169+/-235	+84+/-411	0.59
Kitzman (Exercise)	6 minute walk test (m) $V0_2$ max (ml/kg/min)	106(60,152)‡ +1.2(0.7,1.7)‡	Not reported	<0.0001 <0.0001
Kitzman (Diet)	6 minute walk test(m) $V0_2$ max (ml/kg/min)	85(39,132)‡ +1.3(0.8,1.8)‡	Not reported	0.0005 <0.0001
Quality of Life				
Beck de Silva	MLHF	Not reported	Not reported	Not reported
Evangelista (High Protein)	MLHF	-20.1+/-9.5	-5.1+/-3.9	<0.05
Evangelista (Standard Protein)	MLHF	-12.2+/-4.3	-5.1+/-3.9	NS
Pritchett	KCCQ	+6.1+/-18.6	+1/7+/-10	0.55
Kitzman (Exercise)	MHLF KCCQ	-1(-8,5)‡ 2(-3,7)‡	Not reported	0.7 0.43
Kitzman (Diet)	MHLF KCCQ	-0.6(-12,1)‡ 7 (3,12) ‡	Not reported	0.078 0.004

NYHA Classification				
Beck de Silva	NYHA	+0.6+/-0.5	-0.2+/-0.8	0.25
Kitzman (Exercise)	NYHA	-0.4(-0.6,0.2)‡	Not reported	0.001
Kitzman (Diet)	NYHA	-0.4(-0.5,-0.2)‡	Not reported	0.001
BNP				
Beck de Silva	BNP (pg/ml)	-32.3+/-313.5	-67.5+/-95.1	0.742
Pritchett	BNP(pg/ml)	-5(-28,20.5)	+4(-39,18)	1
Left ventricular Ejection Fraction				
Beck de Silva	EF(%)	Not reported	Not reported	NS
Kitzman (Exercise)	EF(%)	0(-2,2)‡	Not reported	NS
Kitzman (Diet)	EF(%)	-1(-3,1)‡	Not reported	NS

BNP: brain natriuretic peptide, EF: ejection fraction, NS: non-significant, KCCQ: Kansas City cardiomyopathy questionnaire, MLHF: Minnesota living with heart failure questionnaire, NYHA: New York heart association classification, SD: standard deviation

Table 3b results: observational studies

		Intervention Group			Control Group•			P value	
Study	**Measure**	**Baseline measure group Mean+/- sd**	**Final measure group**	**Mean change measure group***	**Baseline measure group Mean+/-sd**	**Final measure group**	**Mean change measure group**	**Intervention change vs control change**	**Intervention baseline vs final**
Weight									
Miranda‡	kg	146(98-210)	99(63-164)	ND	132(112-147)	140(124-128)	ND	<0.001	ND
Ramani	kg×	153.1+/-20	110+/-23	ND	136+/-12	136+/-12	ND	ND	<0.01
Vest	kg×	47.2+/-10	ND	22.6*	38.2+/-7	NS	0.08*	<0.001	ND
Pischke•	kg	90.5+/-17.1	84.1+/-15.8	ND	NA	NA	NA	NS	<0.001
Alpert•	kg	128+/-16	ND	33+/-4*	NA	NA	NA	NS	ND
Marriotti	kg	92.9+/-10.6	88.5+/-10.4	ND	No control	No control	No control	No control	<0.004
McCloskey	kg×	147+/-6	107+/-5	41.9	No control	No control	No control	No control	ND
Exercise Capacity									
Pischke	ETT	8.9+/-3.4	10.6+/-2.7	ND	NA	NA	NA	NS	<0.01
Quality of Life									
Miranda‡	LSAQ	3(0-6)	7(7-10)	5(-10-10)	4.5(3-8)	6(3-8)	0(0-3)	0.06	0.001
Pischke•	MOS SF36-PH MOS SF36-MH	44.8+/-10.3 48.2+/-10.9	49.4+/-8.9 52.9+/-11.4	ND	NA	NA	NA	NS	<0.01 <0.01
Mariotti	KCCQ	59.7+/-21.7	71.2+/-19.3	ND	No control	No control	No control	No control	0.02
Heart Failure symptoms									
Ramani	NYHA	2.9+/-0.7	2.3+/-0.5	ND	2.4+/-0.7	3.3+/-0.9	ND	<0.05	0.02
Alpert•	NYHA	2.5+/-0.5	1.4+/-0.5	ND	N/A	N/A	N/A	N/A	ND
Mariotti	NYHA	2.3+/-0.9	1.9+/-0.7	ND	No control	No control	No control	No control	<0.05
McCloskey	NYHA	2.7+/-0.4	2.2+/-0.4	ND	No control	No control	No control	No control	ND
Left ventricular Function									

Miranda‡	EF(%)	57(35-75)	59(41-75)	ND	57.5(35-65)	62.5(53-65)	ND	NS	NS
Ramani	EF(%)	21.7+/-6.5	35+/-14.8	ND	23.5+/-6.7	28.5+/-14	ND	<0.05	<0.01
Vest	EF(%)	37.8+/-9	ND	+5.1+/-8.3	37.4+/-9	ND	+3.4+/-10.5	ND	P=0.0005
Alpert•	FS(%)	23+/-5	ND	+5+/-5	NA	NA	NA	NS	NS
Mariotti	EF(%)	33.5+/-11.5	37.4+/-12.1	ND	No control	No control	No control	No control	0.02
McCloskey	EF(%)	23+/-6	33+/-14	12.2+/-14.6	No control	No control	No control	No control	0.02

EF: ejection fraction, ETT: exercise tolerance test, FS: fractional shortening, KCCQ: kansas city cardiomyopathy questionnaire, LSAQ: linear analogue self assessment questionnaire, MOS-SF: medical outcomes study-short form survey ND: non described, NS: Non significant, NYHA: new york heart association,

*% weight mean weight loss,

‡median and range values

•control group used patients without heart failure undergoing same intervention

×Weights not defined therefore weight in kg calculated from body mass index figures given using a standard height of 1.7m