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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Comparing the effect of low versus moderate intensity strength training in addition to endurance training in patients with heart failure: a randomized controlled trial

Thomas Keena
Hanne Merkelbach

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Dominique HANSEN

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Research context

This master thesis is situated within a cardiovascular rehabilitation context, more specifically, in the ambulant rehabilitation of people with heart failure. Currently, the standard rehabilitation program in the 'Ziekenhuis Oost-Limburg' contains both aerobic and resistance training. This master thesis investigated the superiority of adding either a low or a moderate intensity resistance training in addition to an aerobic exercise training for improving cardiovascular health.

People suffering from heart failure need to exercise to improve their quality of life during daily activities. A better cardiovascular health correlates with both a higher functional capacity and a higher exercise capacity. Thus, improving cardiovascular health is a crucial factor in patients with heart failure, as a reduced cardiovascular health can result in a diminished exercise tolerance and other symptoms like fatigue, orthopnea and breathlessness.

Aerobic exercise training has been researched extensively in the heart failure population and clear recommendations exist surrounding the intensity and the frequency at which this exercise modality should be trained at. However, research regarding the effect of resistance training is more rare. Current studies compare resistance training to both a combined exercise training program (aerobic and resistance training) as well as to sedentary groups (no exercise intervention). Current evidence demonstrates that resistance training has no significant additional effect in improving cardiovascular on top of aerobic training. Nevertheless, significant improvements are found when resistance training is compared to sedentary groups. Therefore, resistance training can result in improvements in cardiovascular health, as well as muscle strength, which causes a reduced mortality in patients with heart failure. Still, the most optimal intensity for the applied resistance training has yet to be established for this population. Knowledge surrounding the most optimal intensity for the resistance training is a benefit, because this would result in a higher chance of achieving clinically important results in this population. If no superiority can be found regarding intensity for this exercise modality, it could be recommended to train at low intensities to achieve improvements for patients who are not confident or strong enough, as it would be deemed safer.

This master study is an interim report of an ongoing study from Tin Gojević, which is performed at the 'Ziekenhuis Oost-Limburg' in Genk. The research design and study protocol

was already developed before the two students were informed about the study. The recruitment, measurements and rehabilitation sessions commenced in September 2021. The students were informed about the study in January 2022. In April 2022, they received all available data and started the statistical analysis. All results were interpreted by the students and were reported in the study. This master thesis was written by the two students.

1 Abstract

Background: Research affirms the positive effect of aerobic training with or without resistance training in patients with heart failure (HF).

Objectives: The aim of this study was to investigate whether a low or a moderate intensity resistance training with a combined aerobic training has a superior effect in improving cardiovascular health in patients with HF.

Participants: 86 patients with HF from 'Ziekenhuis Oost-Limburg' in Genk were screened. After exclusion, 36 patients were allocated to the low-intensity group (LG) or to the moderate-intensity group (MG).

Measurements: One rep maximum (1RM) strength tests were performed on a leg-press, dips and pulldown machine. Cardiovascular parameters were measured by a cardiopulmonary exercise test (CPET) and the six-minute walk test (6MWT). The quality of life (QoL) was assessed with the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Results: 20 participants were allocated to the LG and 19 to the MG. Between-group analysis showed no significant differences in the strength tests. However, significant differences in favor for the LG were found for the heart rate (HR) at the anaerobic threshold (AT2), the HR_{max} (CPET) and for the HR_{post} (6MWT). The within-group analysis showed significant improvements for both groups in all three strength tests (1RM test), the VO_{2max} (CPET) and the distance (6MWT). Significant changes that were found only for the LG were the wattage, HR at both the aerobic and anaerobic threshold and the HR_{max} (CPET). Additionally, significant improvements were made for HR_{post} and BORG dyspnea before the test (6MWT). Finally, the socio-economic, the psychological-emotional domain and the total score increased significantly (MLHFQ).

Conclusion: In conclusion, a combined resistance and aerobic exercise intervention showed significant improvements in cardiovascular health (mainly measured in VO_{2max}) in HF patients, regardless of the intensity level of the resistance training.

2 Introduction

Heart failure (HF) refers to a dysfunction of the heart in which the heart muscle no longer pumps blood through the body sufficiently[1,2]. This dysfunction may be caused by an impairment of either the filling or the ejection of blood from the heart[2]. In result, this can lead to respiratory problems, as a lack of movement of blood throughout the body can lead to a fluid buildup in the lungs[1]. Additionally, HF causes a disruption in all major body functions[3] and reduces the functional capacity of the patient[2]. People with HF most commonly experience shortness of breath during exercise. Nevertheless, chest pain, palpitations, anorexia, ankle swelling and fatigue are also frequently described[2,4].

HF is caused by many reasons in which structural (e.g. valve stenosis or regurgitation,...) and functional abnormalities (e.g. induced by a myocardial infarction) of the heart are most common[2,4]. On one hand, acute HF may develop due to an acute myocardial infarction, which can cause both structural and functional abnormalities[4]. On the other hand, the development of chronic HF is typically associated with hypertension[4]. Important risk factors that increase the chances of developing HF include coronary heart disease, obesity, chronic pulmonary disease, hypertension, diabetes and smoking[4,6]. Thus, cardiovascular diseases play a strong link in the development of HF[4,5]. Since the COVID-19 crisis, the treatment of cardiovascular diseases has proved to be even more crucial due to a higher hospitalization and mortality rate for these patients when contracting the COVID-19 virus[7,8]. In return, a COVID-19 infection can develop HF or can further worsen the symptoms of patients with HF[8].

Certain lifestyle changes (e.g. diet and nutritional counseling, medication management, smoking cessation, psychosocial management,...) and the addition of physical activity (30-60 min/day)[12] have proven to improve the quality of life (QoL), symptomatology and/or mortality of people with this condition[1,2] or even prevent the development of HF in the first place[9,10]. Due to these aforementioned findings, a multidisciplinary treatment program including physical therapy as well as lifestyle changes would be of great importance for these patients[11,12]. Clinical guidelines suggest to perform aerobic or endurance training at a minimum of 2-3 days/week. Ideally, this should be performed every day of the week to achieve better results. The intensity level should start low, at around 40% of peak aerobic capacity (VO_{2peak}). The end goal is to work towards the second ventilatory threshold (VT2), which corresponds with 65-90% VO_{2peak}. This endurance training should be performed between 15-

30 minutes up to 45-60 minutes/session[12]. Resistance training should be executed with the same frequency of 2-3 days/week, but the intensity level is initially performed at <30% of one rep maximum (1RM) for 5-10 repetitions and later at 40-60% 1RM for 8-15 repetitions[12].

Several studies have shown exercise therapy (which includes both aerobic and resistance training) to improve VO_{2peak}, QoL, muscle strength, aerobic capacity and hospitalization of HF patients[13,15,17,18,19,20]. Additionally, Ostman, Jewiss and Smart (2016)[16] suggests a combined aerobic and resistance training intervention to achieve the greatest increase in health related QoL (HRQoL). Nevertheless, the most optimal exercise pattern, duration, combination or intensity for these patients remains unclear[14]. Though a higher total amount of physical activity performed, has been suggested to be superior for primary prevention of HF[10].

Recent research[23] indicates a superior result in increasing muscle strength when implementing a high-intensity dynamic resistance training (at ≥70% of 1RM) compared to a low-intensity one. More importantly, muscle strength has been proven to reduce mortality risk[22]. In addition, Kim et al. 2018[21] suggests that improving both cardiorespiratory fitness as well as muscle strength results in the largest reduction in mortality risk. Therefore it may be valuable to determine the most effective way to increase muscle strength in patients with cardiovascular disease, as there is currently no literature regarding the most effective exercise intensity to be performed with a broad range of 40-60% 1RM.

The aim of this study was to determine whether greater cardiovascular health would be achieved with the addition of either low or moderate intensity resistance training on top of cardiovascular exercise training. It was hypothesized that moderate resistance training added to a cardiovascular exercise training would result in a significant increase in clinical health benefits in patients with HF, opposed to a low resistance training with a cardiovascular exercise training.

3 Methods

3.1 Study design

A prospective randomized controlled trial was conducted to determine the effects of two different types of resistance training on top of endurance training. Dutch speaking individuals suffering from HF, and treated in the 'Ziekenhuis Oost-Limburg' (ZOL) in Genk, were recruited. Eighty six participants were screened and 39 individuals were randomly allocated in two intervention groups with different training intensities; a low intensity resistance training (35-40% 1RM with 25 repetitions/series) and a moderate intensity resistance training (65-70% 1RM with 12 repetitions/series), both with a concurrent endurance training. Participants were randomized via block-randomization with age and gender taken into account. This was done to achieve a similar distribution in age and gender between both groups. This study was an open-label randomized controlled trial where both the participants and the researchers, who analyzed results, were informed about the applied intervention. A per-protocol analysis was conducted.

3.2 Participants

3.2.1 Recruitment

Recruitment of participants started in September 2021. All HF patients in the ZOL in Genk, who started their rehabilitation after September 2021, were informed about the study. Patients who agreed to participate in this study signed a written informed consent. Afterwards, the participants were screened by performing a maximal cardiopulmonary exercise test (CPET), as this is often used to assess the suitability of a HF patient's treatment[24]. Prof. Dr. W. Mullens supervised this test and determined which patients could participate in the study based on the eligibility criteria.

3.2.2 Eligibility criteria

Inclusion criteria for the patients to participate in this study were; being diagnosed with HF by a physician, being an adult (>18 years) and initiating rehabilitation at the ZOL. Exclusion criteria to participate in this study were the presence of orthopedic or neurological comorbidities which affect muscle strength; a cognitive impairment or unable to understand the exercises; measurements that cannot be performed correctly; a heart or arterial surgery (like

percutaneous coronary intervention, bypass, heart valve surgery...) in the last year; an acute myocardial infarction in the last 6 months; and other interventions during the study.

3.2.3 Allocation

Every participant was randomized into one of the two intervention groups via block randomization by age and gender. Five blocks with six randomizations were made. Each block consisted of three moderate-intensity and three low-intensity groups. Nineteen participants were allocated in the moderate-intensity group (MG) and 20 participants were allocated in the low-intensity group (LG).

3.2.4 Medical Ethics

Ethical approval was obtained from the Medical Ethics of the UHasselt and the 'Ziekenhuis Oost-Limburg, Genk' on the 30th of November of 2020, with a CTU-number of 2020044. Participants signed an informed consent before participating, which was then reviewed by the physiotherapist K. Geladé.

3.3 Procedure

3.3.1 Baseline characteristics

Baseline characteristics were obtained through the medical file when participants commenced the training intervention. This information was collected regarding age, height, body mass, body mass index (BMI), (ex-)smoking status, presence of hypotension, presence of type 2 diabetes mellitus (T2DM), presence of dyslipidemia, presence of obesity as well as medication use and the presence of other comorbidities. Values of the left ventricular ejection fraction (LVEF) and type of HF were objectified by an echocardiography.

3.3.2 Primary Outcome measures

The most important primary outcome was VO_{2peak}. Other primary outcomes were muscle strength, functional capacity and QoL. These outcomes were, respectively, measured by the CPET, the 1RM test, the 6 minute walking test (6MWT) and The Minnesota Living with Heart Failure Questionnaire (MLHFQ). These measurements were never conducted on the same day. In addition, when VO_{2peak}, 1RM or functional capacity was measured, this was always done at the start of an intervention session. If a measurement of the VO_{2peak} was taken by the CPET, this was never followed by a training session. Measurements of the CPET and 6MWT were

taken at baseline (session one), after 20 sessions and finally at the end of the intervention (45 sessions). The 1RM strength test was always performed after nine sessions (Figure 1).

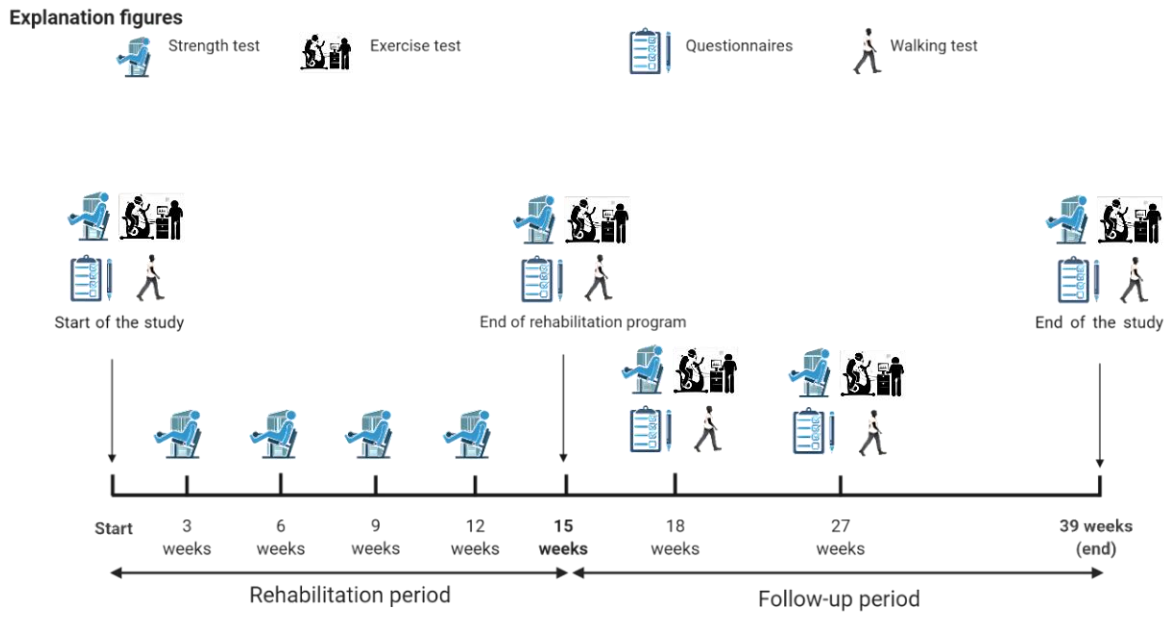

Figure 1 Timeline of the study[85]

3.3.2.1 Cardiopulmonary exercise test

The cardiopulmonary exercise test (CPET) was used to measure the VO_{2peak}. The CPET tests the entire cardiorespiratory system, from the lungs to the skeletal muscles[25]. More recently, this test is used to determine exercise intolerance due to the knowledge that resting cardiac and pulmonary function do not relate to exercise performance or functional capacity[25].

The CPET was performed on an electronically braked cycle ergometer (eBike, GE Medical systems, Milwaukee, Wisconsin, USA) with the goal to achieve volitional exhaustion. This was monitored by the Cardiosoft electrocardiography software (Cardiosoft 6.6, GE Medical systems, Feiburg, Germany). Before every test, a gas and volume calibration was performed according to the manufacturer's instructions. The seat of the bike was adjusted to the correct height based on the anatomy of the patient and reused every time to provide standardization. Hereafter, a 12-lead electrocardiography device (KISS™ Multilead, GE Medical systems, Freiburg, Germany) was placed on the patient to monitor the heart rate (HR) and this device averaged their HR every ten seconds. Finally, a blood pressure monitor was placed on the arm and the CPET mask was placed on the mouth of the patient. Many parameters were collected during the CPET by the pulmonary gas exchange analysis (Jaeger MasterScreen CPX Metabolic

Cart, CareFusion Germany GmbH, Hoechberg, Germany) during the test. The parameters; oxygen uptake (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE), equivalents for oxygen uptake (VE/VO_2) and carbon dioxide production (VE/VCO_2) as well as the respiratory exchange ratio (RER) were collected breath-by-breath and averaged every ten seconds. Furthermore, exercise tolerance was assessed by the peak workload (W_{peak}).

Before initiating the test, the patient was told that a perceived fatigue in the legs was deemed okay, but that they should inform the researcher when any dizziness or pain in the chest (angina pectoris) was noted. During the performance of the test, an environmental temperature of 19-21°C was maintained. The test (ramp protocol) took between 6 and 12 minutes, consisting of a 30-sec pre-exercise resting period sitting upright on the bike, a 1-to-2-min warm-up cycling phase and finally, an incremental exercise cycling period. The warm-up was performed unloaded, whereas the incremental exercise cycling period started at a workload of 10-60W and increased every minute with 5-40W depending on the patient's clinical status. During these two periods, a cycling frequency of 60-70 revolutions per minute (rpm) was maintained. If this dropped under 60 rpm, the test was ended. Maximal effort of the participant was sought-for and this was objectified when RER ≥1.10 was achieved. Additionally, subjective measurements were obtained by an experienced tester who verbally encouraged the subjects and analyzed if a maximal effort was performed based on subjective features (e.g. dyspnea, sweating, facial flushing, clear unwillingness to continue, and/or a sustained drop in the participant's pedaling frequency from 60 rpm despite verbal encouragement).

The training zones were determined by the first ventilatory threshold (VT1) and the second ventilatory threshold (VT2). The zone before the VT1 is considered to be the light-to-moderate intensity zone. The zone between the VT1 and the VT2 is the moderate-to-high intensity zone. Additionally, the VT2 is related to the critical power, which is the upper intensity limit for prolonged aerobic exercise. The VT1 was determined using the V-slope method and the VT2 was determined by the VE vs VCO_2 plot. The latter threshold is reached when the VE increases out of proportion to VCO_2. Both thresholds were double-checked by establishing the nadir of the VE/VCO_2 versus work rate relationship. Three independent observers checked these ventilatory thresholds. Two of them determined the thresholds and cross-checked each other's work, while the third reviewed these thresholds in a random subsample of patients.

After this analysis, the three observers determined the VT1 and VT2 for each patient and a consensus was achieved. The CPET has been proven to be a valuable measurement tool that provides diagnostic and prognostic information for patients with cardiopulmonary diseases[25,26,27].

3.3.2.2 Muscle strength

The maximal strength was measured by a 1RM. During the first session, a standardization of the test was done. In addition, the participant underwent a familiarization period since the reliability of the 1RM test increases after a short warm-up and familiarization period[28]. The standardization of the 1RM test was done by always maintaining the same test order; the leg press was always performed first, second the dips and lastly the pulldown. The testing procedure was further standardized by recording the seat and handlebar height during the first measurement of the pull-down and dip exercise. For the leg press, standardization was achieved by recording the seat distance, the backrest angle and the footplate height. These exercises, as well as, the 1RM tests were always carried out at the patient's specific settings. After performing a warm-up, the participant first completed eight repetitions at 30% 1RM, hereafter two repetitions were performed first at 50% 1RM, then 70% 1RM and finally at 90% 1RM. Lastly, the 1RM was calculated based on the following formula from Brzicky et al. 1993[31]: $1RM = \frac{weight\ lifted}{1.0278 - 0.0278 * repetitions}$. The date, the amount of weight lifted, the number of repetitions and finally, the estimated 1RM were recorded. Additional notes regarding the test were added if this was necessary. For example, if a 1RM test for a specific exercise was not possible to be carried out, the reason was described. This test is the gold standard for assessing muscle strength in a non-laboratory setting[28]. It is a simple test that has been proven to be reliable in patients with heart failure[29] as well as healthy patients regardless of experience with resistance training, age or sex[30].

3.3.2.3 Functional capacity

The 6MWT does not require any sophisticated equipment. In this test, the submaximal level of the functional capacity of the patient is tested. All patients were asked to walk as far as they could in six minutes on a flat, hard surface over a parkour of 30 meters. The description from the ATS guidelines 2002 was followed[32]. Before initiating the test, the therapist informed the participant to use the arms while walking, not to speak during the test and to walk as fast as they could. The participant was asked to stop the test if severe shortness of breath was

experienced. Perceived shortness of breath and fatigue in their legs was rated on a BORG Rating of Perceived Exertion (RPE) scale (0-10)[37]. A score of zero meant no fatigue, while a ten indicated maximal fatigue. In addition, HR and oxygen saturation (SpO_2) were measured via a pulse oximeter (Nonin Onyx Vantage 9590). Both the BORG RPE scale, the HR and the SpO_2 were measured before and immediately after conducting the 6MWT. The assessor always remained at the same position during the entire test instead of walking behind the patient. Standardized verbal encouragement was given every minute based on the ATS guidelines 2002[32]. The 6MWT has been proven to be a simple, reliable and well-tolerated test to determine exercise tolerance and functional capacity in HF patients[33,34,35]. The testing was supervised by the same physiotherapist (T.G.), although intra-reliability has yet to be proven for this test[36].

3.3.2.4 Quality of life

At last, the QoL of the patients was measured by the MLHFQ. The MLHFQ is a self-administered and disease-specific questionnaire for patients with HF. In the MLHFQ, 21 items are rated on a six point Likert scale (0 = none/5 = very much) regarding the impact of their disease on health-related quality of life (HRQoL). The questionnaire consists of questions about the physical, the emotional, the social and the mental domain[39]. The total score ranges from 0 (best) to 105 (worst) in which a score of 23 or lower indicates a good QoL, a score between 24 and 45 suggests a moderate QoL and a score of 46 or higher indicates a poor QoL[39]. The MLHFQ is one of the most widely used HRQoL questionnaires in HF patients and has been proven to be valid in this population[38].

3.3.3 Intervention

All recruited patients followed a multidisciplinary rehabilitation intervention. This is considered to be the standard care treatment of the hospital, with exercise training being one part of this intervention. The exercise training consisted of a combined endurance training and resistance training (Table 1). The intervention program consisted of 45 sessions of approximately 60 minutes during 15 weeks.

All participants followed the same endurance training of 40 minutes, three times a week at an intensity between 50% and 80% VO_{2max}. The intensity started above the first VT1 and progressed over the weeks until the VT2 was reached. The machines that were used to

perform the endurance exercises were a treadmill, a cycle ergometer, an arm ergometer, a stepper, a cross trainer and a rowing machine.

For the resistance training, the same exercises were performed by both groups. Whilst the intensity of the exercises varied between the two intervention groups, an identical volume (intensity x repetitions) was maintained. The exercises performed were the leg press, the dip and the pulldown (Proxomed, Compass, Enraf Nonius). The MG trained at an intensity of 55-70% of 1RM. More specifically, from week one to week four the MG trained at an intensity of 55% 1RM for the upper body exercises (UB) and at an intensity of 65% 1RM for the lower body exercises (LB). In week four until week eight the UB was trained at an intensity of 60% 1RM and at an intensity of 70% 1RM for the LB. The MG always performed the exercises for 12 repetitions over three sets. In contrast, the LG trained between 35% and 40% 1RM. In week one till four the upper extremity was trained at an intensity of 35% 1RM for three sets of 19 repetitions and the lower extremity for 35% 1RM for three sets of 22 repetitions. The next four weeks the LG trained the upper extremity at an intensity of 40% 1RM for three sets of 18 repetitions and the lower extremity at an intensity of 40% 1RM for three sets of 21 repetitions. Every three weeks (the ninth session) the participants performed a new 1RM test. The weights used during the resistance training were constantly matched to provide the same intensity. This was done based on the results of the last 1RM test. This way the patients could continuously progress their weight while maintaining the same intensity as during intake. All the sessions were performed under supervision of well-trained physical therapists.

Table 1.
Exercise training program

Endurance training	**Low intensity (n = 20)**	**Moderate intensity (n = 19)**
Machines	Treadmill, cycle ergometer, arm ergometer, stepper, cross-trainer, rowing machine	
Intensity	50-80% of VO_{2peak}	
Duration	40-60 minutes	
Frequency	3 times/ week	
Resistance training	**Low intensity (n = 24)**	**Moderate intensity (n = 27)**
Machines	Leg press, dips, pulldown	Leg press, dips, pulldown
Intensity	LB session 1-4: 35% 1RM UB session 1-4: 35% 1RM LB session 5-8: 40% 1RM UB session 5-8: 40% 1RM	LB session 1-4: 65% 1RM UB session 1-4: 55% 1RM LB session 5-8: 70% 1RM UB session 5-8: 60% 1RM
Frequency	LB session 1-4: 3x 22 reps UB session 1-4: 3x 19 reps LB session 5-8: 3x 21 reps UB session 5-7: 3x 18 reps	LB session 1-8: 3x 12 reps UB session 1-8: 3x 12 reps
Rest between sets	1 minute	1 minute

LB = lower body exercise (leg press); UB = upper body exercises (dips, pulldown)

3.4 Data-analysis

Data was analyzed by the statistical software package 'JMP Pro 16'[40]. The continuous baseline data from both groups were compared via an unpaired t-test when they were normally distributed, otherwise a rank sum test was used (Appendix 3). The categorical baseline data was compared using the Pearson's chi-squared test if the requirement was met (Expected value >5), elsewise the Fisher's Exact test was used (Appendix 4). The categories "medications" and "comorbidities" of the baseline characteristics were compared individually. Additionally, these separate medications and comorbidities were clustered into groups and once again compared with one another to detect significant differences.

The means for the primary outcomes were compared between the two intervention groups by calculating the difference between the last and the first observed measurement for every participant. Data regarding the primary outcomes was included only when a measurement for a particular variable was taken for at least two different points in time per participant. If only one measurement was present, the data of the participant for that particular variable was excluded from the statistical analysis. All data was checked for normality, homoscedasticity and independency (Appendix 1). To compare the post-pre intervention changes between both groups, an unpaired t-test was used if all requirements were met, otherwise a rank-sum test was used. The post-pre intervention changes within one group were checked to see if the means within the group significantly differed from zero. All these results were dependent, as the difference between two measurements at two different points in time within the same patient were compared with one another. A paired t-test was used when the data was normally distributed, otherwise a signed-rank test was performed. A more detailed overview of the performed test per group for the within-group analysis can be found in the appendix (Appendix 2). The p-value of significance was set at $p < .05$ and the p-value of highly significant was set at $p < .01$.

4 Results

4.1 Participants

Eighty six HF patients were screened, both men and women with an age of 61.26 ± 11.18. Forty seven of these screened patients were excluded or dropped out of the study due to not being able to train at high intensity, not consenting to the study or because they completed

less than 25 training sessions. After exclusion, data of 39 participants remained with 20 in the LG and 19 in the MG (Figure 2). However, for certain outcome variables the sample size (n) of these groups varies, as data was not always collected for at least two different points in time for every patient. Both groups were homogenous, without any significant difference between the baseline characteristics (Table 2). The baseline characteristics regarding medications (Table 3) and comorbidities (Table 4) were grouped together as well as analyzed separately. Significant differences between both groups were found for the cluster of "Other medications" ($p = .0482$), indicating a significantly higher usage in the MG group. However when the different medications within this group were viewed separately, no significant differences were found. Furthermore, a significant difference was found for the use of "Alpha blocker" ($p = .0471$) towards the MG, but no significant differences were found for the cluster "Blood pressure medications". For the comorbidities, only the cluster of "Operations" showed a significantly higher amount of operations in the LG ($p = .0369$).

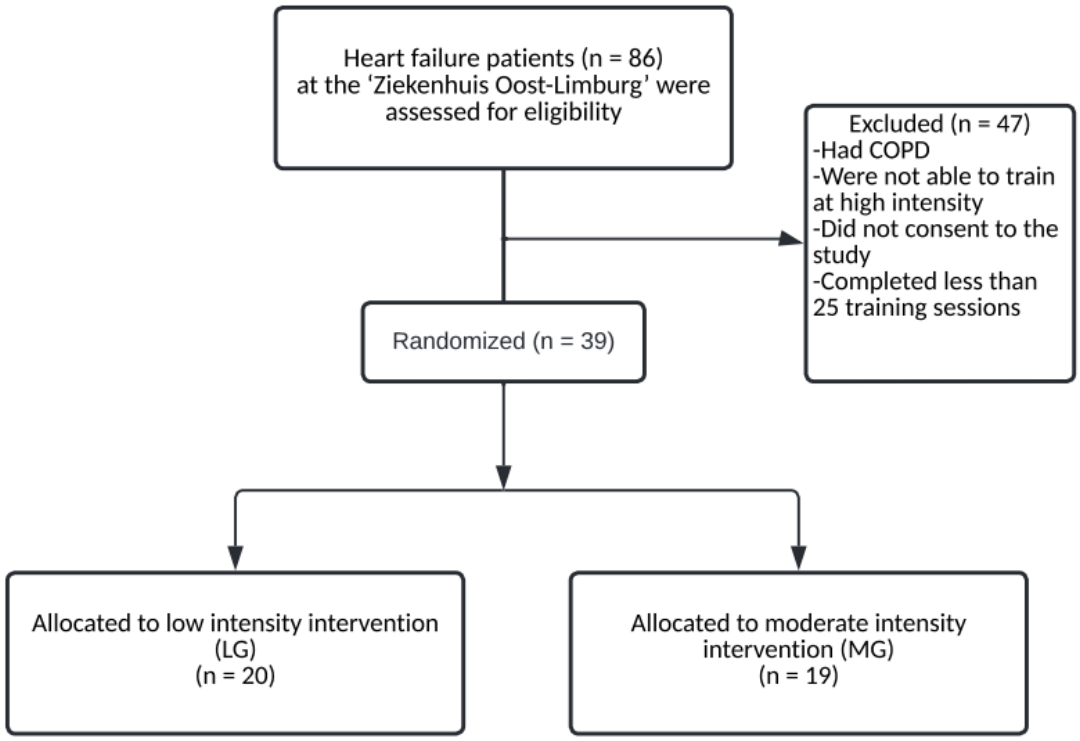

Figure 2 Flowchart of the recruitment process and the included- and excluded participants

Table 2.
Participants' baseline characteristics

	LG (n = 20)	MG (n = 19)	p-value	Amount of participants missing data (n)
Gender (male/female)	16/4	15/4	1.0000	0
Age (years)	59.60 ± 13.26	63.00 ± 8.50	.3495	0
Height (cm)	172.63 ± 8.73	170.5 ± 7.35	.4230	0
Body mass (kg)	84.00 ± 13.07	77.99 ± 14.55	.1833	0
BMI (kg/m^2)	28.17 ± 3.80	26.85 ± 4.92	.3515	0
LVEF (%)	37.69 ± 6.22	35.94 ± 10.34	.5640	6 (4 in LG; 2 in MG)
HFrEF (yes/no)	12/4	10/7	.3245	6 (4 in LG; 2 in MG)
DDF	GR1: 0 GR2: 3 GR3: 0 GR4: 0	GR1: 0 GR2: 2 GR3: 0 GR4: 0	1.0000	34 (17 in LG; 17 in MG)
Smoker (yes/no)	2/18	1/18	1.0000	0
Ex-smoker (yes/no)	10/10	8/11	.6211	0
Arterial hypotension (yes/ no)	12/8	12/7	.8394	0
T2DM (yes/no)	0/19	3/15	.1050	2 (1 in LG; 1 MG)
Dyslipidemia (yes/no)	13/7	13/6	.8208	0
Obesity (yes/no)	6/14	3/16	.4506	0

LG = low-intensity group; MG = moderate-intensity group; BMI = Body Mass Index; LVEF = Left Ventricular Ejection Fraction; T2DM = Type 2 Diabetes Mellitus; HFrEF = Heart Failure with Reduced Ejection Fraction; DDF = Diastolic Dysfunction
Variables are expressed as mean ± standard deviation.

4.2 Difference between low-intensity and moderate intensity training group

Table 5 shows the p-values from the post-pre intervention changes between and within both groups for all primary outcomes. The majority of the results does not show a significant difference ($p < .05$) or a highly significant difference ($p < .01$) between the changes of the two groups. When a significant difference was found, it was mostly the LG that showed these results.

4.2.1 Effects of the intervention on muscle strength

No significant differences were found for the 1RM strength for dips, the leg press or the pulldown between both groups. Nevertheless, within-group analysis found highly significant improvements ($p = < .01$) for all three strength tests in both groups separately (LG and MG). This indicates that, while both interventions resulted in a highly significant improvement in muscle strength, no group has been proven to be significantly superior in increasing this outcome measure.

Table 3.

Participants' baseline characteristics, medications

	LG (n = 20)	MG (n = 19)	Total (n = 39)	p-value
Blood pressure medications (yes/no)	**20/0**	**18/1**	**38/39**	**.4872**
ACE-inhibitor (yes/no)	7/13	10/9	17/39	.2670
Alpha blocker (yes/no)	0/20	4/15	4/39	.0471*
Angiotensin receptor blocker (yes/no)	10/10	6/13	16/39	.2424
Antihypertensive (yes/no)	0/20	1/18	1/39	.4872
Betablocker (yes/no)	19/1	17/2	36/39	.6050
Calcium antagonist (yes/no)	0/20	1/18	1/39	.4872
Diuretic (yes/no)	15/5	11/8	26/39	.2574
Painkillers and anti-inflammatory drugs (yes/no)	**13/7**	**14/5**	**27/39**	**.5570**
Acetylsalicylic acid (yes/no)	9/11	10/9	19/39	.6337
Colchicine (yes/no)	2/18	3/16	5/39	.6614
Corticosteroid (yes/no)	2/18	3/16	5/39	.6614
Non-opioid analgesic (yes/no)	2/18	1/18	3/39	.0000
Opioid (yes/no)	1/19	1/18	2/39	.0000
Spasmolytic (yes/no)	1/19	1/18	2/39	.0000
Sulfasalazine (yes/no)	1/19	0/19	1/39	1.0000
Psychotropic medications (yes/no)	**6/14**	**2/17**	**8/39**	**.1337**
Antipsychotic (yes/no)	1/19	0/19	1/39	1.0000
Non-selective serotonin reuptake inhibitor (yes/no)	2/18	1/18	3/39	1.0000
Selective serotonin reuptake inhibitors (yes/no)	2/18	2/17	4/39	1.0000
Cholesterol-Lowering drugs (yes/no)	**18/2**	**12/7**	**30/39**	**.0648**
Ezetimibe (yes/no)	2/18	2/17	4/39	1.0000
Statin (yes/no)	17/3	14/5	31/39	.4506
Blood sugar regulating drugs (yes/no)	**3/17**	**7/12**	**10/39**	**.1552**
Glucagon (yes/no)	0/20	1/18	1/39	.4827
Hypoglycemic sulfamide (yes/no)	0/20	1/18	1/39	.4872
Insulin (yes/no)	0/20	1/18	1/39	.4827
SGLT2-inhibitor (yes/no)	3/17	7/12	10/39	.1552
Anticoagulants (yes/no)	**14/6**	**11/8**	**25/39**	**.4309**
P2Y12-inhibitor (yes/no)	8/12	8/11	16/39	.8937
Thienopyridine (yes/no)	1/19	2/17	3/39	.6050
Oral anticoagulant (yes/no)	7/13	4/15	11/39	.3333
Arrhythmia drugs (yes/no)	**4/16**	**1/18**	**5/39**	**.3416**
Antiarrhythmic (yes/no)	4/16	1/18	5/39	.3416
Other medications (yes/no)	**11/9**	**16/3**	**27/39**	**.0482***
Antibiotic (yes/no)	0/20	2/17	2/39	.2308
Anticholinergic (yes/no)	0/20	2/17	2/39	.2308
Anti-emetic (yes/no)	1/19	1/18	2/39	1.0000
Anti-epileptic (yes/no)	1/19	0/19	1/39	1.0000
Aromatase inhibitor (yes/no)	0/20	1/18	1/39	.4872
Benzodiazepine agonist (yes/no)	1/19	3/16	4/39	.3416
Betahistine (yes/no)	0/20	1/18	1/39	.4872
Contraceptive (yes/no)	0/20	1/18	1/39	.4872
Glycoside (yes/no)	1/19	1/18	2/39	1.0000
LABA (yes/no)	0/20	1/18	1/39	.4872
Laxative (yes/no)	0/20	1/18	1/39	.4872
Mucolytic (yes/no)	0/20	1/18	1/39	.4872
Immunosuppressor (yes/no)	1/19	3/16	4/39	.3416
Phosphodiesterase-5 inhibitor (yes/no)	0/20	2/17	2/39	.2308
Proton pump inhibitor (yes/no)	9/11	9/10	18/39	.8821
SABA (yes/no)	0/20	1/18	1/39	.4872
Thyromimetic (yes/no)	3/17	0/19	3/39	.2308
Xanthine oxidase inhibitor (yes/no)	4/16	1/18	5/39	.3416

LG = low-intensity group; MG = moderate-intensity group; ACE-inhibitor = Angiotensin-converting enzyme inhibitor; LABA = Long-Acting Beta Agonist; SABA = Short-Acting Beta Agonist

*p-value < .05

Table 4.
Participants' baseline characteristics, comorbidities

	LG (*n* = 20)	MG (*n* = 19)	Total (n)	p-value
Heart and blood vessel conditions (yes/no)	**3/17**	**1/18**	**4/39**	**.6050**
Acute pulmonary embolism (yes/no)	20/0	1/18	1/39	.4872
DVT (yes/no)	1/19	0/19	1/39	1.0000
PAD (yes/no)	1/19	0/19	1/39	1.0000
Valve disease (yes/no)	1/19	0/19	1/39	1.0000
Respiratory conditions (yes/no)	**7/13**	**7/12**	**14/39**	**.9046**
Allergic asthma (yes/no)	0/20	1/18	1/39	.4872
Asthma (yes/no)	1/19	1/18	2/37	1.0000
COPD (yes/no)	0/20	1/18	1/39	.4872
OSA (yes/no)	6/14	3/16	9/39	.4506
Pneumonia (yes/no)	0/20	1/18	1/39	.4872
Internal diseases (yes/no)	**6/14**	**11/8**	**17/39**	**.0791**
Chronic glomerulonephritis (yes/no)	0/20	1/18	1/39	.4872
Chronic renal insufficiency (yes/no)	1/19	2/17	3/19	.6050
Gastro-enteritis (yes/no)	0/20	2/17	2/39	.2308
Gout (yes/no)	2/18	1/18	3/39	1.0000
Hypertensive encephalopathy (yes/no)	0/20	1/18	1/39	.4872
Mechanical ileus (yes/no)	0/20	1/18	1/39	.4872
Nephrolithiasis (yes/no)	1/19	1/18	2/39	1.0000
Esophagitis (yes/no)	0/20	1/18	1/39	.4872
Polymyalgia rheumatica (yes/no)	1/19	0/19	1/39	1.0000
Stomach bleeding (yes/no)	0/20	1/18	1/39	.4872
T1DM (yes/no)	0/20	1/18	1/39	.4872
Ureteral stone (yes/no)	0/20	1/18	1/39	.4872
Urosepsis with pericarditis (yes/no)	1/19	0/19	1/39	1.0000
Operations (yes/no)	**13/7**	**6/13**	**19/39**	**.0369***
Ankle surgery (yes/no)	0/20	1/18	1/39	.4872
Appendectomy (yes/no)	2/18	1/18	16	1.0000
Back operation after accident (yes/no)	1/19	0/19	1/39	1.0000
CABG (yes/no)	1/19	0/19	1/39	1.0000
Cholecystectomy (yes/no)	2/18	1/18	3/39	1.0000
Kidney transplant (yes/no)	0/20	1/18	1/39	.4872
Knee surgery (yes/no)	1/19	0/19	1/39	1.0000
Mastectomy (yes/no)	0/20	1/18	1/39	.4872
Meniscus operation (yes/no)	1/19	0/19	1/39	1.0000
Nose Surgery (yes/no)	1/19	0/19	1/39	1.0000
PTCA (yes/no)	1/19	0/19	1/39	1.0000
Tummy tuck (yes/no)	1/19	0/19	1/39	1.0000
Varicectomy (yes/no)	1/19	0/19	1/39	1.0000
Vasectomy (yes/no)	1/19	0/19	1/39	1.0000
Total hip prothesis (yes/no)	0/20	1/18	1/39	.4872
Cancers (yes/no)	**4/16**	**3/16**	**7/39**	**1.0000**
Adenocarcinoma (yes/no)	1/19	0/19	1/39	1.0000
Bladder carcinoma (yes/no)	1/19	0/19	1/39	1.0000
Breast carcinoma (yes/no)	1/19	1/18	2/39	1.0000
Carcinoid lung tumor (yes/no)	1/19	1/18	2/37	1.0000
Colon adenoma (yes/no)	0/20	1/18	1/39	.4872
Prostate neoplasm (yes/no)	1/19	0/19	1/39	1.0000

LG= low-intensity group; MG = moderate-intensity group; OSA = Obstructive Sleep Apnea; T1DM = Type 1 Diabetes Mellitus; CABG = Coronary Artery Bypass Grafting; PTCA = Percutaneous Transluminal Coronary Angioplasty; PAD = Peripheral Artery Disease; COPD = Chronic Pulmonary Obstructive Disease; DVT = Deep Vein Thrombosis; MSK = Musculoskeletal
*p-value < .05

Table 4.
Continued

Neurological conditions (yes/no)	**2/18**	**2/17**	**4/39**	**1.0000**
Carpal tunnel (yes/no)	1/19	0/19	1/39	1.0000
Facial paralysis (yes/no)	1/19	0/19	1/39	1.0000
Lumbar herniation (yes/no)	0/20	1/18	1/39	.4872
Sliding hernia (yes/no)	0/20	1/18	1/39	.4872
Other (skin conditions, MSK conditions, mental conditions, trauma,…) (yes/no)	**7/13**	**9/10**	**16/39**	**.4325**
Cervical facet arthritis (yes/no)	0/20	1/18	1/39	.4872
Depression (yes/no)	1/19	1/18	2/39	1.0000
Empty sella (yes/no)	1/19	0/19	1/39	1.0000
Erysipelas (yes/no)	1/19	0/19	1/39	1.0000
Fibromyalgia (yes/no)	1/19	0/19	1/39	1.0000
Gynecomastia (yes/no)	1/19	1/18	2/39	1.0000
Infrapatellar bursitis (yes/no)	0/20	1/18	1/39	.4872
Navel rupture (yes/no)	1/19	0/19	1/39	1.0000
Prostate hypertrophy (yes/no)	0/20	2/17	2/39	.2308
Psoriasis (yes/no)	1/19	0/19	1/39	1.0000
Rotator cuff disorder (yes/no)	0/20	1/18	1/39	.4872
Rotator cuff tendinopathy (yes/no)	0/20	1/18	1/39	.4872
Spinal stenosis (yes/no)	0/20	1/18	1/39	.4872
No comorbidities (yes/no)	**4/16**	**5/14**	**9/39**	**.7164**

LG= low-intensity group; MG = moderate-intensity group; OSA = Obstructive Sleep Apnea; T1DM = Type 1 Diabetes Mellitus; CABG = Coronary Artery Bypass Grafting; PTCA = Percutaneous Transluminal Coronary Angioplasty; PAD = Peripheral Artery Disease; COPD = Chronic Pulmonary Obstructive Disease; DVT = Deep Vein Thrombosis; MSK = Musculoskeletal
*p-value < .05

4.2.2 Effects of the intervention on CPET parameters

For the CPET parameters, a significant between-group difference was found for HR at the anaerobic threshold (AT2) (p = .0397). In addition, the HRmax showed a significant difference between both groups (p = .0320) which can be attributed to the highly significant improvements found in HR_{max} (p = .0030) in the LG, but not in the MG (p = .8651). Data implies that the LG is superior to the MG in improving those two variables.. Variables that showed highly significant improvements within both the LG and MG were the VO_{2max} (p = < .0001 in LG; p = .0011 in MG) and the wattage (W) (p = < .0001; p = .0018). Lastly, the LG had significant improvements for the W at the aerobic threshold (AT1) (p = .0168) and the HR at the AT2 (p = .0346). These results once again suggest that the LG is superior to the MG in improving certain CPET parameters.

4.2.3 Effects of the intervention on 6MWT parameters

Aside from the HR_{post} (p = .0067), no other significant between-group differences were found for the 6MWT. This difference was due to a significant increase in the LG for HR_{post} (M = 11.61 ± 17.79; p = .0260), while the MG showed a decrease in HR_{post} (M = -3.88 ± 12.61; p = .2226). Both groups had highly significant improvements on the walking distance with an improvement of 47.05 ± 38.78 meters (p = < .0001) in the LG and 57.83 ± 56.64 meters (p =

.0005) in the MG. This improvement was clinically important as it has been proven that the minimal clinically important difference (MCID) is 36-45 m over a period of 6-12 months in chronic HF patients and the means of both groups surpassed this[41,48]. Nevertheless, no significant difference was observed between the groups. Finally, for the $BORG_{pre}$ dyspnea, a significant improvement was found in the LG (p = .0273). However, a p-value was not calculated for the between-group difference as the requirements were not met. The LG was not normally distributed using the Goodness-of-Fit test (LG: p = .0033; MG: p = .5135) and the variances were not equally distributed based on the Brown-Forsythe test (p = .0356).

4.2.4 Effects of the intervention on QoL

Lastly, the MLHFQ showed no significant differences between the groups for the different domains of the questionnaire nor the total score. For the within-group analysis on the other hand, significant improvements were found on the psychological-emotional domain (p = .0214) and on the total score (p = 0.126) in the LG. The socio-economic domain (p = .0059) also demonstrated a highly significant improvement. No significant improvements were found in the MG for this outcome measure. Based on the category scores, in the LG five patients had a “Good QoL” at baseline, whereas seven patients had a “Moderate QoL” and two had a “Poor QoL”. After the intervention, this distribution changed to twelve, two and zero for the respective categories. Seven out of fourteen participants stayed in the same category, whereas five of them improved by one category and two participants improved by two categories, going from a “Poor QoL” to a “Good QoL”. For the MG, the baseline distribution was eleven, one and two for the categories “Good QoL”, “Moderate QoL” and “Poor QoL” respectively. After the intervention, this distribution changed to ten, two and three respectively. Two participants in this intervention dropped down one category, eleven of the fourteen stayed in the same category and one of the participants improved by one category.

Table 5.

Primary outcome means, changes and p-values

	Group	N	First measurement	Last measurement	Change (Δ last-first)	p-value	Between-group (p-value)
1RM strength							
Dips	LG	20	76.45 ± 18.97	95.2 ± 35.74	18.75 ± 25.58	.0001**	.6190
	MG	18	62.56 ± 19.22	76.83 ± 27.25	14.28 ± 22.26	.0042**	
Leg press	LG	20	153.25 ± 63.77	194.1 ± 80.49	40.85 ± 59.87	.0002**	.5624
	MG	17	134.18 ± 79.4	182.05 ± 162.39	47.88 ± 89.07	.0002**	
Pull down	LG	20	67.15 ± 16.31	73.80 ± 17.74	6.65 ± 5.36	< .0001**	.3403
	MG	18	56.34 ± 16.26	65.44 ± 17.60	9.11 ± 7.50	< .0001**	
CPET							
VO_{2max}	LG	20	16.97 ± 4.87	20.61 ± 5.78	3.65 ± 2.65	< .0001**	.4930
(ml/kgmin)	MG	19	19.08 ± 8.59	22.05 ± 7.36	2.97 ± 3.34	.0011*	
Wattage (Watt)	LG	20	121.2 ± 33.89	144.35 ± 42.52	23.15 ± 16.94	< .0001**	1.000
	MG	19	116.16 ± 51.23	136.84 ± 44.25	20.68 ± 24.62	.0018*	
AT1 (HR)	LG	17	87.18 ± 12.58	93.47 ± 19.76	6.29 ± 14.09	.2106	.1080
	MG	17	94.24 ± 16.12	92.18 ± 17.36	-2.06 ± 11.88	.4851	
AT1 (W)	LG	17	68.18 ± 15.21	81.00 ± 26.31	12.82 ± 19.81	.0168*	.3587
	MG	17	64.47 ± 18.32	70.59 ± 27.36	6.12 ± 22.12	.2709	
AT2 (HR)	LG	12	106.01 ± 19.36	129.25 ± 33.60	23.17 ± 33.29	.0346*	.0397*
	MG	8	109.38 ± 21.04	105.13 ± 14.35	-4.25 ± 12.05	.3515	
AT2 (W)	LG	12	117.67 ± 30.81	124.33 ± 36.78	6.67 ± 30.97	.6719	.6992
	MG	8	120.25 ± 39.02	119.75 ± 38.60	-0.5 ± 26.80	.9594	
HR_{max}	LG	18	109.39 ± 19.50	120.83 ± 23.96	11.44 ± 14.02	.0030**	.0320*
	MG	18	121.89 ± 24.80	122.5 ± 21.29	0.61 ± 15.03	.8651	
6MWT							
HR_{pre}	LG	18	65.33 ± 12.43	67.61 ± 13.93	2.28 ± 17.17	.7524	.1977
	MG	17	74.12 ± 18.73	69.65 ± 10.04	-4.47 ± 17.57	.3098	
HR_{post}	LG	18	76.94 ± 16.13	88.56 ± 16.85	11.61 ± 17.79	.0260*	.0067**
	MG	17	91.29 ± 20.16	87.41 ± 21.69	-3.88 ± 12.61	.2226	
$BORG_{pre}$ LE	LG	19	1.79 ± 1.62	1.58 ± 1.26	-0.21 ± 1.58	.8811	.7296
	MG	17	2.76 ± 1.64	2.71 ± 1.61	-0.06 ± 1.30	.8541	
$BORG_{post}$ LE	LG	19	2.47 ± 2.12	3.21 ± 1.99	0.74 ± 2.00	.1249	.3541
	MG	17	3.53 ± 1.97	3.82 ± 1.98	0.29 ± 1.61	.6833	
$BORG_{pre}$ Dys	LG	19	1.53 ± 1.22	1.00 ± 1.11	-0.53 ± 0.84	.0273*	/
	MG	17	2.41 ± 1.91	2.18 ± 1.59	-0.24 ± 1.68	.5712	
$BORG_{post}$ Dys	LG	19	2.74 ± 1.66	2.68 ± 1.60	-0.05 ± 1.27	.8585	.7691
	MG	17	3.76 ± 1.86	3.59 ± 2.12	-0.18 ± 1.24	.5645	
Distance	LG	20	480.85 ± 80.89	527.90 ± 83.08	47.05 ± 38.78	< .0001**	.4941
	MG	18	482.44 ± 85.62	540.28 ± 66.16	57.83 ± 56.64	.0005*	
$Saturation_{pre}$	LG	18	97.44 ± 1.38	97.89 ± 1.41	0.44 ± 1.50	.1777	.0537
	MG	18	98.22 ± 0.94	97.83 ± 1.38	-0.39 ± 1.54	.2987	
$Saturation_{post}$	LG	18	97.83 ± 1.15	97.61 ± 1.29	-0.22 ± 1.31	.4810	.7313
	MG	18	97.22 ± 1.96	96.89 ± 2.11	-0.33 ± 1.41	.3770	
MLHFQ							
Physical	LG	14	11.57 ± 8.83	6.14 ± 3.03	-5.43 ± 9.67	.0557	.1623
Domain	MG	14	9.57 ± 10.03	8.57 ± 10.12	-1.00 ± 6.26	.5605	
Socio-economic	LG	14	9.07 ± 7.11	3.21 ± 3.02	-5.86 ± 6.67	.0059**	.0923
Domain	MG	14	6.43 ± 8.14	4.57 ± 5.89	-1.86 ± 5.38	.2187	
Psychological-emotional Domain	LG	14	6.86 ± 4.44	3.21 ± 4.21	-3.64 ± 5.21	.0214*	.1093
	MG	14	4.93 ± 7.42	4.57 ± 5.96	-0.36 ± 5.27	.8038	
Total score	LG	14	27.50 ± 17.31	12.57 ± 8.43	-14.93 ± 19.31	.0126*	.0977
	MG	14	20.93 ± 23.06	17.71 ± 21.09	-3.21 ± 12.62	.5304	

LG = low-intensity group; MG = moderate intensity group; CPET = cardiopulmonary exercise testing; VO_{2max} = maximal oxygen consumption; AT1 = aerobic threshold; AT2 = anaerobic threshold; HR = heart rate; W = wattage; 6MWT = 6 minute walk test; pre = before the test; post = after the test: BORG LE = BORG leg effort; BORG Dys = BORG dyspnea; MLHFQ = Minnesota Living with Heart Failure Questionnaire

Values are expressed as mean ± standard deviation.

*p-value < .05

**p-value < .01

5 Discussion

Before the 90's, the application of exercise interventions was not recommended for HF patients because there was simply not enough evidence to support the safety of these interventions on the myocardium. Nowadays, a great amount of research exists that support the safety and the benefits of exercise interventions on physiological, musculoskeletal as well as psychological domains (such as QoL) in chronic HF patients[13,15,18,45,60,61], Heart Failure patients with Preserved Ejection Fraction (HFpEF)[55,56,57,58] and Heart Failure patients with a Reduced Ejection Fraction (HFrEF)[62]. In addition, exercise therapy has been shown to be a cost-effective intervention for this population[59]. While the mode, frequency, duration and intensity of the exercise training play a critical role in maintaining safety for HF patients, medical status (e.g. medication, comorbidities, contraindications) also needs to be accounted for[45].

Overall, the aim of this study was to improve the cardiovascular health in the population of interest. Moreover, cardiorespiratory fitness is clearly linked to prognosis in HF[65]. Studies indicate that cardiovascular health is most accurately quantified in an increase in VO_{2peak}[19]. However, not only VO_{2peak} is one of the most important clinical measures in HF patients with links to cardiovascular mortality[15,42,43,73], as research has shown that both VO_{2peak} and the 6MWT are potential predictors of mortality and HRQoL in HF patients[63]. While this study used VO_{2max} as one of the most important primary outcome measures, both VO_{2max} and VO_{2peak} are often used interchangeably in literature[68]. VO_{2max} reflects the highest oxygen consumption that is attainable for the entire body. This is when a plateau is reached and oxygen uptake can no longer increase. VO_{2peak}, on the other hand, is more specific and can be applied to one specific muscle (for example the quadriceps during a squat exercise). In addition, VO_{2peak} can be measured by a submaximal exercise test, when the plateau in oxygen uptake is never achieved. To measure the VO_{2max}, a maximal exercise test is conducted. When the entire body is exercised, VO_{2peak} and VO_{2max} are typically equal[66,67,68].

Hence, improvements in either of these variables can produce comparable clinical effects. In this discussion these terms will be used interchangeably, though literature most commonly uses VO_{2peak} instead of VO_{2max} as an outcome measure. The VO_{2peak} is likely used more often because verifiable evidence is necessary to label the plateau as the VO_{2max}. This is because the plateau is reached at a maximum effort that could not rise any further. If a maximum effort is not reached, this value is marked as the VO_{2peak}[68]. This maximum effort was accounted for in

this study by achieving a RER ≥1.10, as well as measuring subjective effort as described more detailed in the “Methods'' section.

When comparing the superiority of the type of exercise intervention in increasing VO_{2peak}, the meta-analysis from Jewiss, Ostman, and Smart 2016[19] showed no significant difference for increase in VO_{2peak} between aerobic training and combined aerobic and resistance training. Resistance training exhibited superior improvements for VO_{2peak} only when this was compared to a sedentary control group. Similar results were found for HFrEF patients, as Gomes-Neto et al. 2019[62] showed no significant improvements in the combined intervention group compared to the aerobic intervention group for VO_{2peak}. However, significant improvements were found for the combined intervention group as opposed to a control group[62]. In this study, both the LG and the MG showed highly significant improvements for the previously mentioned variable. Studies indicate that this change is mainly attributed to aerobic training[19,54]. Nevertheless, Giuliano, Karahalios, Neil, Allen, and Levinger 2017[15] showed the opposite and Boulmpu et al. 2021[55] found no significant difference between aerobic and resistance training in increasing VO_{2peak} in patients with HFpEF. Thus, whether aerobic or the resistance training plays a significantly more important role in increasing the VO_{2peak}, and if a combined intervention results in the greatest improvements in VO_{2peak}, remains up for debate.

Another parameter that reflects the physical functional capacity is the distance covered during the 6MWT[48]. Significant improvements were found for both groups, though Cahalin et al. 2013[50] states that the distance covered during this test mainly provides prognostic information in patients with more advanced HF[69]. In result, this strengthens the findings of this study, as a larger proportion of the included participants had a reduced ejection fraction (LVEF < 40%). More importantly, this improvement was clinically important in both groups, as an improvement of at least 36-45m is considered as the MCID for this test[41,48].

However, research suggests working with heart rate reserve (HRR). This is because a decrease in heart rate after exercise or a CPET has been shown to be a valuable prognosticator in patients with HF, favoring a higher HRR[70,71,72]. Furthermore, Cahalin et al. 2013a[50] and Cahalin et al. 2013b[51] show a very strong correlation between the HRR after both the CPET and the 6MWT. Consequently, 6MWT HRR could be used prognostically in future work. These findings are assumed to be equal for patients with HFpEF and HFrEF[50,51]. While the HRR was not measured in this study, the HR_{post} and HR_{pre} were and the HRR could have easily been

calculated by subtracting the former from the latter. In this study, the HR_{post} in the LG was the only variable regarding HR for the 6MWT to provide a significant improvement. This implies that an increase in cardiac output, and in return, a higher exercise capacity was achieved by the training[52]. Even though the HRR was not calculated in this study, it can be assumed that the HRR would have been increased in this group due to this change. In the MG a decrease was found for both the HR_{post} and the HR_{pre}, but these changes were not significant. Even so, research has shown that HR, and more specifically, resting HR or HR_{pre} is an important variable that should be measured to assess cardiovascular risk, mortality and morbidity[82,83,84]. A lower heart rate indicates a decreased cardiovascular risk and repeated measures can provide valuable prognostic information[83,84]. This decrease in HR in the MG might have been due to a significantly higher usage of alpha blockers in the MG (LG: n = 0; MG: n = 4). While the main function of this medication is to reduce blood pressure, a possible side effect is causing an increase in heart rate. Thus, it is possible that the exercise intervention somehow counteracted this side effect. Although unlikely, the discrepancy in change of heart rate between both groups could possibly be accredited to a learning effect. Hamilton and Haennel (2000)[53] have stated that the results on the 6MWT improved by 6% over three tests. A larger amount of data exists in the LG for this test (LG: n = 10, MG: n = 7), thus it is possible that a larger number of patients in this group performed the test three times instead of only twice. While the study is still ongoing, no significant differences were found in the total sessions performed between the two groups (LG = 37.74; MG = 35.84).

Contrary to our results, literature recommends training at a moderate intensity of 60-80% of 1RM in combination with aerobic training to improve cardiovascular endurance, hypertension, hyperlipidemia, and the capacity to perform activities of daily living in chronic HF patients[45,46,47]. Despite the fact that both intervention groups trained at different levels of intensity during the resistance training, no significant differences were found between the two groups for the 1RM tests. Thus, it is implied that the intensity of the resistance training is an insignificant factor for improving muscle strength in this population. The volume at which this resistance training is performed, might be the predominant factor in increasing muscle strength for these patients, as an equal volume was always accounted for in both groups. Nonetheless, both groups had significant within-group improvements. This remains valuable

due to the strong correlation exists between 1RM test strength for the upper limb and the VO_{2peak} in patients with CHF[64].

At last, significant improvements were observed in the LG for the QoL, while there were none in the MG. These improvements in the LG also were clinically important for both the emotional domain as well as the total score, as the MCID for the MLHFQ has been shown to be 3.59 (2.52-4.66) and 19.14 (16.04-22.24) for the respective scores[89]. The change obtained in the LG for the emotional domain was 3.64 and 14.93 for the total score. All baseline scores on the MLHFQ were higher in the LG than in the MG. In addition, the distribution in the categories was significantly different between both groups, with a higher number of participants in the category of "Good QoL" in the MG group. A possible cause for this might have been due to a significantly higher amount of operations in the LG (LG: n = 13; MG: n = 6). These operations could have reduced the baseline QoL of these patients, whereafter the exercise intervention resulted in an improved QoL, based on research in HF patients[13,15,18,45,55,56,57,58,60,61,62]. Moreover, postoperative exercise has shown to significantly improve QoL in patients undergoing a pulmonary resection88. Another possible reason why QoL only increased in the LG could be attributed to the significant improvements observed for the HR at the AT2, the W at AT1, the HRmax and the HR_{post}, which were not present in the MG.

5.1 Strengths of the study

As mentioned earlier, the increase in VO_{2max} is one of the most important factors regarding improvements in cardiovascular healt[15,42,43,45]. Literature states that the best way to improve this, is to train three to five times per week for 15 to 60 minutes at an intensity of 50-80% of the VO_{2max}[45]. This was performed identically in this study with an additional gradual build-up of this intensity, starting at the lower end of this range, which was also recommended in the literature[45]. Intermediate measurements were taken for the CPET and 6MWT after 20 sessions and for the 1RM strength test every three weeks. This ensured that the patients always trained at the same intensity when progress in muscle strength or VO_{2max} was achieved throughout the intervention. Despite that the resistance training was performed at different intensities for both groups, an equal volume was always maintained between both groups trained due to the difference in the amount of repetitions performed.

Because of the use of a blocked randomized controlled trial, both groups had similar distributions for age and gender. It is important that this was accounted for since significant

differences in strength and endurance for men and women as well as different ages are known to exist. Men have been shown to have greater strength than women[76,77]. In addition, increased age causes a decline in muscle quality as well as strength[78,80,81]. This decrease in muscle strength can range from 16.6% all the way to up to 40.9% between people younger than 40 and older than 40[79]. Moreover, the use of a blocked randomization reduces the risk of having a treatment imbalance as both groups were equal in size[49,86]. Nevertheless, this type of randomization does cause a larger chance of bias when assessing the treatment effects, especially in unmasked trials[86]. This is due to an increase in the predictability of the allocation process in unmasked trials and for small sample sizes[49]. Though, in this study, randomization was performed as a block, rather than individually. In result, selection bias was eliminated even though the trial was unmasked[49]. Furthermore, blinding is highly recommended in open-label studies to reduce bias. For example, patients may be more optimistic when assigned to an experimental treatment and the opposite can occur in the control group, which could influence the results[91]. Even so, both groups received an intervention in this study. Therefore, an overestimation might have occurred in both treatment groups. Finally, a large number of the participants of this study were patients with a HFrEF. This is relevant because there is less available research regarding this population and "healthier" HF patients are more frequently investigated.

5.2 Limitations of the study

This study contains a lot of limitations. The most noteworthy limitation is that a lot of data was missing for the different primary outcomes. For each patient a baseline measurement was to be taken for the 1RM strength tests, the CPET, the 6MWT and the MLHFQ. However, for many patients this data was not obtained. This was a consequence of a lack of execution or reporting of these measurements. For the 1RM test, certain patients received a pacemaker throughout the intervention. This prohibited any upper limb exercises for a period of six weeks, as advised by their physician, disabling them to perform the dip or pulldown exercise[87].

During the testing of the CPET, the equipment did not function three times, which resulted in the inability to perform the test. On the MLHFQ, several data was absent because one question was not filled in. In consequence, this affected the total results and the data had to be excluded for these particular patients, as it would not be a correct representation of the

total score. A solution would have been to conduct the questionnaire digitally, so the patient would not been able to submit the questionnaire before answering every question.

Further, the first executed measurement was always used to calculate the change before and after the intervention (post-pre comparison). This led to a difference of the training effect of minimally 6 weeks between patients. Similarly, the last measurement (after 15 weeks) was not always completed yet, because the study currently is still ongoing and many patients have yet to finish the entire rehabilitation program. Thus, "Last observation carried forward" (LOCF) was often performed. LOFC produces a biased estimate of the treatment effect because it presumes no changes were made for the specific outcome measure since the last measurement[74]. Consequently, the final measurement used to calculate the change before and after the intervention also differed greatly from patient to patient. Some individuals had completed 45 sessions, while others had completed no more than 20. In addition, some patients were not present at their intermediate measurement. In return, the training schedule for these individuals was not recalculated to the correct intensities of VO_{2max} (50-80% VO_{2max}) or 1RM ranges (LG: 35-40% 1RM and MG: 55-70% 1RM).

All strength exercises were performed at an individualized weight. which was calculated from the 1RM test for each patient and further based on the intervention group. However, certain patients reached the maximum available weight on the given strength machine, particularly for the leg press. When this occurred, the patient was asked to perform as many repetitions as possible for this maximum weight. The amount of repetitions performed on this weight was then used in the formula from Brzicky et al. 1993[31], just like all the other 1RM strength calculations. Yet, it must be noted that when the amount of repetitions exceeds that of three, an overestimation of the 1RM strength is perceived when using the aforementioned formula[75]. Even when this estimation was correct, it was possible that some patients had to surpass the maximum weight that was available on the machines and therefore trained under their required intensity level. In addition, the BORG scale that was admitted to assess the leg effort and dyspnea, was color coded. This has an influence on the grading of the scale and possibly caused a systematic bias with an over- or underestimation of the results[90]. Finally, it was difficult to check for adherence of the participants to the given intensity levels. Some patients changed their weights manually when they felt like they wanted an easier day or to train more intensively. This caused a non-adherence to the imposed intensity level of the given

intervention which possibly influenced the results. All tests were conducted by unmasked investigators which could also lead to a detection bias and thus to a biased interpretation of the results.

6 Conclusion

Based on the results of this study, the LG obtained slightly superior results than the MG. Nevertheless, the VO_{2max} is considered to be one of the most clinically important outcome measures for cardiovascular health. Both intervention groups showed similar improvements for this variable. Thus, this study indicates that a combined aerobic and resistance training intervention should be included in the treatment of patients with HF. Nevertheless, a consensus has yet to be found regarding the intensity at which the resistance training should be performed to improve cardiovascular health in these patients. Further research is necessary to determine the most optimal exercise modality and intensity level for the population of interest due to the small sample size and missing data in this study.

7 Referenties

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8 Appendix

Appendix 1.
Requirements statistical analysis between groups

	Independency	Normality LG	Normality MG	Homo/hetero	Test	p-value
1RM strength						
Dips	Independent	Abnormal	Abnormal	Homo	Rank-sum test	.6190
Leg press	Independent	Abnormal	Abnormal	Homo	Rank-sum test	.5624
Pull down	Independent	Abnormal	Normal	Homo	Rank-sum test	.3403
CPET						
VO_{2max}	Independent	Normal	Normal	Homo	Unpaired t-test	.4930
Wattage	Independent	Abnormal	Normal	Homo	Rank-sum test	1.000
AT1 (HR)	Independent	Abnormal	Normal	Homo	Rank sum test	.1080
AT1 (W)	Independent	Normal	Normal	Homo	Unpaired t-test	.3587
AT2 (HR)	Independent	Normal	Normal	Homo	Unpaired t-test	.0397*
AT2 (W)	Independent	Abnormal	Normal	Homo	Rank sum test	.6992
HR_{max}	Independent	Normal	Normal	Homo	Unpaired t-test	.0320*
6MWT						
HR_{pre}	Independent	Abnormal	Normal	Homo	Rank sum test	.1977
HR_{post}	Independent	Abnormal	Normal	Homo	Rank sum test	.0067**
$BORG_{pre}$ LE	Independent	Abnormal	Normal	Homo	Rank sum test	.7296
$BORG_{post}$ LE	Independent	Normal	Abnormal	Homo	Rank sum test	.3541
$BORG_{pre}$ Dys	Independent	Abnormal	Normal	Hetero	/	/
$BORG_{post}$ Dys	Independent	Normal	Normal	Homo	Unpaired t-test	.7691
Distance	Independent	Normal	Normal	Homo	Unpaired t-test	.4941
$Saturation_{pre}$	Independent	Abnormal	Normal	Homo	Rank-sum test	.0537
$Saturation_{post}$	Independent	Normal	Abnormal	Homo	Rank-sum test	.7313
MLHFQ						
Physical Domain	Independent	Normal	Normal	Homo	Unpaired t-test	.1623
Socio-economic Domain	Independent	Normal	Normal	Homo	Unpaired t-test	.0923
Psychological-emotional Domain	Independent	Normal	Normal	Homo	Unpaired t-test	.1093
Total score	Independent	Normal	Abnormal	Homo	Rank sum test	.0977

LG = low-intensity group; MG = moderate intensity group; CPET = cardiopulmonary exercise testing; VO_{2max} = maximal oxygen consumption; AT1 = aerobic threshold; AT2 = anaerobic threshold; HR = heart rate; W = wattage; 6MWT = 6 minute walk test; pre = before the test; post = after the test: BORG LE = BORG leg effort; BORG Dys = BORG dyspnea; MLHFQ = Minnesota Living with Heart Failure Questionnaire
*p-value < .05
**p-value < .01

Appendix 2.

Requirements statistical analysis within groups

	Independency	Normality LG	Test LG	p-value LG	Normality MG	Test MG	p-value MG
1RM strength							
Dips	Dependent	Abnormal	Signed-rank test	.0001**	Abnormal	Signed-rank test	.0042**
Leg press	Dependent	Abnormal	Signed-rank test	.0002**	Abnormal	Signed-rank test	.0002**
Pull down	Dependent	Abnormal	Signed-rank test	< .0001**	Normal	Paired t-test	< .0001**
CPET							
VO_{2max}	Dependent	Normal	Paired t-test	< .0001**	Normal	Paired t-test	.0011**
Wattage	Dependent	Abnormal	Signed-rank test	< .0001**	Normal	Paired t-test	.0018*
AT1 (HR)	Dependent	Abnormal	Signed-rank test	.2106	Normal	Paired t-test	.4851
AT1 (W)	Dependent	Normal	Paired t-test	.0168*	Normal	Paired t-test	.2709
AT2 (HR)	Dependent	Normal	Paired t-test	.0346*	Normal	Paired t-test	.3515
AT2 (W)	Dependent	Abnormal	Signed rank test	.6719	Normal	Paired t-test	.9594
HR_{max}	Dependent	Normal	Paired t-test	.0030**	Normal	Paired t-test	.8651
6MWT							
HR_{pre}	Dependent	Abnormal	Signed rank test	.7524	Normal	Paired t-test	.3098
HR_{post}	Dependent	Abnormal	Signed rank test	.0260*	Normal	Paired t-test	.2226
$BORG_{pre}$ LE	Dependent	Abnormal	Signed rank test	.8811	Normal	Paired t-test	.8541
$BORG_{post}$ LE	Dependent	Normal	Paired t-test	.1249	Abnormal	Signed rank test	.6833
$BORG_{pre}$ Dys	Dependent	Abnormal	Signed rank test	.0273*	Normal	Paired t-test	.5712
$BORG_{post}$ Dys	Dependent	Normal	Paired t-test	.8585	Normal	Paired t-test	.5645
Distance	Dependent	Normal	Paired t-test	< .0001**	Normal	Paired t-test	.0005**
$Saturation_{pre}$	Dependent	Abnormal	Signed rank test	.1777	Normal	Paired t-test	.2987
$Saturation_{post}$	Dependent	Normal	Paired t-test	.4810	Abnormal	Signed rank test	.3770
MLHFQ							
Physical Domain	Dependent	Normal	Paired t-test	.0557	Normal	Paired t-test	.5605
Socio-economic Domain	Dependent	Normal	Paired t-test	.0059**	Normal	Paired t-test	.2187
Psychological-emotional Domain	Dependent	Normal	Paired t-test	.0214*	Normal	Paired t-test	.8038
Total score	Dependent	Normal	Paired t-test	.0126*	Abnormal	Signed rank test	.5304

LG = low-intensity group; MG = moderate intensity group; CPET = cardiopulmonary exercise testing; VO_{2max} = maximal oxygen consumption; AT1 = aerobic threshold; AT2 = anaerobic threshold; HR = heart rate; W = wattage; 6MWT = 6 minute walk test; pre = before the test; post = after the test; BORG LE = BORG leg effort; BORG Dys = BORG dyspnea; MLHFQ = Minnesota Living with Heart Failure Questionnaire

*p-value < .05

**p-value < .01

Appendix 3.

Requirements statistical analysis baseline characteristics (continuous)

	Independency	Normality LG	Normality MG	Homo/hetero	Test	p-value
Baseline characteristics (continuous)						
Age (years)	Independent	Normal	Normal	Homo	Unpaired t-test	.3495
Height (cm)	Independent	Normal	Normal	Homo	Unpaired t-test	.4230
Body mass (kg)	Independent	Normal	Normal	Homo	Unpaired t-test	.1833
BMI (kg/m^2)	Independent	Normal	Normal	Homo	Unpaired t-test	.3515
LVEF (%)	Independent	Normal	Normal	Homo	Unpaired t-test	.5640

LG = low-intensity group; MG = moderate intensity group; BMI = Body Mass Index; LVEF = Left Ventricular Ejection Fraction

Appendix 4.

Requirements statistical analysis baseline characteristics (categorical)

	Conditions met (Expected values > 5)	Test	p-value
Baseline characteristics (categorical)			
Gender (male/female)	No	Fisher's Exact test	1.0000
HFrEF (yes/no)	Yes	Rank-sum test	.3245
DDF	No	Fisher's Exact test	1.0000
Smoker (yes/no)	No	Fisher's Exact test	1.0000
Ex-smoker (yes/no)	Yes	Rank-sum test	.6211
Arterial hypotension (yes/ no)	Yes	Rank sum test	.8394
T2DM (yes/no)	No	Fisher's Exact test	.1050
Dyslipidemia (yes/no)	Yes	Rank Sum test	.8208
Obesity (yes/no)	No	Fisher's Exact test	.4506
Blood pressure medications (yes/no)	No	Fisher's Exact test	.4872
ACE-inhibitor (yes/no)	Yes	Rank-sum test	.2670
Alpha blocker (yes/no)	No	Fisher's Exact test	.0471*
Angiotensin receptor blocker (yes/no)	Yes	Rank-sum test	.2424
Antihypertensive (yes/no)	No	Fisher's Exact test	.4872
Betablocker (yes/no)	No	Fisher's Exact test	.6050
Calcium antagonist (yes/no)	No	Fisher's Exact test	.4872
Diuretic (yes/no)	Yes	Rank-sum test	.2574
Painkillers and anti-inflammatory drugs (yes/no)	Yes	Rank-sum test	.5570
Acetylsalicylic acid (yes/no)	Yes	Rank-sum test	.6337
Colchicine (yes/no)	No	Fisher's Exact test	.6614
Corticosteroid (yes/no)	No	Fisher's Exact test	.6614
Non-opioid analgesic (yes/no)	No	Fisher's Exact test	.0000
Opioid (yes/no)	No	Fisher's Exact test	.0000
Spasmolytic (yes/no)	No	Fisher's Exact test	.0000
Sulfasalazine (yes/no)	No	Fisher's Exact test	1.0000
Psychotropic medications (yes/no)	No	Fisher's Exact test	.1337
Antipsychotic (yes/no)	No	Fisher's Exact test	1.0000
Non-selective serotonin reuptake inhibitor (yes/no)	No	Fisher's Exact test	1.0000
Selective serotonin reuptake inhibitors (yes/no)	No	Fisher's Exact test	1.0000
Cholesterol-Lowering drugs (yes/no)	No	Fisher's Exact test	.0648
Ezetimibe (yes/no)	No	Fisher's Exact test	1.0000
Statin (yes/no)	No	Fisher's Exact test	.4506
Blood sugar regulating drugs (yes/no)	No	Fisher's Exact test	.1552
Glucagon (yes/no)	No	Fisher's Exact test	.4827
Hypoglycemic sulfamide (yes/no)	No	Fisher's Exact test	.4872
Insulin (yes/no)	No	Fisher's Exact test	.4827
SGLT2-inhibitor (yes/no)	No	Fisher's Exact test	.1552
Anticoagulants (yes/no)	Yes	Rank-sum test	.4309
P2Y12-inhibitor (yes/no)	Yes	Rank-sum test	.8937
Thienopyridine (yes/no)	No	Fisher's Exact test	.6050
Oral anticoagulant (yes/no)	Yes	Rank-sum test	.3333
Arrhythmia drugs (yes/no)	No	Fisher's Exact test	.3416
Antiarrhythmic (yes/no)	No	Fisher's Exact test	.3416
Other medications (yes/no)	Yes	Rank-sum test	.0482*
Antibiotic (yes/no)	No	Fisher's Exact test	.2308
Anticholinergic (yes/no)	No	Fisher's Exact test	.2308
Anti-emetic (yes/no)	No	Fisher's Exact test	1.0000
Anti-epileptic (yes/no)	No	Fisher's Exact test	1.0000
Aromatase inhibitor (yes/no)	No	Fisher's Exact test	.4872
Benzodiazepine agonist (yes/no)	No	Fisher's Exact test	.3416
Betahistine (yes/no)	No	Fisher's Exact test	.4872
Contraceptive (yes/no)	No	Fisher's Exact test	.4872
Glycoside (yes/no)	No	Fisher's Exact test	1.0000
LABA (yes/no)	No	Fisher's Exact test	.4872
Laxative (yes/no)	No	Fisher's Exact test	.4872
Mucolytic (yes/no)	No	Fisher's Exact test	.4872
Immunosuppressor (yes/no)	No	Fisher's Exact test	.3416
Phosphodiesterase-5 inhibitor (yes/no)	No	Fisher's Exact test	.2308
Proton pump inhibitor (yes/no)	Yes	Rank-sum test	.8821
SABA (yes/no)	No	Fisher's Exact test	.4872
Thyromimetic (yes/no)	No	Fisher's Exact test	.2308
Xanthine oxidase inhibitor (yes/no)	No	Fisher's Exact test	.3416
Heart and blood vessel conditions (yes/no)	No	Fisher's Exact test	.6050
Acute pulmonary embolism (yes/no)	No	Fisher's Exact test	.4872
DVT (yes/no)	No	Fisher's Exact test	1.0000
PAD (yes/no)	No	Fisher's Exact test	1.0000
Valve disease (yes/no)	No	Fisher's Exact test	1.0000
Respiratory conditions (yes/no)	Yes	Rank-sum test	.9046
Allergic asthma (yes/no)	No	Fisher's Exact test	.4872
Asthma (yes/no)	No	Fisher's Exact test	1.0000
COPD (yes/no)	No	Fisher's Exact test	.4872
OSA (yes/no)	No	Fisher's Exact test	.4506
Pneumonia (yes/no)	No	Fisher's Exact test	.4872
Internal diseases (yes/no)	Yes	Rank-sum test	.0791
Chronic glomerulonephritis (yes/no)	No	Fisher's Exact test	.4872
Chronic renal insufficiency (yes/no)	No	Fisher's Exact test	.6050
Gastro-enteritis (yes/no)	No	Fisher's Exact test	.2308
Gout (yes/no)	No	Fisher's Exact test	1.0000
Hypertensive encephalopathy (yes/no)	No	Fisher's Exact test	.4872
Mechanical ileus (yes/no)	No	Fisher's Exact test	.4872
Nephrolithiasis (yes/no)	No	Fisher's Exact test	1.0000
Esophagitis (yes/no)	No	Fisher's Exact test	.4872
Polymyalgia rheumatica (yes/no)	No	Fisher's Exact test	1.0000
Stomach bleeding (yes/no)	No	Fisher's Exact test	.4872
T1DM (yes/no)	No	Fisher's Exact test	.4872
Ureteral stone (yes/no)	No	Fisher's Exact test	.4872

Urosepsis with pericarditis (yes/no)	No	Fisher's Exact test	1.0000
Operations (yes/no)	Yes	Fisher's Exact test	.0369*
Ankle surgery (yes/no)	No	Fisher's Exact test	.4872
Appendectomy (yes/no)	No	Fisher's Exact test	1.0000
Back operation after accident (yes/no)	No	Fisher's Exact test	1.0000
CABG (yes/no)	No	Fisher's Exact test	1.0000
Cholecystectomy (yes/no)	No	Fisher's Exact test	1.0000
Kidney transplant (yes/no)	No	Fisher's Exact test	.4872
Knee surgery (yes/no)	No	Fisher's Exact test	1.0000
Mastectomy (yes/no)	No	Fisher's Exact test	.4872
Meniscus operation (yes/no)	No	Fisher's Exact test	1.0000
Nose Surgery (yes/no)	No	Fisher's Exact test	1.0000
PTCA (yes/no)	No	Fisher's Exact test	1.0000
Tummy tuck (yes/no)	No	Fisher's Exact test	1.0000
Varicectomy (yes/no)	No	Fisher's Exact test	1.0000
Vasectomy (yes/no)	No	Fisher's Exact test	1.0000
Total hip prothesis (yes/no)	No	Fisher's Exact test	.4872
Cancers (yes/no)	No	Fisher's Exact test	1.0000
Adenocarcinoma (yes/no)	No	Fisher's Exact test	1.0000
Bladder carcinoma (yes/no)	No	Fisher's Exact test	1.0000
Breast carcinoma (yes/no)	No	Fisher's Exact test	1.0000
Carcinoid lung tumor (yes/no)	No	Fisher's Exact test	1.0000
Colon adenoma (yes/no)	No	Fisher's Exact test	.4872
Prostate neoplasm (yes/no)	No	Fisher's Exact test	1.0000
Neurological conditions (yes/no)	No	Fisher's Exact test	1.0000
Carpal tunnel (yes/no)	No	Fisher's Exact test	1.0000
Facial paralysis (yes/no)	No	Fisher's Exact test	1.0000
Lumbar herniation (yes/no)	No	Fisher's Exact test	.4872
Sliding hernia (yes/no)	No	Fisher's Exact test	.4872
Other (skin conditions, MSK conditions, mental conditions, trauma,…) (yes/no)	Yes	Rank-sum test	.4325
Cervical facet arthritis (yes/no)	No	Fisher's Exact test	.4872
Depression (yes/no)	No	Fisher's Exact test	1.0000
Empty sella (yes/no)	No	Fisher's Exact test	1.0000
Erysipelas (yes/no)	No	Fisher's Exact test	1.0000
Fibromyalgia (yes/no)	No	Fisher's Exact test	1.0000
Gynecomastia (yes/no)	No	Fisher's Exact test	1.0000
Infrapatellar bursitis (yes/no)	No	Fisher's Exact test	.4872
Navel rupture (yes/no)	No	Fisher's Exact test	1.0000
Prostate hypertrophy (yes/no)	No	Fisher's Exact test	.2308
Psoriasis (yes/no)	No	Fisher's Exact test	1.0000
Rotator cuff disorder (yes/no)	No	Fisher's Exact test	.4872
Rotator cuff tendinopathy (yes/no)	No	Fisher's Exact test	.4872
Spinal stenosis (yes/no)	No	Fisher's Exact test	.4872
No comorbidities (yes/no)	No	Fisher's Exact test	.7164

T2DM = Type 2 Diabetes Mellitus; HFrEF = Heart Failure with Reduced Ejection Fraction; DDF = Diastolic Dysfunction; ACE-inhibitor = Angiotensin-converting enzyme inhibitor; LABA = Long-Acting Beta Agonist; SABA = Short-Acting Beta Agonist; OSA = Obstructive Sleep Apnea; T1DM = Type 1 Diabetes Mellitus; CABG = Coronary Artery Bypass Grafting; PTCA = Percutaneous Transluminal Coronary Angioplasty; PAD = Peripheral Artery Disease; COPD = Chronic Pulmonary Obstructive Disease; DVT = Deep Vein Thrombosis; MSK = Musculoskeletal

*p-value < .05