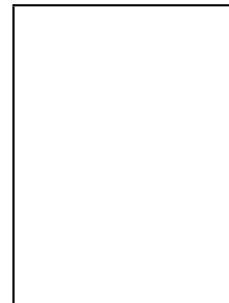


Journal Pre-proof

Effectiveness of a cardiac rehabilitation program in women with heart failure

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PII: S0870-2551(25)00218-5

DOI: <https://doi.org/doi:10.1016/j.repc.2025.02.010>

Reference: REPC 2460

To appear in: *Revista Portuguesa de Cardiologia*

Received Date: 4 June 2024

Accepted Date: 25 February 2025

Please cite this article as: Campinas A, Schmidt C, Oliveira MI, Magalhães S, Gomes C, Nogueira-Ferreira R, Ribeiro F, Santos M, Effectiveness of a cardiac rehabilitation program in women with heart failure, *Revista Portuguesa de Cardiologia* (2025), doi: <https://doi.org/10.1016/j.repc.2025.02.010>

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Title: Effectiveness of a cardiac rehabilitation program in women with heart failure

Título: Eficácia de um Programa de Reabilitação Cardíaca em Mulheres com Insuficiência Cardíaca

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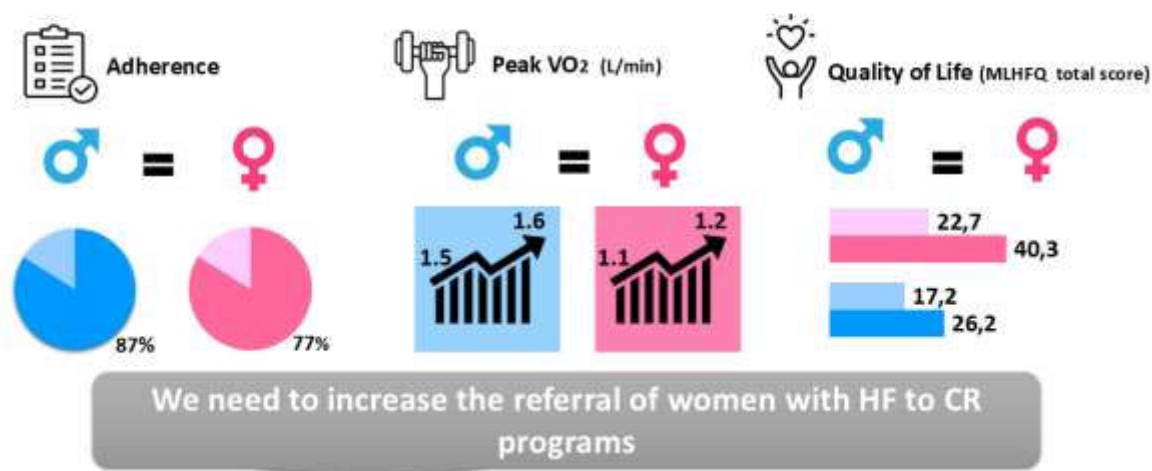
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Graphical Abstract

Effectiveness of a Cardiac Rehabilitation Program in Women with Heart Failure

To compare the **adherence** and **effectiveness** of a Cardiac Rehabilitation program of women and men with Heart Failure (HF)

Prospective single-center study of **93** consecutive **HF patients** were divided into two groups according to **gender**



Resumo:

Introdução e Objetivos: A eficácia da reabilitação cardíaca (RC) na melhoria da capacidade de exercício e qualidade de vida (QoL) na insuficiência cardíaca (IC) está bem estabelecida. No entanto, continua subutilizada em mulheres. Foi o nosso objetivo comparar a adesão e a eficácia de um programa de RC entre mulheres e homens com IC.

Métodos: Realizámos um estudo unicêntrico prospetivo com 93 doentes consecutivos com IC referenciados ao programa de RC no nosso hospital entre setembro de 2019 e julho de 2021. Definimos a adesão pela percentagem de sessões que os doentes frequentaram. A eficácia foi avaliada pelas diferenças no pico de consumo de oxigénio (VO₂pico) e na pontuação da QoL antes e após o programa de RC. O VO₂pico foi estimado durante uma prova cardiorrespiratória máxima. A QoL foi avaliada utilizando o Minnesota Living with Heart Failure Questionnaire® (MLHFQ).

Resultados: Dos 93 doentes, 32.3% eram mulheres. Em relação à adesão, 84% dos completaram o programa de RC e não foram encontradas diferenças significativas entre os grupos ($p=0.232$). O aumento no VO₂pico não diferiu entre os sexos ($p=0.938$). Foi observada uma redução significativa na pontuação total, física e emocional do MLHFQ em ambos os sexos (todos $p<0.05$). Não foram encontradas diferenças significativas na análise de eficácia da QoL entre os grupos (todos $p=NS$).

Conclusão: As mulheres com IC apresentaram uma adesão semelhante ao programa de RC e o mesmo aumento no VO₂pico, um marcador prognóstico robusto e validado na IC. As mulheres beneficiaram tanto quanto os homens em todas as dimensões da QoL. Estes dados reforçam a necessidade de aumentar a referência das mulheres com IC para programas RC.

Palavras-chave: prevenção secundária, reabilitação cardíaca, insuficiência cardíaca, mulher, qualidade de vida, prova cardiopulmonar

Abstract:

Introduction and Objectives: The effectiveness of cardiac rehabilitation (CR) in improving exercise capacity and quality of life (QoL) in heart failure (HF) is well established. However, it remains underutilized in women. We aimed to compare the adherence and effectiveness of a CR program between women and men with HF.

Methods: Prospective single-center study of consecutive 93 HF patients referred to a CR program between September 2019 and July 2021. We defined adherence as the percentage of sessions patients attended. The effectiveness outcomes were changes in peak oxygen uptake (VO_2 peak) and QoL measurements before (baseline) and after the CR program (12wk). VO_2 peak was assessed by a maximal effort cardiopulmonary exercise testing on a treadmill. QoL was assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Results: Among 93 patients, 32.3% were female. Regarding adherence, 84% of patients completed the CR program, and no significant differences were found between groups ($p=0.232$). The increase in VO_2 peak did not differ between genders ($p=0.938$). A significant reduction in the total, physical and emotional MLHFQ scores in both genders was observed (all $p<0.05$). There were no significant differences in QoL effectiveness analysis between the groups (all $p=NS$).

Conclusion: Women with HF adhered to the CR program similarly to men and had a similar increase in VO_2 peak, a robust and validated prognostic marker for HF in this setting. Women

benefited as much as men in all dimensions of QoL. Together, these data emphasize the need to increase the referral of women with HF to CR programs.

Keywords: secondary prevention, cardiac rehabilitation, heart failure, women, quality of life, cardiopulmonary exercise testing

INTRODUCTION

Heart failure (HF) continues to be a significant global health concern associated with reduced survival; it is one of the leading causes of morbidity and mortality in both genders.¹ It affects millions of people worldwide and prevalence is rising due to aging populations and improvements in survival rates for other cardiac conditions.² Despite evidence from randomized clinical trials demonstrating the equal efficacy of pharmacological therapy in both men and women, a concerning issue of undertreatment among women persists.³

Cardiac rehabilitation (CR) is strongly recommended as a Class I Level A intervention for managing HF, as it has been shown to improve functional capacity and quality of life (QoL), as well as to reduce the risk of hospitalization and mortality.⁴⁻⁶ CR programs offer a multidisciplinary approach to secondary prevention, which includes patient assessment, cardiovascular risk management, exercise training, dietary advice, physical activity counseling, psychosocial support and vocational assistance.^{7,8} Despite its benefits, CR remains widely underused⁹, especially among women.^{6,10} Several studies have shown that women are referred less frequently to CR programs, partially due to a misperception of its reduced effectiveness by healthcare professionals compared to men.⁶ In addition, it has been reported that females are less likely than males to attend CR sessions and complete the CR program.^{6,11,12} It is important to note that despite the low participation rates of females in CR, research has

demonstrated that CR can lead to similar or even greater mortality benefits in females when compared with males in post-acute myocardial infarction patients.^{13–15} However, studies comparing the impact of CR between men and women with HF patients are lacking. These studies could provide valuable insights into potential differences in treatment responses, further emphasizing the need for gender-specific strategies in CR.

OBJECTIVES

The aim of our study was, therefore, to compare the impact of a CR program on functional capacity, exercise session adherence, and QoL between men and women with HF.

METHODS

Study design and study population

We conducted a prospective single-center study of 93 consecutive patients with HF referred to a CR program from September 2019 to July 2021. Our study population comprised patients diagnosed with HF based on the diagnostic criteria outlined by the European guidelines⁴ and who were eligible to participate in the CR program based on CR recommendations.^{4,5,8,16} The patients included in our study were divided into two groups according to gender. The study was conducted at a tertiary university public hospital. The study was approved by the ethics committee and was conducted in accordance with the Declaration of Helsinki.

Intervention: Cardiac rehabilitation program

The CR program included a total of 24 exercise training sessions over 12-week (two sessions *per wk*). Each session comprised 5–10 minutes of warm-up with calisthenics and stretching exercises, followed by 25 minutes of resistance exercises using elastic bands (two sets of 12–15 repetitions for each exercise), followed by 30 minutes of moderate to vigorous aerobic training at 60%–80% of peak oxygen uptake (VO_{2peak}) or guided by Borg's scale (11–14). Finally, a 5-minute cool-down period with stretching exercises was conducted. In addition to the supervised sessions, patients were encouraged to boost their daily physical activity levels on the other days. Throughout the supervised exercise sessions, patient's heart rate and electrocardiogram were monitored using a real-time heart rate monitor (Polar M200 model; Polar Electro Ltd). The intensity of the resistance training was progressively increased based on the patient's perceived exertion, as measured using the Borg scale.¹² Additionally, the CR program included weekly group sessions, scheduled on the same days as the exercise sessions, to address dietary goals for improving modifiable cardiovascular risk factor control, encourage lifestyle behavior changes, and offer psychological and/or psychiatric consultations as clinically necessary.

Assessments

Demographics and clinical data

Demographic data (age), anthropometric (body mass index), comorbidities, HF-related characteristics (HF phenotype, etiology, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), B-type natriuretic peptide (BNP) plasma levels], pharmacological and non-pharmacological treatments were captured from patients' files and/or during the CR consult.

The analysis of the effectiveness of the outcomes of interest was conducted by comparing the baseline values (measured before the CR program) with the final values (measured after completing the 12-week CR program).

Functional capacity

Functional capacity was evaluated using VO_2 peak (ml/min/kg) and the ventilatory efficiency [minute ventilation to carbon dioxide production (VE/VCO_2) slope] assessed during the cardiopulmonary exercise test (CPX). All patients underwent a CPX on a treadmill (Medisoft, Model 870C) with continuous electrocardiographic monitoring throughout the entire protocol. Exercise testing protocol, the modified Naughton or Bruce, was chosen according to the patient's physical activity level and orthopedic/musculoskeletal condition. VO_2 peak is currently recognized as the gold standard for objectively evaluating the functional capacity of HF patients.¹⁷ However, since the VE/VCO_2 slope has prognostic value for submaximal exercise levels and several studies have recently demonstrated that it appears the most powerful predictor of prognosis in HF patients, this parameter was also used to estimate the impact and effectiveness of the CR program.¹⁷ Respiratory gas exchange measurements were obtained at each breath cycle and recorded every 30 seconds using the stationary metabolic cart system (Geratherm® Respiratory Ergostik, BLUE CHERRY®). Heart rate and blood pressure were regularly recorded throughout the test. VO_2 peak was determined as the highest achieved VO_2 during exercise. Patients were strongly encouraged to achieve a respiratory exchange ratio (RER) above 1.05¹⁸¹⁹ and a Borg rating of perceived exertion score > 17 on the 6 to 20 scale (6 to 20 scale).²⁰

Exercise sessions adherence

Adherence to the exercise sessions was assessed as the total percentage of exercise sessions attended by participants. Adherence to the CR program was defined as completing at least 80% of the prescribed exercise sessions, as described in the literature.^{21,22}

Quality of life

Quality of life was assessed using the Minnesota Living with Heart Failure Questionnaire® (MLHFQ). The MLHFQ was specifically developed and validated to evaluate the impact of HF systematically and comprehensively on patient's QoL.^{23,24} This questionnaire consists of 21 questions that cover the physical dimension (eight questions, scored from 0 to 40), emotional dimension (five questions, scored from 0 to 25), and socioeconomic factors that can potentially negatively affect the QoL of HF patients. The total MLHFQ score ranges from 0 to 105, with higher scores indicating a poorer QoL. Therefore, the total score as well as the scores for the physical and emotional dimensions were evaluated for each group.

Statistical analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) software, version 26.0. Continuous variables with a normal distribution were reported as means and standard deviations (SD), while continuous variables without a normal distribution were reported as medians and interquartile ranges (IQR). Categorical variables were presented as absolute numbers and percentages (%). The male and female genders were compared for each variable using the Student's t-test or Wilcoxon rank-sum test for continuous variables. The chi-square test or Fisher's exact tests were used for categorical variables to evaluate any differences between the two genders. Paired t-tests were employed to compare the mean values between baseline and final for each variable. Analysis of Covariance was also

employed to adjust for baseline CPX and MLHFQ measurements. $P < 0.05$ was considered statistically significant.

RESULTS

Study population

Among a total of 93 patients with HF referred to the CR program, the mean age was 62 ± 12 years. Baseline demographic and clinical characteristics of the study population by gender are shown in Table 1. In general, men and women showed similar characteristics, including age, body mass index, comorbidities and treatment. Hypertension was the most frequent (61.3%) in the total sample, as well as both genders, while chronic kidney disease (CKD) was more prevalent in men (20.6% vs. 3.3%, $p = 0.032$). Most patients were in NYHA functional class II (69.2%) and the average of LVEF in men was lower compared with women (34% vs. 42%, $p = 0.002$). HF with reduced Ejection Fraction (HFrEF) was the most prevalent phenotype in men (92.1% vs. 73.3%, $p = 0.024$), whereas HF with preserved ejection fraction (HFpEF) was the most observed in women (20% vs. 3.2%, $p = 0.013$). In the male group, ischemic etiology was statistically more prevalent (48.4% vs. 20%, $p = 0.012$).

Adherence

In our study, the overall adherence to the CR program was 84%, with adherence rates of 87% in men and 77% in women. No statistically significant differences were observed between genders regarding adherence to the CR program ($p = 0.232$). Of the 15 patients who did not adhere to the CR program, the majority were male (8, 53.3%) with a non-ischemic etiology (9, 60%).

Functional capacity

Table 2 presents the baseline and final functional capacity evaluations in the study population by gender. A significant increase in VO_2 peak was observed in both genders after the CR program compared to baseline (men: $+1.2 \pm 2.4$ ml/min/kg; women: $+1.5 \pm 2.1$ ml/min/kg), with no between-group difference (0.39 ml/min/kg, 95% CI: -0.81 to 0.81), $p=0.516$). Furthermore, no significant difference was observed between men and women in the O_2 pulse after adjusting for baseline values ($p=0.989$). Regarding ventilatory efficiency (VE/VCO_2 slope), only women experienced significant improvements (-2.1 ± 3.6 , $p=0.014$), with a significant between-group difference (2.16, 95% CI: 0.33 to 4.00, $p=0.022$). Both genders saw a small increase in RER peak after CR program; however, there were no significant difference within each group ($p=\text{NS}$). There was a significant difference between-group (-0.065 , 95% CI: -0.11 to 0.01, $p=0.012$) when adjusted to baseline values, with men showing a slightly greater increase in RER peak compared to women.

Quality of life

A significant decrease was observed in both groups after the CR program in the total score of MLHFQ (-9 ± 14.8 , $p<0.001$ in males and -17.6 ± 19.7 , $p<0.001$ in females). The physical dimension score significantly improved in both groups (-4 ± 7.8 , $p=0.001$ in males and -9.6 ± 9.3 , $p<0.001$ in females). On the other hand, in the emotional dimension score a significant improvement was observed only in men (-2.1 ± 4.9 , $p=0.004$), but not in women (-2.5 ± 7.4 , $p=0.133$). Regarding the analysis of effectiveness in QoL, no significant differences were observed between genders in the MLHFQ total score ($p=0.529$), as well as in the scores for the physical dimension ($p=0.705$) and the emotional dimension ($p=0.353$).

DISCUSSION

The main findings of our study indicate that women with HF adhere to a 12-week CR program similarly to men and have similar improvements in both VO₂ peak and QoL.

Peak VO₂ is a prognostic factor with significant clinical implications, as it has been associated with a reduced risk of rehospitalization in HF patients.⁶ In our study, we found no significant gender-based differences in the effectiveness of the CR program regarding functional capacity improvement. Several studies on the effectiveness of CR in ischemic heart disease and HF, particularly in functional capacity improvement assessed by VO₂ peak after CR, point to inferior results observed in women.^{25–28} These findings suggest that women experience a comparatively smaller increase in VO₂ peak from each session. It has been hypothesized that women may require a specific CR program with a longer duration.^{26,29,30} The prescription of more a conservative exercise plans due to older age and the higher burden of comorbidities in women when referred to CR programs has been identified as one of the factors that limit functional capacity and QoL improvement in women.²⁸ In our sample, the groups were relatively homogeneous, regarding age and comorbidities, which may partially explain the results obtained. Furthermore, although the exercise training program was the same for both genders, patients received an individualized exercise intensity prescription. Similarly, a study of patients with cardiovascular disease compared the improvement in VO₂ peak between genders after a high-intensity program, with results showing that men and women experienced similar improvements in VO₂ peak (8.8% vs 9.0%, $p=0.273$).³¹

Additionally, there were significant differences between groups in terms of the RER. Less muscle mass and strength³², hormonal influences (as estrogen promotes greater fat oxidation over carbohydrate use),³³ psychological factors in perceived exertion (women may end exercise

testing earlier due to perceived discomfort or exhaustion at lower intensities than men)³⁴ and a lower lactate threshold³² may contribute to lower average RER values in women's CPETs. However, we believe these results should not hinder the interpretation of the present data.

On the other hand, the effectiveness of CR in ventilatory efficiency improvement differed between genders, as only the women's group showed a significant VE/VCO₂ slope improvement after CR. This result might be attributed to the small sample size of our study. Further larger studies are warranted to comprehensively elucidate the impact of CR programs on ventilatory efficiency between genders.

Results from a meta-analysis on adherence to CR programs show that the average adherence rate is approximately 66.5±18.2% across studies.³⁵ However, in our study, the overall adherence to the CR program was 84%. Implementing measures described in the literature that have been shown to increase women's adherence to CR, such as self-monitoring of physical activity, planning, and personalized counseling by healthcare professionals³⁵, may explain the higher adherence observed in our study. Some studies have shown lower adherence to CR in women for several reasons, principally due to family responsibilities, transportation problems and advanced age with more comorbidities.³⁵ Our findings reveal that despite women comprising less than half of the participants enrolled in our CR program (30 women vs. 63 men), no significant differences were observed in adherence between genders. Strategies including automatic referral systems, liaison/nurse-patient contact, and early post-hospital referral are warranted to increase women's referral to CR programs. In addition, since women are more likely than men to perceive exercise as tiring or painful³⁴, future research should explore exercise prescription strategies that employ alternative approaches. Incorporating specific aerobic training programs, such as dance-based programs, could provide considerable benefits for adherence and cardiovascular outcomes in women.^{6,36} Dance-based aerobics are

often seen as enjoyable, social, and engaging, which can greatly boost motivation and, in turn, enhance adherence to CR programs.^{6,36} In addition, a meta-analysis showed a significant difference in VO₂ peak and QoL in HF patients, demonstrating that dance therapy was as efficient as conventional exercise training in VO₂ peak and QoL.³⁶ Thus, randomized studies are needed to evaluate the innovative CR programming strategies for women.

Regarding the impact of our CR program on the QoL, our findings demonstrate a significant increase in QoL improvement, evidenced by a significant reduction in total, physical, and emotional dimension MLHFQ scores in both groups. These results are consistent with findings reported by other authors.^{37,38}

Research indicates that women tend to have a lower QoL than men due to several factors, including a higher number of comorbidities associated with aging, a greater prevalence of psychosocial risk factors (including stress, anxiety, and depression), as well as the need for more frequent and intense exercise sessions to achieve desired outcomes within the program.³⁹ Consistent with the aforementioned, our study revealed that women had lower QoL (higher scores) than men in all dimensions assessed by the MLHFQ prior to the CR program. However, according to our analysis, the effectiveness of the CR program in QoL improvement shows similar results for both genders. Results from a meta-analysis also demonstrated that women achieve similar benefits to men in terms of QoL improvement after CR, namely in the physical dimension.⁴⁰ These results hold significance, considering the potential vulnerability of women to poorer prognosis due to older age and pre-existing clinical conditions.^{6,41} Furthermore, some authors have shown that women experienced greater long-term QoL improvement after a CR program that incorporates aerobic and resistance training (as in our CR program) compared to a program consisting of aerobic training alone,⁴² which might explain our results.

The implementation of a personalized training plan in our CR program, tailored according to the progression of symptoms, addressing specific fears and concerns related to exercise, is widely acknowledged to enhance exercise confidence and self-efficacy. This, in turn, promotes adherence to our CR program and, subsequently, contributes to the improvement in QoL. These strategies emerged as particularly important for women, who often report more negative perceptions toward exercise, higher levels of demotivation,^{43–45} stress, anxiety, and depression compared to men.³⁸ Likewise, the interaction with other participants, facilitating the sharing of experiences, also promotes specific emotional support, thereby reducing anxiety and apprehension in women.⁴⁶ This aspect may also contribute to our results. Regarding the emotional domain, although the effectiveness was similar between the groups, some authors argue that when psychosocial components specifically designed for women's needs are added to traditional CR models, women may benefit more than men.⁴⁰

Our study has some limitations and strengths that deserve to be discussed. It is a prospective study, which was conducted at a single hospital, so the generalization of these results should be viewed with caution. The study included only 93 patients, with a significant imbalance between men (63) and women (30). Therefore, a larger sample, particularly including more women, could yield more robust and representative results. Additionally, this limitation made it impossible to evaluate patients with different heart failure phenotypes (HFrEF and HFpEF), which may influence the response to the program. Finally, as we only included women referred by the attending physician to the CR unit, selection bias cannot be excluded.

CONCLUSIONS

In our study population, women with HF experience similar improvements in both VO₂ peak and QoL and equal adherence to the CR program compared to men. These findings highlight the importance of improving the referral of women with HF to CR programs.

All authors declare no conflicts of interest.

ACKNOWLEDGMENTS

None.

Ética de la publicación

1. ¿Su trabajo ha comportado experimentación en animales?:

No

2. ¿En su trabajo intervienen pacientes o sujetos humanos?:

No

3. ¿Su trabajo incluye un ensayo clínico?:

No

4. ¿Todos los datos mostrados en las figuras y tablas incluidas en el manuscrito se recogen en el apartado de resultados y las conclusiones?:

Sí

REFERENCES

1. Samayoa L, Grace SL, Gravely S, et al. Sex Differences in Cardiac Rehabilitation Enrollment: A Meta-analysis. *Canadian Journal of Cardiology*. 2014;30(7):793-800. doi:10.1016/j.cjca.2013.11.007
2. Savarese G, Becher PM, Lund LH, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res*. 2023;118(17):3272-3287. doi:10.1093/cvr/cvac013
3. Bozkurt B, Khalaf S. Heart Failure in Women. *Methodist Debaquey Cardiovasc J*. 2017;13(4):216. doi:10.14797/mdcj-13-4-216
4. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368
5. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of

- Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18). doi:10.1161/CIR.0000000000001063
6. Smith JR, Thomas RJ, Bonikowske AR, et al. Sex Differences in Cardiac Rehabilitation Outcomes. *Circ Res*. 2022;130(4):552-565. doi:10.1161/CIRCRESAHA.121.319894
 7. Balady GJ, Williams MA, Ades PA, et al. Core Components of Cardiac Rehabilitation/Secondary Prevention Programs: 2007 Update. *Circulation*. 2007;115(20):2675-2682. doi:10.1161/CIRCULATIONAHA.106.180945
 8. Ambrosetti M, Abreu A, Corrà U, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol*. 2021;28(5):460-495. doi:10.1177/2047487320913379
 9. Suaya JA, Shepard DS, Normand SLT, et al. Use of Cardiac Rehabilitation by Medicare Beneficiaries After Myocardial Infarction or Coronary Bypass Surgery. *Circulation*. 2007;116(15):1653-1662. doi:10.1161/CIRCULATIONAHA.107.701466
 10. Bozkurt B, Fonarow GC, Goldberg LR, et al. Cardiac Rehabilitation for Patients With Heart Failure. *J Am Coll Cardiol*. 2021;77(11):1454-1469. doi:10.1016/j.jacc.2021.01.030
 11. Peters AE, Keeley EC. Trends and Predictors of Participation in Cardiac Rehabilitation Following Acute Myocardial Infarction: Data From the Behavioral Risk Factor Surveillance System. *J Am Heart Assoc*. 2018;7(1). doi:10.1161/JAHA.117.007664
 12. Ritchey MD, Maresh S, McNeely J, et al. Tracking Cardiac Rehabilitation Participation and Completion Among Medicare Beneficiaries to Inform the Efforts of a National

- Initiative. *Circ Cardiovasc Qual Outcomes.* 2020;13(1).
doi:10.1161/CIRCOUTCOMES.119.005902
13. Goel K, Lennon RJ, Tilbury RT, et al. Impact of Cardiac Rehabilitation on Mortality and Cardiovascular Events After Percutaneous Coronary Intervention in the Community. *Circulation.* 2011;123(21):2344-2352.
doi:10.1161/CIRCULATIONAHA.110.983536
 14. Eijsvogels TMH, Maessen MFH, Bakker EA, et al. Association of Cardiac Rehabilitation With All-Cause Mortality Among Patients With Cardiovascular Disease in the Netherlands. *JAMA Netw Open.* 2020;3(7):e2011686.
doi:10.1001/jamanetworkopen.2020.11686
 15. Ekblom Ö, Cider Å, Hambraeus K, et al. Participation in exercise-based cardiac rehabilitation is related to reduced total mortality in both men and women: results from the SWEDHEART registry. *Eur J Prev Cardiol.* 2022;29(3):485-492.
doi:10.1093/eurjpc/zwab083
 16. Price KJ, Gordon BA, Bird SR, et al. A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus? *Eur J Prev Cardiol.* 2016;23(16):1715-1733. doi:10.1177/2047487316657669
 17. Guazzi M, Bandera F, Ozemek C, et al. Cardiopulmonary Exercise Testing. *J Am Coll Cardiol.* 2017;70(13):1618-1636. doi:10.1016/j.jacc.2017.08.012
 18. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to Cardiopulmonary Exercise Testing in Adults. *Circulation.* 2010;122(2):191-225.
doi:10.1161/CIR.0b013e3181e52e69
 19. Glaab T, Taube C. Practical guide to cardiopulmonary exercise testing in adults. *Respir Res.* 2022;23(1):9. doi:10.1186/s12931-021-01895-6

20. Squires RW, Kaminsky LA, Porcari JP, et al. Progression of Exercise Training in Early Outpatient Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev.* 2018;38(3):139-146. doi:10.1097/HCR.0000000000000337
21. Conraads VM, Deaton C, Piotrowicz E, et al. Adherence of heart failure patients to exercise: barriers and possible solutions. *Eur J Heart Fail.* 2012;14(5):451-458. doi:10.1093/eurjhf/hfs048
22. Marti CN, Georgiopoulou V V., Giamouzis G, et al. Patient-Reported Selective Adherence to Heart Failure Self-Care Recommendations: A Prospective Cohort Study: The Atlanta Cardiomyopathy Consortium. *Congestive Heart Failure.* 2013;19(1):16-24. doi:10.1111/j.1751-7133.2012.00308.x
23. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: Reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. *Am Heart J.* 1992;124(4):1017-1025. doi:10.1016/0002-8703(92)90986-6
24. Rector TS, Kubo SH, Cohn JN, et al. Validity of the minnesota living with heart failure questionnaire as a measure of therapeutic response to enalapril or placebo. *Am J Cardiol.* 1993;71(12):1106-1107. doi:10.1016/0002-9149(93)90582-W
25. Schutter A, Kachur S, Lavie CJ, et al. Cardiac rehabilitation fitness changes and subsequent survival. *Eur Heart J Qual Care Clin Outcomes.* Published online June 2, 2018. doi:10.1093/ehjqcco/qcy018
26. Savage PD, Antkowiak M, Ades PA, et al. Failure to Improve Cardiopulmonary Fitness in Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev.* 2009;29(5):284-291. doi:10.1097/HCR.0b013e3181b4c8bd

27. Nguyen CH, Thomas SG, Marzolini S, et al. Factors Associated With Change in Cardiovascular Fitness for Patients With Peripheral and Coronary Artery Disease in Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev.* 2021;41(4):230-236. doi:10.1097/HCR.0000000000000559
28. Rengo JL, Khadanga S, Savage PD, et al. Response to Exercise Training During Cardiac Rehabilitation Differs by Sex. *J Cardiopulm Rehabil Prev.* 2020;40(5):319-324. doi:10.1097/HCR.0000000000000536
29. Witvrouwen I, Pattyn N, Gevaert AB, et al. Predictors of response to exercise training in patients with coronary artery disease – a subanalysis of the SAINTEX-CAD study. *Eur J Prev Cardiol.* 2019;26(11):1158-1163. doi:10.1177/2047487319828478
30. Montero D, Lundby C. Refuting the myth of non-response to exercise training: ‘non-responders’ do respond to higher dose of training. *J Physiol.* 2017;595(11):3377-3387. doi:10.1113/JP273480
31. Vidal-Almela S, Way KL, Terada T, et al. Sex differences in physical and mental health following high-intensity interval training in adults with cardiovascular disease who completed cardiac rehabilitation. *Applied Physiology, Nutrition, and Metabolism.* 2022;47(1):9-17. doi:10.1139/apnm-2021-0265
32. Hafen P, Vehrs P. Sex-Related Differences in the Maximal Lactate Steady State. *Sports.* 2018;6(4):154. doi:10.3390/sports6040154
33. Delp M, Chesbro GA, Pribble BA, et al. Higher rating of perceived exertion and lower perceived recovery following a graded exercise test during menses compared to non-bleeding days in untrained females. *Front Physiol.* 2024;14. doi:10.3389/fphys.2023.1297242

34. Grace SL, Gravely-Witte S, Kayaniyl S, et al. A Multisite Examination of Sex Differences in Cardiac Rehabilitation Barriers by Participation Status. *J Womens Health*. 2009;18(2):209-216. doi:10.1089/jwh.2007.0753
35. Oosenbrug E, Marinho RP, Zhang J, et al. Sex Differences in Cardiac Rehabilitation Adherence: A Meta-analysis. *Canadian Journal of Cardiology*. 2016;32(11):1316-1324. doi:10.1016/j.cjca.2016.01.036
36. Gomes Neto M, Menezes MA, Carvalho VO, et al. Dance therapy in patients with chronic heart failure: a systematic review and a meta-analysis. *Clin Rehabil*. 2014;28(12):1172-1179. doi:10.1177/0269215514534089
37. Candelaria D, Randall S, Ladak L, et al. Health-related quality of life and exercise-based cardiac rehabilitation in contemporary acute coronary syndrome patients: a systematic review and meta-analysis. *Quality of Life Research*. 2020;29(3):579-592. doi:10.1007/s11136-019-02338-y
38. McGregor G, Powell R, Kimani P, et al. Does contemporary exercise-based cardiac rehabilitation improve quality of life for people with coronary artery disease? A systematic review and meta-analysis. *BMJ Open*. 2020;10(6):e036089. doi:10.1136/bmjopen-2019-036089
39. Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *The Lancet*. 2004;364(9438):937-952. doi:10.1016/S0140-6736(04)17018-9
40. Chung S, Candelaria D, Gallagher R, et al. Women's Health-Related Quality of Life Substantially Improves With Tailored Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev*. 2022;42(4):217-226. doi:10.1097/HCR.0000000000000692

41. Berger JS, Elliott L, Gallup D, et al. Sex Differences in Mortality Following Acute Coronary Syndromes. *JAMA*. 2009;302(8):874. doi:10.1001/jama.2009.1227
42. Hung MJ. Reduction of High-Sensitivity C-Reactive Protein after Treatment with Anti-Spastic Agents in Patients with Coronary Vasospastic Angina and No Hemodynamically Significant Coronary Artery Disease. *Chest*. 2004;126(4):825S. doi:10.1378/chest.126.4.1026
43. Rogerson MC, Murphy BM, Bird S, et al. "I don't have the heart": a qualitative study of barriers to and facilitators of physical activity for people with coronary heart disease and depressive symptoms. *International Journal of Behavioral Nutrition and Physical Activity*. 2012;9(1):140. doi:10.1186/1479-5868-9-140
44. McCarthy MM, Vaughan Dickson V, Chyun D, et al. Barriers to Cardiac Rehabilitation in Women With Cardiovascular Disease. *Journal of Cardiovascular Nursing*. 2011;26(5):E1-E10. doi:10.1097/JCN.0b013e3181f877e9
45. Broadbent E, Petrie KJ, Ellis CJ, et al. Patients with acute myocardial infarction have an inaccurate understanding of their risk of a future cardiac event. *Intern Med J*. 2006;36(10):643-647. doi:10.1111/j.1445-5994.2006.01150.x
46. McSweeney JC, Crane PB. An Act of Courage: Women's Decision-Making Processes Regarding Outpatient Cardiac Rehabilitation Attendance. *Rehabilitation Nursing*. 2001;26(4):132-140. doi:10.1002/j.2048-7940.2001.tb01935.x

TABLES

Table 1 - Characterization of overall study population and by gender.

	Overall (n=93)	Men (n=63)	Women (n=30)	P-value
Demographic characteristics				
Age (yrs), mean (SD)	62.4 (±11.7)	62.2 (±10.9)	62.6 (±13.2)	0.89
Anthropometric data				
BMI, mean (SD)	28.2 (0.5)	28.1 (0.6)	28.4 (1.1)	0.774
Comorbidities				
Hypertension, n (%)	57 (61.3)	42 (66.7)	15 (50)	0.123
DM, n (%)	38 (40.9)	25 (39.7)	13 (43.3)	0.823
Dyslipidemia, n (%)	54 (58.1)	13 (20.6)	14 (46.7)	0.124
AF, n (%)	23 (24.7)	13 (20.8)	10 (33.3)	0.185
Smoking				<0.001
Smoker, n (%)	16 (17.4)	12 (19)	4 (13.8)	
Ex-smoker, n (%)	37 (40.2)	33 (52.4)	4 (13.8)	
MI, n (%)	24 (25.8)	19 (30.2)	5 (16.7)	0.165
COPD, n (%)	11 (11.8)	8 (12.7)	3 (10)	1
CKD, n (%)	14 (15.1)	13 (20.6)	1 (3.3)	0.032
Heart failure phenotype				
HFrEF, n (%)	80 (86)	58 (92.1)	22 (73.3)	0.024
HFpEF, n (%)	8 (8.6)	2 (3.2)	6 (20)	0.013
Recovered HFrEF, n (%)	5 (5.4)	3 (4.7)	2 (6.7)	0.156
LVEF (%), mean (SD)	36.6 (±11.3)	34.1 (±9.5)	41.9 (±12.9)	0.002

Heart failure etiology					
Non-ischemic, n (%)	52 (55.9)	31 (49.2)	21 (70)	0.078	
Ischemic, n (%)	36 (38.7)	30 (47.6)	6 (20)	0.012	
Mixed, n (%)	2 (2.2)	0 (0)	2 (6.7)	0.104	
Indeterminate, n (%)	2 (2.2)	1 (1.6)	1 (3.3)	0.548	
Missing, n (%)	1 (1)	1 (1.6)	-	-	
NYHA Functional Class					
I, n (%)	22 (23.6)	19 (30.2)	3 (10)	0.063	
II, n (%)	63 (67.7)	40 (63.5)	23 (76.6)	0.223	
III, n (%)	6 (6.5)	4 (6.3)	2 (6.7)	0.660	
Missing, n (%)	2 (2.2)	-	2 (6.7)	-	
BNP (pg/ml), median (IQR)	355 (179,1075)	444 (167,1152)	331.5 (223,795)	0.864	
Pharmacological treatment					
AAS, n (%)	36 (38.7)	24 (38.1)	12 (40)	0.860	
Statin, n (%)	70 (75.3)	53 (84.1)	17 (56.7)	0.004	
Beta-blockers, n (%)	86 (92.5)	58 (92.1)	28 (93.3)	1	
ACE-I/ARB, n (%)	45 (48.4)	26 (41.3)	19 (63.3)	0.047	
Sacubitril-Valsartan, n (%)	38 (39.8)	28 (44.4)	9 (30)	0.183	
SLTG2i, n (%)	50 (53.8)	34 (54)	16 (53.3)	0.954	
MRA, n (%)	70 (75.3)	49 (77.8)	21 (70)	0.416	
Loop diuretics, n (%)	58 (62.4)	36 (57.1)	22 (73.3)	0.132	
Non-pharmacological treatment					
ICD, n (%)	11 (11.8)	10 (15.9)	1 (3.3)	0.097	
CRT, n (%)	11 (11.8)	9 (14.3)	2 (6.7)	0.493	

Abbreviations: AAS: Acetylsalicylic acid; ACE-I: Angiotensin-converting enzyme inhibitor; AF: Atrial fibrillation; ARB: Angiotensin receptor blockers; BMI: Body mass index; BNP: B-type natriuretic peptide; COPD: Chronic obstructive pulmonary disease; CR: Cardiac rehabilitation; CRT: Cardiac resynchronization therapy; CKD: Chronic kidney disease; DM: Diabetes mellitus; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; IQR: Interquartile range; ICD: Implantable cardioverter-defibrillator; LVEF: Left ventricular ejection fraction; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; SD: standard deviation; SLTG2: Sodium-glucose co-transporter 2.

Table 2 - Baseline and final functional capacity and quality of life in the study population by gender.

	Baseline women	Final Women	Change from baseline	p- value	Baseline men	Final men	Change from baseline	p- value	Baseline adjusted Between-Group Difference in Change	P-value
Peak VO₂ (L/min)	1.1 (0.1)	1.2 (±0.1)	+0.1 (±0.1)	0.009	1.5 (±0.1) ^a	1.6 (±0.1)	+0.1 (±0.2)	0.004	-0.01 (-0.10 to 0.09)	0.846
Peak VO₂ (ml/min/kg)	15.5 (±0.6)	17 (±0.8)	+1.5 (±2.1)	0.004	18.8 (±0.7) ^a	20 (±0.8)	+1.2 (±2.4)	<0.001	0.39 (-0.81 to 1.6)	0.516
% Predicted VO₂ peak	80.8 (±20.2)	83.3 (±21.4)	-2.5 (±11.6)	0.342	72.4 (±15.9)	76 (±17)	-3.7 (±9.9)	0.018	-0.58 (-5.94 to 4.78)	0.829
VE/VCO₂ slope	32.1 (±0.7)	30 (±0.7)	-2.1 (±3.6)	0.014	31.3 (±0.8)	31.6 (±0.8)	+0.07 (±3.6)	0.885	2.16 (0.33 to 4.0)	0.022
Peak RER	1.02 (±0.03)	1.03 (±0.02)	+0.01 (±0.2)	0.929	1.10 (±0.01) ^a	1.11 (±0.01)	+0.01 (±0.1)	0.537	-0.065 (-0.11 to -0.01)	0.012
O₂ pulse	9.44 (±2.5)	10.2 (±2.6)	+0.76 (±1.3)	0.010	12.3 (±3.03) ^a	12.67 (±3.3)	+0.37 (±2.1)	0.199	-0.01 (-1.03 to 1.02)	0.989
Test duration (min)	8.1 (±2.2)	9.6 (±2)	-1.52 (±1.5)	<0.001	10.1 (±3.4)	11.1 (±3.2)	-0.58 (±2.5)	0.031	0.76 (-0.62 to 2.12)	0.298
MLHFQ total	40.3 (±4.2)	22.7 (±3.9)	-17.6 (±19.7)	<0.001	26.2 (±2.9) ^a	17.2 (±2.5)	-9.0 (±14.8)	<0.001	2.31 (4.9 to 9.6)	0.529
MLHFQ physical dimension	20 (±1.8)	10.4 (±1.8)	-9.6 (±9.3)	<0.001	10.8 (±1.4) ^a	6.8 (±1.1)	-4.0 (±7.8)	0.001	0.69 (2.93 to 4.31)	0.705

MLHFQ emotional dimension	9.5	7.1	-2.5	0.133	6.4	4.3	-2.1	0.004	1.11	0.353
	(±1.5)	(±1.5)	(±7.4)		(±0.9)	(±0.7)	(±4.9)		(1.35 to 3.73)	

Data are presented as mean $\pm$ SD. Abbreviations: MLHFQ: Minnesota Living with Heart Failure Questionnaire; RER: respiratory exchange Ratio; SD: standard deviation; VE/VCO₂: minute ventilation/carbon dioxide output ratio; VO₂: oxygen consumption.

^asignificantly different from baseline women, $p < 0.05$

SUPPLEMENTARY MATERIAL:

Table 1. Baseline characterization of patients included at final analyses by gender.

	Overall (n=78)	Men (n=55)	Women (n=23)	P-value
Demographic characteristics				
Age (years), mean (SD)	62.8 (11.4)	63.1 (10.7)	62.1 (13)	0.731
Anthropometric data				
BMI, mean (SD)	28.4 (5)	28 (4.7)	29.4 (5.7)	0.263
Comorbidities				
Hypertension, n (%)	51 (65.4)	39 (70.9)	12 (52.2)	0.126
DM, n (%)	32 (41)	22 (40)	10 (43.5)	0.805
Dyslipidemia, n (%)	45 (57.7)	36 (65.5)	9 (39.1)	0.045
AF, n (%)	17 (21.8)	10 (18.2)	7 (30.4)	0.367
Smoking				<0.001
Smoker, n (%)	12 (15.6)	9 (16.4)	3 (13.6)	
Ex-smoker, n (%)	32 (41.6)	31 (56.4)	1 (4.5)	
MI, n (%)	19 (24.4)	16 (29.1)	3 (13)	0.159
COPD, n (%)	8 (10.3)	7 (12.7)	1 (4.3)	0.424
CKD, n (%)	13 (16.7)	12 (21.8)	1 (4.3)	0.094
Heart failure phenotype				
HFrEF, n (%)	68 (87.2)	51 (92.7)	17 (73.9)	0.056
HFpEF, n (%)	6 (7.7)	1 (1.8)	5 (21.7)	0.008
Recovered HFrEF, n (%)	4 (5.1)	3 (5.5)	1 (4.4)	1
LVEF (%), mean (SD)	36.3 (10.8)	33.7 (9.1)	42.7 (12.1)	0.001
Heart failure etiology				
Non-ischemic, n (%)	43 (55.1)	25 (45.5)	18 (78.3)	0.012
Ischemic, n (%)	32 (41)	28 (50.9)	4 (17.4)	0.006
Mixed, n (%)	1 (1.3)	0 (0)	1 (4.3)	0.299
Indeterminate, n (%)	1 (1.3)	1 (1.8)	0 (0)	1
Missing, n (%)	1 (1.3)	1 (1.8)	-	-
NYHA Functional Class				
I, n (%)	17 (21.8)	15 (27.3)	2 (8.7)	0.129

II, n (%)	54 (69.2)	36 (65.4)	18 (78.3)	0.596
III, n (%)	5 (6.4)	4 (7.3)	1 (4.3)	1
Missing, n (%)	2 (2.6)	-	2 (8.7)	-
BNP (pg/ml), median (IQR)	308	301	383.5	0.417
Pharmacological treatment				
AAS, n (%)	31 (39.7)	22 (40)	9 (39.1)	1
Statin, n (%)	58 (74.4)	46 (83.6)	12 (52.2)	0.006
Beta-blockers, n (%)	75 (96.2)	53 (96.4)	22 (95.7)	1
ACE-I/ARB, n (%)	41 (52.6)	23 (41.8)	18 (78.3)	0.006
Sacubitril-Valsartan, n (%)	30 (38.5)	25 (45.5)	5 (21.7)	0.073
SLTG2i, n (%)	42 (53.8)	30 (54.5)	12 (52.2)	1
MRA, n (%)	59 (75.6)	44 (80)	15 (65.2)	0.246
Loop diuretics, n (%)	48 (61.5)	32 (58.2)	16 (69.6)	0.447
Non-pharmacological treatment				
ICD, n (%)	10 (12.8)	10 (18.2)	0 (0)	0.056
CRT, n (%)	11 (14.1)	9 (16.4)	2 (8.7)	0.492
CPET measurements				
Peak VO ₂ (L/min), mean (SD)	1.4 (±0.05)	1.5 (±0.1)	1.1 (±0.1)	0.001
Peak VO ₂ (ml/min/kg), mean (SD)	18.1 (±0.5)	18.8 (±0.7)	15.5 (±0.6)	0.001
VE/VCO ₂ slope, mean (SD)	31.4 (±0.6)	31.3 (±0.8)	32.1 (±0.7)	0.567
Peak RER, mean (SD)	1.1 (±0.01)	1.1 (±0.01)	1.02 (±0.03)	0.006
QoL evaluation				
MLHFQ total, mean (SD)	31.2 (±2.3)	26.2 (±2.9)	40.3 (±4.2)	0.008
MLHFQ physical dimension, mean (SD)	13.7 (±1.2)	10.8 (±1.4)	20 (±1.8)	<0.001
MLHFQ emotional dimension, mean (SD)	7.8 (±0.7)	6.4 (±0.9)	9.5 (±1.5)	0.071

Abbreviations: AAS: Acetylsalicylic acid; ACE-I: Angiotensin-converting enzyme inhibitor; AF: Atrial fibrillation; ARB: Angiotensin receptor blockers; BMI: Body mass index; BNP: B-type natriuretic peptide; COPD: Chronic obstructive pulmonary disease; CPET: cardiopulmonary exercise test; CR: Cardiac rehabilitation; CRT: Cardiac resynchronization therapy; CKD: Chronic kidney disease; DM: Diabetes mellitus; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; IQR: Interquartile range; ICD: Implantable cardioverter-defibrillator; LVEF:

Left ventricular ejection fraction; MI: myocardial infarction; MLHFQ: Minnesota Living with Heart Failure Questionnaire; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; RER: Respiratory Exchange Ratio; SD: standard deviation; SLTG2: Sodium-glucose co-transporter 2; VE/VCO₂: minute ventilation/carbon dioxide output ratio; VO₂: oxygen consumption.