PHYSICAL AND PSYCHOSOCIAL EFFECTS OF CARDIAC REHABILITATION PARTICIPATION IN PATIENTS WITH AND THOSE WITHOUT CORONARY ARTERY DISEASE AND WOMEN COMPARED TO MEN

PHYSICAL AND PSYCHOSOCIAL EFFECTS OF CARDIAC REHABILITATION PARTICIPATION IN PATIENTS WITH AND THOSE WITHOUT CORONARY ARTERY DISEASE AND WOMEN COMPARED TO MEN

By

Ihab Yassin

A Dissertation Submitted to the Faculty of Harvard Medical School

in Partial Fulfillment of

the Requirements for the Degree of Master of Medical Sciences in Clinical Investigation (MMSCI)

Harvard University

Boston, Massachusetts

April 2022

Area of Concentration: Cardiac Rehabilitation/Cardiology
Project Advisor Dr. Hicham Skali, MD, MSc.

I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

Primary Mentor: Hicham Skali, MD, MSc

Dr. Amil Shah
Division of Cardiovascular Medicine, BWH
Harvard Medical School

Dr. Sahir Kalim
Nephrology Division, MGH
Harvard Medical School

Dr. Sanjay Divakaran
Division of Cardiovascular Medicine, BWH
Harvard Medical School

Contents

Acknowledgement

I would like to express my gratitude to my primary mentor, Dr. Hicham Skali, who guided me throughout this thesis. I would also like to thank my friends and family who supported me and offered deep insight into the study.

Overview of thesis manuscripts

Two -thematically similar- studies addressing two less studied groups of patients (women, and those referred for non-coronary artery disease (non-CAD)) in cardiac rehabilitation (CR) programs. Common research question was to assess CR benefits in these groups compared to men and those referred for coronary artery disease (CAD). The primary aim of the first study was to evaluate and compare exercise capacity and psychological well-being between patients referred to CR for CAD diagnoses and those for non-CAD diagnoses. We sought in the second study to demonstrate whether women enrolled in a contemporary CR program derived similar benefits as men.

Primary endpoint was improvement in 6-minute walking distance (6MWD). Secondary endpoints included change in proportion of patients exercising more than 150 minutes per week (≥150 minutes/week) (EMW150), depression scores (PHQ9), anxiety scores (GAD7) and overall quality of life (COOP) scores.

Between January 2015 and February 2020, 617 patients (26% women) completed the 12-week-CR program and were divided into: group I (referred for non-CAD diagnosis) (N=188) and group II (referred for CAD diagnosis) (N=429). At the completion of their cardiac rehabilitation program, both groups improved their 6MWD without statistical difference (non-CAD group: +188 (110, 274) feet) vs. +200 (89, 290) feet in CAD group, P=0.86).

By the end of the CR program, women had similar improvement in their 6MWD as men (women: median (IQR): 14 [7, 20] % (increase from baseline) vs. men: 13[6, 21] % (increase from baseline), p-value=0.87). Women with mild anxiety improved significantly more than men.

First manuscript

Physical and psychosocial effects of cardiac rehabilitation participation in patients with and without coronary artery disease.

Title Page

Original Investigation

Physical and psychosocial effects of cardiac rehabilitation participation in patients with and those without coronary artery disease.

Ihab Yassin, MD[1]; Hicham Skali, MD, MSc [2,3]

Total word count: 3904

1. Master of Medical Sciences in Clinical Investigation Program, Harvard Medical School, Boston, MA

2. Cardiovascular division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Cardiac Rehabilitation program, Brigham and Women's Hospital, Foxborough, MA

Key words: Cardiac Rehabilitation, coronary artery disease, non-coronary artery disease, heart failure, myocardial infarction, stable angina, heart transplantation, percutaneous coronary intervention, valvular heart disease, coronary artery bypass graft.

Funding: Authors deny any financial affiliation for the performance of this investigation.

Disclosures: Authors deny any relationships with the industry.

*Corresponding Author

Hicham Skali, MD, MSc, FACC

Cardiovascular Division, Department of Medicine

Brigham and Women's Hospital

75 Francis Street

Boston, MA, 02115

Phone: 857-307-1988

Email: hskali@bwh.harvard.edu

Structured Abstract

Background

Patients participating in cardiac rehabilitation (CR) referred for coronary artery disease (CAD) diagnoses have improvements in physical capacity and psychological well-being. The primary aim of this study is to evaluate and compare exercise capacity and psychological well-being between patients referred to CR for CAD diagnoses and those referred for non-CAD diagnoses.

Methods

Primary endpoint was improvement in 6-minute walking distance (6MWD). Secondary endpoints included change in exercise minutes per week (≥150 minutes/week) (EMW150), depression scores (PHQ9), anxiety scores (GAD7) and overall quality of life (COOP) scores.

Results

Between January 2015 and February 2020, 617 patients completed the 12-week-CR program and were divided into: group I (referred for non-CAD diagnosis) (N=188) and group II (referred for CAD diagnosis) (N=429). At the completion of their cardiac rehabilitation program, both groups improved their 6MWD without statistical difference (non-CAD group: +188 (110, 274) feet) vs. +200 (89, 290) feet in CAD group, P=0.86)

Improvements in EMW150 following CR were also similar between both groups (non-CAD group: (%) 54% vs. 51%, in CAD group, P= 0.75). Psychological health scores improved with reduction in GAD7, PHQ9 and COOP scores but changes in scores were not statistically different between both groups. PHQ9 categories showed a significant improvement in the moderate to severe category in patients referred for CAD patients. By adjusting for other covariates, CAD status was not associated with change in 6MWD.

Conclusions

Patients referred to CR for non-CAD diagnoses showed a similar and non-inferior improvement in physical and psychological parameters as patients referred for CAD diagnoses.

Clinical implications

The study emphasizes the importance of enrollment of patients in the CR for a wide spectrum of cardiac diseases including non-CAD in addition to CAD.

Introduction

Cardiac rehabilitation (CR) program referral is a Class IA recommendation by AHA/ACC guidelines [1] after myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), stable angina (SA), valvular heart surgeries (VHD), stable heart failure with reduced ejection fraction ≤40% (HFrEF) and cardiac transplantation (HT). Participation in CR is widely recommended in selected patients with cardiovascular (CV) diseases for secondary prevention [2].

CR in heart diseases is a prognostically vital program, decreases readmission rate and improves quality of life [3]. Most of the evidence supporting the benefits of CR is based on subjects enrolled with coronary artery disease (CAD) related diagnoses. There is less evidence for CR benefits in patients enrolled with non-CAD [4] diagnoses such as stable heart failure with reduced ejection fraction (LVEF≤40%), following valve procedures, and post heart transplantation. No direct comparison was found between the roles of CR in CAD patients versus non-CAD patients.

We aimed to compare the effect of CR on the change in the 6-minute walking distance (6MWD) as a reliable measurement [5] for the mortality and morbidity outcomes chosen in many other studies.

We hypothesized that after completion of CR, subjects enrolled for non-CAD diagnoses will demonstrate improvements in parameters of physical and psychological well-being similar to subjects enrolled for CAD diagnoses.

Methods

This analysis was performed in our prospectively collected Brigham and Women's Hospital CR database (Foxborough, Boston, MA) between January 1,2015 and February 1,2020 (N=848).

The patients were divided into two groups: patients referred for a diagnosis related to CAD such as SA, MI, PCI, CABG; and patients enrolled with a non-CAD related diagnosis as HFrEF, VHD and HT. Patients who did not complete the CR program were excluded. Among our enrolled cohort, 617 patients completed the program and had paired pre- and post-CR data.

The CR program in BWH consists of an outpatient 12-week program in Foxborough, MA. The program included two one-hour sessions per week that incorporated 30-40 minutes of cardiovascular conditioning, 5-15 minutes of resistance training, 10 minutes of warm-up and cool down, and 5 minutes of stretching or relaxation. Exercise prescription for almost all patients was based on a maximal exercise tolerance test (ETT), or on an entry 6MWD test when an ETT was not performed.

Exercise intensity was prescribed based on two parameters: 1) Heart rate (HR): To maintain their HR below the peak from their ETT and 2) RPE (rate of perceived exertion): an RPE 11-13 was prescribed. The physical training was based on the peak heart rate achieved during an initial ETT. Additionally, there was one weekly 60-minute educational session that covered different prevention-related topics, such as nutrition, physical exercise, stress reduction, and medication adherence. Furthermore, five educational sessions were dedicated to heart-healthy diet, including one session that, specifically, addressed weight loss.

The primary outcome was the change from the start of CR to completion in a 6MWD test.

The secondary outcomes consisted of the change in: Exercise minutes per Week (EMW150) (defined as patients who exercised more than 150 minutes per week as recommended by the American heart association(AHA)), overall health related quality of life score determined by the Dartmouth Cooperative Functional assessment (COOP)[6], depression scores by Patient Health Questionnaire-9 (PHQ9)[7] (is a 9-item questionnaire to estimate the prevalence of major depressive symptoms [7]), and anxiety scores by General anxiety disorder-7(GAD7)[7] (is a 7-item questionnaire that measure anxiety frequency) . Reduced scores are better in terms of depression (PHQ9), anxiety (GAD7) and overall quality of life (COOP). Anxiety scores were divided into clinical categories (30): (0-4: no/minimal anxiety, 5-9: Mild anxiety, 10-14: Moderate anxiety, 15-21: Severe anxiety) and depression scores (31) (0-4: No depression, 5-9: Mild depression, 10-14: Moderate depression, 15-19: Moderately severe depression, 20-27: Severe depression). Exercise capacity was assessed by ETT and/or 6MWD.

EMW150 was collected from patient's questionnaires. All parameters were collected at the beginning and at the end of the CR. The study protocol was approved by the Internal Review Board (IRB) at Brigham and Women's hospital.

Statistical analysis

Values are presented as mean +/- standard deviation for normally distributed variables, median and interquartile range for non-normally distributed variables and frequencies or percentage as appropriate. T-test and Wilcoxon signed rank-test were used to compare continuous variables between groups according to normality of distribution. Chi-squared test was used for the analysis of categorical data. We chose to do available case analysis to resolve the issue of missing data.

Multiple linear regression analysis was used to determine if the enrollment diagnosis for CAD was independently related with change in 6MWD. The multivariable adjustment model included: age, sex, body mass index (BMI), CAD, PHQ9, GAD7, COOP (all at baseline). A level of significance of $P \leq 0.05$ was used for statistical significance. The statistical analyses were carried out using Stata statistical package (Stata 16.1).

Results

Between January 2015 and February 2020, 848 subjects participated in our CR program, among them 617 completed the 12-week-CR program and were divided into two groups: patients enrolled for non-CAD diagnoses composed of 188 patients (30%) and patients enrolled for CAD diagnoses composed of 429 patients (70%) (**figure 1)**. Both groups had no significant statistical difference regarding age, weight, BMI, hypertension, and waiting time before enrollment. Compared to subjects enrolled for non-CAD diagnoses, those enrolled for CAD diagnoses were more likely to be men (P=0.007), have diabetes and hyperlipidemia, to be on statins (P=0.02), and have a higher American association of cardiovascular and pulmonary rehabilitation (AACVPR) risk category (P<0.001) **(table 1).** They also had a higher aerobic capacity (P<0.001). Patients enrolled for CAD diagnoses had higher baseline 6MWD than non-CAD participants (median (IQR): 1535 (1293,1755) vs. 1414 (1176,1670) feet, P=0.003). the proportion of patients exercising more than 150 minutes per week was low and similar in both groups (EMW150 N (%): 34 (18%) vs. 83 (19%), P= 0.71). No statistical difference between both groups regarding psychological outcomes except for less GAD7 anxiety scores at baseline in patients referred for non-CAD (P=0.045). Demographic and clinical characteristics by CAD are listed in **table 1.**

The changes in parameters at baseline pre-CR and at follow-up post-CR are described in Tables 2,3: there was a significant improvement (P<0.001) of all parameters in the enrolled for non-CAD group 6MWD (median(IQR): +188 (110, 274) feet or 12%(increase from baseline), EMW150 (%: 18% v. 70%, P<0.001), anxiety and depression categories showed a significant reduction

towards the lowest category as well as the COOP scores were significantly reduced (P<0.001). But no significant change was found in weight and BMI in the enrolled as non-CAD group **(figures 3,4).**

There was a significant improvement (P<0.001) of all parameters in the enrolled for CAD group: 6MWD (+200 (89, 290) feet or 13% (increase from baseline)). Also, anxiety and depression categories showed a significant reduction towards the lowest category as well as the COOP scores were significantly reduced (P<0.001) **(figures 3,4).**

While 6MWD improved in both groups, there was no statistical difference (increase from baseline in the enrolled for non-CAD group 12% vs. 13% in the enrolled for CAD group, P=0.86) **(figure 2).** Improvements in EMW150 following CR were also similar between both groups (enrolled for non-CAD group vs. CAD group: 54% vs. 51%, P=0.75). Psychological health scores (anxiety and depression categories and COOP scores) were not statistically different post CR. (**table 4,5)**.

In a multivariable linear regression model, the enrollment diagnosis for CAD was not independently associated with change in 6MWD (**table 6)**.

Discussion

We studied a contemporary cohort of real-world patients referred to CR for CAD or for non-CAD related diagnoses and demonstrated that patients referred for non-CAD diagnoses derived at least similar physical and psychosocial benefits as participants referred for CAD related diagnoses.

Our results show a strong and significant improvement in all outcomes in both groups.

Both study groups experienced similar improvements in exercise capacity evidenced by comparable increases in 6MWD and EMW150 following CR program participation despite significantly higher baseline heart rate, lower baseline aerobic capacity and lower left ventricular ejection fraction in the referred for non-CAD group. Although the group referred for CAD diagnoses had significantly older patients, more males and more smokers.

An association between the CR program and amelioration of physical and psychological parameters after several cardiac diseases or procedures has been investigated in previous studies[10,11,12,13,14].

Several controlled cohort studies and meta-analyses have found a survival benefit for patients receiving CR after acute coronary syndromes (26% reduction of cardiac mortality, 18% reduction in recurrent hospitalization), even in the modern era of early revascularization and statins, with a proven cost-effectiveness[15]. These benefits appear to be through direct physiological effects of exercise training, but, also, through the effects on risk factors control.

Our results showed a significant decrease in LDL-cholesterol and blood pressure measurements before and after CR program.

In the study by Pollmann et al. [19], they assessed the effect of CR by a 6-minute walk test (6MWT) on 211 patients of 250 who underwent heart valve surgery. There was an improvement in this test distance by 13% from 1145 feet pre-CR to 1289 feet post-CR (P = 0.0016). in a subset analysis of our data, Jafri et al. [20] found that in 115 patients with aortic valve replacement and in 46 patients with mitral valve replacement improved their 6MWD by 14.5 and 12%, respectively. They found that the psychological outcomes (GAD7, PHQ9 and COOP) improved minimally and similarly.

Also, in CAD patients, Sokhteh et al [21] assessed the effect of CR on functional capacity through the 6MWT. They found that there was a significant improvement of nearly 70% in the 6MWT from 974 feet pre-CR to 1670 feet post-CR. The patients in this study had at least three times walking sessions at home per week.

Whereas Gardiner et al [22] found an improvement of 7% in 6MWT in both coronary heart disease patients and non-coronary heart disease patients (n = 78) from 1633 feet to 1751feet ($p \leq 0.001$). For psychological outcomes, PHQ9 score was reduced significantly in the rehab. arm ($P<0.01$).

A meta-analysis by Ciani et al. [23] showed an improvement from 100 feet to 164 feet in patients with stable heart failure with reduced ejection fraction (≤40%). Zhang et al. [24] demonstrated in his study on 130 patients (65 in a CR program vs. 65 controls) referred after PCI post-MI that patients included in the CR arm had their 6MWT improved significantly more than the control arm ($P<0.001$)

Several studies pointed out that exercise is a diagnostic and prognostic tool as well as a therapeutic intervention in stable chronic heart failure which led -widely- to recommend the enrollment of these patients in CR programs. Although the heart failure patients in our study were included, collectively, in the enrolled as non-CAD group of which they represent 27% (50 patients). The results of the study confirm the CR benefit in stable heart failure with reduced ejection fraction (≤40%)[16].

As it was previously mentioned, we would like to emphasize the role of CR in enrolled for non-CAD patients, of them, a relatively new indication is cardiac transplantation patients. This specific cohort of patients represents 3% (5 patients) in our enrolled for non-CAD group. CR in these patients may be effective in reversing the complex pathophysiological consequences associated with cardiac denervation and prevention of immunosuppression-induced adverse effects. The results in this study may help to elaborate the evidence for this new indication[17].

Cardiac valves repair or replacement including TAVR (Transaortic valve replacement) represents 70% (132 patients) which is most of the enrolled for non-CAD group in our study.

Previous studies found in this group of patients a short-term improvement in physical capacity, may positively affects return to work and being cost effective. Voller et al. [18] found; by using the 6MWD; that TAVR patients reached a longer walking distance at discharge after the three-week inpatient structured CR program.

Guidelines emphasize that CR program is essential prognostically for the whole spectrum of CAD from stable angina to acute myocardial infarction to PCI and CABG.

6MWD is a strong outcome to assess CR effect given its validity, reliability and responsiveness as a CR outcome found in a systematic review done by Bellet et al [(5)] (on 11 high-quality

studies). The mean change of 6MWD in the aforementioned systematic review is the same mean change in our study (198 feet, 10 to 28% increase from baseline).

Multivariable linear regression model showed that the enrollment diagnosis is not associated with a change in 6MWD.

Psychological wellbeing measured by PHQ9, GAD7 and COOP scores showed similar improvement in patients enrolled for CAD or non-CAD diagnoses, and a significant decrease in the proportion of subjects with greater than minimal anxiety or depression after CR participation in both groups.

In patients with HFrEF, Middleton et al [25] noticed a significant improvement in PHQ-9 after CR participation (n=19, 5 ± 5 to 3 ± 4, P=0.05). Also, in another study of 79 patients enrolled in CR for various diagnoses including atrial fibrillation (AF), and patients' high risk of coronary artery disease (CAD), an improvement in PHQ9 was observed (n=79, 4.8 to 2.42 (median values), p=<0.01) [25]. The average anxiety and depression scores in our analysis were, however, lower than in these studies.

In a large study of 1403 CR participants, psychological and quality of life measures were assessed pre- and post-CR through three questionnaires [27]. There was a significant improvement in each domain of the COOP score with the smallest change in the 'social support' score (0.11) and the largest change in the 'physical fitness' score (0.82).

One of the major strengths of our analysis is to include a large cohort of well-characterized contemporary patients treated with current standards and using validated outcomes measures of physical and psychosocial wellbeing. However, our study has several limitations: this was an observational cohort, and our analysis included only subjects with paired data who completed

the program. About 25% of patients were non completers with missing follow-up data (with similar baseline data). The patients were classified according to their main referral diagnosis without objective assessment of CAD prevalence or severity. Though it is conceivable that patients in this age group likely have some degree of CAD without it being obstructive. The non-CAD group as well as the CAD group included patients with different pathophysiological mechanisms which could have influenced the outcomes differently. We did not have access to medication dosing and adjustments throughout the program, including antidepressants or anxiety interventions that could affect depression and anxiety scores.

Conclusions

Patients enrolled for a non-CAD diagnosis showed an important and non-inferior improvement in physical and psychological wellbeing parameters comparable to patients enrolled for CAD diagnosis. Our study emphasizes the need to encourage CR participation in all eligible patients including those with CAD or those with non-CAD related diagnoses.

References

1. Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs: Human Kinetics, Incorporated; 2013: p. 4.

2. Simon M, Korn K, Cho L, Blackburn GG, Raymond C. Cardiac rehabilitation: A class 1 recommendation. Cleve Clin J Med. 2018;85(7):551-8.

3. Anderson, L., et al., Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis. J Am Coll Cardiol, 2016. 67(1): p. 1-12.

4. McLaughlin MA. Rehabilitation of the patient with coronary heart disease. In: Fuster V, Harrington RA, Narula J, Eapen ZJ, editors. Hurst's The Heart, 14e. New York, NY: McGraw-Hill Education; 2017.

5. Bellet RN, Adams L, Morris NR. The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness--a systematic review. Physiotherapy. 2012;98(4):277-86.

6. Eaton T, Young P, Fergusson W, Garrett JE, Kolbe J. The Dartmouth COOP Charts: a simple, reliable, valid and responsive quality of life tool for chronic obstructive pulmonary disease. Qual Life Res. 2005;14(3):575-85.

7. Ivanovs R, Kivite A, Ziedonis D, Mintale I, Vrublevska J, Rancans E. Association of depression and anxiety with cardiovascular co-morbidity in a primary care population in Latvia: a cross-sectional study. BMC Public Health. 2018;18(1):328.

8. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 ;140(11) : e596-e646.

9. Gaalema DE, Savage PD, Leadholm K, Rengo J, Naud S, Priest JS, et al. Clinical and Demographic Trends in Cardiac Rehabilitation: 1996-2015. J Cardiopulm Rehabil Prev. 2019;39(4):266-73.

10. Piotrowicz R, Wolszakiewicz J. Cardiac rehabilitation following myocardial infarction. Cardiol J. 2008;15(5):481-7.

11. Taylor RS, Long L, Mordi IR, Madsen MT, Davies EJ, Dalal H, et al. Exercise-Based Rehabilitation for Heart Failure: Cochrane Systematic Review, Meta-Analysis, and Trial Sequential Analysis. JACC Heart Fail. 2019;7(8):691-705.

12. La Rovere MT, Pinna GD, Maestri R, Olmetti F, Paganini V, Riccardi G, et al. The 6-minute walking test and all-cause mortality in patients undergoing a post-cardiac surgery rehabilitation program. Eur J Prev Cardiol. 2015;22(1):20-6.

13. Dendale P, Hansen D, Berger J, Lamotte M. Long-term cost-benefit ratio of cardiac rehabilitation after percutaneous coronary intervention. Acta Cardiol. 2008;63(4):451-6.

14. Patel DK, Duncan MS, Shah AS, Lindman BR, Greevy RA, Jr., Savage PD, et al. Association of Cardiac Rehabilitation with Decreased Hospitalization and Mortality Risk After Cardiac Valve Surgery. JAMA Cardiol. 2019;4(12):1250-9.

15. Gaalema, D.E., et al., Clinical and Demographic Trends in Cardiac Rehabilitation: 1996-2015. J Cardiopulm Rehabil Prev, 2019. 39(4): p. 266-273.

16. Pourafkari L, Ghaffari S, Shahamfar J, Tokhmechian L, Nader ND. The psychological effects of cardiac rehabilitation after coronary revascularization. Turk Kardiyol Dern Ars. 2016;44(3):228-36.

17. Perrier-Melo RJ, Figueira F, Guimarães GV, Costa MDC. High-Intensity Interval Training in Heart Transplant Recipients: A Systematic Review with Meta-Analysis. Arq Bras Cardiol. 2018;110(2):188-94.

18. Völler H, Salzwedel A, Nitardy A, Buhlert H, Treszl A, Wegscheider K. Effect of cardiac rehabilitation on functional and emotional status in patients after transcatheter aortic-valve implantation. Eur J Prev Cardiol. 2015;22(5):568-74.

19. Pollmann AGE, Frederiksen M, Prescott E. Cardiac Rehabilitation After Heart Valve Surgery: Improvement in exercise capacity and morbidity. J Cardiopulm Rehabil Prev. 2017;37(3):191-8.

20. Jafri SH, Hushcha P, Dorbala P, Bousquet G, Lutfy C, Klein J, et al. Physical and Psychological Well-being Effects of Cardiac Rehabilitation on Patients Following Mitral Valve and Aortic Valve Procedures. J Cardiopulm Rehabil Prev. 2022;42(2):90-6.

21. Sahabazi Deh Sokhteh A, Pishkar ZM, Rafizadeh O, Yaghoubinia F. The effect of cardiac rehabilitation program on functional capacity and waist to hip ratio in patients with coronary artery disease: A clinical trial. Jpn J Nurs Sci. 2021;18(2): e12386.

22. Gardiner FW, Regan E, Nwose EU, Bwititi PT, Crockett J, Wang L. Outpatient cardiac rehabilitation: Effects on patient improvement outcomes. Diabetes Metab Syndr. 2017;11 Suppl 2: S1025-s30.

23. Ciani O, Piepoli M, Smart N, Uddin J, Walker S, Warren FC, et al. Validation of Exercise Capacity as a Surrogate Endpoint in Exercise-Based Rehabilitation for Heart Failure: A Meta-Analysis of Randomized Controlled Trials. JACC Heart Fail. 2018;6(7):596-604.

24. Zhang Y, Cao H, Jiang P, Tang H. Cardiac rehabilitation in acute myocardial infarction patients after percutaneous coronary intervention: A community-based study. Medicine (Baltimore). 2018;97(8): e9785.

25. Middleton WA, Savage PD, Khadanga S, Rengo JL, Ades PA, Gaalema DE. Benchmarking Depressive Symptoms in Cardiac Rehabilitation. J Cardiopulm Rehabil Prev. 2021.

26. Patel DK, Duncan MS, Shah AS, Lindman BR, Greevy RA, Jr., Savage PD, et al. Association of Cardiac Rehabilitation with Decreased Hospitalization and Mortality Risk After Cardiac Valve Surgery. JAMA Cardiol. 2019;4(12):1250-9.

27. Turner SC, Evans JA, Bethell HJ, Goddard J. Psychological assessments for cardiac rehabilitation patients. Int J Cardiol. 2003;92(2-3):201-7.

28. Nilsson BB, Lunde P, Holm I. Implementation and evaluation of the Norwegian Ullevaal model as a cardiac rehabilitation model in primary care. Disabil Rehabil. 2019;41(4):481-8.

29. Nilsson BB, Lunde P, Grøgaard HK, Holm I. Long-Term Results of High-Intensity Exercise-Based Cardiac Rehabilitation in Revascularized Patients for Symptomatic Coronary Artery Disease. Am J Cardiol. 2018;121(1):21-6.

30. Spitzer, R.L., et al., A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med, 2006. 166(10): p. 1092-7.

31. Kroenke, K., R.L. Spitzer, and J.B. Williams, The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med, 2001. 16(9): p. 606-13.

Figure and Table LEGENDS

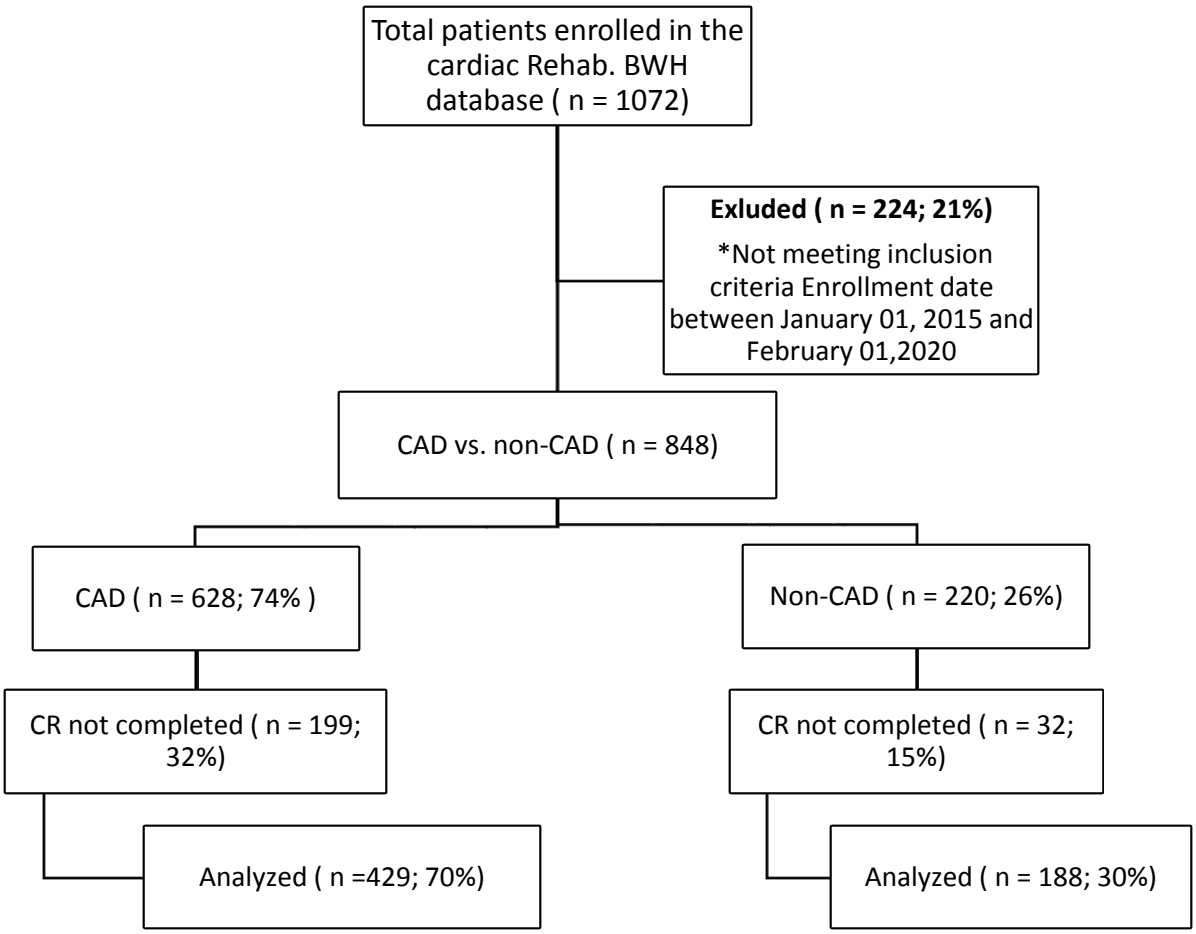


Figure1. Consort diagram for the study patients.

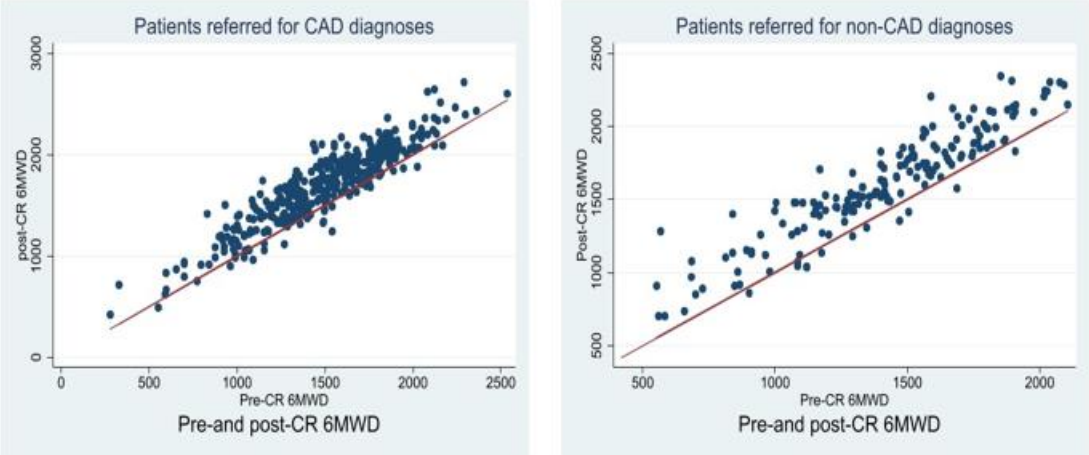


Figure 2. Scatterplot of the 6MWD pre and post CR in non-CAD and CAD groups.

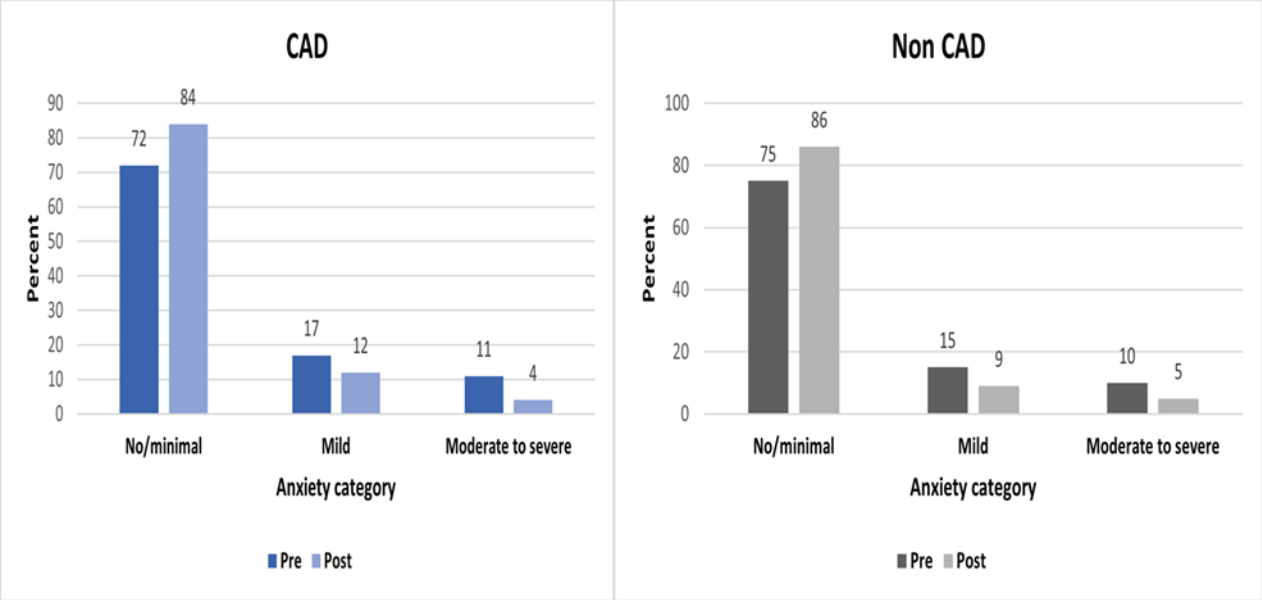


Figure 3. GAD7 anxiety categories before and after CR for both groups.

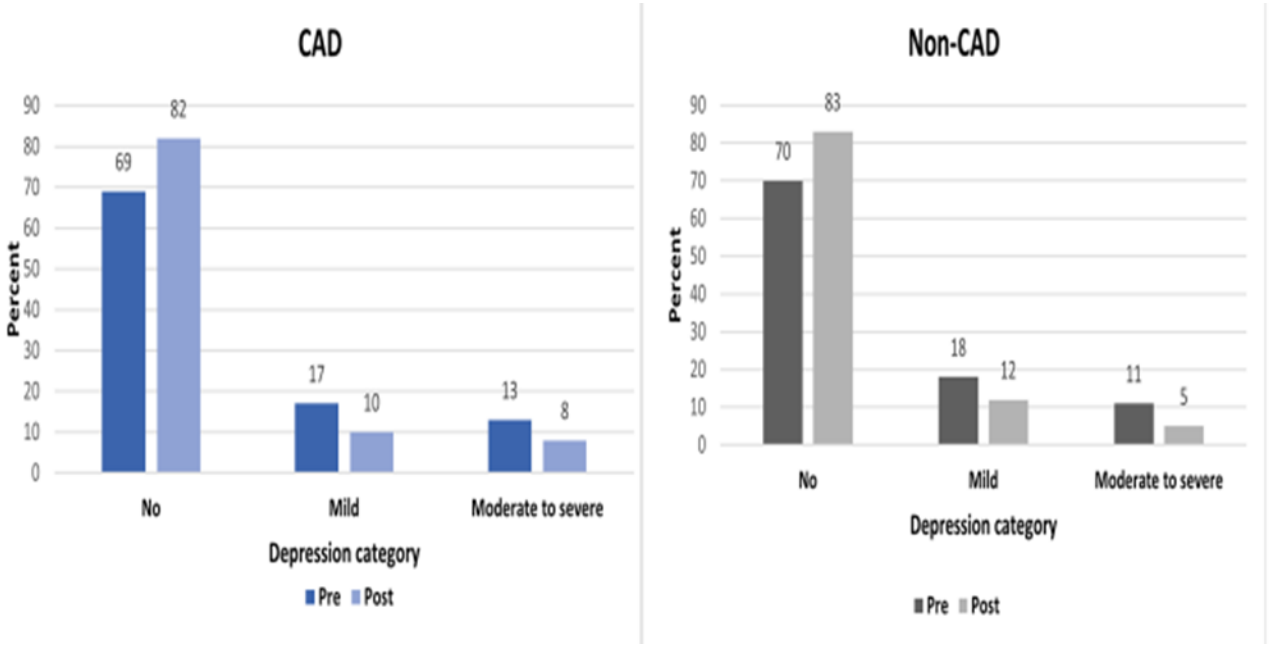


Figure 4. PHQ9 depression categories before and after CR for both groups.

Table 1. Baseline clinical and demographic characteristics (N=617) among CR completers:

Variable name	**Non-CAD (N=188, 30%)**	**CAD (N=429, 70%)**	**P-value**
Demograhics and cardiac risk factors			
Age,years	63 ± 14	64 ± 10	0.51
Males	126(67%)	332(77%)	0.007
Weight,lbs	193 ± 46	194 ± 39	0.76
BMI,kg/m²	29 ± 5.9	29 ± 5	0.99
Hypertension	157(83%)	347(80.9%)	0.44
Smoking	15(8%)	52(12%)	0.13
Diabetes	30(16%)	108(25%)	<0.001
Hyperlipidemia	126(67%)	391(91%)	<0.001
Hemoglobin A1C,% (N = 384)	5.8 ± 0.9	6.1 ± 1	0.009
LDL cholesterol,mg/dl.	83.4 ± 33.8	71.2 ± 33.0	<0.001
Cardiac surgical procedure	138(73%)	146(34%)	<0.001
AACVPR Risk profile			
Low Medium High	41(21%) 56(29%) 91(48%)	163(38 %) 139(32%) 124(29%)	<0.001
Pre CR markers			

Baseline HR,bpm	73 ± 13	68 ± 11	<0.001
Peak HR, bpm	121 ± 23	125 ± 21	0.044
Baseline SBP,mmHg.	126 ± 18.9	127 ± 17	0.57
Baseline DBP,mmHg.	73 ± 9	73 ± 9	0.80
PeakSBP,mmHg.	144 ± 24	157 ± 22	<0.001
PeakDBP,mmHg.	71 ± 10	72 ± 9	0.39
Exercise test, mets (N =573)	6 ± 3	8 ± 3	<0.001
Left ventricular EF, % (N=588)	50 ± 16	56 ± 9	<0.001
Medications			
Beta Blockers	157(83%)	376(87%)	0.17
Calcium Blocker	25(13%)	70(16%)	04
ACEI	83 (44%)	216(50%)	0.15
Statin	124(66%)	410(95.6%)	<0.001
Antidepressant	43(22.9%)	115(26.8%)	0.3
Days to enrollment	39 ± 25	35 ± 35	0.21
Enrollment diagnoses			
AMI	2(1.1 %)	154(35.9%)	<0.001
PCI	5(2.7 %)	241(56.2%)	<0.001
CABG	26(13.8%)	146(34.0%)	<0.001
Heart valve replacement/repair	132(70.2%)	0	<0.001
Heart transplantation	5(2.7 %)	0	<0.001
Heart failure	50(26.6%)	0	<0.001
Stable angina	0	40(9.3 %)	<0.001

Other	12(6.4%)	0	<0.001
Outcomes at baseline			
6MWD, feet	1414 (1176,1670)	1535 (1293,1755)	0.003
EMW150†N (%)	34(18%)	83(19%)	0.71
GAD7[b]	1 (0, 4)	2(0, 5)	0.045
GAD7(clinical interpretation) [c] No/minimal anxiety (0-4) Mild anxiety (5-9) Moderate to severe anxiety (≥10)	 139(74%) 28(15%) 18(9.6 %)	 295(69%) 73(17%) 47(11%)	0.59
PHQ9[d]	2(1, 5)	3(1, 5)	0.93
PHQ9 (clinical interpretation) [e] No depression (0-4) Mild depression (5-9) Moderate to severe depression (≥10)	 130(69%) 31(17%) 24(13%)	 286(67%) 83(19%) 47(11%)	0.60
COOP [f]	18(15, 22)	18(15, 22)	0.51

Abbreviations: AACVPR, American association of cardiovascular and pulmonary rehabilitation; BMI, body mass index; Ibs, pounds; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ETT, exercise tolerance test; AMI, acute myocardial infarction; CR, cardiac rehabilitation; ACEi, angiotensin converting enzyme inhibitors; 6MWD, 6 minute-walking distance; † EMW150, exercise minutes per week if>150 minutes per week.

[a]Data reported as mean ± standard deviations, n (%) or median (interquartile range)
[b]Anxiety scores
[c]Anxiety scores categories: 0-4: no/minimal anxiety, 5-9: Mild anxiety, 10-14: Moderate anxiety, 15-21: Severe anxiety).[265]
[d]Depression scores
[e]Depression scores categories: 0-4: No depression, 5-9: Mild depression, 10-14: Moderate depression, 15-19: Moderately severe depression, 20-27: Severe depression). [27]
[f]Overall health quality

Table 2.Clinical and demographic characteristics pre and post cardiac rehabilitation between both groups (N=617):

Variable name	Non-CAD(N=188, 30%)	CAD(N=429, 70%)	P-value
Weight,lbs			
pre	193 ± 46	194 ± 39	0.76
post	193 ± 45	191 ± 38	0.66
change	0 ± 3	-1 ± 5	0.001
BMI,kg./m²			
pre	29.7 ± 5.9	29.7 ± 5.3	0.99
post	29.5 ± 5.7	29.2 ± 5	0.42
change	-0.1 ± 1	-0.5 ± 0.9	0.001
SBP,mmHg.			
pre	122 ± 19	123 ± 18	0.63
post	117 ± 14	119 ± 12	0.10
change	-5 ± 16	-4 ± 16	0.09
DBP,mmHg.			
pre	71 ± 11	70 ± 10	0.34
post	67 ± 9	68 ± 9	0.26
change	-3 ± 9	-1 ± 10	0.05
LDL cholesterol,mg./dl.			
pre	83 ± 33	71 ± 33	<0.001
post	83 ± 30	60 ± 25	<0.001
change	-0.5 ± 29	-11 ± 30	<0.001

Table 3. Primary and secondary outcomes in both groups pre and post CR(N=617)

Variable name	Non-CAD(N=188,30%)	CAD(N=429,70%)	P-value
6MWD,ft.			
pre	1414 (1176, 1670)	1535 (1293, 1755)	0.003
post	1618 (1417, 1855)	1738 (1475, 1960)	0.004
change	188 (110, 274)	200 (89, 290)	0.86
change,%	12 (5 , 21)	13 (5 , 20)	0.46
EMW150, N (%)			
pre	34(18%)	83(19.3%)	0.71
post	133(71%)	300(70%)	0.84
change	101(54%)	220(51%)	0.75
GAD7			
pre	1 (0 , 4)	2 (0 , 5)	0.045
post	1 (0 , 3)	1 (0 , 3)	0.33
change	0 (-2 , 0)	0 (-3 , 0)	0.21
PHQ9			
pre	2 (1 , 5)	3 (1 , 5)	0.93
post	1 (0 , 3)	1 (0 , 3)	0.75
change	-1 (-3 ,0)	-1 (-3 , 0)	0.98
COOP			
pre	18 (15 , 22)	18 (15 , 22)	0.51
post	16 (13 , 19)	15 (12 , 19)	0.75
change	-3 (-6 , 0)	-2 (-5 , 0)	0.20

Table 4. Multivariable linear regression analysis in study patients for delta 6MWD(N=617)

Variable	Coef.(feet)(95%CI)	P-value
CAD††	2.39(-5.08,29.86)	0.86
Age, years	-2.19(-3.30,-1.07)	<0.001
Sex†	29.41(-0.22,59.03)	0.05
BMI, kg./m^2	-2.79(-5.18,-0.41)	0.02
GAD7	0.27(-4.11,4.64)	0.90
PHQ9	-1.12(-5.77,3.53)	0.64
COOP	0.79(-2.56,4.13)	0.64

Abbreviations:†† CAD, coronary artery diseases (0=NonCAD),1=CAD), BMI, body mass index, 6MWD, 6 minutes walking distance; †sex: one unit increase=men
[a] Values at baseline
[b] Anxiety score
[c] Depression score
[d] Quality of life score

Second manuscript

Physical and psychosocial effects of cardiac rehabilitation participation in women compared to men.

Title Page

Original Investigation

Physical and psychosocial effects of cardiac rehabilitation participation in women compared to men.

Ihab Yassin[1], Majed Malak[1], Pavel Hushcha[3], S. Hammad Jafri[1], Gisele Bousquet[3], Lauren Mellett[3], Lexie Cabral[3], Lindsay Sonis[3], Christine Lutfy[3], Donna Polk[3], Hicham Skali[2,3]

Total word count: 3416

1. Master of Medical Sciences in Clinical Investigation Program, Harvard Medical School, Boston, MA, USA

2. Cardiovascular division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

3. Cardiac Rehabilitation program, Brigham and Women's Hospital, Foxborough, MA, USA

Key words: Cardiac Rehabilitation, sex, gender, females, males, men, women, coronary artery disease, non-coronary artery disease, heart failure, myocardial infarction, stable angina, heart transplantation, percutaneous coronary intervention, valvular heart disease, coronary artery bypass graft.

Funding: Authors deny any financial affiliation for the performance of this investigation.

Disclosures: Authors deny any relationships with the industry.

*Corresponding Author

Hicham Skali, MD, MSc, FACC

Cardiovascular Division, Department of Medicine

Brigham and Women's Hospital

75 Francis Street

Boston, MA, 02115

Phone: 857-307-1988

Email: hskali@bwh.harvard.edu

STRUCTURED ABSTRACT

Background

Despite its proven benefits, cardiac rehabilitation (CR) remains markedly underutilized, particularly among eligible women. We sought to demonstrate whether women enrolled in a contemporary CR program derived similar benefits as men.

Methods

Using a clinical registry of CR participants between January 2015 and February 2020 who completed a standard 12-week CR program, we analyzed changes in physical and psychosocial well-being parameters. Primary endpoint was improvement in 6-minute walking distance (6MWD). Secondary endpoints included change in exercise minutes per week (EMW150)(only patients with more than 150 minutes per week of reported exercise are included), depression scores (PHQ9), anxiety scores (GAD7), and overall quality of life (COOP) scores (lower scores are better)(1) .

Results

There were 617 patients (mean age 64 ± 12 years, 26% women) with complete pre- and post-CR data. At baseline, women had lower 6MWD, lower EMW150, higher GAD7, PHQ9, COOP, heart rate and LV EF. Women were more likely to be referred following a valvular procedure and had fewer CABG. By the end of the CR program, women had similar improvement in their 6MWD as men (women: median (IQR): 14 [7, 20] % (increase from baseline) vs. men: 13[6, 21] % (increase from baseline), p-value=0.87). Women with mild anxiety improved significantly more than men (table 3).

Conclusions

Women who complete a CR program derive similar physical benefits as men and may have greater psychosocial well-being improvements. Efforts to increase CR participation should certainly target eligible women.

Clinical implications

Physical and psychosocial improvements observed in women completing CR are similar to men. Efforts that increase women participation in CR need to be encouraged.

Introduction

Cardiac rehabilitation (CR) is a highly effective secondary prevention measure in patients with cardiovascular disease (CVD) proven to reduce cardiovascular mortality and re-hospitalization in observational and randomized controlled studies[1].

There are known differences between men and women in several aspects of CVD, including risk factors (smoking rate is decreasing less in women), presentation (often an atypical presentation of ischemic heart disease in women), management (diagnosis of ischemic heart disease is often missed more in women), response to therapy, quality of care and outcome [2]. The use of evidence-based treatments appears to be imbalanced according to patient gender as was shown in the study by Rathore et al.[(2)] For the more frequent use of cardiac catheterization in men than women.

Previous studies highlighted the underutilization of CR in women compared to men with lower rates of referral (31 vs 42%), participation (19 vs 29%) and completion (26 vs 28%) [(4)]. The percent of women with improved cardiorespiratory fitness (CRF)-best measured by the vO2 (peak oxygen uptake)[(3)]- is less than men at baseline even after adjusting for age (13 vs 17%). CRF does not improve in women as much as men after CR [(3)]. CR is tied to behavioral or psychosocial factors in women. Some of these barriers are present for both men and women but are more prevalent in women or have a larger impact[(3)].

In this study, we aimed to compare the changes in physical and psychosocial outcomes by sex after CR completion. We hypothesized that after participation in CR, women will demonstrate

similar improvements in physical and psychological parameters to men.

Methods

All enrolled patients in the outpatient CR program (a prospectively collected cohort) from the Brigham and Women's Hospital database (Foxborough, Boston, MA) during the time period between January 1, 2015, and February 1, 2020 (N=848) were included in our study. Patients were grouped according to self-reported sex in medical charts.

The CR program in BWH consists of an outpatient 12-week program in Foxborough, MA. The program included two one-hour sessions per week that incorporated 30-40 minutes of cardiovascular conditioning, 5-15 minutes of resistance training, 10 minutes of warm-up and cool down, and 5 minutes of stretching or relaxation. Exercise prescription for almost all patients was based on a maximal exercise tolerance test (ETT), or an entry 6-minute walking distance (6MWD) when an ETT was not performed. The physical training was based on the peak heart rate achieved during an initial ETT. Additionally, there was one weekly 60-minute educational session that covered different prevention-related topics, such as nutrition, physical exercise, stress reduction, and medication adherence. Furthermore, five educational sessions were dedicated to heart-healthy diet and weight loss.

Among our enrolled cohort, 617 patients completed the program and had paired pre- and post-CR data.

The primary outcome was the change in the 6MWD from the start of CR to completion.

The secondary outcomes consisted of the change in: Exercise minutes per Week (EMW150) (defined as patients who exercised more than 150 minutes per week as recommended by the American heart association(AHA)), overall health related quality of life scores determined by the Dartmouth Cooperative Functional assessment (COOP), depression scores by Patient Health Questionnaire-9 (PHQ9) (is a 9-item questionnaire to estimate the prevalence of major depressive symptoms), and anxiety scores by General anxiety disorder-7(GAD7) (is a 7-item questionnaire that measure anxiety frequency) . Reduced scores are better in terms of depression (PHQ9), anxiety (GAD7) and overall quality of life scores (COOP). Anxiety scores were divided into clinical categories [20]: (0-4: no/minimal anxiety, 5-9: Mild anxiety, 10-14: Moderate anxiety, 15-21: Severe anxiety) and depression scores [21] (0-4: No depression, 5-9: Mild depression, 10-14: Moderate depression, 15-19: Moderately severe depression, 20-27: Severe depression). Exercise capacity was assessed by ETT and/or 6MWD.

EMW150 was collected from patient's questionnaires. All parameters were collected at the beginning and at the end of the CR. The study protocol was approved by the Internal Review Board (IRB) at Brigham and Women's hospital.

Statistical analysis

Values are presented as mean ± standard deviation for normally distributed variables, median and interquartile range for non-normally distributed variables, and frequencies and percentage as appropriate. T-test and Wilcoxon signed rank-test were used to compare continuous variables between groups, and chi-squared test for categorical variables. Only patients with complete paired pre- and post-CR data were included.

Adjusted linear regression was used to assess the association of sex with the change in 6MWD between pre- and post-CR. The multivariable linear regression model included: age, body mass index (BMI), sex, PHQ9, GAD7, COOP (all at baseline). A level of significance of $P \leq 0.05$ was used for statistical significance. Statistical analyses were carried out using Stata statistical package (Stata 16.1).

Results

Between January 2015 and February 2020, 848 subjects were enrolled and participated in our CR program, among them 617 (73%) completed the 12-week-CR program including 159 women (26%) (**figure 1)**. Compared to men, women had higher baseline: heart rate (71 ± 12 vs. 68 ± 12 bpm, P=0.035), and were more likely to be enrolled in CR following non-CAD than CAD diagnoses. Men were more likely to have hypertension, diabetes mellitus, hyperlipidemia, and cardiac surgical procedures (224 (48%) vs. 60 (37%), P=0.01). Both groups had no statistical difference regarding age, BMI, American association of cardiovascular and pulmonary rehabilitation risk score (AACVPR), other exercise tolerance test (ETT) parameters and waiting time before enrollment.

Baseline 6MWD was higher in men than women (median (IQR):1540 (1296, 1760) vs. median (IQR):1405 (1145, 1642) feet, P=0.003). Baseline depression, anxiety and COOP scores were low in both groups but significantly better in men. (Demographic and clinical characteristics by sex are listed in **table 1).**

Tables 2 and 3 show that both groups improved their 6MWD (P<0.001) with a similar increase for women and men (women: median (IQR): 179 [100, 247] feet or 14% [7, 20] vs. 203 [90, 298] feet, P=0.13 or 13% [6, 21] (increase from baseline) in men, P=0.87) **(figure 2).**

Psychological health scores improved significantly in each sex (P<0.001) proved by a reduction in GAD7, PHQ9 and COOP scores. After CR participation, there was a significant increase in the proportion of patients in the no/mild anxiety (figure 3) and no depression (figure 4) categories for both women and men, and the increase was greater in women.

The multivariable linear regression analysis showed that sex was independently correlated with the change in 6MWD **(table 4).**

Discussion

Our study demonstrates that in a large group of contemporary CR participants, improvements in physical outcomes at the end of the CR program were overall important, and similar in men and women, whereas improvements in psychosocial parameters appeared greater in women than men.

Our primary physical endpoint of change in 6MWD improved similarly in men and women.

Our study shows that women had lower percent of all studied traditional risk factors as in a study done by Izawa et al. [4]. Hypertension and obesity rates were elevated in our women cohort, with prevalence rates similar in the literature[5]. Overweight prevalence in women can be a strong factor leading to a poorer physical performance during CR.

For the referral diagnoses for CR, women were more likely to be referred following heart failure, valvular heart diseases, AMI (possibly due to less referral of women for revascularization) and less likely following CABG like it was found by the study done by DeFeo et al.[6].

Our study shows some trends in CR as a study done by Gaalema et al. [8] with an average participant's age of 64 years old and an increase in women participation up to 30%.

Verill et al.[7] found in a short study of 12 weeks a 15% improvement in the 6MWD for each sex with significant statistical difference pre- and post-CR: they found a similar finding with more baseline 6MWD in men than women (1463±339 ft vs, 1243±301, P<0.001) and at follow-up (1683±346 vs. 1435±298 ft., P<0.001). Same results were found in a study by Hamilton et al. with men walking farther than women (P<0.01) [8]. A plausible explanation was mentioned by

Verill et al.[7] referring this difference due to men's longer stride during 6MWD, greater baseline functional capacity or both. Studies done by Lane et al. [9] and O'Farell et al. [10]concluded that men usually have higher levels of physical activity than women leading to better adherence to CR.

In the United States, Brody et al., [11] and Canuto et al., [12]found that women have twice the rate of depression than men, accordingly, the women anxiety and depression impact their participation and attendance in CR. Social relationships impacts the women more, especially, the caregiving for others[3].

Nevertheless, there are inconsistent findings on the correlation between the improvement in physical and psychosocial wellbeing in CR by sex: results range from no correlation[7] to a strong correlation[13] to the hypothesis that the psychosocial improvement will not happen in a short-term CR[14]. Although there were better baseline GAD7, PHQ9 and COOP in men, the scores improvements were more significant in women (P<0,001). However, the anxiety and depression clinical categories were only significantly improved in the mild anxiety category in women (P<0,01) (**figure 3**).

Adjusting for other covariates, sex was found to be associated with the change in 6MWD post CR program. This result is in agreement with multivariable linear regression analysis of a large systematic review including eleven highly selected randomized controlled trials by Bellet et al.,2012 [15].

This study has some strengths by including real-world patients and comparing women to men as the main study group using the 6MWD as the primary outcome post CR: on one hand, The submaximal nature and the self-paced aspect of the 6MWD makes it a very safe evaluation,

because, the test is relatively low intensity, it allows the assessment of individuals who are otherwise limited by their symptoms during an evaluation of their functional status or exercise capacity. The 6MWD has been proven to be a reliable, valid, and reproducible test of functional capacity [15].The majority of previous studies discussing women in CR program focused on their referral, adherence and compliance [17]. However, our study has several limitations: this was an observational cohort, and our analysis included only subjects with paired data who completed the program. About 25% of patients were non completers with missing follow-up data (with similar baseline data). As it was mentioned previously, despite that our primary outcome was physical improvement in 6MWD, women improved significantly psychologically than men. In our study, significantly more women were found to be on antidepressant treatment at baseline than men which affect the generalizability of our results. The discrepancy in the enrollment diagnoses between women and men may add to the lack of generalizability of our results. Also, it has been found by the study by Mamataz et al.[18] That women-targeted CR had better physical improvement by adopting other exercise modalities like dancing and aerobics.

Conclusion

We demonstrate that women who participate in CR derive similar improvements in functional capacity, and possibly greater improvements in psychological wellbeing than men. Accordingly, efforts to increase referral to, and CR participation for all eligible patients should be encouraged, especially if targeting women and groups traditionally less likely to participate. A female-targeted CR may improve physical outcomes.

References

1. Mosca, L., et al., Guide to Preventive Cardiology for Women.AHA/ACC Scientific Statement Consensus panel statement. Circulation, 1999. 99(18): p. 2480-4.

2. Rathore, S.S., et al., Sex differences in cardiac catheterization after acute myocardial infarction: the role of procedure appropriateness. Ann Intern Med, 2002. 137(6): p. 487-93.

3. Verbrugge LM. Gender and health: an update on hypotheses and evidence. J Health Soc Behav. 1985;26(3):156-82.

4. Khadanga, S., et al., Underutilization of Cardiac Rehabilitation in Women: BARRIERS AND SOLUTIONS. J Cardiopulm Rehabil Prev, 2021. 41(4): p. 207-213.

5. Izawa, H., et al., Standard Cardiac Rehabilitation Program for Heart Failure. Circ J, 2019. 83(12): p. 2394-2398.

6. Beckie, T.M., et al., Adverse baseline physiological and psychosocial profiles of women enrolled in a cardiac rehabilitation clinical trial. J Cardiopulm Rehabil Prev, 2008. 28(1): p. 52-60.

7. De Feo, S., et al., Gender differences in cardiac rehabilitation programs from the Italian survey on cardiac rehabilitation (ISYDE-2008). Int J Cardiol, 2012. 160(2): p. 133-9.

8. Verrill, D.E., et al., Six-minute walk performance and quality of life comparisons in North Carolina cardiac rehabilitation programs. Heart Lung, 2003. 32(1): p. 41-51.

9. Hamilton, D.M. and R.G. Haennel, Validity and reliability of the 6-minute walk test in a cardiac rehabilitation population. J Cardiopulm Rehabil, 2000. 20(3): p. 156-64.

10. Lane, D., et al., Predictors of attendance at cardiac rehabilitation after myocardial infarction. J Psychosom Res, 2001. 51(3): p. 497-501.

11. O'Farrell, P., et al., Sex differences in cardiac rehabilitation. Can J Cardiol, 2000. 16(3): p. 319-25.

12. Brody, D.J., L.A. Pratt, and J.P. Hughes, Prevalence of Depression Among Adults Aged 20 and Over: United States, 2013-2016. NCHS Data Brief, 2018(303): p. 1-8.

13. Canuto A, Weber K, Baertschi M, Andreas S, Volkert J, Dehoust MC, et al. Anxiety Disorders in Old Age: Psychiatric Comorbidities, Quality of Life, and Prevalence According to Age, Gender, and Country. Am J Geriatr Psychiatry. 2018;26(2):174-85.

14. Haggerty, M.C., R. Stockdale-Woolley, and R. ZuWallack, Functional status in pulmonary rehabilitation participants. J Cardiopulm Rehabil, 1999. 19(1): p. 35-42.

15. Jungbauer, J.S. and B. Fuller, Feasibility of a multi-state outcomes program for cardiopulmonary rehabilitation. J Cardiopulm Rehabil, 1999. 19(6): p. 352-9.

16. Bellet, R.N., L. Adams, and N.R. Morris, The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness--a systematic review. Physiotherapy, 2012. 98(4): p. 277-86.

17. Rejeski, W.J., et al., Older adults in cardiac rehabilitation: a new strategy for enhancing physical function. Med Sci Sports Exerc, 2002. 34(11): p. 1705-13.

18. Midence, L., et al., Women's Health Behaviours and Psychosocial Well-Being by Cardiac Rehabilitation Program Model: A Randomized Controlled Trial. Can J Cardiol, 2016. 32(8): p. 956-62.

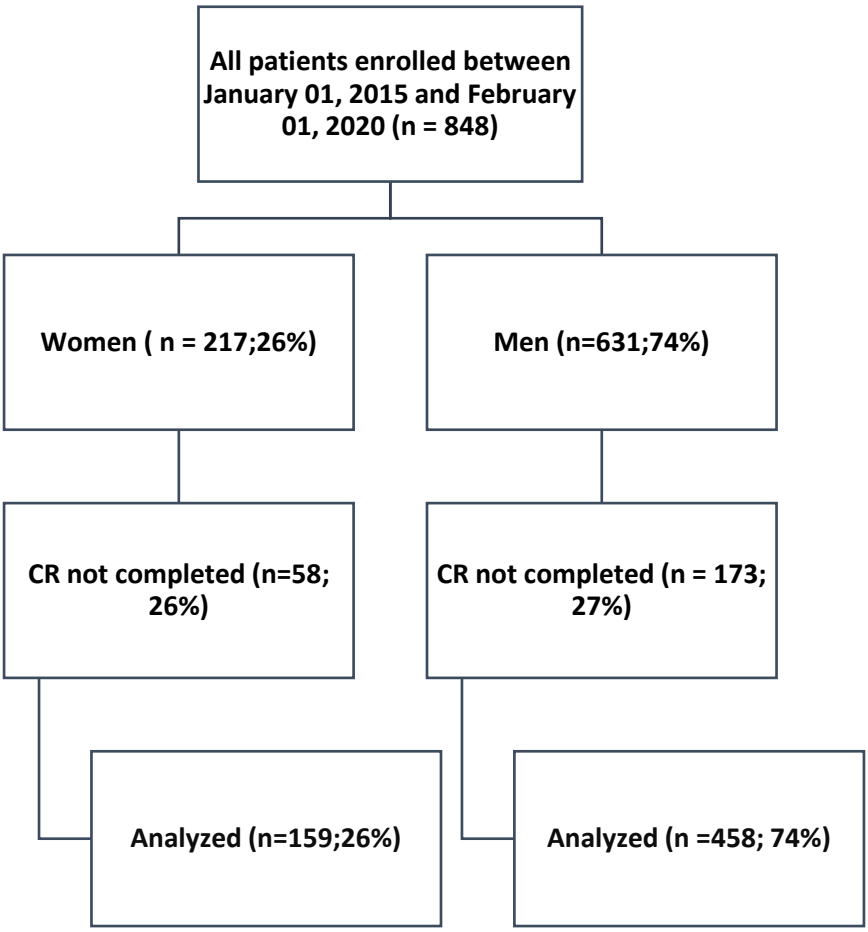
19. Mamataz, T., et al., Nature, availability, and utilization of women-focused cardiac rehabilitation: a systematic review. BMC Cardiovasc Disord, 2021. 21(1): p. 459.

20. Spitzer, R.L., et al., A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med, 2006. 166(10): p. 1092-7.

21. Kroenke, K., R.L. Spitzer, and J.B. Williams, The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med, 2001. 16(9): p. 606-13.

Figure and Table LEGENDS

Figure 1. Consort diagram for the study patients



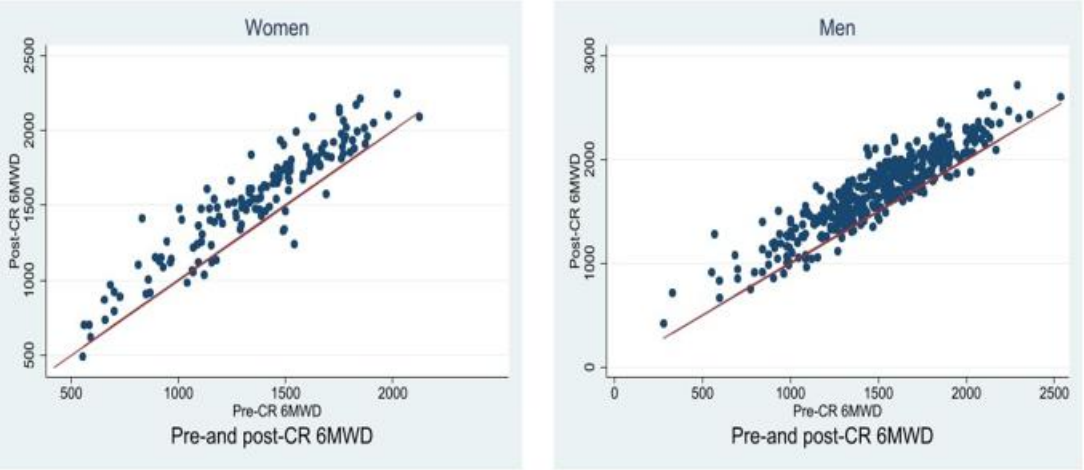


Figure 2. Scatterplot of the 6MWD pre- and post- CR by sex

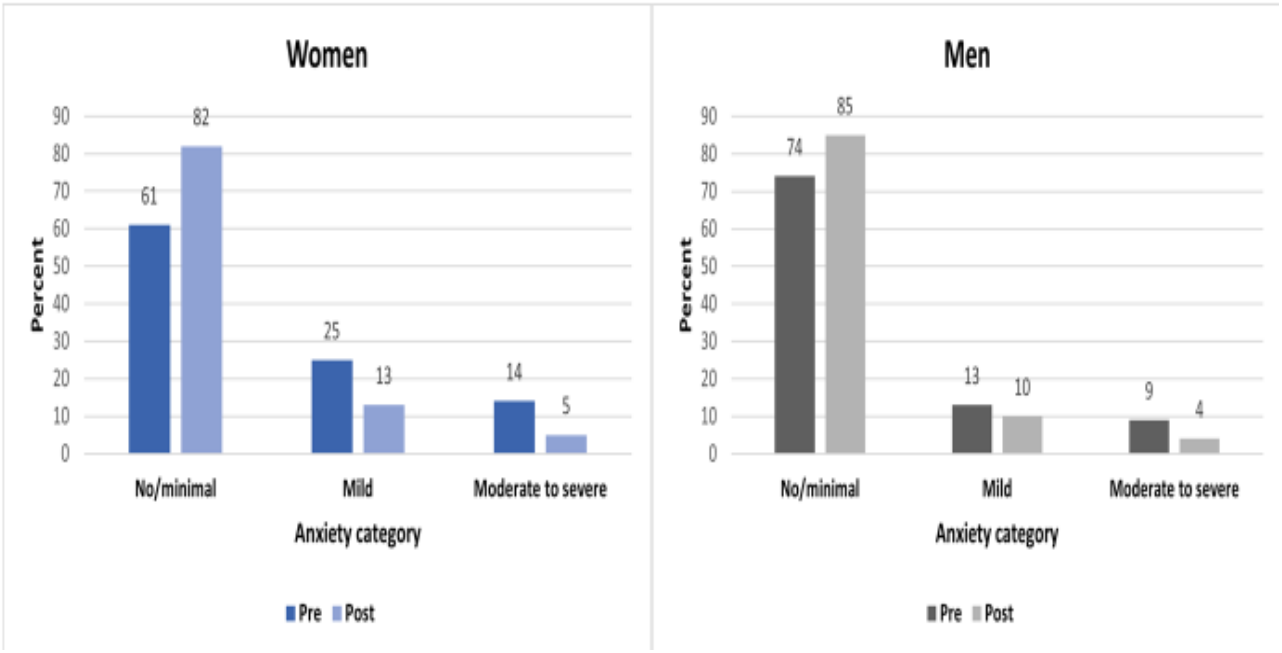


Figure 3. GAD7 anxiety categories before and after CR by sex.

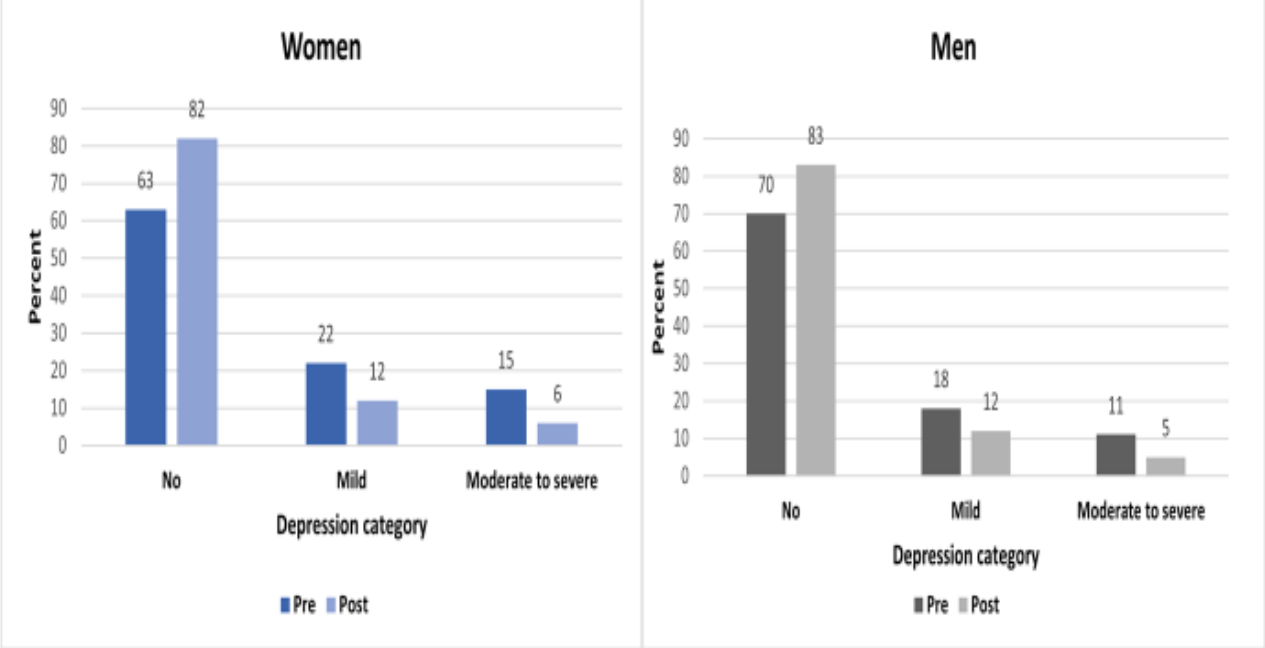


Figure 4. PHQ9 depression categories before and after CR by sex.

Table 1. Baseline clinical and demographic characteristics

Variable name	Women (N=159;26%)	Men (N=458;74%)	P-value
Demograhics and cardiac risk factors			
Age,yrs	64 ± 12	64 ± 11	0.85
Weight,lbs	168 ± 40	203 ± 38	<0.001
Height,in.	63.4 ± 3	69.3 ± 2.9	<0.001
BMI,kg/m²	29 ± 6	29 ± 5	0.50
AACVPR Risk profile			0.55
Low	50(31%)	154(33%)	
Medium	56(35%)	139(30%)	
High	53(33%)	162(35%)	
Pre CR markers			
Baseline HR,bpm	71 ± 12	68 ± 12	0.035
Peak HR, bpm	122 ± 22	125 ± 22	0.16
Baseline SBP, mmHg.	125 ± 18	127 ± 17	0.25
Baseline DBP,mmHg.	71 ± 9	74 ± 9	0.009
Peak SBP,mmHg.	149 ± 23	155 ± 23	0.010
Peak DBP,mmHg.	71 ± 10	72 ± 9	0.19
ETT,mets	6 ± 3	8 ± 3	<0.001
Cardiac risk factors			
Hypertension	122 (76%)	382 (83%)	0.06
Smoking	12 (7.5%)	55 (12%)	0.12
Diabetes	29(18%)	109(24%)	0.014
Hyperlipidemia	123 (77%)	394(86%)	0.011
HbA1C	6 ± 1	6 ± 1	0.73
LDL-cholesterol	87 ± 35	70 ± 32	<0.001
Left ventricular EF	56 ± 12	54 ± 12	0.035
Medications			
Beta blockers	137(86%)	396 (86%)	0.92
Calcium blockers	22 (13%)	73(15%)	0.53
ACEI	63 (39%)	236 (51%)	0.009
Statins	12(7 %)	50 (10%)	0.22
Antidepressant	62(39%)	96(21%)	<0.001
Days to enrollment	36 ± 23	37± 35	0.90
Enrollment diagnoses			
AMI	45 (28%)	111(24%)	<0.001
PCI	66 (41%)	180(39%)	0.62
CABG	21(13%)	151(33%)	<0.001

Heart valve repair/replacement	42(26%)	90(19%)	0.07
Heart transplant	2(1 %)	3(0 .7%)	0.47
Heart failure	17(10%)	33(7 %)	0.17
Stable angina	13(8 %)	27(5 %)	0.31
Other	3(1 %)	9(2 %)	0.95
Cardiac surgical procedure	60(37%)	224(48%)	0.015
Outcomes at baseline			
6MWD	1405 (1145, 1642)	1540 (1296,1760)	<0.001
EMW150†	19(12%)	98(21%)	0.009
GAD7[b]	3(1, 7)	2 (0, 4)	<0.001
Anxiety (GAD7) [c]			0.002
No/minimal (0-4)	94(59%)	340(74%)	
Mild (5-9)	38 (24%)	63(14%)	
Mod. to severe (≥10)	21(13%)	44(10 %)	
PHQ9[d]	3 (1, 6)	2(1, 5)	0.003
PHQ9 [e]			0.17
No (0-4)	97(61%)	319(70%)	
Mild (5-9)	33(21%)	81(18%)	
Mod. to severe (≥15)	23(15%)	48(11%)	
COOP[e]	21 (18, 24)	18 (15, 21)	<0.001

Abbreviations: AACVPR, American association of cardiovascular and pulmonary rehabilitation; BMI, body mass index; Ibs, pounds; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ETT, exercise tolerance test; AMI, acute myocardial infarction; CR, cardiac rehabilitation; ACEi, angiotensin converting enzyme inhibitors; 6MWD, 6 minute-walking distance; EMW150, exercise minutes per week if>150 minutes per week.

[a]Data reported as mean ± standard deviations, n (%) or median (interquartile range)

[b]Anxiety scores

[c]Anxiety scores clinical interpretation: 0-4: no/minimal anxiety, 5-9: Mild anxiety, 10-14: Moderate anxiety, 15-21: Severe anxiety).[(19)]

[c]Depression scores

[d]Depression scores clinical interpretation: 0-4: No depression, 5-9: Mild depression, 10-14: Moderate depression, 15-19: Moderately severe depression, 20-27: Severe depression). [(20)]

[e]Overall health quality

Table 2. Clinical and demographic characteristics pre and post cardiac rehabilitation by sex

Variable name	Women(N=159)	Men(N=458)	P-value
Weight,lbs.			
pre	168 ± 40	203 ± 38	<0.001
post	166 ± 39	200 ± 36	<0.001
change	-0.8 ± 2	-1 ± 5	0.34
change %	0.4 ± 1.7 %	0.6 ± 3%	0.64
BMI, kg. /m²			
pre	29 ± 6	29 ± 5	0.50
post	29 ± 6	29 ± 5	0.67
change	-0.8± 2	-1 ± 5	0.34
SBP,mmHg.			
pre	123 ± 21	122 ± 18	0.90
post	116 ± 12	119 ± 13	0.02
change	-6 ± 18	-3 ± 16	0.05
DBP,mmHg.			
pre	69 ± 9	70 ± 11	0.26
post	67 ± 8	68 ± 9	0.09
change	-2 ± 9	-2 ± 10	0.67
LDL cholesterol, mg./dl.			
pre	87 ± 35	70 ± 32	<0.001
post	76.2 ± 31.7	64 ± 27	<0.001
change	-11 ± 31	-8 ± 31	0.39

Table 3. Primary and secondary outcomes in pre and post CR by sex

Variable name	Women (N=159,26%)	Men(N=458,74%)	P-value
6MWD, ft.			
pre	1405 (1145, 1642)	1540 (1296, 1760)	<0.001
post	1585 (1340, 1820)	1738 (1484, 1992)	<0.001
change	179 [100,247]	203 [90,298]	0.13
change, %	14 [7, 20]	13[6, 21]	0.87
EMW150, N (%)			
pre	19(12%)	98(21%)	0.009
post	99(62%)	334(73%)	0.011
change	81(51%)	240(52%)	0.90
GAD7			
pre	3(1, 7)	2(0, 4)	<0.001
post	1(0, 3)	1(0, 3)	0.41
change	-1(-4, 0)	0(-2, 0)	<0.001
PHQ9			
pre	3(1, 6)	2(1, 5)	0.003
post	1(0, 4)	1(0, 3)	0.13
change	-1(-4, 0)	-1(-2, 0)	0.02
COOP			
pre	21(18, 24)	18(15, 21)	<0.001
post	17(13, 19)	15(12, 18)	0.03
change	-4(-6, 0)	-2(-5, 0)	<0.001

Table 4. Multivariable linear regression analysis for change in 6MWD

6MWD change(feet)	Coef.(feet) (95% CI)	P-value
Sex†	29.65(0.20,59.11)	0.048
Age, years	-2.18(-3.29, -1.07)	<0.001
BMI[a], kg./m^2	-2.79(-5.17, -0.40)	0.022
GAD7[ab]	0.31(-4.01,4.65)	0.886
PHQ9[ac]	-1.14(-5.78,3.48)	0.626
COOP[ad]	0.77(-2.56,4.11)	0.648

Abbreviations: BMI, body mass index, 6MWD, 6 minute-walking distance, †sex: one unit increase=men.
[a] Values at baseline
[b] Anxiety score
[c] Depression score
[d] Quality of life score

1. Mosca, L., et al., Guide to Preventive Cardiology for Women.AHA/ACC Scientific Statement Consensus panel statement. Circulation, 1999. 99(18): p. 2480-4.

2. Rathore, S.S., et al., Sex differences in cardiac catheterization after acute myocardial infarction: the role of procedure appropriateness. Ann Intern Med, 2002. 137(6): p. 487-93.

3. Khadanga, S., et al., Underutilization of Cardiac Rehabilitation in Women: BARRIERS AND SOLUTIONS. J Cardiopulm Rehabil Prev, 2021. 41(4): p. 207-213.

4. Izawa, H., et al., Standard Cardiac Rehabilitation Program for Heart Failure. Circ J, 2019. 83(12): p. 2394-2398.

5. Beckie, T.M., et al., Adverse baseline physiological and psychosocial profiles of women enrolled in a cardiac rehabilitation clinical trial. J Cardiopulm Rehabil Prev, 2008. 28(1): p. 52-60.

6. De Feo, S., et al., Gender differences in cardiac rehabilitation programs from the Italian survey on cardiac rehabilitation (ISYDE-2008). Int J Cardiol, 2012. 160(2): p. 133-9.

7. Verrill, D.E., et al., Six-minute walk performance and quality of life comparisons in North Carolina cardiac rehabilitation programs. Heart Lung, 2003. 32(1): p. 41-51.

8. Hamilton, D.M. and R.G. Haennel, Validity and reliability of the 6-minute walk test in a cardiac rehabilitation population. J Cardiopulm Rehabil, 2000. 20(3): p. 156-64.

9. Lane, D., et al., Predictors of attendance at cardiac rehabilitation after myocardial infarction. J Psychosom Res, 2001. 51(3): p. 497-501.

10. O'Farrell, P., et al., Sex differences in cardiac rehabilitation. Can J Cardiol, 2000. 16(3): p. 319-25.

11. Brody, D.J., L.A. Pratt, and J.P. Hughes, Prevalence of Depression Among Adults Aged 20 and Over: United States, 2013-2016. NCHS Data Brief, 2018(303): p. 1-8.

12. Canuto A, Weber K, Baertschi M, Andreas S, Volkert J, Dehoust MC, et al. Anxiety Disorders in Old Age: Psychiatric Comorbidities, Quality of Life, and Prevalence According to Age, Gender, and Country. Am J Geriatr Psychiatry. 2018;26(2):174-85.

13. Haggerty, M.C., R. Stockdale-Woolley, and R. ZuWallack, Functional status in pulmonary rehabilitation participants. J Cardiopulm Rehabil, 1999. 19(1): p. 35-42.

14. Jungbauer, J.S. and B. Fuller, Feasibility of a multi-state outcomes program for cardiopulmonary rehabilitation. J Cardiopulm Rehabil, 1999. 19(6): p. 352-9.

15. Bellet, R.N., L. Adams, and N.R. Morris, The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness--a systematic review. Physiotherapy, 2012. 98(4): p. 277-86.

16. Rejeski, W.J., et al., Older adults in cardiac rehabilitation: a new strategy for enhancing physical function. Med Sci Sports Exerc, 2002. 34(11): p. 1705-13.

17. Midence, L., et al., Women's Health Behaviours and Psychosocial Well-Being by Cardiac Rehabilitation Program Model: A Randomized Controlled Trial. Can J Cardiol, 2016. 32(8): p. 956-62.

18. Mamataz, T., et al., Nature, availability, and utilization of women-focused cardiac rehabilitation: a systematic review. BMC Cardiovasc Disord, 2021. 21(1): p. 459.

19. Spitzer, R.L., et al., A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med, 2006. 166(10): p. 1092-7.

20. Kroenke, K., R.L. Spitzer, and J.B. Williams, The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med, 2001. 16(9): p. 606-13.

Thesis Conclusions

Patients referred to CR for non-CAD diagnoses showed a similar and non-inferior improvement in physical and psychological parameters as patients referred for CAD diagnoses.

We demonstrate that women who participate in CR derive similar improvements in functional capacity, and possibly greater improvements in psychological wellbeing than men.

Discussion and future perspectives

One of the major strengths of our analysis is to include a large cohort of well-characterized contemporary patients treated with current standards and using validated outcomes measures of physical and psychosocial wellbeing. However, our study has several limitations: this was an observational cohort, and our analysis included only subjects with paired data who completed the program. About 25% of patients were non completers with missing follow-up data (with similar baseline data). The patients in the first study were classified according to their main referral diagnosis without objective assessment of CAD prevalence or severity. Though it is conceivable that patients in this age group likely have some degree of CAD without it being obstructive. The non-CAD group included patients with different pathophysiological mechanisms which could have influenced the outcomes differently.

Our study emphasizes the need to encourage CR participation in all eligible patients including those with CAD or those with non-CAD related diagnoses. Also, efforts to increase referral to, and CR participation for all eligible patients should be encouraged, especially if targeting women and groups traditionally less likely to participate. A female-targeted CR may improve physical outcomes.

Bibliography

Anderson, L., et al., Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis. J Am Coll Cardiol, 2016. 67(1): p. 1-12.

Arnett, D.K., et al., 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation, 2019. 140(11): p. e596-e646.

Baig, M., et al., Cardiac rehabilitation in women; comparison of enrollment, adherence and outcomes between heart failure and coronary artery disease. Heart Lung, 2021. 50(2): p. 223-229.

Beckie, T.M., et al., Adverse baseline physiological and psychosocial profiles of women enrolled in a cardiac rehabilitation clinical trial. J Cardiopulm Rehabil Prev, 2008. 28(1): p. 52-60.

Bellet, R.N., L. Adams, and N.R. Morris, The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness--a systematic review. Physiotherapy, 2012. 98(4): p. 277-86.

Brody, D.J., L.A. Pratt, and J.P. Hughes, Prevalence of Depression among Adults Aged 20 and Over: United States, 2013-2016. NCHS Data Brief, 2018(303): p. 1-8.

Canuto, A., et al., Anxiety Disorders in Old Age: Psychiatric Comorbidities, Quality of Life, and Prevalence According to Age, Gender, and Country. Am J Geriatr Psychiatry, 2018? 26(2): p. 174-185.

Ciani, O., et al., Validation of Exercise Capacity as a Surrogate Endpoint in Exercise-Based Rehabilitation for Heart Failure: A Meta-Analysis of Randomized Controlled Trials. JACC Heart Fail, 2018. 6(7): p. 596-604.

De Feo, S., et al., Gender differences in cardiac rehabilitation programs from the Italian survey on cardiac rehabilitation (ISYDE-2008). Int J Cardiol, 2012. 160(2): p. 133-9.

Dendale, P., et al., Long-term cost-benefit ratio of cardiac rehabilitation after percutaneous coronary intervention. Acta Cardiol, 2008. 63(4): p. 451-6.

Eaton, T., et al., The Dartmouth COOP Charts: a simple, reliable, valid and responsive quality of life tool for chronic obstructive pulmonary disease. Qual Life Res, 2005. 14(3): p. 575-85.

Gaalema, D.E., et al., Clinical and Demographic Trends in Cardiac Rehabilitation: 1996-2015. J Cardiopulm Rehabil Prev, 2019. 39(4): p. 266-273.

Gardiner, F.W., et al., Outpatient cardiac rehabilitation: Effects on patient improvement outcomes. Diabetes Metab Syndr, 2017. 11 Suppl 2: p. S1025-s1030.

Ghisi, G.L., et al., Assessment of patient knowledge of cardiac rehabilitation: Brazil vs Canada. Arq Bras Cardiol, 2013. 101(3): p. 255-62.

Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs. 2013: Human Kinetics, Incorporated.

Haggerty, M.C., R. Stockdale-Woolley, and R. ZuWallack, Functional status in pulmonary rehabilitation participants. J Cardiopulm Rehabil, 1999. 19(1): p. 35-42.

Hamilton, D.M. and R.G. Haennel, Validity and reliability of the 6-minute walk test in a cardiac rehabilitation population. J Cardiopulm Rehabil, 2000. 20(3): p. 156-64.

Ivanovs, R., et al., Association of depression and anxiety with cardiovascular co-morbidity in a primary care population in Latvia: a cross-sectional study. BMC Public Health, 2018. 18(1): p. 328.

Izawa, H., et al., Standard Cardiac Rehabilitation Program for Heart Failure. Circ J, 2019. 83(12): p. 2394-2398.

Jafri, S.H., et al., Physical and Psychological Well-being Effects of Cardiac Rehabilitation on Patients Following Mitral Valve and Aortic Valve Procedures. J Cardiopulm Rehabil Prev, 2022. 42(2): p. 90-96.

Jungbauer, J.S. and B. Fuller, Feasibility of a multi-state outcomes program for cardiopulmonary rehabilitation. J Cardiopulm Rehabil, 1999. 19(6): p. 352-9.

Khadanga, S., et al., Underutilization of Cardiac Rehabilitation in Women: BARRIERS AND SOLUTIONS. J Cardiopulm Rehabil Prev, 2021. 41(4): p. 207-213.

Kim, C., et al., Clinical Practice Guideline for Cardiac Rehabilitation in Korea: Recommendations for Cardiac Rehabilitation and Secondary Prevention after Acute Coronary Syndrome. Korean Circ J, 2019. 49(11): p. 1066-1111.

Kroenke, K., R.L. Spitzer, and J.B. Williams, The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med, 2001. 16(9): p. 606-13.

La Rovere, M.T., et al., The 6-minute walking test and all-cause mortality in patients undergoing a post-cardiac surgery rehabilitation program. Eur J Prev Cardiol, 2015. 22(1): p. 20-6.

Lane, D., et al., Predictors of attendance at cardiac rehabilitation after myocardial infarction. J Psychosom Res, 2001. 51(3): p. 497-501.

Mamataz, T., et al., Nature, availability, and utilization of women-focused cardiac rehabilitation: a systematic review. BMC Cardiovasc Disord, 2021. 21(1): p. 459.

McGregor, G., 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): p. e036089.

McLaughlin, M.A., REHABILITATION OF THE PATIENT WITH CORONARY HEART DISEASE, in Hurst's The Heart, 14e, V. Fuster, et al., Editors. 2017, McGraw-Hill Education: New York, NY.

Middleton, W.A., et al., Benchmarking Depressive Symptoms in Cardiac Rehabilitation. J Cardiopulm Rehabil Prev, 2021.

Midence, L., et al., Women's Health Behaviours and Psychosocial Well-Being by Cardiac Rehabilitation Program Model: A Randomized Controlled Trial. Can J Cardiol, 2016. 32(8): p. 956-62.

Nilsson, B.B., et al., Long-Term Results of High-Intensity Exercise-Based Cardiac Rehabilitation in Revascularized Patients for Symptomatic Coronary Artery Disease. Am J Cardiol, 2018. 121(1): p. 21-26.

Nilsson, B.B., P. Lunde, and I. Holm, Implementation and evaluation of the Norwegian Ullevaal model as a cardiac rehabilitation model in primary care. Disabil Rehabil, 2019. 41(4): p. 481-488.

O'Farrell, P., et al., Sex differences in cardiac rehabilitation. Can J Cardiol, 2000. 16(3): p. 319-25.

Patel, D.K., et al., Association of Cardiac Rehabilitation With Decreased Hospitalization and Mortality Risk After Cardiac Valve Surgery. JAMA Cardiol, 2019. 4(12): p. 1250-1259.

Patel, D.K., et al., Association of Cardiac Rehabilitation With Decreased Hospitalization and Mortality Risk After Cardiac Valve Surgery. JAMA Cardiol, 2019. 4(12): p. 1250-1259.

Perrier-Melo, R.J., et al., High-Intensity Interval Training in Heart Transplant Recipients: A Systematic Review with Meta-Analysis. Arq Bras Cardiol, 2018. 110(2): p. 188-194.

Piotrowicz, R. and J. Wolszakiewicz, Cardiac rehabilitation following myocardial infarction. Cardiol J, 2008. 15(5): p. 481-7.

Pollmann, A.G.E., M. Frederiksen, and E. Prescott, Cardiac Rehabilitation After Heart Valve Surgery: IMPROVEMENT IN EXERCISE CAPACITY AND MORBIDITY. J Cardiopulm Rehabil Prev, 2017. 37(3): p. 191-198.

Pourafkari, L., et al., The psychological effects of cardiac rehabilitation after coronary revascularization. Turk Kardiyol Dern Ars, 2016. 44(3): p. 228-36.

Rathore, S.S., et al., Sex differences in cardiac catheterization after acute myocardial infarction: the role of procedure appropriateness. Ann Intern Med, 2002. 137(6): p. 487-93.

Rejeski, W.J., et al., Older adults in cardiac rehabilitation: a new strategy for enhancing physical function. Med Sci Sports Exerc, 2002. 34(11): p. 1705-13.

Sahabazi Deh Sokhteh, A., et al., The effect of cardiac rehabilitation program on functional capacity and waist to hip ratio in patients with coronary artery disease: A clinical trial. Jpn J Nurs Sci, 2021. 18(2): p. e12386.

Shabani, R., et al., Effect of cardiac rehabilitation program on exercise capacity in women undergoing coronary artery bypass graft in hamadan-iran. Int J Prev Med, 2010. 1(4): p. 247-51.

Simon, M., et al., Cardiac rehabilitation: A class 1 recommendation. Cleve Clin J Med, 2018. 85(7): p. 551-558.

Spitzer, R.L., et al., A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med, 2006. 166(10): p. 1092-7.

Taylor, R.S., et al., Exercise-Based Rehabilitation for Heart Failure: Cochrane Systematic Review, Meta-Analysis, and Trial Sequential Analysis. JACC Heart Fail, 2019. 7(8): p. 691-705.

Terada, T., et al., Sex differences in psychosocial and cardiometabolic health among patients completing cardiac rehabilitation. Appl Physiol Nutr Metab, 2019. 44(11): p. 1237-1245.

Turner, S.C., et al., Psychological assessments for cardiac rehabilitation patients. Int J Cardiol, 2003. 92(2-3): p. 201-7.

Verbrugge, L.M., Gender and health: an update on hypotheses and evidence. J Health Soc Behav, 1985. 26(3): p. 156-82.

Verrill, D.E., et al., Six-minute walk performance and quality of life comparisons in North Carolina cardiac rehabilitation programs. Heart Lung, 2003. 32(1): p. 41-51.

Völler, H., et al., Effect of cardiac rehabilitation on functional and emotional status in patients after transcatheter aortic-valve implantation. Eur J Prev Cardiol, 2015. 22(5): p. 568-74.

Zhang, Y., et al., Cardiac rehabilitation in acute myocardial infarction patients after percutaneous coronary intervention: A community-based study. Medicine (Baltimore), 2018. 97(8): p. e9785.