Universidade de Évora - Instituto de Investigação e Formação Avançada

Programa de Doutoramento em Motricidade Humana

Tese de Doutoramento

Phase III Cardiac Rehabilitation in coronary patients: High-intensity interval training or moderate-intensity continuous training?

Catarina Joaquim Gonçalves

Orientador(es) | Armando Manuel Mendonça Raimundo

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«Education is the most powerful weapon that you can use to change the world».

Nelson Mandela (2004)

DEDICATION

I would like to dedicate this study to all the "sick" and/or apparently "healthy" people who crossed my life in a less good period of theirs, and who were and are sensitive to changes in behavior and lifestyles capable of being, educating and generating happy, strong and healthy human beings!

To my parents and to all the people, who directly or indirectly helped me on this journey.

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I confess that this path has not always been easy, especially to start this Cardiac Rehabilitation project in a region that, despite the high number of patients with heart disease, does not have this or any service for the population. In addition to the difficulties in starting the study, such as obtaining the sample, this study was "caught" by a global pandemic, forcing us to interrupt the intervention several times due to the high risk of contagion associated with heart disease. Therefore, I could not fail to express my gratitude to the people and institutions that helped to make this possible despite all the obstacles, helping in my personal growth as a professional.

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Confesso que este caminho nem sempre foi fácil, sobretudo para conseguir iniciar este projeto de Reabilitação Cardíaca numa região que, apesar do elevado número de doentes com doença cardíaca, não dispõe deste nem de nenhum serviço para a população. A somar às dificuldades em iniciar o estudo, como na obteção da amostra, este estudo ainda foi "apanhado" por uma pandemia mundial, tendo-se que interromper as intervenções por várias vezes, pelo risco elevado associado à doença cardíaca. Por isso, não poderia deixar de expressar a minha gratidão para com as pessoas e instituições que contribuíram para que o mesmo fosse possível apesar de todos os obstáculos, ajudando no meu crescimento pessoal como profissional.

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ClinicalTrials.gov registration**:** This thesis was conducted in accordance with the Declaration of Helsinki and registered at ClinicalTrials.gov (Ref. No. NCT03538119) – **APPENDIX 2**

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Abbreviations and Acronyms

6MWT	Six-minute walking test
AACVPR	American Association of Cardiovascular and Pulmonary Rehabilitation
ACSM	American College of Sports Medicine
AHA	American Heart Association
BMI	Body mass index
bpm	Beats per minute
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CPET	Cardiopulmonary exercise test
CNS	Central nervous system
CR	Cardiac rehabilitation
CRF	Cardiorespiratory fitness
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
HADS	Hospital anxiety and depression scale
HDL	High-density lipoprotein cholesterol
HIIT	High-intensity interval training
HR	Heart rate
HRQOL	Health-related quality of life
HRV	Heart rate variability
LDL	Low-density lipoprotein cholesterol
MI	Myocardial infarction
MICT	Moderate-intensity continuous training
MVPA	Moderate-to-vigorous physical activity
NYHA	The New York Heart Association Functional Classification

PA	Physical Activity
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trial
RPE	Rating of perceived exertion
SBP	Systolic blood pressure
QoL	Quality of life
VO_2peak	Maximal oxygen consumption
WHO	World Health Organization

Measurements

ºC	celsius
dl	decilitre
g	gram
kg	kilogram
l	litre
m	metre
MET	metabolic equivalent
mg	milligram
mm Hg	millimetre of mercury
mmol	millimole
ms	milliseconds
s	seconds

ABSTRACT

This thesis is part of the Ph.D. Program in Human Motricity at the University of Évora, as a branch of deepening skills for research in the scientific field, which aimed to investigate the problem of cardiovascular diseases (CVD). CVD are the number one cause of death worldwide and also in Portugal. The increase in the prevalence of CVD is a public health concern in Portugal. Given the high prevalence of risk factors and the growing number of cases of CVD in Alentejo, where there is no cardiac rehabilitation (CR) coverage, there is an urgent need to implement a CR program. Initially, a systematic review (Paper 1) was carried out to identify the program's ideal exercise intensity and length to improve VO_2peak in patients with CVD in CR. In conclusion, CR performed at moderate to vigorous intensity, namely, high-intensity interval training (HIIT), allows greater benefits for cardiac patients compared to moderate-intensity continuous training (MICT) over 6-12 weeks to increase aerobic capacity and reverse CVD. Next, we produced a case study (Paper 2) to analyze the physiological parameters of people with CVD who belong to CR programs in HIIT and MICT compared with healthy people without CVD. We found that participants with CVD in the MICT group had more than twice as much central nervous system (CNS) fatigue compared to healthy people who did the same protocol, but both groups who did the HIIT protocol (participants with and without CVD) had almost the same CNS fatigue. Furthermore, participants with CVD in the exercise groups (HIIT and MICT) had higher chest temperatures during exercise compared to healthy participants. Thus, after perceiving the physiological responses of a patient with CVD compared to a person without CVD, randomized controlled studies 3, 4, and 5 appear, where we compare 6-week HIIT and MICT interventions (a total of 18 sessions) and their direct and indirect associations in patients with CVD in CR in phase III in the lipid, glycemic and endocrine profile, blood pressure and body composition (Paper 3); physical fitness (body composition, aerobic capacity, and muscle strength), level of physical activity and sedentary behavior (Paper 4); in quality of life and levels of anxiety and depression (Paper 5), where we also compare it with a control group that only performs the usual medical recommendations. In all three studies was found that both exercise groups improved all variables studied compared to the control group and that, within the exercise groups, HIIT could improve health outcomes more positively than MICT. These findings indicate that HIIT may be an effective alternative training method in CR programs for patients with CVD. On the other hand, not participating in any

exercise-based program after a cardiovascular problem is harmful. Finally, we wanted to assess whether there were changes in the lifestyle of these patients and the association of cardiovascular risk factors over time by performing follow-up assessments at 6 and 12 months (Paper 6). We conclude that both CR programs were effective in reducing cardiovascular risk factors over time, as well as in changing the lifestyle of these cardiac patients since there were lower results than at the beginning of the intervention. The HIIT group showed additional improvements compared to MICT over time.

In summary, across all of these studies, we found that both programs showed clinical benefits and are safe for these cardiac patients. It can also be concluded that exercise-based CR is an important service for cardiac patients, given the low dissemination of CR services in the national territory, observing a very asymmetrical distribution with a total absence of centers in Alentejo, it is urgent to promote and create strategies so that CR programs reach a greater number of patients with CVD.

Keywords: Aerobic Exercise; Cardiovascular Diseases; Cardiac Rehabilitation; Cardiovascular Risk Factors; Secondary Prevention.

RESUMO

A presente tese encontra-se enquadrada no programa de Doutoramento em Motricidade Humana da Universidade de Évora, enquanto ramo de aprofundamento de competências para a investigação no domínio científico, a qual procurou investigar a problemática das doenças cardiovasculares (DCV). As DCV são a causa número um de morte no mundo e também em Portugal. O aumento da prevalência das DCV é uma preocupação para a saúde pública em Portugal. Dada a elevada prevalência de fatores de risco e o número crescente de casos de DCV no Alentejo, onde não existe cobertura de reabilitação cardíaca (RC), urge a necessidade de implementar um programa de RC. Inicialmente foi feita uma revisão sistemática (Estudo 1) que teve como objetivo identificar a intensidade do exercício e a duração do programa ideais para melhorar o VO_2pico em pacientes com DCV em RC. Concluindo-se que a RC realizada em intensidade moderada-a-vigorosa, nomeadamente, o treino intervalado de alta intensidade (HIIT), permite maiores benefícios para o doente cardíaco em comparação com o treino contínuo de intensidade moderada (TCM), numa duração de 6-12 semanas, para aumento da capacidade aeróbia e reversão da DCV. De seguida, produzimos um estudo de caso (Estudo 2) para analisar os parâmetros fisiológicos de pessoas com DCV que pertencem a programas de RC, em HIIT e TCM, em comparação com pessoas saudáveis, sem DCV. Verificámos que as pessoas com DCV do grupo TCM apresentam mais que o dobro da fadiga no sistema nervoso central (SNC) em comparação às pessoas saudáveis que realizaram o TCM, mas ambos os grupos que realizaram o HIIT (pessoas com e sem DVC) têm quase a mesma fadiga no SNC. Além disso, ambos os grupos de exercício (HIIT e TCM) das pessoas com DVC apresentaram temperaturas mais elevadas na zona do peito durante o exercício em comparação aos doentes saudáveis. Assim, depois de percebermos as respostas fisiológicas de um doente com DVC em comparação a uma pessoa sem DCV, surgem os estudos controlados randomizados 3, 4 e 5, onde comparamos intervenções de HIIT e TCM de 6 semanas (no total de 18 sessões) e as suas associações diretas e indiretas em pacientes com DCV em RC na fase III no perfil lipídico, glicémico e endócrino, pressão arterial e na composição corporal (Estudo 3); na aptidão física (composição corporal, capacidade aeróbia e força muscular), nível de atividade física e comportamento sedentário (Estudo 4); na qualidade de vida e níveis de ansiedade e depressão (Estudo 5), onde comparámos ainda com um grupo controlo que realiza

apenas as recomendações médicas habituais. Verificou-se nos três estudos controlados randomizados que ambos os grupos de exercício melhoraram todas as variáveis estudadas em comparação ao grupo controlo, e que dentro dos grupos de exercício, o HIIT conseguiu melhorar os resultados de saúde de forma mais positiva do que o TCM. Esses achados indicam que o HIIT pode ser um método de treino alternativo eficaz em programas em CR para pacientes com DCV. Por outro lado, não participar em nenhum tipo de programa baseado em exercícios após um problema cardiovascular mostrou ser prejudicial. Por fim, quisemos avaliar se estes pacientes mantiveram o estilo de vida adquirido com os programas e a associação dos fatores de risco cardiovascular ao longo do tempo realizando avaliações de follow-up aos 6 e aos 12 meses (Estudo 6). Concluímos que ambos os programas de RC mostraram-se eficazes na diminuição dos fatores de risco cardiovascular ao longo do tempo, bem como na mudança do estilo de vida desses pacientes cardíacos visto que houve mantiveram resultados mais baixos que no início da intervenção. Contudo, o grupo HIIT mostrou melhorias adicionais em comparação com o TCM ao longo do tempo.

Em suma, verificámos com estes estudos que ambos os programas mostraram benefícios clínicos e são seguros para estes pacientes cardíacos. Podendo-se concluir que a RC baseada em exercício é um serviço importante para os doentes cardíacos, e dado ao facto que existe uma baixa difusão no território nacional de serviço de RC, observando-se uma distribuição muito assimétrica com ausência total de centros no Alentejo, é urgente promover e criar estratégias para que os programas de RC possam chegar a um maior número de pacientes com DCV.

Palavras-chave: Doenças Cardiovasculares; Exercício Aeróbio; Fatores de Risco Cardiovascular; Prevenção Secundária; Reabilitação Cardíaca.

CHAPTER 1

General Introduction

CHAPTER 1 – General Introduction

Cardiovascular diseases (CVD) is the leading cause of death worldwide, accounting for 30% (16.7 million) of all deaths. Coronary artery disease (CAD) makes up the highest proportion of CVD mortalities and is projected to show an increase of 16.6% by 2030 (WHO, 2018). In Portugal, CVD signify 29.5% of all causes of death, which makes evident the importance in the public health scenario and the need to implement measures aimed at primary and secondary prevention (Andrade et al., 2018). Cardiac rehabilitation (CR) is a secondary prevention tool used worldwide to improve prognosis in patients with various forms of CVD. A key component of a CR program is exercise training which has been shown to influence patients' physical, psychological, and social condition, benefit their quality of life, and control potential complications (Mishra et al., 2022). The CR programs have different phases that support patients from hospitals (phase I, acute) with the transition to their daily activities through phase II (subacute), phase III (outpatient), and phase IV (maintenance) (Mandic et al., 2018).

Exercise programs for patients with CVD traditionally involve mostly low- to moderate- intensity continuous aerobic exercise training, with the consensus that one of the benefits of aerobic exercise is the increase in peak oxygen uptake (VO_2peak) (Mezzani et al., 2013; Moholdt et al., 2011). The current consensus recommends that exercise intensity prescribed for patients with CVD should be approximately 60% of the maximal heart rate (MHR), 50% of the heart rate reserve (HRR), or 12–13 on the Borg scale. Intensities around 85% MHR, 80% HRR, or 15–16 on the Borg scale should represent the upper limits (Mezzani et al., 2013). High-intensity protocols (85–100% of VO_2peak) appear to be of particular interest to scientists, considering their application in patients with CVD based on the effects on the cardiorespiratory and muscle systems (Moholdt et al., 2011). In addition, high-intensity interval training (HIIT) appears to improve the limiting factors of VO_2peak, and VO_2peak itself has been found to be more effective in improving cardiovascular risk factors than moderate-intensity exercise (McGregor et al., 2023; Taylor et al., 2020). As a reference, improving aerobic capacity by 3.5 mL kg^{-1} min^{-1} is associated with a ~15% reduction in CAD/cardiovascular-related mortality (Boden et al., 2013).

A recent meta-analysis (Mitchell et al., 2018) reported higher improvements in maximal aerobic capacity after HIIT programs compared to moderate-intensity programs.

Nevertheless, the optimum exercise intensity prescription in patients with CVD is still a subject of debate (Mitchell et al., 2018). Another recent systematic review on the topic (Hannan et al., 2018) did not report optimal intensity prescription (e.g., the intensity interval that is most effective during exercise interventions to induce favorable changes in aerobic capacity). Thus, despite the literature being replete with studies showing that regular and structured exercise is beneficial for CVD patients, the optimal intensity and length of exercise interventions that bring about greater benefits remain equivocal. Hence, the objective of the systematic review with meta-analysis included in this thesis (**Paper 1**) was to identify, through randomized controlled trials (RCTs) of exercise-based CR, the most effective exercise intensity and intervention length to optimize VO_2peak in patients with CVD.

CR programs' benefits are internationally consensual (WHO, 2018; Corrà et al., 2010), but during the exercise, progressive physiological effects occur on the body temperature, heart rate variability (HRV), blood pressure, and cortical arousal, which have not been studied yet in CR programs. The real question is, what are the physiological differences between cardiac patients and healthy people during exercise, and is it possible to predict the appearance of the disease in people who are clinically healthy or who present an equivocal cardiac clinical condition? Actually, new evaluation and control methods are applied to different sport areas such as performance, but also health. One of these is the analysis of the HRV as a tool to understand the autonomous nervous system status and response to different stimulus (Aguilera et al., 2021; Sánchez-Conde & Clemente-Suárez, 2021), facts directly related to heart and cardiovascular pathologies (Huikuri & Stein, 2013). The analysis of HRV is based in the study of differences in milliseconds (ms) between RR waves of the electrocardiogram; then, using linear, frequency, or nonlinear analysis methods, we can analyze the autonomic nervous system response (Mendoza-Castejón & Clemente-Suárez, 2020; Bustamante-Sánchez et al., 2020). The other method is the use of thermography analysis, which allow us to study microcirculation abnormalities and capillarity disorders to prevent injuries and detect in early stages (Viegas et al., 2020; Sillero-Quintana et al., 2015). Thus, the case control of the thesis (**Paper 2**) aimed to analyze the physiological parameters of thermography, HRV, blood pressure, and cortical arousal in cardiac patients who belong to CR programs of HIIT and MICT, compared to healthy participants.

As stated earlier, exercise-based CR at different intensities can affect the training endurance, aerobic capacity, and intervention effects. Precisely, HIIT has been found to be as effective, if not superior, to MICT in improving clinical outcomes for patients with CVD, including body composition, HR response to exercise, blood pressure, blood lipids, insulin dynamics, physical fitness, heart rate variability (HRV), quality of life (QoL), depression and anxiety (Taylor et al., 2019; Sjölin et al., 2020; Long et al., 2019; Zhang et al., 2016; Smith et al., 2017). Importantly, HIIT also appears to be as safe as MICT for CVD patients (Dun et al., 2019).

However, despite all health improvements, participation in CR is low around the world, which is largely because of limited access (Ades et al., 2017; Mamataz et al., 2021). In Portugal, less than 8% of survivors of any CVD enrolled in CR programs, and adherence is relatively poor among patients who do enroll in CR settings (Andrade et al., 2018). Unfortunately, to date, there are few exercise-based CR programs in the country and the geographic distribution of these centers is poor, with no CR center in the Alentejo region, where there is a higher prevalence of CVD. Although the effect of HIIT has gradually proven beneficial, little is explored about the role and the validity of HIIT on CAD patients in the country. The first RCT present in this thesis (**Paper 3**) aimed to investigate the effects of two different six-week exercise-based programs, HIIT and MICT, on the body composition and blood biomarkers in cardiovascular risk factors and compare them with a control group.

Physical inactivity is an independent risk factor in people with CAD (Stewart et al., 2017). Therefore, within CR programs participants are encouraged to meet the public health physical activity (PA) guidelines to improve health outcomes, namely, achieve at least 150 minutes of moderate-to-vigorous intensity physical activity (MVPA) per week (Woodruffe et al., 2015; Piepoli et al., 2014; Baçady et al., 2007). Also, major health care organizations recommend that CR patients consistently accumulate 30 to 60 minutes of moderate intensity PA per day on more than 5 days of the week and minimize the amount of time that is spent in sedentary behavior (SB) (Balady et al., 2007). Fallavollita et al. (2016) studied coronary artery disease (CAD) patients who underwent a 5-week CR program and verified that CR improved aerobic capacity, while Kim et al. (2015) checked that a 6-week CR exercise program with an intensity of 60–85% heart rate reserve improved aerobic capacity in CVD patients. In addition, resistance training increases muscle strength and endurance, and positively influences cardiovascular risk factors, metabolism, and cardiovascular function in cardiac patients (Vanhees et al. 2012; Fletcher et al., 2013; Williams et al., 2017; Braith & Beck, 2008). Previous studies have shown that exercise-based CR is also beneficial for improving body composition (Pedersen et al., 2019; Giannuzzi et al., 2008; Lear et al., 2006). The objective of the second RCT (**Paper 4**) was to compare the effectiveness of 6-week supervised community-based exercise protocols, a short-duration resting HIIT, and a usual MICT, in improving health indicators among CAD patients. Specifically, the study aimed to assess the impact of these exercise protocols on physical fitness (body composition, aerobic capacity and muscle strength) and PA levels of CAD patients.

As a chronic disease, CAD affects patients' QoL negatively. The presence of depressive symptoms has been associated, more and more, with a higher morbidity and mortality rate in CVD (Schopfer & Forman, 2016). Physical exercise is therefore essential to maximize physical, psychological and social well-being by promoting the development of motor learning skills and cognitive function, which influence QoL (Ståhle & Cider, 2010). Unsar et al. (2007) compared QoL in patients with and without CAD and reported that QoL of patients with CAD is lower in the domains of mobility, hearing, breathing, elimination, usual activities, mental function, discomfort and symptoms, vitality, sexual activity, and total score in compared to patients without this disease. In this regard, there is a need for medical and lifestyle interventions that improve QoL, maintain physical and psychosocial independence, and reduce long-term health and social care utilization. A Cochrane review published in 2016 found that exercise-based CR reduced the risk of cardiovascular mortality and improved QoL, with a reduction in hospital admissions in the short-term, compared with no-exercise control (Anderson et al., 2016). Since the recovery and/or maintenance of QoL is one of the primary goals of CR (Magalhaes et al., 2013) it becomes important to study its impact on QoL, anxiety and depression. However, the comparison effects of HIIT versus MICT on the QoL and mental health in CAD patients are not found in scientific literature. Therefore, the aim of the third RCT of this thesis (**Paper 5**) was to investigate the effects of two community-based exercise CR programs using two protocols: HIIT and MICT on QoL and mental health (anxiety and depression) and compare with a control group (no exercise program).

Patients with CAD are encouraged to maintain an active lifestyle after the completion of exercise-based CR. However, during the observation phase after the completion of CR adherence to structured exercise remains low (Dolansky et al., 2010) and PA engagement decreases significantly (Chase, 2011). Despite the positive impact of MICT and HIIT in community-based CR programs on clinical outcomes, many individuals do not continue to exercise after completion of CR, with only one-third of patients engaging in regular PA when assessed 6 months after completion of CR (Hellman, 1997; Bock et al. 2003). Maintenance of PA is a critical component that is still understudied, particularly in the long term in CAD patients, as any potential benefits of CR are likely to be lost among patients who discontinue their regular exercise routines. The last RCT in the thesis (**Paper 6**) aimed to investigate the effects of two different exercise CR programs (HIIT and MICT) after 6 and 12 months of the end of the intervention on physical fitness, PA, SB, QoL, and mental health; compare the exercise groups with a control group (no intervention), and to assess whether there are changes in the patients' lifestyle and the association with long-term cardiovascular risk factors.

1.1. Pertinence of the study and main objectives

The aging of the Alentejo population is closely related to the increase in the prevalence of CVD in these inhabitants, so this region is an authentic living lab for the implementation of this study which, among other aspects, will allow the monitoring of patients. Thus, it became pertinent to start a CR program in Alentejo, in the district of Évora, an area where there is currently no CR centre-based.

It is essential to encourage the advancement of scientific understanding regarding the most effective type of CR program. By adopting this approach, the program can reach a wider audience and promote preventative measures. The study aims to establish a plan to monitor and evaluate the program's effectiveness through data analysis and document the methodology used. Implementing this will facilitate the implementation of quality improvement methods for effectively coordinating care with other healthcare providers. Additionally, a plan will be created to evaluate the patients' progress after completion of the program.

In addition, we want to use accelerometers in the project (during seven days of a typical week, covering five weekdays and two weekend days) to estimate physical activity levels, sleep behavior, and sedentary behavior and analyze the phenomenon of "Active Couch Potato" which little or nothing has been studied.

Main objective:

- To evaluate the effect of different exercise-based CR programs (HIIT versus MICT) on physical activity levels, health-related quality of life, clinical response, cardiorespiratory fitness, body composition, muscle strength, in reducing sedentary behavior, anxiety, and depression, in patients with coronary artery disease referred to CR phase III.

Specific objectives:

- Start a CR program in Alentejo, in the district of Évora, a region where there is currently no CR center;
- Evaluate the impact of interventions in phase III of the CR on the variables indicated in the general objective:
  - compare the effects of the HIIT versus the MICT program;
  - compare the effects of the intervention groups versus the control group, jointly and separately;
- Assess the impact of interventions at 6 and 12 months after the start of the program on the variables indicated in the general objective;
- Development of knowledge to enable access to CR;
- Compare the results found regarding sedentary behavior with other studies that used the same methodology in different parts of the globe (New Zealand, United States of America, South Africa, Spain, and Australia).

1.2. Contribution in academic and practical terms

With the increase in the prevalence of CVD and the number one cause of death worldwide and in Portugal, this project holds immense significance in terms of scientific knowledge as it promotes and compares the effects of possible CR programs on the population of an area that is still little known with insufficient and almost non-existent scientific studies.

This study is crucial for advancing national knowledge as it tackles one of the most significant issues in Portuguese society – Cardiovascular Diseases – and especially in the Alentejo region, where sedentary lifestyles are common, it is crucial to offer a service that is, currently unavailable for the population – Cardiac Rehabilitation. By implementing this project in the most disadvantaged region, we can provide access and knowledge of CR to those in need. Another aspect to be highlighted, in addition to its innovative character, is the possibility of this CR program being subsequently developed safely and effectively in national terms.

With the implementation of this study, the incentive for the rational development of CR centers will increase, as these should be multiplied throughout the country, with particular attention to the neediest regions of the country, as well as knowledge of the specific training of professionals in health in the area of CR, for inclusion in multidisciplinary teams, which can be carried out in hospitals, centers, and universities, by accredited professionals.

It is important to note that the costs of morbidity related to CVD are substantial, and the publications will address measures to reduce the risk of morbidity in these patients, highlighting the importance of increasing physical activity and reducing sedentary time, which can represent a significant reduction in costs of this disease. In this way, we cannot fail to highlight the economic impact of this intervention, as it will reduce the costs associated with absenteeism and medical treatment, increasing productivity and the quality of life of citizens.

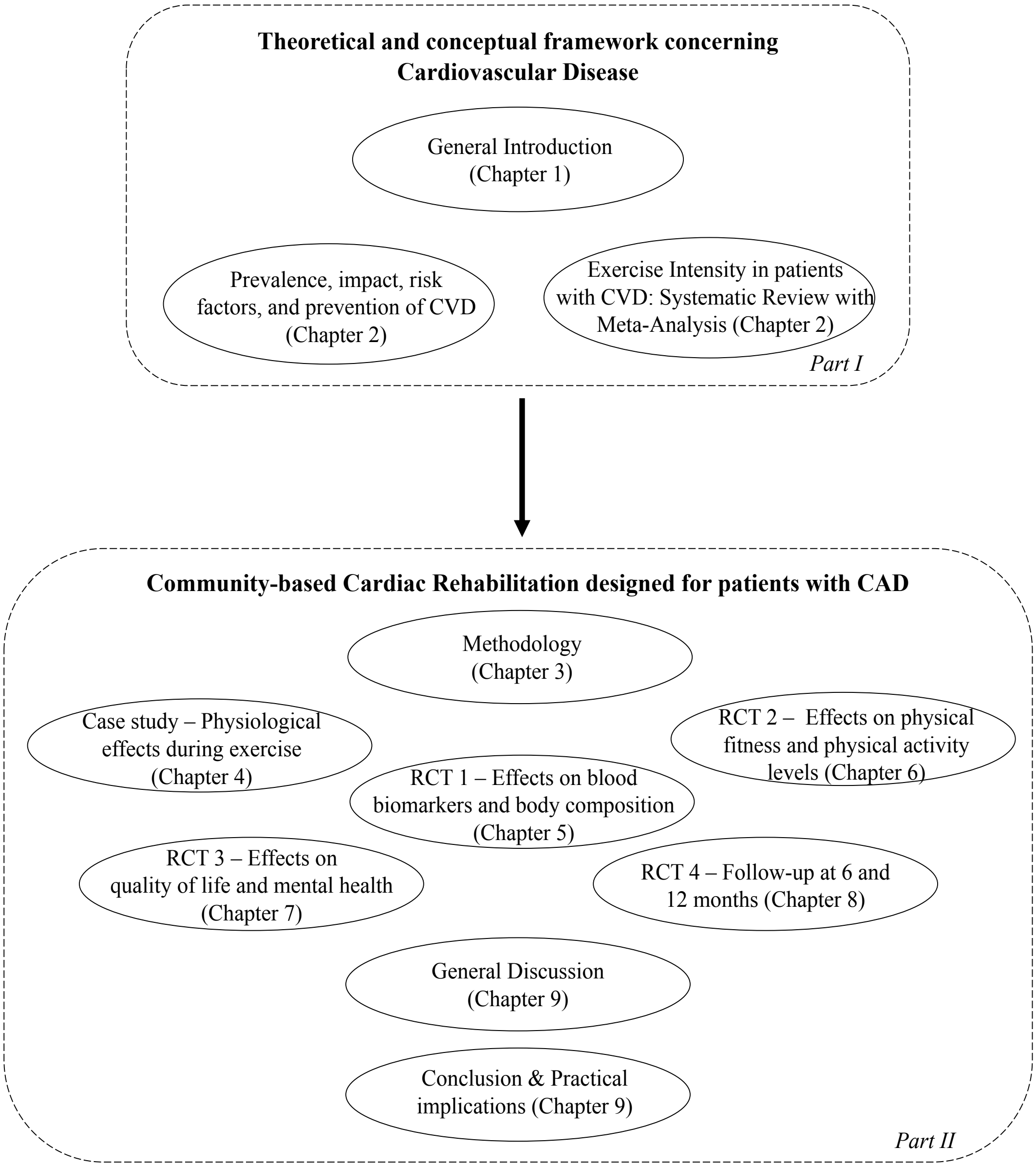
In the present study, Higher Education Institutions articulated with district Hospitals and local Associations, producing relevant knowledge that will be transferable to the community. This thesis is aligned with the Alentejo RS3 initiative, which seeks to connect regional scientific expertise in specific areas like health with social organizations and companies focused on social and health issues. Creating publications that promote physical activity and exercise is crucial for individuals with CVD who are participating in Cardiovascular Rehabilitation.

1.3. Structure of the Thesis

This thesis follows the Scandinavian model (accomplished by scientific papers) and is divided into ten chapters. **Chapter 1** refers to the introduction, where the objectives and hypotheses of the study are explained. In this chapter, we also refer what we expect from this study for scientific knowledge and how the thesis is structured. **Chapter 2** is a literature review, with the theoretical and conceptual framework on cardiovascular diseases exposed, namely their prevalence, the impact of CVD worldwide, risk factors, and primary and secondary preventions. In the latter, we address Cardiac Rehabilitation, exposing the phases that characterize it, the risk stratification of cardiac patients, exercise prescription, benefits, safety, contraindications, and existing CR programs. At the end of this chapter, we present our systematic review with meta-analysis (Paper 1). **Chapter 3** reports the methodology, outlining the study design, procedures, and materials. **Chapters 4**, **5**, **6**, **7**, and **8** are the other published and submitted scientific Papers that describe the thesis's results. **Chapter 9** is the general discussion where we relate the papers. Finally, **Chapter 10** has the conclusions and recommendations for future work/practical implications. An overview of this thesis is presented in **Figure 1.1.**

Figure 1.1.

Outline of this thesis



1.4. Articles included in this Thesis

Paper I: Gonçalves, C., Raimundo, A., Abreu, A., & Bravo, J. (2021). Exercise Intensity in Patients with Cardiovascular Diseases: Systematic Review with Meta-Analysis. *International journal of environmental research and public health*, *18*(7), 3574. https://doi.org/10.3390/ijerph18073574

Paper II: Gonçalves, C., Parraca, J. A., Bravo, J., Abreu, A., Pais, J., Raimundo, A., & Clemente-Suárez, V. J. (2022). Influence of Two Exercise Programs on Heart Rate Variability, Body Temperature, Central Nervous System Fatigue, and Cortical Arousal after a Heart Attack. *International journal of environmental research and public health*, *20*(1), 199. https://doi.org/10.3390/ijerph20010199

Paper III: Gonçalves, C., Raimundo, A., Abreu, A., Pais, J., & Bravo, J. (2024). Effects of High Intensity Interval Training vs Moderate Intensity Continuous Training on Body Composition and Blood Biomarkers in Coronary Artery Disease Patients: A Randomized Controlled Trial. *Reviews in Cardiovascular Medicine*. https://doi.org/10.31083/j.rcm2503102

Paper IV: Gonçalves, C., Bravo, J., Pais, J., Abreu, A., & Raimundo, A. (2024). Improving health outcomes in coronary artery disease patients with short-term protocols of High Intensity Interval Training and Moderate Interval Continuous Training: A community-based randomized controlled trial. *Cardiovascular Therapeutics*. https://doi.org/10.1155/2023/6297302

Paper V: Gonçalves, C., Raimundo, A., Abreu, A., Pais, J., & Bravo, J. (2024). Reviving Hearts Post-Myocardial Infarction: High-Intensity Interval Training vs. Moderate-Intensity Continuous for Enhanced Quality of Life and Mental Well-being: a Randomized Controlled Trial. *Portuguese J Public Health* ***(under review)***

Paper VI: Gonçalves, C., Bravo, J., Pais, J., Abreu, A., & Raimundo, A. (2024). A Comparison of High versus Moderate Intensity of Exercise Training in Patients with Coronary Artery Disease: a Randomized Controlled Trial with 6 and 12 months Follow-up. *J Public Health*. https://doi.org/10.1007/s10389-024-02224-z

Conferences

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Gonçalves, C., Bravo, J., Pais, J., & Raimundo, A. (2023). Exercise-based Programs for cardiac patients: HIIT vs MICT – A Randomized Controlled Trial comparing Fat Loss and Blood Biomarkers. *4th Annual Summit Comprehensive Health Research Centre (CHRC)*. May. Evora, Portugal.

Gonçalves, C., Bravo, J., Pais, J., & Raimundo, A. (2022). Physiological responses during two types of training after Acute Myocardial Infarction Patients. *3rd Annual Summit Comprehensive Health Research Centre (CHRC)*. Nov. Lisbon, Portugal.

Gonçalves, C., Bravo, J., Pais, J., & Raimundo, A. (2022). Relationship between age and cardiac factors in Patients with Coronary Artery Disease. *2nd Annual Summit Comprehensive Health Research Centre (CHRC)*. May. Evora, Portugal.

Gonçalves, C., Bravo, J., Pais, J., Abreu, A., & Raimundo, A. (2021). Correlation Between Endocrine Function, Inflammation, Body Composition, Cardiorespiratory And Muscular Function In Coronary Patients. *Coimbra Health School abstract supplement of Annual Meeting*. Jun. Coimbra, Portugal.

Gonçalves, C., Bravo, J., Abreu, A., Parraça, J., & Raimundo, A. (2020). High-intensity interval training exercise for ambulatory cardiac patients: preliminary results. In: *25th Annual Congress of the European College of Sport Science*. 28th - 30th Oct. Seville, Spain.

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Books

Gonçalves, C., Bravo, J., Abreu, A., Parraça, J., & Raimundo, A. (2020). High-intensity interval training exercise for ambulatory cardiac patients: preliminary results. In: Dela, F., Müller E., Tsolakidis, *E (Eds) Book of Abstracts of the 25th Annual Congress of the European College of Sport Science*. 173-74. Seville, Spain. ISBN: 978-3-9818414-3-5

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Posters

Gonçalves, C., Bravo, J., Pais, J., & Raimundo, A. (2023). Improving health outcomes in myocardial infarction patients with two short-term protocols: A randomized controlled trial. *4th Comprehensive Health Research Centre Annual Summit*. May. Evora, Portugal.

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Master's thesis coordinator

Diogo André Grilo de Oliveira – "Effects of exercise-based cardiac rehabilitation programs with Moderate-intensity continuous training versus High-intensity interval training on Sleep Quality Risk Factors in patients with Cardiovascular Diseases". (2021–2023)

Liliana Correia Faria – "Effects of a Moderate-intensity continuous training versus High-intensity interval training on the Metabolic Syndrome risk Factors in patients with Cardiovascular Diseases enrolled in Exercise-based Cardiac Rehabilitation." (2021–2023)

Awards

Honorable mention by the Portuguese Olympic Committee and the Millennium BCP Foundation in the Sports Medicine category at the 2020 Sports Science Awards.

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CHAPTER 2

Literature Review

CHAPTER 2 – Literature Review

2.1. Cardiovascular Diseases

2.1.1. Definition and Risk Factors

Cardiovascular diseases (CVD) are a group of disorders of the heart and blood vessels and they include:

- **coronary artery disease** – disease of the blood vessels supplying the heart muscle;
- **cerebrovascular disease** – disease of the blood vessels supplying the brain;
- **peripheral arterial disease** – disease of blood vessels supplying the arms and legs;
- **rheumatic heart disease** – damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria;
- **congenital heart disease** – malformations of heart structure existing at birth;
- **deep vein thrombosis and pulmonary embolism** – blood clots in the leg veins, which can dislodge and move to the heart and lungs.

Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain. The most common reason for this is a build-up of fatty deposits on the inner walls of the blood vessels that supply the heart or brain. Strokes can also be caused by bleeding from a blood vessel in the brain or from blood clots.

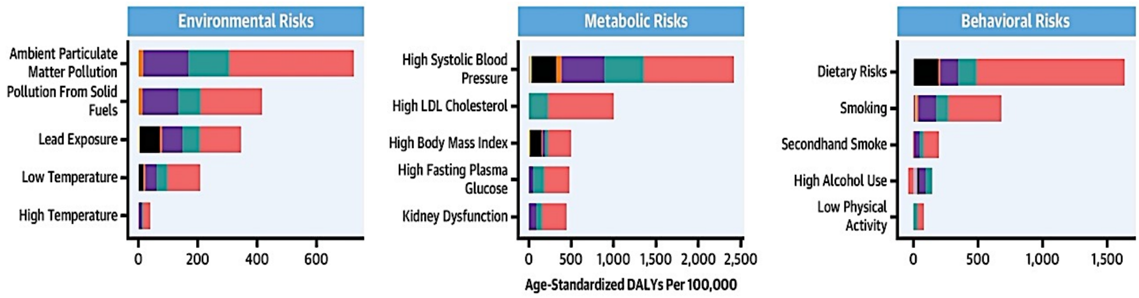
The cause of heart attacks and strokes are usually the presence of a combination of risk factors (**Figure 2.1**), such as tobacco use, unhealthy diet, physical inactivity and harmful use of alcohol, causing increased blood pressure (hypertension), raised blood glucose (diabetes) and lipid levels (hyperlipidemia), overweight and obesity (Wilkins et al., 2017).

Some of the known individual determinants for CVD, such as age, sex, race/ethnicity and family history, are intrinsic to the individual and cannot be modified, whereas others are external and can be at least partially modified. Established risk factors that can be modified to reduce CVD risks include:

- **clinical risk factors** such as high blood pressure, high blood cholesterol, excess weight and obesity, and diabetes. Some of these may be partly hereditary;
- **behavioral risk factors** such as unhealthy diet, lack of physical activity, smoking and alcohol use;
- **environmental risk factors** like exposure to air pollution, noise and chemicals in the environment and the workplace, second-hand smoke, some infectious agents, thermal stress, and limited accessibility to settings that facilitate physical activity like green spaces.

Figure 2.1.

Cardiovascular Risk Factors



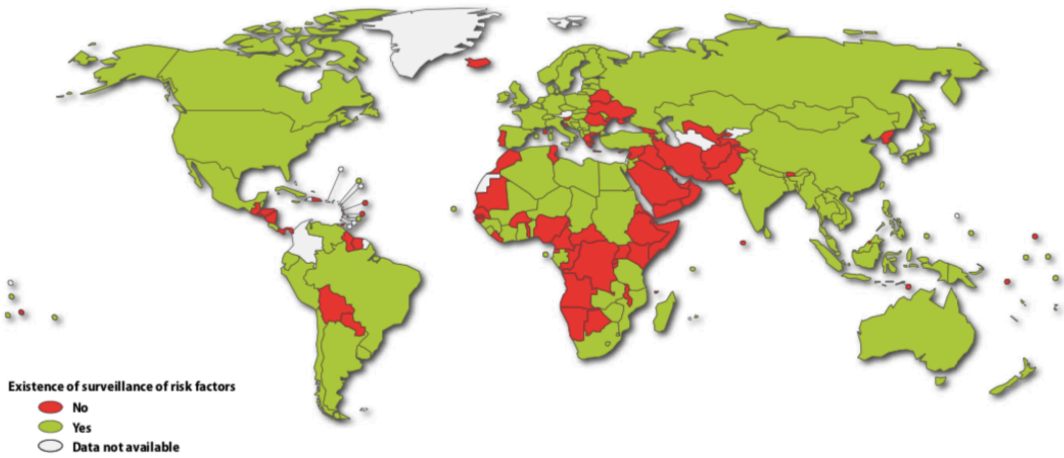
Note. Data Source: Wilkins et al. (2017).

In 2021, according to the World Heart Report (2023), high blood pressure was the leading modifiable risk factor globally for mortality and contributed to 10.8 million CVD deaths worldwide (**Figure 2.2**). Modifiable risk factors that contributed to CVD deaths in 2021 include:

- High blood pressure (10.8 million deaths)
- Air pollution (4.8 million deaths)
- Elevated LDL cholesterol (3.8 million deaths)
- High fasting plasma glucose 2.3 million deaths)
- Tobacco use (3.0 million deaths)
- High body-mass index (2.0 million deaths)
- Low physical activity (397 000 deaths) (Mariachiara et al., 2023).

Figure 2.2.

World map showing countries with surveillance data for risk factors



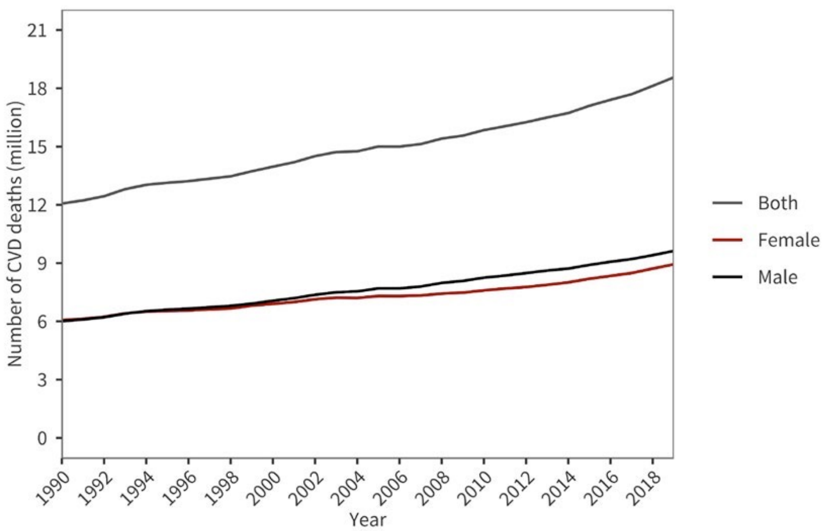
Note. Data Source: World Heart Report (2023).

2.1.2. Prevalence and Impact

Cardiovascular diseases are the number 1 cause of death globally, taking an estimated 17.9 million lives each year, an estimated 31% of all deaths worldwide. More than half a billion people around the world is affected by CVD (**Figure 2.3**), which accounted for 20.5 million deaths in 2021, close to a third of all deaths globally and an overall increase on the estimated 121 million CVD deaths (**Figure 2.4**) (Lindstrom et al., 2021).

Figure 2.3.

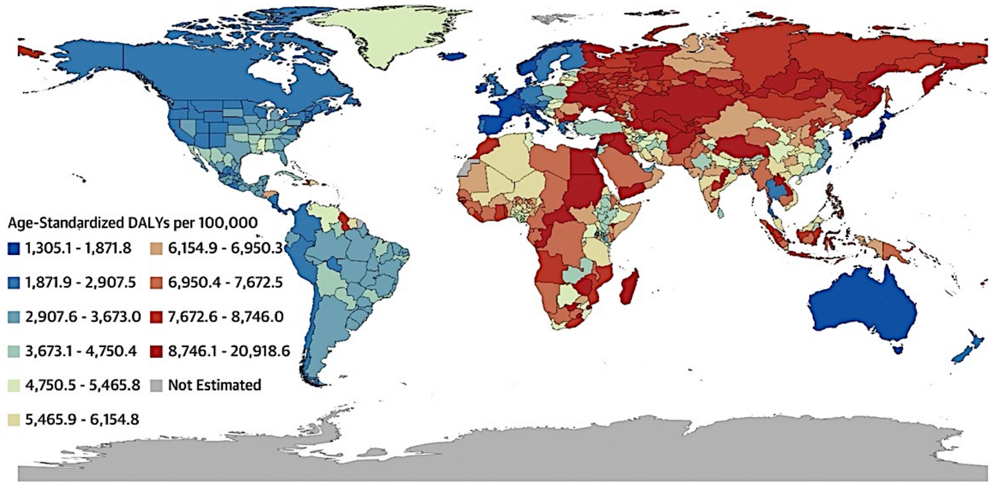
Global trends in number of deaths due to cardiovascular diseases between 1990-2019



Note. Data Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2020. Available from http://vizhub.healthdata.org/gbd-compare (1 July 2023).

Figure 2.4.

Global burden of cardiovascular diseases worldwide

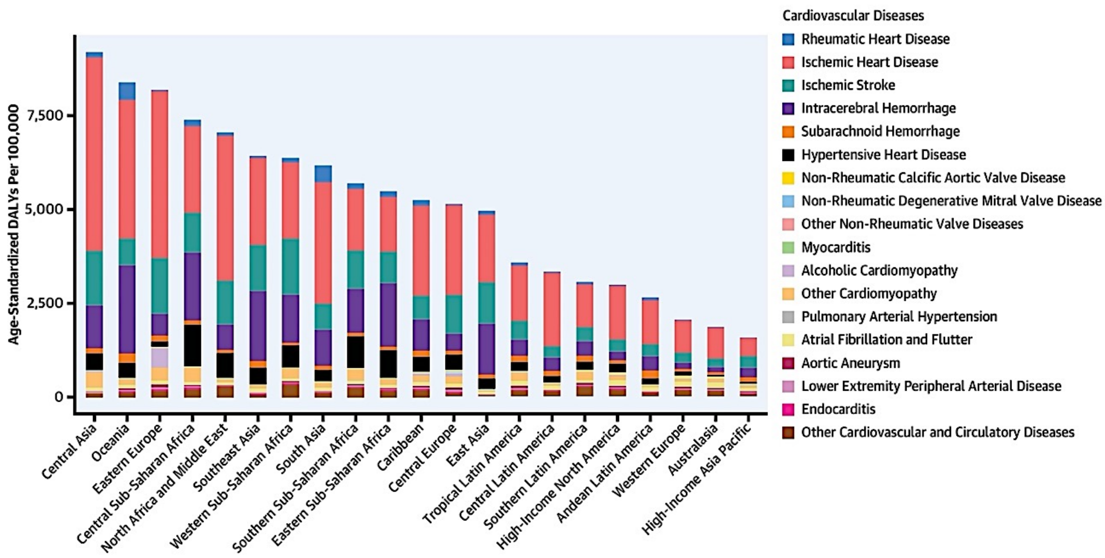


Note. Data Source: Vaduganathan et al. (2022).

The situation regarding CVD in Europe has improved in recent decades. Every year in the Europe, more than 6 million new cases of CVD are diagnosed and over 1.7 million people die from diseases of the circulatory system, representing around 37% of all deaths (Timmis et al., 2022; WHO, 2022). The burden of disease from CVD is generally higher in eastern and central Europe than in northern, southern and western Europe (IHME, 2020; Timmis et al., 2022). The most common heart diseases are coronary artery disease (CAD), congestive heart failure, heart valve disease and arrhythmia (**Figure 2.5**).

Figure 2.5.

Global burden of specific cardiovascular diseases by region

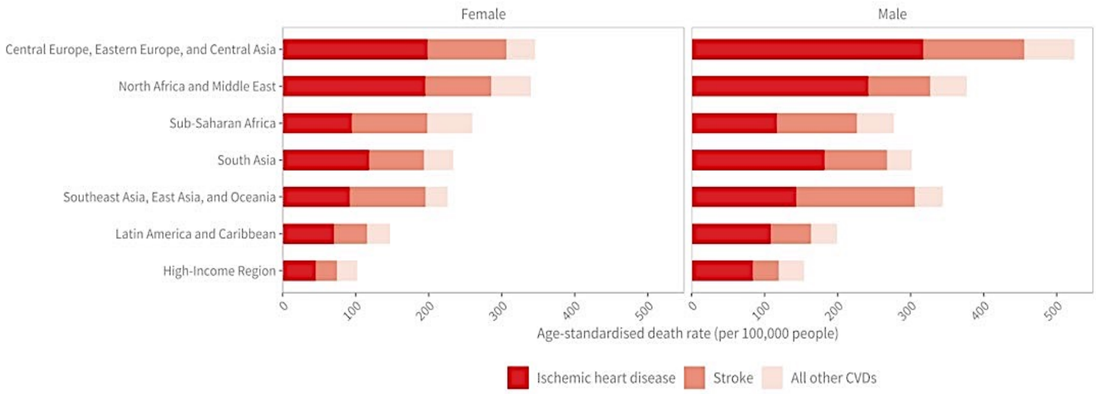


Note. Data Source: Vaduganathan et al. (2022).

In all regions, ischaemic heart disease is the leading cause of CVD mortality across males and females (**Figure 2.6**), accounting for 9.44 million deaths in 2021 and 185 million Age-standardized disability-adjusted life years (DALYs).

Figure 2.6.

Cause-specific regional age-standardised CVD death rate in 2019

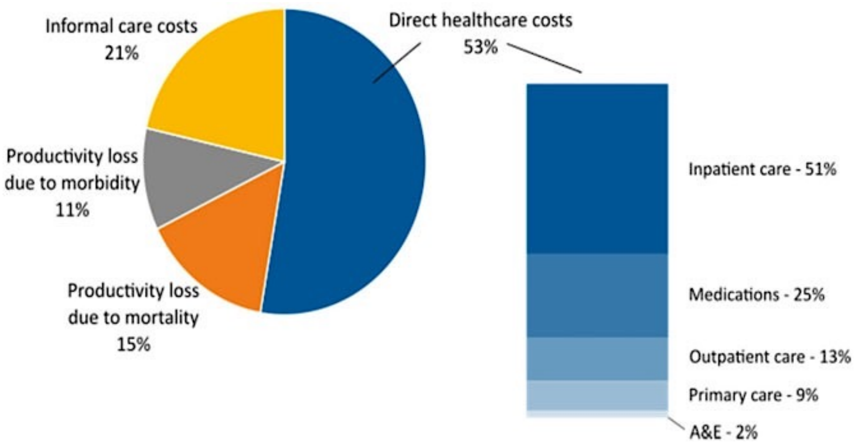


Note. Data Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2020. Available from http://vizhub.healthdata.org/gbd-compare (1 July 2023).

The global burden of CVD is not only a health issue, but an economic challenge to healthcare systems that is expected to grow exponentially in future years (Anand & Yusuf, 2011). Health-care costs associated with CVD in the European Union are estimated to amount for over €100 billion a year, almost 10% of the total healthcare expenses (Wilkins et al., 2017). The cost of CVD, ischemic heart disease, and stroke in the Europe by category are exposed in **Figure 2.7**.

Figure 2.7.

Cost of cardiovascular diseases, ischaemic heart disease, and stroke in Europe by category in 2015

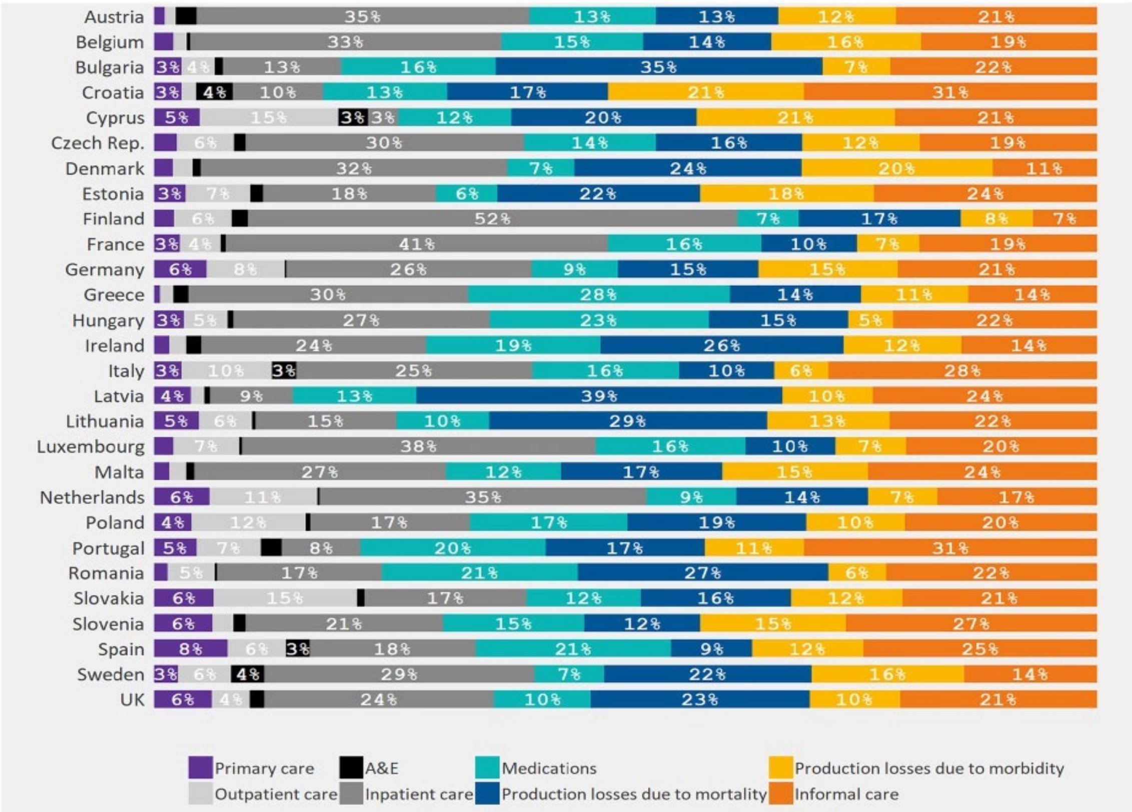


Note. Data source: Wilkins et al. (2017).

The World Disease Heart Federation has estimated that by 2030, the total global cost of CVD is set to rise from approximately €781 billion in 2010 to a staggering €945 billion (Wilkins et al., 2017). The distribution of costs of CVD in the Europe member countries by category in 2015 is exposed in **Figure 2.8**.

Figure 2.8.

Distribution of costs of cardiovascular diseases in the Europe member countries by category in 2015



Note. Data source: Wilkins et al. (2017).

2.1.3. Prevention

Prevention of CVD and its recurrence (secondary prevention) can be achieved by adopting a healthy lifestyle, consisting of regular physical activity, cessation of tobacco use, reduction of salt in the diet, consuming fruits and vegetables, reducing stress levels and avoiding harmful use of alcohol (Rippe, 2018) (**Figure 2.9**). Physical exercise has shown to reduce cardiovascular risk factors (e.g. reduced blood pressure, decreased triglyceride levels and increased HDL cholesterol) and has a direct influence on the heart and cardiovascular system (Franczyk et al., 2023). With physical exercise, the myocardial oxygen demand decreases, endothelial function improves, and the development of coronary collateral vessels is stimulated (Nystoriak & Bhatnagar, 2018; Nickolay et al., 2020). Services, such as cardiac rehabilitation, are used to enhance patient outcomes in functional capacity and quality care. Therefore, physical exercise is considered a crucial part of CR (Taylor et al., 2022).

2.2. Cardiac Rehabilitation

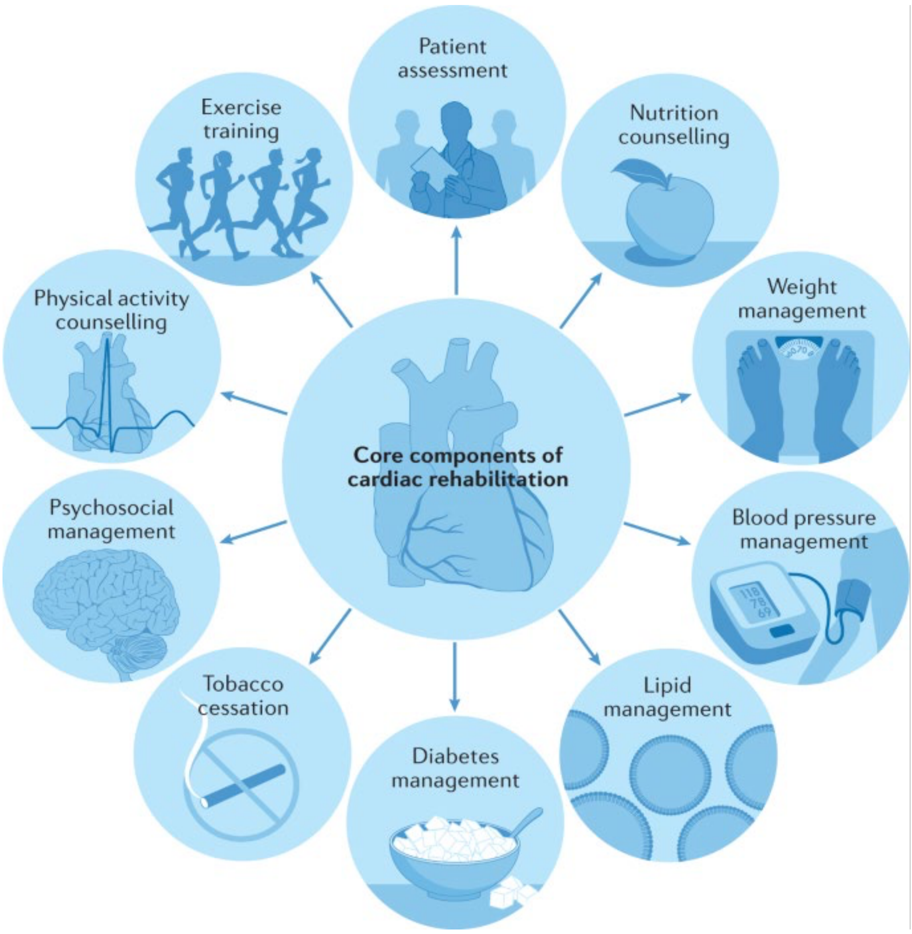
Cardiac Rehabilitation also known as a Secondary Prevention Program, is a multidimensional intervention provided to patients after a cardiac event (myocardial infarction, angina pectoris) or intervention (percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) and/or pharmacological treatment) (Visseren et al., 2021; Arnett et al., 2019; Piepoli et al., 2016).

- **Phase 1** consists of nutritional counseling and education addressing steps to recovery while trying to get the patient physically stable to return to their home in a self-sufficient status (Mampuya, 2012).
- **Phase 2** of CR is a voluntary, outpatient program that consists of up to 36 weeks, with 3 sessions per week of a medically observed, individually tailored exercise program. After a heart event such as an MI, the optimal time to plan Phase 2 of CR is 2-4 weeks after being released from the hospital depending upon the patient's condition. The main goal is to help the patient return to their normal activities of daily living by increasing their functional capacity, implementing a plan to stop smoking, improving the individual's psychosocial wellness, and learning strategies for reducing associated risks of CVD by implementing healthy behavior modifications (Sandercock et al., 2013).
- **Phase 3** (the focus of this thesis) generally lasts for 6-12 weeks, and the main goals are to increase the patient's aerobic capacity, reach a stable psychosocial status, manage risk factors and achieve a heart-healthy lifestyle to maintain health, and avoid a recurrent MI (Balady et al. 2007; Piepoli et al., 2016). Achieving these diverse CR goals (**Figure 2.9**) requires the collaboration of a multidisciplinary team comprising physiotherapists, nurses, psychologists, social workers, dieticians, cardiologists, rehabilitation physicians, and sports physicians. As part of the CR program, patients can choose to become members of the gymnasium available at the facility or continue practicing the skills they have acquired at home (Mampuya, 2012).

Extensive evidence have shown that structured exercise-based CR programs (**Figure 2.9**) reduce mortality, prevent hospital readmission, improve psychosocial well-being, and improve quality of life in patients with CVD in a cost-effective manner (Ambrosetti et al., 2021; Salzwedel et al., 2020; Mandic et al., 2016). Despite the clear benefits associated with CR, uptake is poor worldwide, with the reported uptake rate varying between 20% and 50% (Visseren et al., 2021; Kotseva et al., 2019; Back et al., 2017). Health policies that create conducive environments for making healthy choices affordable and available are essential for motivating people to adopt and sustain healthy behavior. CR has shown to be effective in improving health-related quality of life (HRQOL) and aerobic capacity, and in decreasing the risk for mortality and hospital readmissions in populations of patients with CAD (Uijl et al., 2022; Yue et al., 2022; Li et al., 2023). Previously conducted studies also found that standard exercise-based CR programs are cost-effective (Batalik et al., 2023; Brouwers et al., 2023).

Figure 2.9.

A visual summary of the major components of comprehensive cardiac rehabilitation



Note. Source: Taylor et al. (2022).

The CR program had a multidisciplinary team composed of cardiologists, exercise physiologists, nurses, and a nutritionist/dietitian, psychologists/psychiatrists, physiotherapists and social workers, in order to achieve the general objectives of the program and those specific to each patient (Giannuzzi et al., 2003). This team will have the following functions:

- medical assessment concerning carrying out the program and risk stratification;
- changing risk factors, counseling, and education;
- exercise prescription, individualized and based on the plan drawn up;
- weight control during the six weeks;
- nutritional counseling;
- support and motivate.

Before joining a cardiac rehabilitation program, patients are evaluated to be classified by cardiologists as low, moderate, or high risk through anamnesis, a physical examination, and an exercise test (Liguori, 2022).

2.2.1. Indications and Contraindications for Cardiac Rehabilitation

A safe, progressive plan of exercise should be formulated before leaving the hospital. A pre-discharge low-level submaximal exercise test is useful for prognostic assessment, evaluation of medical therapy or coronary interventions, and physical activity counseling (Gibbons et al., 1997). Until evaluated with an exercise test or entry into a clinically supervised outpatient CR program, the upper limit of exercise should not exceed those levels observed during the inpatient program while closely monitoring for signs and symptoms of exercise intolerance. Patients should be counseled to identify abnormal signs and symptoms suggesting exercise intolerance and the need for medical evaluation. All patients also should be educated and encouraged to investigate outpatient exercise program options with appropriately qualified staff and be provided with information regarding the use of home exercise equipment. All patients, especially moderate- to high-risk patients, should be strongly encouraged to participate in a clinically supervised outpatient CR program (Gibbons et al., 1997; American Association of Cardiovascular and Pulmonary Rehabilitation, 2020).

Before beginning formal physical activity in the inpatient setting, a baseline assessment should be conducted by a health care provider who possesses the skills and competencies necessary to assess and document vital signs, heart and lung sounds, and musculoskeletal strength and flexibility. Initiation and progression of physical activity depends on the findings of the initial assessment and varies with level of risk. Thus, inpatients should be risk stratified as early as possible following their acute cardiac event or procedure. The American College of Sports Medicine has adopted the risk stratification system established by the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) for patients with known CVD because it considers the overall prognosis of the patient and their potential for rehabilitation (Fletcher et al., 2013; Liguori, 2022).

The risk stratification criteria for people with CVD developed by the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) consist of dividing them into three risk categories: low risk, moderate risk, and high risk. The categories are based on data obtained through an exercise test and clinical data.

In the low-risk category, the following data obtained from performing an exercise test must be positive: absence of complex arrhythmias during the exercise test and recovery; absence of angina and other symptoms during the exercise test and recovery; normal hemodynamic response during the exercise test and recovery and functional capacity ≥ 7 METs. Regarding clinical data, the following characteristics must also be positive for the patient considered to be at low risk: safe ejection fraction ≥ 50%; uncomplicated myocardial infarction or revascularization; absence of complex arrhythmias safely; absence of congestive heart failure; absence of signs or symptoms of post-event/post-intervention ischemia and absence of clinical depression (AACVPR, 2013).

In the moderate-risk category, the presence of any one or a combination of the following data obtained by performing an exercise test places the patient at moderate risk: the presence of angina or other significant symptoms, such as shortness of breath or dizziness, on exertion ≥ 7 MET; levels moderate levels of silent ischemia during the exercise test or recovery and functional capacity < 5 METs. In clinical data, the presence of an ejection fraction between 40-49% also places the patient in this category (AACVPR, 2013).

In the high-risk category, the presence of any one or a combination of the following data obtained by performing a stress test places the patient at high-risk: the presence of complex arrhythmias during the stress test or recovery; the presence of angina or other significant symptoms during low levels of effort (< 5 METs) or during recovery; silent high levels of ischemia during the exercise test or recovery; abnormal presence of hemodynamic interruptions during the exercise test or recovery. In clinical data, the presence of the following characteristics also places the patient in this category: safe ejection fraction < 40%; history of cardiorespiratory arrest or death; complex arrhythmias safely; acute myocardial infarction or revascularization with complications; presence of congestive heart failure; presence of signs or symptoms of post-event/post-intervention ischemia and presence of clinical depression (AACVPR, 2013).

At program entry, the following assessments should be performed:

- Medical and surgical history including the most recent cardiovascular event, comorbidities, and other pertinent medical history.
- Physical examination with an emphasis on the cardiopulmonary and musculoskeletal systems.
- Review of recent cardiovascular tests and procedures including 12-lead electrocardiogram (ECG), coronary angiogram, echocardiogram, stress test (AACVPR, 2020; Liguori, 2022).

Indications and contraindications for inpatient and outpatient cardiac rehabilitation according, to the ACSM Guidelines, are described in the following **Table**.

Table 2.1.

Indications and Contraindications for Inpatient and Outpatient Cardiac Rehabilitation (Liguori, 2022)

INDICATIONS	CONTRAINDICATIONS
• Medically stable post–myocardial infarction • Stable angina • Coronary artery bypass graft surgery • Percutaneous transluminal coronary angioplasty • Stable heart failure caused by either systolic or diastolic dysfunction (cardiomyopathy) • Heart transplantation • Valvular heart surgery • Peripheral arterial disease • At risk for coronary artery disease with diagnoses of diabetes mellitus, dyslipidemia, hypertension, or obesity • Other patients who may benefit from structured exercise and/or patient education based on physician referral and consensus of the rehabilitation team	• Unstable angina • Uncontrolled hypertension — that is, resting systolic blood pressure (SBP) >180 mm Hg and/or resting diastolic BP (DBP) >110 mm Hg • Orthostatic BP drop of >20 mm Hg with symptoms • Significant aortic stenosis (aortic valve area <1.0 cm^2) • Uncontrolled atrial or ventricular arrhythmias • Uncontrolled sinus tachycardia (>120 beats, min^{-1}) • Uncompensated heart failure • Third-degree atrioventricular block without pacemaker • Active pericarditis or myocarditis • Recent embolism • Acute thrombophlebitis • Acute systemic illness or fever • Uncontrolled diabetes mellitus • Severe orthopedic conditions that would prohibit exercise • Other metabolic conditions, such as acute thyroiditis, hypokalemia, hyperkalemia, or hypovolemia (until adequately treated)

2.2.2. Exercise Training and Physical Activity Recommendations in Cardiac Rehabilitation

Physical Activity (PA) reduces the risk of many adverse health outcomes and risk factors in all ages and both sexes. There is an inverse relationship between moderate-to-vigorous PA and all-cause mortality, cardiovascular morbidity and mortality, as well as incidence of type 2 diabetes mellitus (Fletcher et al., 2013; Gupta et al., 2023). Exercise Training and Physical Activity Recommendations in CR are exposed in **Table 2.2.**

Table 2.2.

Exercise Training and Physical Activity Recommendations in Cardiac Rehabilitation

Recommendations	**Class[a]**	**Level[b]**
It is recommended for adults of all ages to strive for at least 150-300 min a week of moderate-intensity or 75-150 min a week of vigorous-intensity aerobic physical activity, or an equivalent combination thereof, to reduce all-cause mortality, cardiovascular mortality, and morbidity (Kraus et al., 2019; Powell et al., 2018).	**I**	**A**
It is recommended that adults who cannot perform 150 min of moderate-intensity physical activity a week should stay as active as their abilities and health condition allow (Sattelmair et al., 2011; Hupin et al., 2015).	**I**	**B**
It is recommended to reduce sedentary time to engage in at least activity throughout the day to reduce all-cause and cardiovascular mortality and morbidity (Ekelund et al., 2019; Patterson et al., 2018; Biswas et al., 2015).	**I**	**B**
Performing resistance exercise, in addition to aerobic activity, is recommended on 2 or more days per week to reduce all-cause mortality (Liu et al., 2019; Saeidifard et al., 2019).	**I**	**B**
Lifestyle interventions, such as group or individual education, behavior-change techniques, telephone counselling, and use consumer-based wearable activity trackers, should be considered to increase physical activity participation (Cradock et al., 2017; Howlett et al., 2019; Brickwood et al., 2019).	**IIa**	**B**

Note. [a]Class of recommendation (Class I. Conditions for which there is evidence for and/or general agreement that a procedure or treatment is beneficial, useful, and effective; Class IIa. Weight of evidence/opinion is in favor of usefulness/efficacy); [b]Level of evidence (Level of Evidence A. Data derived from multiple randomized clinical trials or meta-analyses; Level of Evidence B. Data derived from a single randomized clinical trial or large non-randomized studies).

2.2.3. Exercise Prescription for Patients with Cardiovascular Diseases

As mentioned previously, the American College of Cardiology (ACC) and American Heart Association (AHA) Guideline Update for Exercise Testing states exercise testing at baseline is essential for the development of an exercise prescription in patients who suffered from myocardial infarction (MI) with (Class I recommendation) or without (Class IIa recommendation) revascularization, as well as those patients who have undergone coronary revascularization alone (Class IIa recommendation). The test should be completed while the patient is stable on guideline-based medications (Gupta et al., 2023).

Exercise-based CR guidelines emphasis a progressive training regimen with aerobic exercise intensities ranging from moderate to high levels, combined with strength training at least three times per week, according to the FITT (frequency, intensity, time, type) guidelines (Liguori, 2022). In addition, patients are encouraged to incorporate a minimum of 30 minutes of moderately vigorous aerobic activity most days, as a part of their daily routines (Bull et al., 2020; Liguori, 2022).

The prescription of the intensity can be made by taking into account whether or not an exercise test has been carried out. The ACSM recommends an intensity of 40-80% of heart rate reserve, VO_2reserve, or VO_2peak, for people performing an exercise test. For people who do not execute an exercise test, the ACSM recommends using the resting heart rate with an addition of 20 to 30 bpm or using the subjective perception of exertion, between 12 and 16, on a scale of 6 to 20. For people recognized with an ischemia threshold, the maximum training heart rate is set below the value at which ischemia was identified, usually 10 bpm less (Liguori, 2022). Attention should also be yielded to the type of pharmacological therapy taken by participants due to the influence that this may have on certain training variables, in this case, the intensity, which may interfere with the correct prescription of physical exercise. An example of this is participants under beta-blocking therapy, who must perform the exercise test under the influence of medication so that the exercise prescription can be carried out using the data from the exercise test. Whenever the medication is changed, performing a new exercise test should be considered (AACVPR, 2013; Pelliccia et al., 2021).

A well-structured CR program must include aerobic training, resistance training, and flexibility training (Liguori, 2022). Regarding time, it is recommended to practice aerobic exercise for 20 to 60 minutes per session. For people with reduced functional capacity, it is initially recommended to practice aerobic exercise for a period equal to or less than 10 minutes per day, or several times a day, to gradually achieve the recommendations described previously (Liguori, 2022).

The type of exercise must include activities that stimulate the upper and lower extremities and must take into account the patient's characteristics, limitations, and preferences, with the most common exercises being walking or running on a treadmill, elliptical, bicycle, rowing, or even arm ergometers. Preferably, rhythmic activities that involve large muscle groups should be incorporated so that it is possible to achieve a high caloric expenditure to lose/maintain weight and reach all the benefits mentioned above (Liguori, 2022).

2.2.3.1. Aerobic Training

For aerobic training, the ACSM recommends practicing at least three days a week, which is preferable to practicing at least five or more days. Exercise frequency should depend on several factors, including the patient's initial exercise tolerance, exercise intensity (**Figure 2.10**), health goals, and types of exercise included in the CR program (Liguori, 2022).

Figure 2.10.

Classification of exercise intensity: relative and absolute intensity for aerobic exercise

Aerobic exercise				
Relative intensity				Absolute intensity
Intensity	%HRR or %VO_2R	%HR_{max}	%VO_{2max}	METs
Very light	<30	<57	<37	<2
Light	30–39	57–63	37-45	2.0–2.9
Moderate	40–59	64–76	46-63	3.0–5.9
Vigorous	60–89	77–95	64-90	6.0–8.7
Near-maximal to maximal	≥90	≥96	≥91	≥8.8

Note. HRmax: maximal heart rate; HRR: heart rate reserve; MET: metabolic equivalent; VO_2max: maximal volume of oxygen consumed per minute; VO_2R: oxygen uptake reserve.

Currently there is no international consensus on exercise prescription for CR, and exercise intensity recommendations vary considerably between countries from light-moderate intensity to moderate intensity to moderate-vigorous intensity. As cardiorespiratory fitness [peak oxygen uptake (VO_2peak)] is a strong predictor of mortality in patients with coronary heart disease and heart failure, exercise prescription that optimizes improvement in cardiorespiratory fitness and exercise capacity is a critical consideration for the efficacy of CR programming.

In cardiovascular regulation and disease prevention, low-, moderate-, and vigorous-intensity exercise have all exhibited some degrees of health benefit (Bernardo et al., 2018). A significant dose-response relationship exists between exercise intensity and overall cardiovascular benefit (Eijsvogels et al., 2016). High-intensity interval training (HIIT) is a type of advanced aerobic training that is equally safe and effective in improving cardiorespiratory fitness and is characterized by alternating periods of high-intensity exercise (90-95% of HRpeak) with periods of moderate intensity (60-70% of HRpeak). Practicing this type of training requires a gradual progression of effort intensity over time and carrying it out for approximately 40 minutes a day, three times a week, appears to promote improvement in VO_2peak in people with stable coronary artery disease and heart failure (Liguori, 2022).

In the last decade, it has been intensely discussed whether HIIT specifically outperforms moderate-intensity continuous training (MICT) with regard to improvements in cardiorespiratory fitness, cardiovascular risk factors, cardiac and vascular function, and quality of life (QoL). There is a fundamental physiological difference between exercising at a continuous moderate-intensity vs. HIIT. Compared with moderate intensity, vigorous-intensity exercise takes less time to obtain the same benefits of improving cardiorespiratory fitness and preventing CVD. For example, exercise at moderate intensity for 30 min produces roughly the same as that of 15 min of vigorous-intensity exercise (Piercy et al., 2018). The study found that exercise performed at higher relative intensity led to a greater increase in aerobic capacity and greater cardiac protection than exercise at moderate intensity (Siasos et al., 2016). However, vigorous activity can also acutely and transiently increase the risk of sudden cardiac death and myocardial infarction in susceptible people (Way et al., 2019). Consequently, it was recommended that people of different ages should engage in moderate (40–59% HRR or VO_2R) to vigorous (60–89% HRR or VO_2R) aerobic exercise; people in poor health should undergo low- (30–39% HRR or VO_2R) to moderate-intensity aerobic exercise to improve cardiorespiratory fitness and prevent CVD (O'Donovan et al., 2018). It is noted that the elderly, and the frail should exercise under the guidance of caregivers, doctors, and professional trainers to ensure safety (O'Donovan et al., 2018).

2.2.3.2. Resistance Training

The ACSM recommends practicing strength training 2 to 3 days a week on non-consecutive days, with an intensity of 40% to 60% of 1-RM or a subjective perception of effort of 11 to 13 on a scale of 6 to 20 perform 8 to 10 exercises for the large muscle groups, 1 to 3 sets of each exercise and 10 to 15 repetitions in each set without reaching a very high degree of fatigue. The types of exercise can be free weights, guided machines, or other materials that are safe and comfortable for the patient, and to choose which exercise to perform, the patient's characteristics, limitations, and preferences must be taken into account. The exercise physiologist must be able to educate participants and inform them that strength exercises must be carried out in a controlled manner and breathing must be regular, avoiding blocking as much as possible (Valsava maneuver). The Valsava maneuver and handles that are too tight can increase blood pressure and should therefore be avoided. The training volume can be increased by 2% to 10% when a patient is already able to perform 1 or 2 repetitions above the number of repetitions established for a given exercise in 2 consecutive training sessions (Liguori, 2022).

2.2.3.3. Flexibility Training

For flexibility training, the ACSM recommends practicing at least 2 to 3 days a week, and preferably this type of training should be carried out daily. The exercises should be performed until you feel slight discomfort, 15 seconds for each exercise, and perform 4 or more sets for each exercise. Flexibility exercises can be static or dynamic and should focus mainly on the large joints and lumbar spine (Liguori, 2022).

In all exercise sessions, warming up and returning to calm must be carried out and must incorporate activities such as static and dynamic stretching and low or very low-intensity aerobic activities that last approximately 5 to 10 minutes (Liguori, 2022).

2.2.4. Home-based Cardiac Rehabilition

To address the aforementioned barriers, CR programs should be better tailored to patients' individual needs, constraints and preferences, without losing its clinical effectiveness. A proposed solution is exercise-based CR in the home environment. Home-based CR does not require journeys to the outpatient clinic, training sessions can be scheduled individually and independently, and CR can be combined with work resumption (De Vos et al., 2013; Oerkild et al., 2012). In addition, home-based CR provides the opportunity to combine evidence-based behavioral change-strategies with modern wearable sensor techniques in the telemonitoring guidance, during the integration of exercise training in daily routine. Previous studies have shown that structured home-based CR is safe and short-term results of home-based cardiac rehabilitation are similar to the results of centre-based CR (Arthur et al., 2002, Aamot et al., 2013, Oerkild et al., 2015; Taylor et al., 2015). However, it is important to note that the interventions described in these studies vary considerably with respect to both the prescribed training protocols and the telemonitoring guidance provided during home-based training. There is no general guideline for home-based training yet, hence training protocols from centre-based CR are often translated to the home environment (Vanhees et al., 2012). However, those recommendations cannot be translated directly to home-based training. For instance, fitness equipment used in the outpatient clinic is seldom available at home and high-intensity interval training is difficult to perform during outdoor walking or cycling. Therefore, we should define the characteristics of exercise training that determine the improvement in physical fitness, so we can provide recommendations for designing a feasible and effective home-based training program for CR patients (Vanhees et al., 2012).

2.2.5. Adverse Responses to Inpatient Exercise Leading to Exercise Discontinuation

The exercise physiologist must be alert to symptoms such as angina pectoris induced by exercise, which is relieved through rest or nitroglycerin, as it can be a sign of myocardial ischemia (Liguori, 2022). Other adverse responses to inpatient exercise leading to exercise discontinuation are:

- Diastolic blood pressure (DBP) ≥ 110 mm Hg;
- Decrease in systolic blood pressure (SBP) >10 mm Hg during exercise with increasing workload;
- Significant ventricular or atrial arrhythmias with or without associated signs/symptoms;
- Second- or third-degree heart block;
- Signs/symptoms of exercise intolerance including angina, marked dyspnea, and electrocardiogram (ECG) changes suggestive of ischemia (Liguori, 2022).

2.3. References

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2.4. Paper 1:

Exercise Intensity in Patients with Cardiovascular Diseases – Systematic Review with Meta-Analysis

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Abstract: Exercise-induced improvements in the VO_2peak of cardiac rehabilitation participants are well documented. However, optimal exercise intensity remains doubtful. This study aimed to identify the optimal exercise intensity and program length to improve VO_2peak in patients with cardiovascular diseases (CVD) following cardiac rehabilitation. Randomized controlled trials (RCTs) included a control group and at least one exercise group. RCTs assessed cardiorespiratory fitness (CRF) changes resulting from exercise interventions and reported exercise intensity, risk ratio, and confidence intervals (CIs). The primary outcome was CRF (VO_2peak or VO_2 at anaerobic threshold). Two hundred and twenty-one studies were found from the initial search (CENTRAL, MEDLINE, CINAHL and SPORTDiscus). Following inclusion criteria, 16 RCTs were considered. Meta-regression analyses revealed that VO_2peak significantly increased in all intensity categories. Moderate-intensity interventions were associated with a moderate increase in relative VO_2peak (SMD = 0.71 mL-kg^{-1}-min^{-1}; 95% CI = [0.27–1.15]; $p = 0.001$) with moderate heterogeneity ($I^2 = 45\%$). Moderate-to-vigorous-intensity and vigorous-intensity interventions were associated with a large increase in relative VO_2peak (SMD = 1.84 mL-kg^{-1}-min^{-1}; 95% CI = [1.18–2.50], $p < 0.001$ and SMD = 1.80 mL-kg^{-1}-min^{-1}; 95% CI = [0.82–2.78] $p = 0.001$, respectively), and were also highly heterogeneous with I2 values of 91% and 95% ($p < 0.001$), respectively. Moderate-to-vigorous and vigorous-intensity interventions, conducted for 6–12 weeks, were more effective at improving CVD patients' CRF.

Keywords: cardiac rehabilitation; cardiorespiratory fitness; exercise therapy; heart diseases; high-intensity intermittent exercise.

2.4.1. Introduction

Cardiovascular diseases (CVD) are the leading cause of mortality in today's society, being responsible for up to one-third of all deaths worldwide and 50% of all deaths in Europe, and this scenario is expected to worsen in the coming years (WHO, 2011).

The concept of cardiac rehabilitation (CR) has been defined as the effort towards cardiovascular risk factor reduction, designed to lessen the chance of a subsequent cardiac event, and to slow and perhaps stop the progression of the disease process. In the context of CR programs, exercise training has been recognized as one of the main components, combined with education, control, pharmacological adherence and lifestyle changes of cardiovascular risk factors (Corrà et al., 2010). Physical exercise inclusion in CR programs resulted in several beneficial effects on cardiovascular functional capacity, quality of life, risk factor modification, psychological profile, hospital readmissions, and mortality (Mohammed & Shabana, 2018; Arnett et al., 2019). Such benefits can be justified by a 20% reduction in mortality from all causes and in the levels of cardiorespiratory fitness (CRF) for each metabolic equivalent improvement (MET) in CRF of patients with CVD (Anderson et al., 2016).

Exercise programs for patients with CVD traditionally involve mostly low- to moderate- intensity continuous aerobic exercise training, with the consensus that one of the benefits of aerobic exercise is the increase in peak oxygen uptake (VO_2peak) (Mezzani et al., 2013; Moholdt et al., 2011; Wisloff et al., 2011). Continuous aerobic exercise training implicates higher durations under moderate-intensity and nonvariable aerobic activity (60–80% of VO_2peak) (Abolahrari-Shirazi et al., 2018; Giallauria et al., 2009; Giallauria et al., 2012; Giallauria et al., 2013), compared to high-intensity protocols, which consist of intermittent, short high-intensity work periods (85–100% of VO_2peak) with relative resting periods (Villelabeitia-Jaureguizar et al., 2017; Tamburús et al., 2015).

Exercise intensity appears to influence the number of cardioprotective benefits achieved from aerobic exercise (Beckie et al., 2014; Rivera-Brown et al., 2012). The current consensus recommends that exercise intensity prescribed for patients with CVD should be approximately 60% of the maximal heart rate (MHR), 50% of the heart rate reserve (HRR), or 12–13 on the Borg scale. Intensities around 85% MHR, 80% HRR, or 15–16 on the Borg scale should represent the upper limits (Mezzani et al., 2013).

Additionally, high-intensity protocols (85–100% of VO_2peak) appear to be of particular interest to scientists, considering their application in patients with CVD based on the effects on the cardiorespiratory and muscle systems (Moholdt et al., 2011). High-intensity protocols elicit a greater training stimulus than moderate continuous exercise in improving maximal aerobic capacity (Wisloff et al., 2011; Abolahrari-Shirazi et al., 2018; Giallauria et al., 2009; Giallauria et al., 2012; Giallauria et al., 2013; Villelabeitia-Jaureguizar et al., 2017; Tamburús et al., 2015; Beckie et al., 2014; Rivera-Brown et al., 2012; Warburton et al., 2005; Rognmo et al., 2004; Cornish et al., 2010). In addition, high-intensity exercise appears to improve the limiting factors of VO_2peak, and VO_2peak itself has been found to be more effective in improving cardiovascular risk factors than moderate-intensity exercise (Warburton et al., 2005; Rognmo et al., 2004; Cornish et al., 2010).

Training sessions based on moderate-intensity continuous exercise have shown improvements in HRR after eight weeks (Ghroubi et al., 2012) and after 12 weeks (Blumenthal et al., 2005; Kitzman et al., 2013). Moderate- to high- intensity continuous exercise (6 and 12 MET, corresponding to 21 and 42 $mL\text{-}kg^{-1}\text{-}min^{-1}$ of VO_2peak) has also been shown to reduce all-cause mortality in healthy individuals, independent of activity duration (Moholdt et al., 2011), and reduce the risk of heart disease (Beckie et al., 2014), supporting the need to further investigate the potential health effects of protocols based on higher intensities. Therefore, during the last two decades, several studies have demonstrated that high-intensity exercise protocols induce more beneficial cardiovascular adaptations in patients with mild-to-severe heart disease when compared to moderate-intensity exercise protocols (Wisloff et al., 2011; Warburton et al., 2005; Rognmo et al., 2004; Cornish et al., 2010).

A recent meta-analysis (Mitchell et al., 2019) reported higher improvements in maximal aerobic capacity after high-intensity interval training (HIIT) programs compared to moderate-intensity programs. Nevertheless, the optimum exercise intensity prescription in patients with CVD is still a subject of debate. A recent systematic review on the topic (Hannan et al., 2018) did not report optimal intensity prescription (e.g., the intensity interval that is most effective during exercise interventions to induce favorable changes in aerobic capacity). Thus, despite the literature being replete with studies showing that regular and structured exercise is beneficial for CVD patients, the optimal intensity and length of exercise interventions that bring about greater benefits remain equivocal. Hence, the objective of this systematic review with meta-analysis was to identify, through Randomized Controlled Trials (RCTs) of exercise-based CR, the most effective exercise intensity and intervention length to optimize VO_2peak in patients with CVD.

2.4.2. Materials and Methods

The systematic review was undertaken as detailed in the protocol registered with PROSPERO (Registration Number CRD42018097319).

2.4.2.1. Search Strategy

The search strategies were designed in accordance with the methods suggested by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011). The following databases were searched from their inception to January 2021: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), CINAHL (EBSCO) and SPORTDiscus. Data are provided as the risk difference (95% CI), based on RCTs published until January 2021, ensuring that all studies have been included if reporting data on established outcomes. Reference lists of eligible studies were also systematically searched.

We used the PICO model (Leonardo, 2018) to identify free text terms and controlled vocabulary terms to create our searches. The following key concepts were chosen: “Patients with cardiovascular diseases” AND “Cardiac Rehabilitation” AND “Exercise Intensity” AND “Cardiorespiratory Fitness”. The search strategy for the MEDLINE (Ovid) database is available in the Supplementary Materials of this manuscript.

2.4.2.2. Inclusion Criteria

The inclusion criteria were full-length research articles published in peer-reviewed journals in the English language with no limits set on the date of first publication or gender. Only RCTs up to January 2021 were eligible. Studies included participants who were diagnosed with CVD, such as those involved in some exercise programs, assessed by analyzing expired air during a maximal cardiopulmonary exercise test at baseline and postintervention.

We included RCTs to compare aerobic capacity changes resulting from exercise interventions, with an exercise group (or groups), that described exercise intensities, including data for risk ratio and CI.

Studies were required to detail the exercise prescription in patients with CVD, including the frequency, intensity and duration of each session, mode of exercise and the overall length of intervention. The main authors of studies and experts in this field were asked for any missed, unreported, or ongoing trials. The quantitative synthesis included studies reporting sample size and the mean and standard deviations (SDs) for VO_2peak preintervention and postintervention.

2.4.2.3. Exclusion Criteria

Abstracts, conference presentations or posters, letters to editors or book chapters, unpublished papers, and retrospective design studies were excluded. In addition, studies were excluded if participants had documented heart failure (ejection fraction < 40%) or arrhythmia, they were targeting a specific comorbidity (e.g., diabetes, chronic obstructive pulmonary disease, or stroke) and they featured interventions involving resistance exercises only. We also excluded studies based on exercise prescriptions including testing food supplements and nutritional or pharmacological aids.

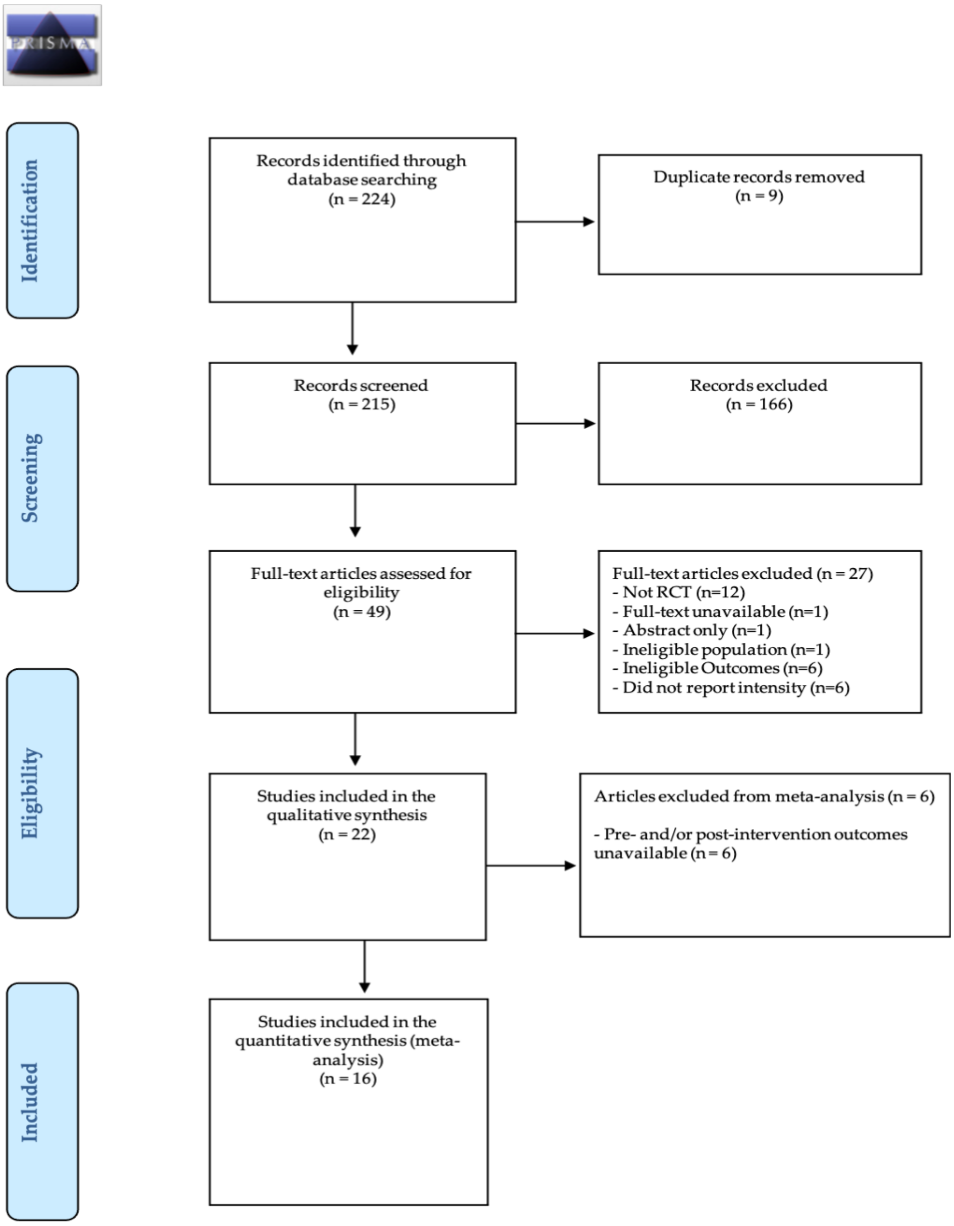
Studies were also excluded if baseline or postintervention data were not published, and the authors were not available for contact or did not wish to provide the missing data.

2.4.2.4. Study Selection and Data Extraction

All data were extracted by the principal investigator and their accuracy was assessed by the second author. The EndNote software (Clarivate Analytics, Philadelphia, PA, USA) was used to import, manage and remove duplicated articles for final review. After removing the duplicates, the two reviewers independently reviewed titles and abstracts against the inclusion/exclusion criteria. If in doubt, the full texts were evaluated to verify if they met the criteria. Subsequently, abstracts were selected for eligibility, and full manuscripts were retrieved for further evaluation of eligibility. Discrepancies were resolved between both authors, and a third expert, not involved in the previous procedures, was consulted to verify the ratings. The selection process was entered into a Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) diagram (Moher et al., 2009) (**Figure 2.11**).

Figure 2.11.

PRISMA diagram of literature search strategies. Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis



For each RCT, the author, year of publication, participant characteristics (age, gender, and primary diagnosis), description of the exercise testing protocol and description of the intervention (session frequency and duration, intervention length, exercise modality, resistance training, type of training (interval/continuous), supervision (clinic/home) and intervention type) were extracted. The pre- and post-VO_2peak values, change in VO_2peak, were also extracted to assess change in CRF. Outcomes were extracted in relative (mL-kg^{-1}-min^{-1}) and absolute (L-min^{-1}) terms. Outcomes reported in METs were converted to relative terms (METs × 3.5mL-kg^{-1}-min^{-1}).

2.4.2.5.Assessment of Potential Bias

The risk of bias was assessed using the modified Cochrane collaboration tool (Higgins et al., 2011), developed in 2005 to assess and report the risk of bias in RCTs. Bias assessment results from the judgment (high, low, or unclear) of individual elements from seven sources of bias covered six domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias (criteria for selected patients in the studies and the country in which the study was conducted). A detailed description of each source of bias and support for judgement is available elsewhere (Higgins et al., 2011). The lead reviewer found 16 studies, and discrepancies were discussed and resolved.

2.4.2.6.Data Treatment and Analysis

The systematic review was stratified by intensities based on proposed cut-offs (ACSM, 2017). Thereby, each exercise program was ranked as being prescribed light-, moderate- and vigorous-intensity aerobic exercise (**Table 2.3**.

Table 2.3.

Classification of exercise intensity based on physiological and perceived exertion responses

	%VO_{2max}	**%HR_{peak}**	**%$HR_{reserve}$/%$VO_{2reserve}$**	**Perceived exertion ***
Light	37–45	57–63	30–39	RPE 9–11
Moderate	46–63	64–76	40–59	RPE 12–13
Vigorous	64–90	77–95	60–89	RPE 14–17
Near maximal to maximal	≥91	≥95	≥90	RPE ≥18

Note. Table adapted from American College of Sports Medicine (ACSM, 2017) and Mitchell et al. (2019). *As per the Borg 6–20 RPE scale. %VO_2max, percentage of maximal oxygen uptake; %HRpeak, percentage of peak heart rate; %HRreserve, percentage of heart rate reserve; %VO_2reserve, percentage of oxygen uptake reserve; RPE, rating of perceived exertion.

Studies reporting an intensity that covers the categories of moderate intensity and vigorous intensity (e.g., 60–70% of VO_2peak) were classified as “moderate-to-vigorous” intensity (ACSM, 2017). A separate meta-analysis was performed for each intensity category and length of the trial — e.g., “short-term” (0–6 weeks), “medium-term” (7–12 weeks), and “long-term” (>12 weeks). Separate meta-analysis was performed for each intensity category and length of the trial duration, e.g., ’short-term’ (0 to 6 weeks), ’medium-term’ (7 to 12 weeks), and ’long-term’ (> 12 weeks).

The following subgroup analysis was conducted to explore significant heterogeneity: participant characteristics, including (1) age, (2) gender, and (3) primary diagnosis; description of the exercise testing protocol and description of the intervention (4) session frequency and (5) duration, (6) intervention length, (7) exercise modality, (8) resistance training, (9) type of training (interval/continuous), (10) supervision (clinic/home), (11) intervention type (exercise only/comprehensive); and (12) pre- and post-peak VO_2 values or change in VO_2peak.

Heterogeneity amongst included studies was first explored qualitatively by comparing characteristics of included trials and then by visually inspecting forest plots. It was also assessed quantitatively by the Chi^2 and I^2 statistics. Heterogeneity was considered minimal if I^2 fell between 0% and 30%, moderate if 30–50%, substantial if 50–90%, and considerable if >90% (Higgins et al., 2011). I^2 was considered significant at $p < 0.1$.

Due to the heterogeneity of the protocol, mean differences (MDs) were used, dividing the mean values between different intensities. The differences in means were grouped using the random-effects model. A random-effects model and a standardized means model of averages were used to explain the differences in the methodology of the studies including both in the intensities and length of intervention to ensure a conservative estimate was calculated. A sensitivity analysis was conducted to investigate the possible effects of specific studies on heterogeneity and overall effect.

The dichotomous and continuous variables of the studies were compared with the extracted potential VO_2peak moderator factors. The effect of treatment was calculated for each study for the change in VO_2peak over the intervention using the pooled between-subject SD at both time points. Effects were quantified as trivial (<0.20), small (0.21–0.60), moderate (0.61–1.20), large (1.21–2.00), and very large (>2.00) (Hopkins et al., 2009), with the precision of effect size estimates assessed using 95% CI. Pooled SMD was back-transformed using the pooled between-subject SD at baseline within each intensity category. If SD for the mean change in VO_2peak across the intervention was not published (Cochrane, 2014), it was used for p-value entry. If no p-values or standard deviations were published, the standard error (SE) of the MD was inputted based on the correlation between preintervention and postintervention outcomes (Elbourne et al., 2002). The imputed SE was then used to calculate the 95% CI for the standardized effect of each study. For outcomes expressed as change in relative VO_2peak (mL-kg^{-1}-min^{-1}), a correlation of r = 0.54 from a similar meta-analysis (Sandercock et al., 2013) was used. A sensitivity analysis was performed using the estimated correlations of r = 0.30 and 0.70.

Publication bias was analyzed using a funnel plot derived in *RevMan 5.3 software* (Cochrane, 2014). The publication bias for the different conditions analyzed (pre- vs. post-intervention) was assessed by examining the asymmetry of a funnel plot using Egger's test, and $p \leq 0.05$ was considered to be statistically significant.

2.4.3. Results

The initial search resulted in 221 studies. All data were extracted by the principal investigator and their accuracy was assessed by a second author. Search results were entered into EndNote software (Clarivate Analytics, Philadelphia, PA, USA), a reference management tool, and duplicates were removed. After the duplicates were removed, the titles of 212 studies were reviewed. Following a screening of potential records, 49 articles were reviewed for eligibility and their reference lists screened. Twenty-two RCTs met eligibility criteria for the systematic review and meta-analysis. According to our inclusion criteria, sixteen studies (Abolahrari-Shirazi et al., 2018; Giallauria et al., 2009; Giallauria et al., 2012; Giallauria et al., 2013; Villelabeitia-Jaureguizar et al., 2017; Tamburús et al., 2015; Ghroubi et al., 2012; Blumenthal et al., 2005; Kitzman et al., 2013; Wu et al., 2006; Zheng et al., 2008; Giallauria et al., 2006; Chuang et al., 2005; Legramante et al., 2006; Kraal et al., 2013; Kubo et al., 2004) were included in this systematic review (**Figure 2.11.**

The main characteristics of the studies and training interventions are described in **Table 2.4.** and **Table 2.5.**

Table 2.4.

Subgroup analyses assessing potential moderating factors for VO_2peak increase in studies included in the meta-analysis by population characteristics

Group	**N**	**References**	**MD (95%CI)**	I^2	p [a]	p-Difference [b]
		Research Studies	**Peak VO_2**			
No. of participants						
<20	4	Ghroubi et al. (2012), Tamburus et al. (2015), Wu et al. (2006), Chuang et al. (2008)	2.62 (1.65, 3.58)	88	<0.001	0.78
≥20	12	Abolahrari-Shirazi et al. (2018), Blumenthal et al. (2005), Giallauria et al. (2006, 2009, 2012, 2013), Kitzman et al. (2013), Kraal et al. (2005), Kubo et al. (2005), Legramante et al. (2007), Villelabeitia et al. (2017), Zheng et al. (2006)	2.75 (2.58, 2.93)	97	<0.001	
Age, years						
<60	9	Abolahrari-Shirazi et al. (2018), Ghroubi et al. (2012), Giallauria et al. (2006, 2009, 2013), Kraal et al. (2013), Kubo et al. (2005), Tamburus et al. (2015), Villelabeitia et al. (2017)	4.40 (0.79, 8.01)	97	0.02	0.75
≥60	6	Blumenthal et al. (2005), Chuang et al. (2008), Giallauria et al. (2012), Kitzman et al. (2013), Legramante et al. (2007), Wu et al. (2006)	3.48 (2.09, 4.87)	79	<0.001	
Not reported	1	Zheng et al. (2006)	3.10 (2.06, 4.14)	0	<0.001	
Diagnosis						
CAD only	3	Blumenthal et al. (2005), Tamburus et al. (2015), Villelabeitia et al. (2017)	6.41 (−2.70, 15.53)	99	0.17	0.03
CABG only	4	Chuang et al. (2008), Ghroubi et al. (2012), Legramante et al. (2007), Wu et al. (2006)	4.27 (1.60, 6.94)	85	0.002	
PCI only	1	Abolahrari-Shirazi et al. (2018)	8.20 (4.68, 11.72)	0	<0.001	
CABG/ PCI	1	Kraal et al. (2013)	3.20 (0.36, 6.04)	0	0.03	
MI	6	Giallauria et al. (2006, 2009, 2012, 2013), Kubo et al. (2005), Zheng et al. (2006)	2.65 (0.56, 4.74)	91	0.01	
FMD	1	Kitzman et al. (2013)	1.60 (−0.13, 3.33)	0	0.07	
Study location						
America	2	Kitzman et al. (2013), Tamburus et al. (2015)	1.38 (0.39, 2.36)	0	0.006	0.01
Africa	1	Ghroubi et al. (2012)	1.70 (−1.07, 4.47)	0	0.23	
Asia	5	Abolahrari-Shirazi et al. (2018), Chuang et al. (2008), Kubo et al. (2005), Wu et al. (2006), Zheng et al. (2006)	5.33 (2.90, 7.76)	80	<0.001	
Europe	8	Blumenthal et al. (2005), Giallauria et al. (2006, 2009, 2012, 2013), Kraal et al. (2013), Legramante et al. (2007), Villelabeitia et al. (2017)	4.23 (1.50, 6.95)	98	0.002	

Note: 95% CI, 95% confidence interval. I^2, heterogeneity. MD, mean difference. Peak VO_2, peak oxygen uptake. Conditions: MI, myocardial infarction. CABG, coronary artery bypass graft. PCI, percutaneous coronary intervention. CAD, coronary artery disease. FMD, endothelial- dependent flow-mediated arterial dilation. Certain enrolled studies were not included because the value used for subgroup analysis was not reported in them. [a] Test for overall effect. [b] Test for subgroup differences.

Table 2.5.

Subgroup analyses assessing potential moderating factors for VO2peak Increase in studies included in the meta-analysis by population characteristics

Research Studies			**Peak VO_2**			
Group	**N**	**References**	**MD (95%CI)**	**I^2**	**p [a]**	**p-Difference [b]**
Length, weeks						
<6	1	Legramante et al. (2007)	2.60 (2.41, 2.79)	0	<0.001	
6–12	9	Abolahrari-Shirazi et al. (2018), Chuang et al. (2008), Ghroubi et al. (2012), Giallauria et al. (2006, 2009), Kraal et al. (2013), Kubo et al. (2005), Villelabeitia et al. (2017), Wu et al. (2006)	5.31 (1.24, 9.38)	97	0.01	0.42
>12	6	Blumenthal et al. (2005), Giallauria et al. (2012, 2013), Kitzman et al. (2013), Tamburus et al. (2015), Zheng et al. (2006)	2.50 (1.60, 3.41)	52	<0.001	
Frequency, sessions/week						
1–2	2	Chuang et al. (2008), Kraal et al. (2013)	3.98 (1.96, 6.01)	0	0.001	
3–4	13	Abolahrari-Shirazi et al. (2018), Blumenthal et al. (2005), Ghroubi et al. (2012), Giallauria et al. (2006, 2009, 2012, 2013), Kitzman et al. (2013), Kubo et al. (2005), Tamburus et al. (2015), Villelabeitia et al. (2017), Wu et al. (2006), Zheng et al. (2006)	4.21 (1.82, 6.60)	96	0.006	0.17
5–7	1	Legramante et al. (2007)	2.60 (2.41, 2.79)	0	<0.001	
Supervision						
Clinic	12	Blumenthal et al. (2005), Chuang et al. (2008), Ghroubi et al. (2012), Giallauria et al. (2009, 2012, 2013), Kitzman et al. (2013), Kubo et al. (2005), Legramante et al. (2007), Tamburus et al. (2015), Villelabeitia et al. (2017), Zheng et al. (2006)	4.01 (2.30, 5.72)	96	<0.001	0.02
Home	1	Wu et al. (2006)	8.50 (5.78, 11.22)	0	<0.001	
Mixed	3	Abolahrari-Shirazi et al. (2018), Giallauria et al. (2006), Kraal et al. (2013)	2.99 (−2.89, 8.87)	94	0.32	
Intervention type						
Continuous	13	Abolahrari-Shirazi et al. (2018), Blumenthal et al. (2005), Chuang et al. (2008), Giallauria et al. (2006, 2009, 2012, 2013), Kitzman et al. (2013), Kraal et al. (2013), Kubo et al. (2005), Legramante et al. (2007), Wu et al. (2006), Zheng et al. (2006)	3.27 (2.23, 4.32)	87	<0.001	0.44
Interval	2	Tamburus et al. (2015), Villelabeitia et al. (2017)	8.67 (−5.86, 23.21)	99	0.24	
Mixed	1	Ghroubi et al. (2012)	1.70 (−1.07, 4.47)	0	0.23	
Mode						
Cycle ergometer	7	Ghroubi et al. (2012), Giallauria et al. (2009, 2012, 2013), Tamburus et al. (2015), Villelabeitia et al. (2017), Zheng et al. (2006)	4.90 (1.52, 8.27)	97	0.005	
Treadmill	1	Chuang et al. (2008)	4.80 (1.91, 7.69)	0	0.001	
Walking	1	Blumenthal et al. (2005)	1.90 (0.20, 3.60)	0	0.03	0.23
Mixed (treadmill, walking, cycling, calisthenics or/and arm/leg ergometer)	7	Abolahrari-Shirazi et al. (2018), Giallauria et al. (2006), Kitzman et al. (2013), Kraal et al. (2013), Kubo et al. (2005), Legramante et al. (2007), Wu et al. (2006)	3.28 (1.17, 5.39)	92	0.002	
Exercise type						

Aerobic	13	Blumenthal et al. (2005), Chuang et al. (2008), Ghroubi et al. (2012), Giallauria et al. (2006, 2009, 2013), Kitzman et al. (2013), Kraal et al. (2013), Kubo et al. (2005), Tamburus et al. (2015), Villelabeitia et al. (2017), Wu et al. (2006), Zheng et al. (2006)	3.94 (1.55, 6.34)	96	0.001	0.86
Aerobic and Resistance	3	Abolahrari-Shirazi et al. (2018), Giallauria et al. (2012), Legramante et al. (2007)	4.24 (1.82, 6.67)	81	0.001	
Intensity						
Moderate	3	Giallauria et al. (2009), Kubo et al. (2005), Villelabeitia et al. (2017)	2.90 (1.64, 4.16)	0	<0.001	
Moderate-to-vigorous	10	Abolahrari-Shirazi et al. (2018), Chuang et al. (2008), Giallauria et al. (2006, 2012, 2013), Legramante et al. (2007), Kitzman et al. (2013), Kraal et al. (2004), Wu et al. (2006), Zheng et al. (2006)	5.07 (3.43, 6.72)	92	<0.001	0.03
Vigorous	5	Blumenthal et al. (2005), Ghroubi et al. (2012), Giallauria et al. (2009), Tamburus et al. (2015), Villelabeitia et al. (2017)	2.43 (1.33, 3.54)	75	<0.001	

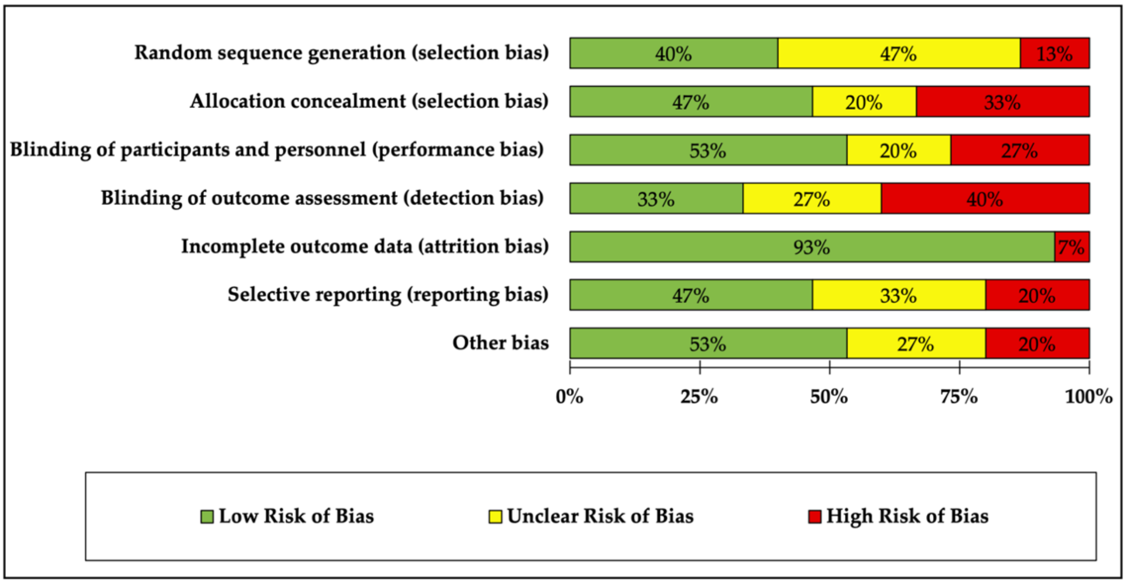
Note: 95% CI, 95% confidence interval. I^2, heterogeneity. MD, mean difference. Peak VO_2, peak oxygen uptake. Certain enrolled studies were not included because the value used for subgroup analysis was not reported in them. a Test for overall effect. b Test for subgroup differences.

2.4.3.1. Risk of Bias

Sixteen studies were scored by two reviewers, and an absolute agreement (r = 0.94) was obtained from the intraclass correlation coefficient (ICC). Bias was assessed as a judgment (high, low, or unclear) for individual elements from seven sources of bias and the following ICCs for absolute agreement between the two reviewers were obtained: random sequence generation for selection bias (r = 0.90), allocation concealment for selection bias (r = 0.92), blinding of participants and personnel for performance bias (r = 0.98), blinding of outcome assessment for detection bias (r = 0.94), incomplete outcome data for attrition bias (r = 0.79), selective reporting for reporting bias (r = 0.98) and inclusion criteria of patients in the studies and the country in which the study was conducted for other bias (r = 0.88). The risk of bias in the 16 included trials is summarized in **Figure 2.12**.

Figure 2.12.

Assessment of risk of bias in included randomized controlled trials



Of the 16 studies, the risk was low in four or more of the seven domains. Many studies were attributed to high risk in random sequence generation, allocation concealment, and blinding of outcome assessment due to the nature of the exercise program. It was high in almost all studies due to the lack of blinding of participants and personnel. However, this issue could not be omitted due to the peculiarity of the intervention (exercise vs. no exercise) and should be taken into consideration.

The most prevalent methodological issues were an inadequate description of randomization (60%), allocation of concealment (50%), and blinding of outcome assessment (70%). Most studies were low risk for incomplete outcome data (90%).

2.4.3.2. Study and Participants Characteristics

The total number of CVD participants analyzed across all studies was 969 (267 coronary artery disease (CAD) only, 200 Coronary Artery Bypass Graft (CABG) only, 75 Percutaneous Coronary Intervention (PCI) only, 50 CABG/PCI, 310 myocardial infarction (MI), and 63 Carotid artery stiffness (CAS)). A summary of study characteristics is shown in the Supplementary Materials.

The number of participants per group raged between 15 and 48, with four studies reporting < 20 participants and twelve studies reporting ≥ 20 participants, composed of more males ($n = 419$). The age range of participants was 52 – 69 years, with nine studies reporting mean ages < 60 years, six studies reporting mean ages ≥ 60 years, and one did not report. Individual patient characteristics for each study can be seen in **Table 2.4.**

Regarding the characteristics of the patients, the meta-analysis identified statistically significant improvements in VO_2peak in each subgroup of patients with PCI analyzed ($p < 0.001$), as well as in patients with MI ($p < 0.01$), patients with CABG ($p < 0.02$) and patients with both CABG/PCI ($p < 0.03$).

2.4.3.3. Intervention Characteristics

The included trials tested a variety of interventions to increase VO_2peak (**Table 2.5**. In many trials, the interventions were performed with exercise-based clinical supervision (Giallauria et al., 2009, 2012, 2013; Villelabeitia-Jaureguizar et al., 2017; Tamburús et al., 2015; Ghroubi et al., 2012; Blumenthal et al., 2005; Kitzman et al., 2013; Zheng et al., 2008; Legramante et al., 2007; Kraal et al., 2013), a few studies implemented an unsupervised home-based program (Wu et al., 2006), and some studies performed both programs (Giallauria et al., 2006, Abolahrari-Shirazi et al. 2018, Chuang et al., 2005).

Exercise training was typically continuous (Abolahrari-Shirazi et al., 2018; Blumenthal et al., 2005; Chuang et al., 2008; Giallauria et al., 2006, 2009, 2012, 2013; Kitzman et al., 2013; Kraal et al., 2013; Kubo et al., 2005; Legramante et al., 2007; Wu et al., 2006; Zheng et al., 2006), as opposed to interval (Tamburus et al., 2015; Villelabeitia et al., 2017), or mixed training (Ghroubi et al., 2012), and this type of training was shown to be significantly superior in improving VO_2peak (3.27 $mL\text{-}kg^{-1}\text{-}min^{-1}$; 95% CI = 2.23–4.32; $p < 0.001$; $I^2 = 87\%$).

The frequency of training was typically 3–4 days/week (Abolahrari-Shirazi et al., 2018; Blumenthal et al., 2005; Ghroubi et al., 2012; Giallauria et al., 2006, 2009, 2012, 2013; Kitzman et al., 2013; Kubo et al., 2005; Tamburus et al., 2015; Villelabeitia et al., 2017; Wu et al., 2006; Zheng et al., 2006), and aerobic training was the most used type of intervention (Blumenthal et al., 2005; Chuang et al., 2008; Ghroubi et al., 2012; Giallauria et al., 2006, 2009, 2013; Kitzman et al., 2013; Kraal et al., 2013; Kubo et al., 2005; Tamburus et al., 2015; Villelabeitia et al., 2017; Wu et al., 2006; Zheng et al., 2006). Three studies tested aerobic and resistance training together during the intervention (Abolahrari-Shirazi et al., 2018; Giallauria et al., 2012; Legramante et al., 2007). The meta-analysis identified that cycle-ergometers ($p < 0.05$) and treadmill ($p < 0.01$) significantly favored changes in VO_2peak.

Studies were separated into three groups depending upon length (<6, 6–12, and >12 weeks). The intervention length ranged from two to 24 weeks, with one study that reported data for less than six weeks (Legramante et al., 2007), nine studies reported data for 6 to 12 weeks (Abolahrari-Shirazi et al., 2018; Chuang et al., 2008; Ghroubi et al., 2012; Giallauria et al., 2006, 2009; Kraal et al., 2013; Kubo et al., 2005; Villelabeitia et al., 2017; Wu et al., 2006), and six studies reported data for >12 weeks (Blumenthal et al., 2005; Giallauria et al., 2012, 2013; Kitzman et al., 2013; Tamburus et al., 2015; Zheng et al., 2006). The subgroup that included studies of >12 weeks in length was significantly superior in terms of improvements in VO_2peak (2.50 mL-kg^{-1}-min^{-1}; 95% CI = 2.23–4.32; $p < 0.001$; $I^2 = 52\%$). Interventions 6 to 12 weeks in length also produced a large increase ($p < 0.01$), demonstrating moderate heterogeneity (5.31 mL-kg^{-1}-min^{-1}; 95% CI = 1.24–9.38; $I^2 = 52\%$).

Based on the American College of Sports Medicine (ACSM, 2017) cut-off points, three studies prescribed moderate-intensity exercise (n = 75%) (Giallauria et al., 2009; Kubo et al., 2005; Villelabeitia et al., 2017), three prescribed vigorous-intensity exercise (n = 75%) (Blumenthal et al., 2005; Ghroubi et al., 2012; Tamburus et al., 2015), and ten interventions (n = 62,5%) (Abolahrari-Shirazi et al., 2018; Chuang et al., 2008; Giallauria et al., 2006, 2012, 2013; Legramante et al., 2007; Kitzman et al., 2013; Kraal et al., 2004; Wu et al., 2006; Zheng et al., 2006) prescribed a range of intensities that placed them within both the moderate-intensity and vigorous-intensity categories. The meta-analyzed effects found the intervention was beneficial in terms of changing VO_2peak in both intensities ($p < 0.001$).

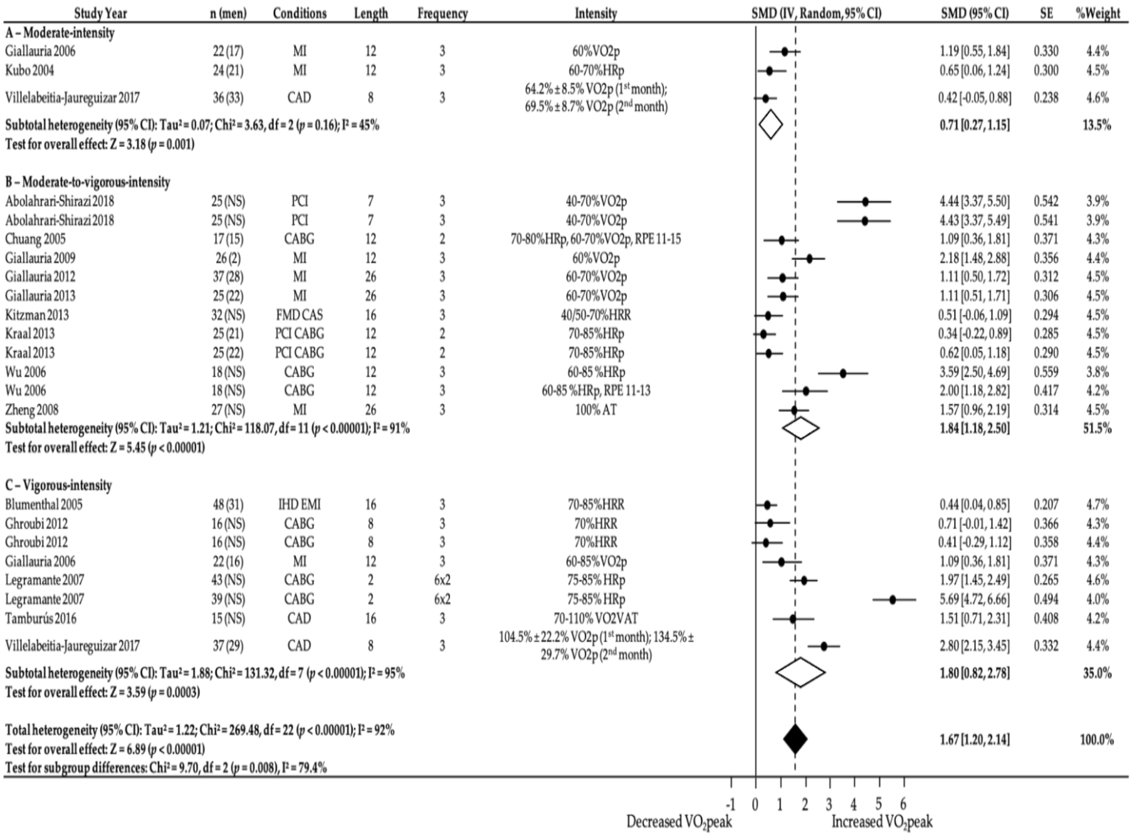
2.4.3.4. Subgroup Analyses – Intensity

When interpreting these results (**Figure 2.13**), it is essential to consider how exercise intensity was classified. We used a categorical-based approach, in which interventions were categorized according to the prescribed exercise intensity reported in each study, based on the recommendations of the ACSM (2017).

The meta-regression analysis displayed in **Figure 2.13** revealed that relative VO_2peak was significantly increased in all intensity categories. Moderate-intensity interventions produced a moderate increase in relative VO_2peak (0.71 mL-kg^{-1}-min^{-1}; 95% CI = 0.27–1.15; $p = 0.001$) with moderate heterogeneity ($I^2 = 45\%$). Moderate-to-vigorous-intensity and vigorous-intensity interventions produced a large increase in relative VO_2peak (1.84 mL-kg^{-1}-min^{-1}; 95% CI = 1.18–2.50; $p < 0.001$ and 1.80 mL-kg^{-1}-min^{-1}; 95% CI = 0.82–2.78; $p = 0.0003$, respectively), and were also highly heterogeneous with I^2 values of 91 and 95% ($p < 0.001$), respectively.

Figure 2.13.

Effect of moderate-, moderate-to-vigorous- and vigorous-intensity exercise during exercise programs on change in relative VO_2peak (mL-kg^{-1}-min^{-1})



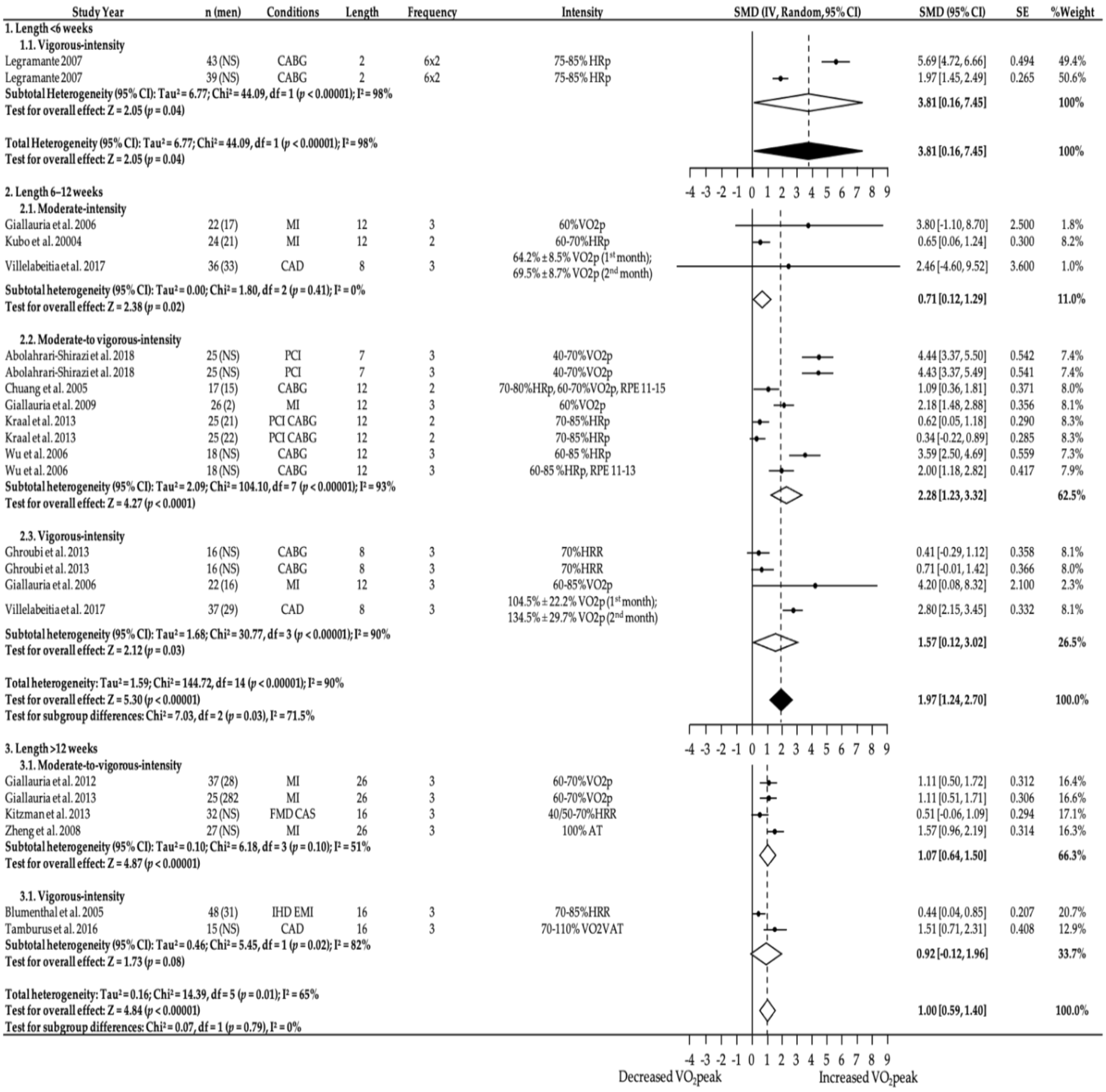
Note. NS, not stated/missing. HRR, heart rate reserve. HRp, heart rate peak. RPE, rate of perceived exertion. AT, anaerobic threshold. VAT, ventilatory anaerobic threshold. 95%CI, 95% confidence interval. SMD, standardized mean differences. IV, Random: a random-effects meta-analysis was applied, with weights based on inverse variances. SE, standard error. Tau^2 and I^2, heterogeneity. Chi^2, the chi-squared. Z, Z-value for test of the overall effect. P, p-value. Conditions: MI, myocardial infarction. CABG, coronary artery bypass test value. Z, Z-value for test of the overall effect. P, p-value. Conditions: MI, myocardial infarction. CABG, coronary graft. PCI, percutaneous coronary intervention. CAD, coronary artery disease. IHD, ischemic heart disease. EMI, exercise-artery bypass graft. PCI, percutaneous coronary intervention. CAD, coronary artery disease. IHD, ischemic heart disease. EMI, exercise-induced myocardial ischemia. FMD, endothelial-dependent flow-mediated arterial dilation. CAS, carotid artery stiffness.

2.4.3.5. Subgroup Analyses – Intensity and Duration

In the analyses of studies lasting less than six weeks, we evaluated studies that exercised at vigorous-intensity. The results (**Figure 2.14**) showed a large increase in VO_2peak (3.81 mL-kg^{-1}-min^{-1}; 95% CI = 0.16–7.45; p = 0.04) and demonstrated significant heterogeneity (I^2 = 98%).

Figure 2.14.

Effect of length in moderate-, moderate-to-vigorous and vigorous-intensity exercise during exercise programs on change in relative VO_2peak (mL-kg^{-1}-min^{-1})



Note. NS, not stated/missing. HRR, heart rate reserve. HRp, heat rate peak. RPE, rate of perceived exertion. AT, anaerobic threshold. VAT, ventilatory anaerobic threshold. 95%CI, 95% confidence interval. SMD, standardized mean differences. IV, Random: a random-effects meta-analysis was applied, with weights based on inverse variances. SE, standard error. Tau^2 and I^2, heterogeneity. Chi^2, the chi-squared. Z, Z-value for test of the overall effect. P, p-value. Conditions: MI, myocardial infarction. CABG, coronary artery bypass test value. Z, Z-value for test of the overall effect. P, *p*-value. Conditions: MI, myocardial infarction. CABG, coronary graft. PCI, percutaneous coronary intervention. CAD, coronary artery disease. IHD, ischemic heart disease. EMI, exercise-artery bypass graft. PCI, percutaneous coronary intervention. CAD, coronary artery disease. IHD, ischemic heart disease. EMI, exercise-induced myocardial ischemia. FMD, endothelial-dependent flow-mediated arterial dilation. CAS, carotid artery stiffness.

For interventions of 6 to 12 weeks duration, moderate-to-vigorous-intensity showed a further increase in VO_2peak (2.28 mL/kg/min; 95% CI [1.23 – 3.32]; $p < 0.001$; $I^2 = 93\%$) compared to moderate-intensity (0.71 mL/kg/min; 95% CI [0.12 – 1.29]; $p = 0.02$; $I^2 = 0\%$) and vigorous-intensity interventions (1.57 mL/kg/min; 95% CI [0.12 – 3.02]; $p = 0.02$; $I^2 = 0\%$).

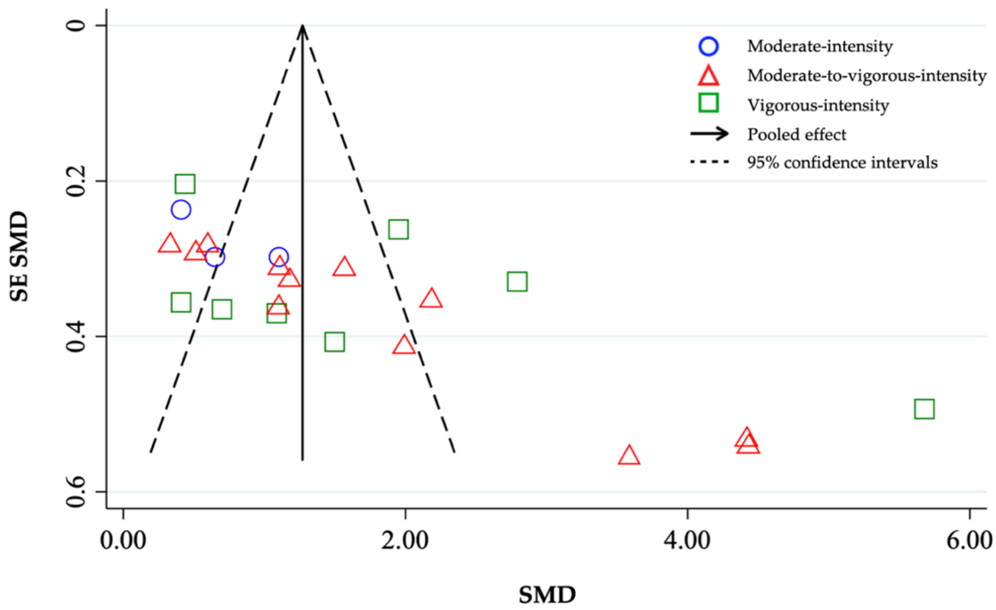
For studies that intervened more than 12 weeks, moderate-to-vigorous-intensity was significantly superior (1.07 mL/kg/min; 95% CI [0.64 – 1.50]; $p < 0.001$; $I^2 = 51\%$) to vigorous-intensity (0.92 mL/kg/min; 95% CI [-0.12 - 1.96]; $p = 0.08$; $I^2 = 82\%$) in improving VO_2peak.

2.4.3.6. Publication Bias

There was no significant publication bias for studies with moderate-intensity (Egger's test: $\beta = 7.29$, $p = 0.26$) and vigorous-intensity (Egger's test: $\beta = 8.67$, $p = 0.15$) interventions reporting relative VO_2peak. However, there was significant publication bias for studies with moderate-to-vigorous-intensity (Egger's test: $\beta = 13.19$, $p = 0.00$). The funnel plot with all studies (**Figure 2.15**) showed a significant degree of asymmetry (Egger's test: $p = 0.00$). Nevertheless, false-positive results may occur due to substantial between-study heterogeneity (Kraal et al., 2013), being the disparity in the number of studies included in each intensity category likely to cause the significant asymmetry in the funnel plot.

Figure 2.15.

Funnel plot with pseudo 95% confidence intervals for change in relative VO_2peak (mL-kg^{-1}-min^{-1}) by exercise intensity (moderate, moderate-to-vigorous, vigorous)



Note. SMD, standardized mean differences. SE SMD, standard error of standardized mean differences.

2.4.4. Discussion

The main aim of this systematic review and meta-analysis was to identify the optimal intensity to optimize VO_2peak in patients with CVD following exercise programs. Furthermore, we aimed to gauge whether the length of interventions had an effect on the results.

Our results support the crucial role of physical exercise in patients with CVD. They have shown significant improvements for all cardiac impairments at all patients ages, regardless of the aerobic exercise mode. A comparison of the mean effects between intensity classifications showed significant improvements, with moderate-to-vigorous-intensity providing the greatest improvements of VO_2peak. The differences were considered clinically significant (p = 0.03) and the retro transformation of the SMD suggested that the differences between the intensities were 3.92 mL-kg^{-1}-min^{-1}. However, when comparing the effects grouped among the intensity classifications, it was found that moderate-to-vigorous-intensity exercises can provide the most significant improvements in VO_2peak. Even so, the differences were not considered clinically significant once the retro transformation of the SMD suggested that the differences between the intensities were, at most, only 1.67 mL-kg^{-1}-min^{-1}. In this regard, our study confirmed the results of previous systematic reviews, pointing that moderate-to-vigorous- and vigorous-intensity interventions improved CRF to a larger extent than moderate-intensity ones (Mitchell et al., 2018).

The difference between moderate-to-vigorous- and vigorous-intensity in our study was 0.4 mL-kg^{-1}-min^{-1} and the difference between moderate- and moderate-to-vigorous-intensity was more significant (1.13 mL-kg^{-1}-min^{-1}). Although these analyses did not yield any consistent findings, they highlighted considerable variability in outcomes for interventions based on VO_2peak that appeared to be consistent across intensities. Although unexpected, this finding is not surprising. Given that VO_2 is not an appropriate variable to regulate intensity during training, in practice, prescriptions are converted to heart rate (HR) estimated to elicit the target VO_2. This approach is confounded in a CR setting by medications (e.g., β-blockers) that alter HR responses, which may cause dissociation of the HR and VO_2 relationship, where a small change in HR may result in varied and disproportionate changes to work rate or VO_2peak (Wisloff et al., 2007; Warburton et al., 2005; Kitzman et al., 2013).

The first meta-analyses that investigated improvements in CRF following exercise-based CR reported a small improvement in CRF (SMD ±: 95% CI = 0.46 ± 0.02) (Conn et al., 2019). Our study confirmed the results of Mitchell et al. (2018) who verified that moderate- and moderate- to-vigorous-intensity interventions were associated with a moderate increase in relative VO_2peak (SMD ±: 95% CI = 0.94 ± 0.30 and 0.93 ± 0.17, respectively), and vigorous- intensity exercise with a large increase (SMD ±: 95% CI = 1.10 ± 0.25), and moderate- and vigorous-intensity interventions were associated with moderate improvements in absolute VO_2peak (SMD ±: 95% CI = 0.63 ± 0.34 and SMD ±: 95% CI = 0.93 ± 0.20, respectively), whereas moderate-to-vigorous- intensity interventions elicited a large effect (SMD ±: 95% CI = 1.27 ± 0.75).

When we subdivided the intensities by length to obtain a more in-depth view of the effect of the different intensities, we found that the vigorous-intensity interventions below six weeks had more significant results in improving the VO_2peak (3.81 mL-kg^{-1}-min^{-1}). Based on the sensitivity analysis, although the results suggest that interventions conducted bidirectionally six times a week resulted in more significant gains of CRF favoring vigorous intensity, the analysis only included two studies and may not be practical to implement. In this sense, not being able to compare with other studies and other intensities within the division by length, the best result obtained was between 6 and 12 weeks in moderate-to- vigorous-intensity exercise, in which there was a significant increase in VO_2peak in relation to the vigorous- and moderate-intensity categories.

Interventions >12 weeks did not show significantly greater gains in CRF compared to other lengths. However, there was a significant improvement in VO_2peak with moderate- to-vigorous intensity. Additionally, there was no significant improvement in VO_2peak with vigorous-intensity interventions, and there were no studies of moderate-intensity RCTs available for comparison. Furthermore, patients with CVD did not obtain significant VO_2peak improvements when the vigorous-intensity protocol was >12 weeks.

Our results indicate that moderate-to-vigorous intensity exercise is superior to other intensities in improving aerobic capacity and is likely to be an underestimation of the true differences between groups. This is supported by the methodological decisions favoring the use of a conservative approach in the meta-analysis (by choosing random effects and SMDs) and using the highest calculated SD for studies where no information was published to allow SD calculations.

Thereby, our findings suggest higher benefits from moderate-to-vigorous-intensity exercise lasting 6 to 12 weeks in terms of VO_2peak improvements in patients with CVD. Overall, our findings are in agreement with reports from previous meta-analyses (Cornish et al., 2019; Mitchell et al., 2018; Sandercock et al., 2013; Vromen et al., 2016; Anderson et al., 2014). Hannan et al. (2018) concluded that HIIT (e.g., of moderate-to-vigorous- and vigorous-intensity) is more effective than moderate-intensity exercise in improving CRF in participants of CR (0.34 $mL\text{-}kg^{-1}\text{-}min^{-1}$; 95% CI = 0.2–0.48; $p < 0.001$; $I^2 = 28\%$). Still, improvements in CRF were higher in >six-week exercise programs, and the largest improvements in CRF for patients with CAD resulted from programs lasting 7 to 12 weeks, as our study confirmed (Hannan et al., 2018).

Some limitations of this systematic review and meta-analysis should be considered. First, the poor level of reporting within the available RCTs made it difficult to evaluate the most effective doses of intensity on CRF in cardiac patients. Second, the RCTs did not use the same methods to control the exercise intensity and the different variables used to establish exercise intensity added complexity to the analyses. While the variables were based on interrelated physiological constructs (e.g., HR and VO_2), they were not directly comparable. Even in what appears to be the narrow domain of HIIT, there is much heterogeneity in clearly defining what high intensity is.

In our study, each reported intervention was categorized according to the prescribed exercise intensity, based on ACSM (2017) recommendations. This approach has two limitations. While some studies reported precise exercise intensities (e.g., 60% VO_2peak), most CR studies prescribed large intervals based on HR responses to exercise (e.g., 40–70% VO_2peak). As these studies often covered several intensity categories, making them difficult to categorize, it was necessary to add an extra intensity category, moderate-to-vigorous intensity. In this category, participants were assumed to have performed similar training interventions, when in fact they may have experienced quite different exercise prescriptions.

We recognized the lack of available data for some intensity analyses when split by program length. For example, in the analysis of subgroups of studies below six weeks, we only had studies that prescribed vigorous-intensity exercise, as well as in the length above 12 weeks, we had no studies that used in their intervention a moderate-intensity program. Furthermore, subgroup analyses for the combined effect of vigorous-intensity programs with lengths below six weeks were based on only two groups of patients, both from the same study that completed the same intervention. As such, we recommend caution when interpreting results where the lack of available data may have limited analyses.

We should consider that medication can influence exercise and therefore should be considered by the therapist when prescribing exercise. Beta-blockers decrease exercise capacity because they create a ceiling effect, meaning the HR will not rise beyond a certain point. Thus, the target HR for monitoring should not be used. Rather, the therapist should use the rate of perceived exertion or calculate the target HR with a graded stress test while the patient is using the medication. Similarly, vasodilators and alpha- and calcium channel blockers may lead to a sudden blood pressure drop while exercising or afterwards. Therefore, the variables that should be taken into consideration are trainability (result of CRF level, muscular endurance and strength) and risk stratification on the basis of completed medical history. Consequently, these factors may provide options for the optimal type of exercise and intensity level.

Future studies would benefit from being between 6 and 12 weeks in length with an intervention activity carried out at least three times weekly, ensuring that the correct intensity is maintained. For example, appropriate goals for vigorous-intensity exercise include ≥85% VO_2peak or ≥85% HRR or ≥90% HRM and, for moderate-intensity, 50–75% VO_2peak or 50–75% HRR or 50–80% HRM. In addition, large ranges of exercise intensities should not be prescribed based on HR responses to exercise. This would allow a more accurate calculation of the exact effects of intensities on CRF and to determine the ideal and most effective "dose" for people with heart problems. Future research should include methods to appropriately describe the compliance of participants with the prescribed exercise intensity and attendance of exercise sessions.

Studies should report standard deviations, conceal allocation, and blind assessors to improve study quality. Moreover, future studies should aim to recruit more women and older participants (<76 years) to ensure vigorous-intensity interventions are more effective than moderate-intensity ones in improving CRF for a broader range of patients with CVD. Finally, further studies that investigate the longer-term benefits of vigorous-intensity interventions and whether these adaptations are maintained would also be beneficial.

2.4.5. Conclusions

The most effective doses of exercise intensity to optimize CRF were moderate-to-vigorous and vigorous exercise. Interventions to enhance CRF in patients with CVD are most effective if conducted for 6 to 12 weeks. More research is needed to understand within the moderate-to-vigorous intensity category which percentage results in increased CRF, assisting in the design of specific prescription protocols.

This review may suggest that countries without guidelines for patients with CVD regarding the intensity of exercise programs, as well as countries with guidelines that recommend lower intensity exercise, should include moderate-to-vigorous intensity and vigorous intensity.

What is already known:

► Cardiovascular diseases are the leading causes of mortality in today's society. They are responsible for up to 30% of all deaths worldwide and 48% of deaths in Europe, and it is expected that these figures will increase in the coming years.

- Exercise programs in patients with cardiovascular disease have several beneficial effects on cardiovascular functional capacity, quality of life, risk factors modification, psychological profile, hospital readmissions, and mortality.
- Exercise-based interventions seem to significantly improve cardiorespiratory fitness in patients following a cardiac event or surgery, but little is known regarding the differential effects of prescribed exercise intensity.

What are the new findings?

- Exercise interventions for patients with cardiovascular disease tend to include large ranges of exercise intensities based on heart rate responses to exercise.
- The most effective doses of exercise intensity to optimize cardiorespiratory fitness were moderate-to-vigorous and vigorous-intensity exercises, being more effective when conducted for 6 to 12 weeks.
- More research is needed to understand within the moderate-to-vigorous- and vigorous-intensity categories the percentage that specifically helps to increase cardiorespiratory fitness and the ability to establish specific prescription protocols.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10 .3390/ijerph18073574/s1. Table S1: Complete search strategy for MEDLINE, searched from inception till January 2021 (**APPENDIX 3**); Table S2: Summary of study characteristics (**APPENDIX 4**); Figure S3: Outcome of the risk of bias assessment (**APPENDIX 5**).

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2.4.6. References

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CHAPTER 3

Methodology

CHAPTER 3: Methodology

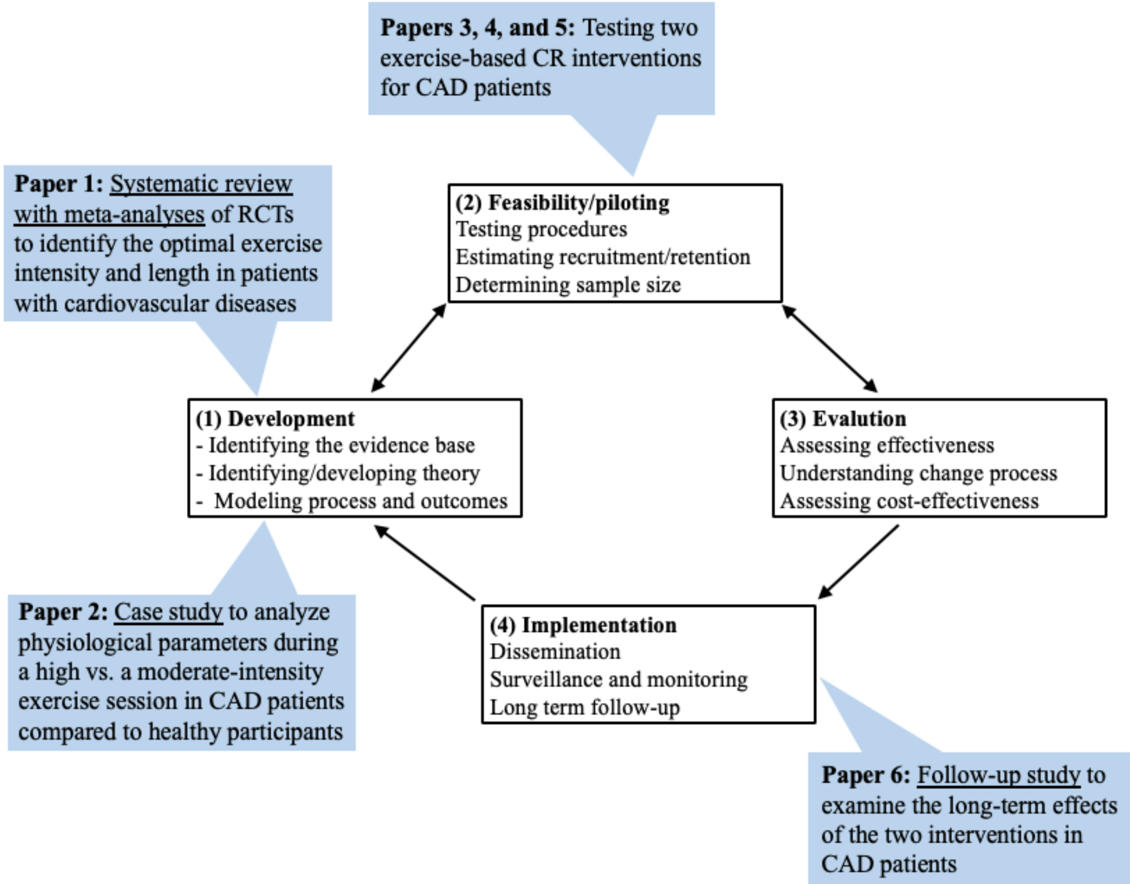
The immediate purpose of this study was to investigate the effectiveness of two cardiac rehabilitation programs in terms of intensity. In order to address the main aim of this thesis, physical, physiological and psychological measurements were collected and statistically analyzed to formulate a conclusion. This study involves six articles: one systematic review with meta-analyses, one case study, and four randomized controlled trials (RCTs) that followed the CONSORT guidelines for RCTs (http://www.consort-statement.org). The systematic review with meta-analyses was registered at PROSPERO with the number CRD42018097319 (**APPENDIX 6**) and described in Chapter 2.3 following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA). All work was conducted following the Declaration of Helsinki and registered at ClinicalTrials.gov (NCT03538119, **APPENDIX 2**). Ethics approval was obtained from the University of Évora Ethics Committee (reference number: 17039, **APPENDIX 1**). Informed written consent was received from all participants in Studies 2, 3, 4, 5, and 6. Participants received an information letter providing details of the study, the name of the principal investigator and an explanation that they could withdraw their consent at any time. All personal data was kept confidential and presented in a way that meant no individual participant was identifiable.

According to the Medical Research Council (MRC), clinical research often prioritizes the evaluation of an intervention without proper development and testing. This can result in weaker interventions that are less likely to be put into practice. The MRC defines complex interventions as those with multiple interconnected components, requiring different behaviors for delivery and reception, and having various outcomes. Such interventions are expected to be tailored to individual needs. Our interventions for survivors of coronary artery disease events meet these criteria.

The MRC suggests that there are four stages involved in the development and evaluation of complex interventions. These stages include the development, feasibility, evaluation, and implementation stages. **Figure 3.1** provides a clear illustration of these stages and how the studies and methods used in this project align with the recommended activities for stages 1, 2, and 4.

Figure 3.1.

The four key stages of developing complex interventions (Adapted from Craig et al., 2008) and how the studies in this thesis match the three stages



On 13 March 2020, the Portuguese Society of Cardiology and the Coordination of the Study Group on Effort Pathophysiology and Cardiac Rehabilitation suspended all Cardiac Rehabilitation Programs at a national level to prevent the spread of the new coronavirus (SARS-CoV-2) due to the high risk of contagion in a cardiac population with multiple risk factors. During the study, we faced challenges and obstacles due to global measures that resulted in home confinement. Unfortunately, we had to interrupt the study several times and experienced withdrawals from some participants in participating in the study.

3.1. Participants

Seventy-two CAD patients were recruited from those entering the cardiology unit at the Hospital do Espírito Santo de Évora (**APPENDIX 7**) between March 2018 and November 2021. The inclusion and exclusion criteria are shown in **Table 3.1**.

Table 3.1.

Inclusion and exclusion criteria of the study

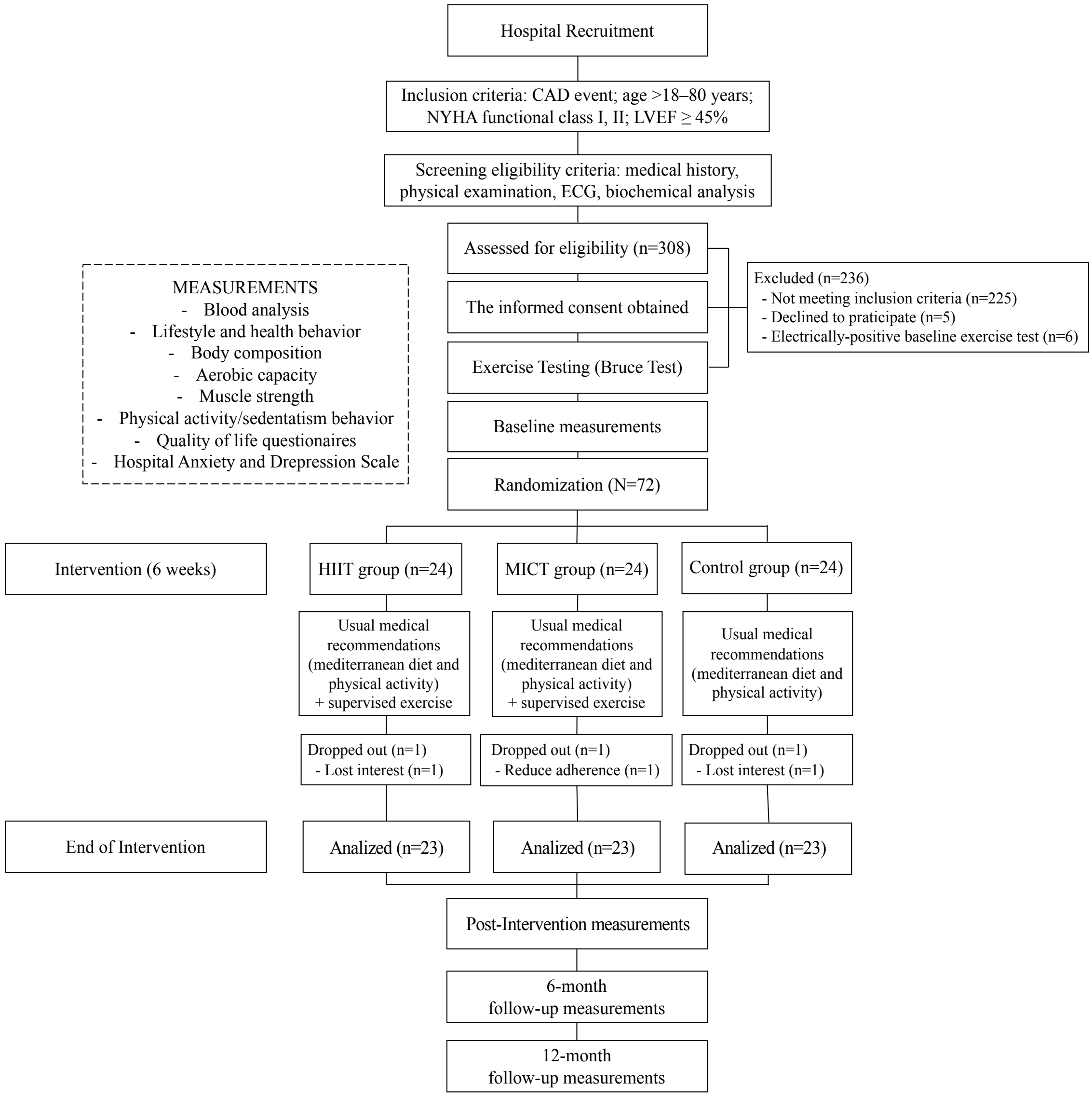
Inclusion Criteria	Exclusion Criteria
(1) age 18–80 years	(1) have symptoms of New York Heart Association class II, III, and IV heart failure (or documented signs and symptoms of chronic heart failure with an ejection fraction < 45%);
(2) low-moderate risk for physical exercise, with the following pathologies/conditions: stable coronary disease; after acute myocardial infarction; after coronary angioplasty; after cardiac surgery (coronary revascularization or valve surgery);	(2) uncontrolled arrhythmias;
(3) left ventricular ejection fraction ≥ 45%	(3) severe chronic obstructive pulmonary disease;
(4) New York Heart Association class I-II stable chronic heart failure;	(4) uncontrolled hypertension;
(5) acceptance of the assumptions of informed consent (**APPENDIX 8**).	(5) symptomatic peripheral arterial disease;
(6) not having participated in physical exercise programs in the 3 months prior to referral;	(6) unstable angina;
(7) not having more than one hour of vigorous PA per week, according to the International PA Questionnaire (IPAQ).	(7) uncontrolled diabetes;
	(8) signs or symptoms of ischemia;
	(9) inability to perform a VO_2max test;
	(10) locomotion exclusively dependent.

3.1.1. Randomization and masking

The sample size was calculated using the online G*Power software, considering an effect size of 0.3, a predefined sample power of 0.8, a predefined error probability defined as 0.05, and statistical power of 95% (El Maniani et al., 2016) (**APPENDIX 9**). Hence, a minimum sample size of 66 participants was determined (22 participants for each group) to identify significant changes. The number of participants was increased to cover an expectable dropout rate. After the baseline assessment and before the start of training protocols, the 72 participants were randomly assigned in a 1:1:1 allocation ratio to one of three groups: HIIT, MICT (traditional), and control (usual medical recommendations) (**Figure 3.2**). To ensure allocation concealment, participants in each group were seen at a specific, prescheduled time, and appointments for each group did not coincide with appointments for any participants in either of the other groups. The three groups were similar regarding age, the extent of coronary artery disease, coronary risk factors, type of coronary event or left ventricular ejection fraction). Whereas patients and physicians allocated to the intervention group were aware of the allocated arm, outcome assessors and data analysts were kept blinded to the allocation.

Figure 3.2.

Diagram of the study



Following health screening, 72 cardiac participants were enrolled in the study and allocated to one of three groups: (1) HIIT; (2) MICT, who did participate in formal exercise training and (3) control, who did not participate in any exercise program training.

3.2. Outcome measures and assessments

3.2.1. Exercise testing

Initially, the participants were submitted to a clinical evaluation performed by a cardiologist. A supervised graded exercise test to record volitional fatigue, risks or symptoms of ischemia was performed on a treadmill with the Bruce protocol (Bires et al., 2013) before the 6-week intervention period. The test was done in non-fasting conditions and under medication. Electrocardiography was recorded continuously, and blood pressure was measured with an arm cuff every 3 minutes. Functional capacity in metabolic equivalent value (METs) was calculated. As a high proportion of participants with CAD are prescribed beta-blocker therapy, this relative method of exercise intensity takes into account the likely lower HRpeak achieved by these participants during the exercise test. To ensure training exercise intensity was reflective of medication effects, all participants were instructed to take their usual medications before the maximal exercise test. A clinically positive CEPT was defined as the development of angina or angina-equivalent with exercise. An electrically positive CEPT was defined as ≥ 1 mm ST-segment depression in ≥ 3 consecutive beats persisting ≥ 1 minute into recovery. The CEPT results were classified as positive (clinically or electrically positive), negative (clinically and electrically negative), or indeterminate (inability to achieve ≥ 85% Maximum Predicted Heart Rate with no ECG changes).

3.2.2. Blood Biomarkers

Blood samples were drawn on the same day as exercise testing but were collected before exercise. All final blood samples were obtained 24-48 hours after completion of the last exercise session. Levels of blood biomarkers: high-sensitive C-reactive protein (hsCRP), fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol, low- and high-density lipoprotein cholesterol (LDL-C and HDL-C) and triglycerides (TG) were collected. Blood samples were collected at baseline and at the end of the study. Based on guidelines, dyslipidemia was defined as an HDL-C level < 50 mg/dL in women or <40 mg/dL in men and a TG level ≥ 150 mg/dL (Wilson et al., 2018). The cutoff for elevated hsCRP was ≥ 3.0 mg/L, according to national guidelines (Pearson et al., 2003). Criteria of diabetes mellitus diagnosis was defined according to the American Diabetic Association's diagnostic criteria: pre-diabetic stage [HbA1c 5.7–6.4 / impaired fasting blood glucose (100–125 mg/dL)] and diabetes mellitus (HbA1c ≥ 6.5 /fasting glucose ≥

126 mg/dL) (Rey & Hawks, 2022). Impaired non-fasting glucose was defined as a glucose value ≥ 100 mg/dL, based on the American Diabetes Association expert recommendations (Rey & Hawks, 2022).

3.2.3. Risk Factor Screening

On the second visit, the participants were submitted to a clinical evaluation of resting heart rate, blood pressure, medical history, body composition, aerobic capacity, muscle strength, physical activity and sedentary behavior, QoL, anxiety and depression tests, performed by a physiologist at the laboratory of the University of Evora (**APPENDIX 10**). Participants were asked to bring any medications that they were taking to the assessments. Initially, each participant completed a standardized questionnaire (**APPENDIX 11**) including demographic data, medical history, medication use, family history of CVD, and smoking status.

3.2.3.1. Health-Related Quality of Life

They also completed the patient-reported QoL questionnaire and the Hospital Anxiety and Depression Scale (HADS). The QoL questionnaire consisted of the rating scale, Short Form 36 (SF-36; Quality Metric, Lincoln, Rhode Island, USA) (**APPENDIX 12).** As physical functioning, role functioning limitations due to physical problems, bodily pain and general health domains of the SF-36 instrument are the most relevant for describing the health status of patients with CVD, the present analysis was restricted to these four domains. For all reported QoL instruments, higher scores correspond to better QoL as perceived by the patient (Ware & Sherbourne, 1992).

3.2.3.2. Anxiety and Depression Scores

The HADS questionnaire (**APPENDIX 13**) has been widely used to screen depression among cardiac patients in the hospitals. The HADS questionnaire has 2 subscales including anxiety and depression, each of which comprised of items rated on 4-point Likert scales (Herrero et al., 2003). The total HADS score ranged between 0-42 with 0-14 being considered as low, 15-28 considered as moderate, and 29-42 being considered as high. For each subscale (anxiety and depression subscales), the scores ranged between 0 to 21, where 0-7 was considered low, 8-14 being moderate, while 15-21 was considered high. After completing the health questionnaires, the participant's blood pressure, height, weight and waist circumference were recorded.

3.2.3.3. Body composition

The participants' height (to nearest 0.5 cm) and weight (to nearest 0.1 kg) were measured. Body mass index (BMI) was calculated directly by the standard formula: *weight(kg)/height(m)*^{2}. Overweight was defined as a BMI 25.0 to 29.9 kg/m^2, and obesity was defined as a BMI ≥ 30 kg/m^2 (Liguori, 2020). The waist circumference (WC) (to nearest 0.5 cm) was measured three times on the midpoint of the lowest rib and the iliac crest, and the mean of measurements was used in analyses (Liguori, 2020). WC was measured by a trained examiner using a standard protocol. In this study, increased WC was defined as > 80 cm in women and > 94 cm in men (Sardinha et al., 2012). Body composition was then assessed by dual-energy x-ray absorptiometry (DXA). DXA scans were performed with QDR 2000 densitometers (DXA, Hologic QDR, Hologic, Inc., Bedford, MA, USA), using the array beam mode. The DXA scans were performed within 1 week before starting and 1 week after the completion of 18 community-based exercise sessions. Scans were used to measure total body mass, body fat mass, body lean mass, body fat percentage, and abdominal region fat percentage (defined as the area between the ribs and the pelvis by GE Healthcare systems). Percentages of the total were calculated accordingly. The scanner was calibrated daily against a manufacturer-supplied standard calibration block to control for possible baseline drift.

3.2.3.4. Aerobic Capacity

Aerobic capacity was represented as peak oxygen consumed (VO_2peak, mL-kg^{-1}-min^{-1}) that was calculated from the equation $VO_2peak = 4.9486 + 0.023 * walk\ distance\ (meters)$ that was determined via using 6-minute walking test (6MWT) as described previously (ACSM, 2013). The 6MWT was performed in a 50m pre-marked University of Evora pavilion, and instructions and encouragements were given following the test's guidelines (Guyatt et al., 1985). This test is well validated for CAD patients and has shown good reliability in this patient group (McDermott et al., 2014).

3.2.3.5. Muscle Strength

To measure the isokinetic muscle strength, we used the Isokinetic Dynamometer (Biodex®, System 3 Pro, Biodex Corp., Shirley, NY, USA). The protocol used was the concentric unilateral mode for the extensor and knee-dominant flexor muscles. Patients were tested in a seated position with hip flexion. Stabilization straps were applied to the trunk, waist, and thigh. Evaluations of peak torque (three repetitions) and fatigue resistance (20 repetitions) were carried out at angular velocities of 90°/s and 180°/s of the dominant knee. The peak torques of the knee extensor and flexor muscles were adjusted by body weight according to the following formula: *strength (Nm) × 100/body weight (kg)*, since it is well known that the peak muscle power is closely associated with body weight (Maffiuletti et al., 2007).

3.2.3.6. Physical Activity and Sedentary Behavior

After completing all clinical evaluations, patients were asked to wear a triaxial accelerometer (ActiGraph GT3X) on their hip placed anterior to the right iliac crest for 7 consecutive days during waking and sleeping hours except when bathing or swimming. Acceleration data from the 3 planes were processed with *ActiGraph software* (ActiLife, version 6) using 15-s epochs (raw data recorded at 30 Hz) and the standard filter and were integrated into a vector magnitude count by taking the square root of the sum of squared axes (vertical, anterior–posterior, and medial–lateral). Daily averages (min/day) of accelerometer-measured PA were calculated for each patient and classified into five activity levels (sedentary time 1.00–1.99 MET, light PA 2.00–3.49 MET, and all activity ≥ 3.50 MET was classified as moderate-to-vigorous PA) using the limits set by the manufacturer41. A valid day was defined as ≥ 10 hours of wear time. All activity with intensities 1 MET (1 Met = 3,5 $mL\text{-}kg^{-1}\text{-}min^{-1}$) or higher was calculated on wear time. Patients with at least four valid days (3 weekdays and 1 weekend day) were included in the analyses (monitor wear time of ≥ 600 min/day) (Prince et al., 2015).

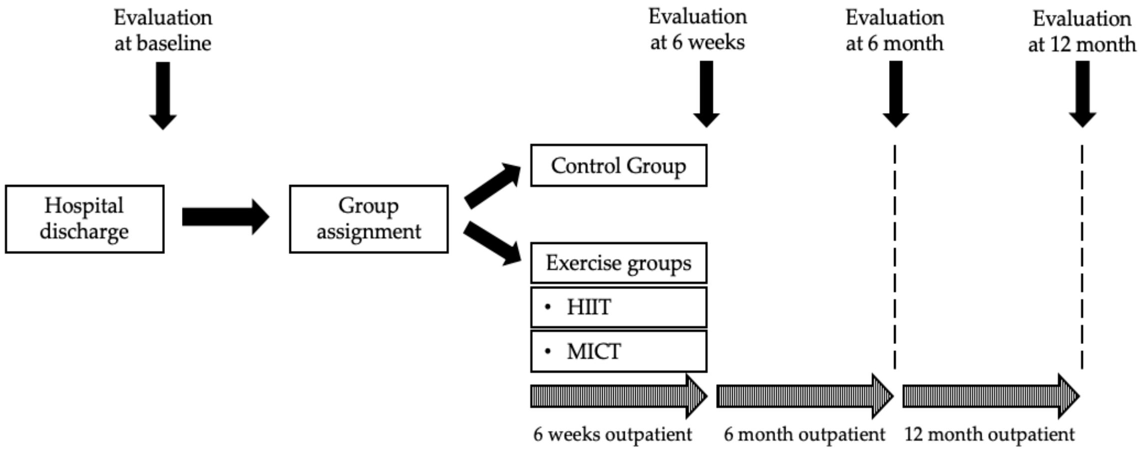
All measurements were taken at the beginning and completion of 18 sessions of community-based exercise programs. The protocols of pre- and post-intervention were the same for each patient. Compliance and adherence to exercise training was determined by recording the number of sessions attended.

3.2.4. Exercise training protocols

After hospital discharge, educational intervention, dietary advice, and psychological support were performed in all participants. The exercise programs consisted of 6 weeks of supervised treadmill exercise, three sessions per week (**Figure 3.3**). If a session was missed, it was made up that week or the following week. Participants performed each exercise session in a group, including a maximum of three participants per session.

Figure 3.3.

Study design and time frame



Note. HIIT = high-intensity interval training; MICT = moderate-intensity continuous training.

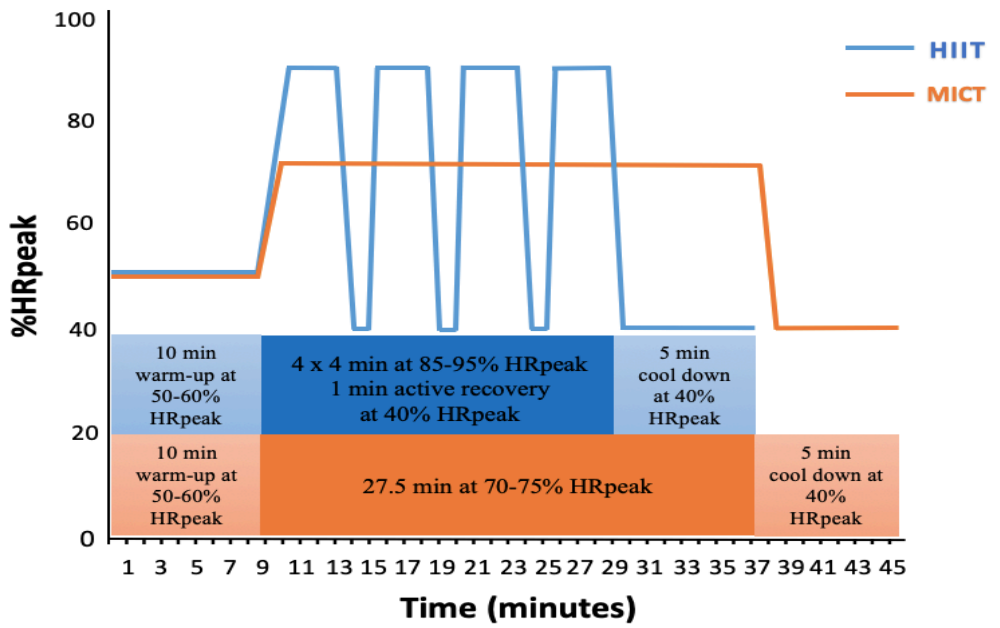
Training sessions were supervised by a physiologist. As training intensity increased, the participant's heart rate, rate of perceived exertion (Borg scale), and cardiac symptoms were also taken into consideration. Heart rates were observed with *Polar heart rate* monitoring (Polar Electro Oy, Kempele, Finland), and blood pressure (using a mercurial sphygmomanometer) was measured at the commencement and the end of each session.

The 10-point Category-Ratio Borg Scale (**APPENDIX 14**), also commonly referred to as the Rating of Perceived Exertion, was used to assess participants' perceived effort during exercise (Scherr et al., 2013). The Borg Scale is a 10-point scale ranging from 0 to 10 with anchors ranging from ''No exertion at all'' (0) to ''Maximal exertion'' (10). Participants were asked to rate their exertion before (pre-exercise), immediately post minute to minute and post-exercise. Buchheit & Laursen (2013) and Levinger et al. (2004) demonstrated that the RPE (Borg Scale) has shown a great correlation with HR, ventilation, and VO_2 in individuals with and without CAD, and the correlation is not impacted by beta-blocker medication, a commonly used HR modulating medication by patients with CAD.

Each training session was initiated with a 5–10-minute warm-up at 50-60% HRpeak and ended with 5 minutes of cool-down at 40% HRpeak. The HIIT group performed 4 × 4-minute high-intensity intervals at 85%–95% HRpeak followed by a 1-minute recovery interval at 40% HRpeak, predicted with a supervised graded exercise test on a treadmill with the Bruce protocol (Bires et al., 2013). During the exercise, the participants were motivated to gradually increase their exercise intensity towards 6–9 (hard to very hard) on a 0 to 10 Borg scale. The MICT protocol consisted of a continuous bout of moderate-intensity exercise to elicit 70–75% HRpeak, rating of perceived exertion 3 to 5 (fairly light to somewhat hard), for 27.5 minutes to equate the energy expenditure with the HIIT protocol (**Figure 3.4**).

Figure 3.4.

Summary of the exercise training protocol



Note. HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; min = minutes; HRpeak = peak heart rate.

Participants' heart rate was recorded using *Polar Heart Rate* monitors minute to minute of exercise (**APPENDIX 15**).

3.2.5. Control group (usual care)

Patients in the control group will receive the usual care. The usual care for this study is defined as following the cardiac procedure, patients get discharged and did not receive any additional follow-up regarding exercise beyond general advice on the importance of exercise and diet. They were evaluated just like the exercise program groups, e.g., before and after the community-based exercise programs, and were called in for the first follow-up assessment at six months and then at 12 months.

3.3. Statistical analyses

According to the Shapiro–Wilk and the Levene test results, repeated measures ANOVA assumptions were not met. Thus, non-parametric statistics were performed. The Friedman test was used for within-group comparisons, and the Kruskal–Wallis test was used for between-group comparisons. Pairwise post hoc tests were also carried out when significant differences were found. Lastly, the Wilcoxon test was performed to compare paired fall data between the baseline and the post-intervention. The means and standard deviations were calculated for all variables. The variation value was calculated between the baseline, post-intervention, and follow-up evaluations as Δ: $moment_{x} - moment_{x-1}$. For significant differences between the evaluation moments, the respective delta percentage was also computed by the following formula: ($\Delta\%$: $[(moment_{x} - moment_{x-1}) / moment_{x-1}] \times 100$). The effect size (ES) was calculated using Cohen's method since the data were not normally distributed. The ES was computed and classified based on Cohen's thresholds (small: $d = 0.10$; medium: $d = 0.30$; and large: $d \geq 0.50$) (Cohen, 2013). Analyses were performed using the SPSS software package (version 24.0 for MacBook, IMB Statistics). A value of $p \leq .05$ was considered statistically significant for all analyses. A code was assigned to each participant to preserve their anonymity.

3.4. Summary of Study Methods

Table 3.2.
Summary of study methods

	PAPER 1 Systematic review with Meta-analyze	**PAPER 2** Case study – Physiological effects during exercise	**PAPER 3** RCT 1 – Effects on blood biomarkers and body composition	**PAPER 4** RCT 2 – Effects on physical fitness and physical activity levels	**PAPER 5** RCT 3 – Effects on quality of life and mental health	**PAPER 6** RCT 4 – Follow-up at 6 and 12 months
Recruitment	Not applicable	Referral from a cardiologist at the Hospital do Espírito Santo de Évora	Referral from a cardiologist at the Hospital do Espírito Santo de Évora	Referral from a cardiologist at the Hospital do Espírito Santo de Évora	Referral from a cardiologist at the Hospital do Espírito Santo de Évora	Referral from a cardiologist at the Hospital do Espírito Santo de Évora
Population	• ≥ 18 years old • CAD patients Studies were eligible if they were: • RCTs studies • Exercise-based CR interventions • With VO_2peak results	• Age 18–80 years • Coronary artery event • Left ventricular ejection fraction ≥ 45% • New York Heart Association functional Class I or II	• Age 18–80 years • Coronary artery event • Left ventricular ejection fraction ≥ 45% • New York Heart Association functional Class I or II	• Age 18–80 years • Coronary artery event • Left ventricular ejection fraction ≥ 45% • New York Heart Association functional Class I or II	• Age 18–80 years • Coronary artery event • Left ventricular ejection fraction ≥ 45% • New York Heart Association functional Class I or II	• Age 18–80 years • Coronary artery event • Left ventricular ejection fraction ≥ 45% • New York Heart Association functional Class I or II
Data collected	• Study and participant characteristics • Primary outcome: VO_2peak • Stratified by intensities based on proposed cut-offs (ACSM, 2017) • Subgroup Analyses: Intensity and length	• Demographic data • Medical history • Medication use • Family history of CVD • Smoking status • Blood Pressure • BMI and WC • Thermography • Heart Rate Variability • Fatigue of central nervous system • Cortical Arousal	• Demographic data • Medical history • Medication use • Family history of CVD • Smoking status • Blood biomarkers • Blood Pressure • BMI and WC • DXA	• Demographic data • Medical history • Medication use • Family history of CVD • Smoking status • BMI and WC • DXA • 6-minute walk test • Biodex • Accelerometers	• Demographic data • Medical history • Medication use • Family history of CVD • Smoking status • SF-36 • HADS	• Demographic data • Medical history • Medication use • Family history of CVD • Smoking status • Blood biomarkers • Blood Pressure • BMI and WC • DXA • 6-minute walk test • Biodex • Accelerometers • SF-36 • HADS

Table 3.4. (cont.)

Summary of study methods

	PAPER 1 Systematic review with Meta-analyze	PAPER 2 Case study – Physiological effects during exercise	PAPER 3 RCT 1 – Effects on blood biomarkers and body composition	PAPER 4 RCT 2 – Effects on physical fitness and physical activity levels	PAPER 5 RCT 3 – Effects on quality of life and mental health	PAPER 6 RCT 4 – Follow-up at 6 and 12 months
Data analysis	• Risk of bias: RoB 2 (RCTs) • Clinical heterogeneity of studies • Effectiveness of exercise interventions summarized as MD or SMD • Data pooled using random effects meta-analyses • Quality of evidence: PRISMA	Summary of survey outcomes: • Mean scores ± SD	• Normality and homogeneity were tested through the Kolmogorov-Smirnov and Levene tests, respectively; • Change in outcomes (mean difference) baseline to end of the intervention: - Kruskal-Wallis Test (comparisons between-group) - Friedman Test (within-group comparisons) - Cohen's method (effect size) - Delta value (Δ) and proportional change delta value (Δ%)	• Normality and homogeneity were tested through the Kolmogorov-Smirnov and Levene tests, respectively; • Change in outcomes (mean difference) baseline to end of the intervention: - Kruskal-Wallis Test (comparisons between-group) - Friedman Test (within-group comparisons) - Cohen's method (effect size) - Delta value (Δ) and proportional change delta value (Δ%)	• Normality and homogeneity were tested through the Kolmogorov-Smirnov and Levene tests, respectively; • Change in outcomes (mean difference) baseline to end of the intervention: - Kruskal-Wallis Test (comparisons between-group) - Friedman Test (within-group comparisons) - Cohen's method (effect size) - Delta value (Δ) and proportional change delta value (Δ%)	• Normality and homogeneity were tested through the Kolmogorov-Smirnov and Levene tests, respectively; • Change in outcomes (mean difference) baseline to follow-up time point: - Kruskal-Wallis Test (comparisons between-group) - Friedman Test (within-group comparisons) - Cohen's method (effect size) - Delta value (Δ) and proportional change delta value (Δ%)

Note. BMI = Body mass index; CAD = Coronary artery disease; CVD = Cardiovascular diseases; DXA = Dual-energy x-ray absorptiometry; HADS = Hospital anxiety and depression scale; MD = Mean difference; RCT = Randomized controlled trial; SF-36 = Short Form 36 questionnaire; SD = Standard deviation; SMD = Standardized mean difference; WC = Waist circumference.

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CHAPTER 4

Paper 2: Influence of Two Exercise Programs on Heart Rate Variability, Body Temperature, Central Nervous System Fatigue, and Cortical Arousal after a Heart Attack

CHAPTER 4

Paper 2: Influence of Two Exercise Programs on Heart Rate Variability, Body Temperature, Central Nervous System Fatigue, and Cortical Arousal after a Heart Attack

Chapter overview

Cardiac rehabilitation (CR) programs' benefits are internationally consensual, but during the exercise, progressive physiological effects occur on the body temperature, heart rate variability, blood pressure, and cortical arousal, which have not been studied yet in CR programs. The real question is, what are the physiological differences between cardiac patients and healthy people during exercise, and is it possible to predict the appearance of the disease in people who are clinically healthy or who present an equivocal cardiac clinical condition? Actually, new evaluation and control methods are applied to different sport areas such as performance, but also health.

This chapter examines the physiological parameters of thermography, heart rate variability, blood pressure, and cortical arousal in cardiac patients who belong to CR programs of High-Intensity Interval Training and Moderate-Intensity Continuous Training, compared to healthy participants.

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Case Report

Influence of Two Exercise Programs on Heart Rate Variability, Body Temperature, Central Nervous System Fatigue, and Cortical Arousal after a Heart Attack

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Abstract: Cardiovascular diseases (CVD) are the leading cause of death globally. Cardiac rehabilitation (CR) programs' benefits are overall consensual; however, during exercise, progressive physiological effects have not been studied yet in cardiac patients. Our study aims to analyze physio- logical parameters of thermography, heart rate variability (HRV), blood pressure, central nervous system (CNS) fatigue, and cortical arousal in heart attack patients (HAP) who belong to CR programs of High-Intensity Interval Training (HIIT) and Moderate-intensity Continuous Training (MICT) com- pared to healthy participants. In this case control study, two HAP patients (both male, age 35 and 48, respectively) and two healthy people (both male, age 38 and 46, respectively) were randomly assigned in a 1:1:1:1 allocation ratio to one of four groups: cardiac MICT, cardiac HIIT, control MICT, and control HIIT. The HIIT at ≈85–95% of peak heart rate (HR) was followed by a one-minute recovery interval at 40% peakHR, and MICT at ≈70–75% of peakHR. Outcome measurements included thermography, HRV, blood pressure, CNS fatigue, and cortical arousal; The HAP presents more than twice the CNS fatigue in MICT than control participants, but HIIT has almost the same CNS fatigue in HAP and control. In addition, both of the HAP groups presented higher temperatures in the chest. The HIIT protocol showed better physiological responses during exercise, compared to MICT in HAP.

Keywords: cardiovascular diseases; heart rate variability; thermography; central nervous system fatigue; prognosis.

4.1. Introduction

According to World Health Organization (WHO, 2011), cardiovascular diseases (CVD) are the number one cause of death globally. An estimated 17.9 million people died from CVD in 2019, representing 32% of all global deaths worldwide. Of these deaths, 85% were due to heart attack and stroke (WHO, 2011). In 2019, there were 3.9 million deaths resulting from CVD in Europe, which corresponded to 45% of all deaths, considerably higher than the second most prevalent cause of death, cancer (Corrà et al., 2010). Furthermore, out of the 17 million premature deaths (under the age of 70) due to noncommunicable diseases in 2019, 38% were caused by CVD (WHO, 2011).

Cardiac rehabilitation (CR) is a multidisciplinary process for patients recovering after an acute cardiac event or chronic CVD that reduces mortality and morbidity and improves the quality of life (Arnett et al., 2019). CR is the gold standard treatment for excellent recovery, not only physical but also mental and social after a cardiac episode so that their inclusion in daily life can be as normalized as possible; however, there is poor adherence to these types of programs, which could condition the recovery of patients (García-Bravo et al., 2020), being that only 10% of patients with a CR indication attend these types of programs (García-Bravo et al., 2019). Two types of training are currently used in CR programs. Moderate-intensity continuous training (MICT) is routinely prescribed for cardiac patients in CR. Typically, the upper limit of intensity that is prescribed during the early stages of phase II cardiac rehab is 60–70% of heart rate reserve. This exercise intensity is performed continuously for 10–30 min, depending on endurance and as tolerated by the patient (Dibben et al., 2021). High-intensity interval training (HIIT) has been used as an effective type of training in healthy adults for many years. However, routine implementation of HIIT into CR programs for higher-risk cardiac patients has yet to be established. Recent clinical studies (Freyssin et al., 2012; Keteyian et al., 2014; Benda et al., 2015) have implemented HIIT into CR programs. The HIIT program allows patients to work at a higher intensity for two to three minutes, while alternating with recovery intervals at a moderate intensity. In these clinical studies, work intervals ranged from an intensity of 80–95% of heart rate reserve, and rest intervals ranged from 50–70% of heart rate reserve with a duration of 30–45 min per rehab session (Freyssin et al., 2012; Keteyian et al., 2014; Benda et al., 2015). A recent meta-analysis which evaluated 16 studies (n = 969 patients) concluded that studies would benefit from being between moderate-to-vigorous and vigorous-intensity (Gonçalves et al., 2021).

Hypertension, hyperlipidemia, diabetes, and obesity are cardiovascular risk factors that can be reduced with this type of exercise program (Hanssen et al., 2022; Fisher et al., 2015), and which consequently have an influence on the reduction of chronic systemic inflammation (Hansen et al., 2022), which has been shown to be an important risk factor for CVD (Chrysohoou et al., 2015). The practice of regular exercise is associated with anti-inflammatory effects that are beneficial for health, mainly in patients with CVD, causing decreased levels of serum C-reactive protein (Fisher et al., 2015), better cardiac output (Haykowsky et al., 2013), stroke volume (Haykowsky et al., 2013), vascular endothelial function (Benda et al., 2015), and changes in heart rate variability (Weston et al., 2014).

CR programs' benefits are internationally consensual (WHO et al. 2011; Corrà et al., 2010), but during the exercise, progressive physiological effects occur on the body temperature, heart rate variability (HRV), blood pressure, and cortical arousal, which have not been studied yet in CR programs. The real question is, what are the physiological differences between cardiac patients and healthy people during exercise, and is it possible to predict the appearance of the disease in people who are clinically healthy or who present an equivocal cardiac clinical condition?

Actually, new evaluation and control methods are applied to different sport areas such as performance, but also health. One of these is the analysis of the HRV as a tool to understand the autonomous nervous system status and response to different stimulus (Aguilera et al., 2021; Sánchez-Conde & Clemente-Suárez, 2021), facts directly related to heart and cardiovascular pathologies (Huikuri & Stein, 2013). The analysis of HRV is based in the study of differences in milliseconds (ms) between RR waves of the electrocardiogram; then, using linear, frequency, or nonlinear analysis methods, we can analyze the autonomic nervous system response (Mendoza-Castejón & Clemente-Suárez, 2020; Bustamante-Sánchez et al., 2020). The other method is the use of thermography analysis, which allow us to study microcirculation abnormalities and capillarity disorders to prevent injuries and detect in early stages (Viegas et al., 2020; Sillero-Quintana et al., 2015).

This case control study aims to analyze the physiological parameters of thermography, HRV, blood pressure, and cortical arousal in cardiac patients who belong to CR programs of HIIT and MICT, compared to healthy participants.

4.2. Materials and Methods

4.2.1. Participants

Two patients were recruited within the cardiology unit of the Hospital do Espírito Santo de Évora (Portugal). Two patients who had undergone a heart attack and were referred by their cardiologist to the cardiac rehabilitation (CR) phase III, two months after angioplasty and low-risk medical recommendations, were evaluated for inclusion in this case control study. The inclusion criteria were age 18–80 years, who had left ventricular ejection fraction ≥ 45%, and were New York Heart Association (NYHA) functional Class I or II. In addition, patients were excluded from the study if the following criteria were met: severe exercise intolerance, uncontrolled arrhythmia, uncontrolled angina pectoris, severe kidney or lung diseases, musculoskeletal or neuromuscular conditions preventing exercise testing or training, and signs or symptoms of ischemia. The control group included two healthy participants without CVD.

4.2.1.1. Randomization and Masking

This case control study had four participants, two HAP patients (both male, age 35 and 48, respectively) and two healthy controls (both male, age 38 and 46, respectively) who were randomly assigned in a 1:1:1:1 allocation ratio to one of four groups: cardiac HIIT (n = 1), cardiac MICT (n = 1), control HIIT (n = 1), and control MICT (n = 1) (**Table 4.1**). All groups are comparable in age and weight, and the two heart attack patients (HAP) were similar in the extent of coronary artery disease, coronary risk factors, type of coronary event, or left ventricular ejection fraction (**Table 4.1**).

Table 4.1.

Participant characteristics

	HAP Group (n = 2)		Healthy Group (n = 2)	
	HIIT (n = 1)	MICT (n = 1)	HIIT (n = 1)	MICT (n = 1)
Demographics				
Age (years)	35	48	38	46
VO_2peak (mL-kg^{-1}-min^{-1})	30.7	30.4	33.3	32.7
Risk factors or comorbidities				
Body Mass index (kg/m^2)	28.2	29.4	29.0	28.4
Waist Circumference (cm)	98.4	101.1	99.5	100.5
Left ventricular ejection fraction (%)	52	46	-	-
Diabetes mellitus	Y	Y	Y	Y
Hypertension	N	Y	N	N
Dyslipidemia	Y	Y	N	N
Active smoker	N	N	N	N
Family history of CVD	Y	Y	Y	N

Note. CVD = cardiovascular diseases; HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; VO_2peak = maximal oxygen consumed; Y = Yes; N = No.

4.2.2. Outcome Measures and Assessments

4.2.2.1. Exercise Testing

Initially, participants read and signed an informed consent form on the first visit, and the two HAP were submitted to a clinical evaluation performed by a cardiologist. A supervised graded exercise test to record volitional fatigue, risks, or symptoms of ischemia was performed on a treadmill, using the Bruce protocol, before the intervention. The test was done in non-fasting conditions and under medication. Electrocardiography was recorded continuously, and blood pressure was measured with an arm cuff every 3 min.

4.2.2.2. Thermography, Heart Rate Variability, and Cortical Arousal

On the second visit, each participant completed a standardized questionnaire including demographic data, medical history, medication use, family history of CVD, and smoking status; then, the peripheral vascular response was collected using a thermography system in two different moments: pre- and post-treadmill protocol. All thermal images were collected in compliance with the European Association of Thermology guidelines (Ring & Ammer, 2012). The thermograms of each participant were obtained in a room with a controlled and constant temperature of 20ºC and 40% humidity. Participants were in the test room 20 min prior to the data collection in order to acclimatize, and all the data collection occurred in the morning to control circadian rhythms (Li & Wang, 2005). To analyze the thermographic images, we divided the body in different sections: head, chest, abdomen, right arm, right hand, left arm, left forearm, and left hand. The analysis of the skin surface temperature was conducted by locating the middle point of each body section, and through a circle at the center of each dorsal and palmar hand (diameter 70 × 70 mm), following previous procedures (Clemente-Suárez et al., 2021).

The Heart Rate Variability (HRV) was measured by a H10 chest strap (Polar ©nc., Kempele, Finland) and recorded using a RS800CX monitor (Polar Inc., Kempele, Finland). This wireless device was placed below the participants' chest muscles, allowing a reliable recording (Barbosa et al., 2016); then, the Kubios HRV software (v.3.3) (Tarvainen et al., 2014) was used to pre-process and analyze the HRV data. A median filter was applied to correct possible artifacts. This filter allows the identification of RR intervals shorter/longer than 0.25s, compared to the average of the previous beats. Correction replaces the identified artifacts with cubic spline interpolation. All HRV indices were extracted using the MATLAB Release 2019a (The MathWorks, Inc., Natick, MA, USA). Time-domain, frequency-domain, and non-linear measures were extracted. For this study, we only considered the time domain and non-linear domains. The following metrics were calculated:

• Time-domain analysis: (a) square root of differences between adjacent RR intervals (RMSSD);

• Non-linear analyses:©) non-linear metrics: the RR variability from heartbeat to short-term Poincaré graph (width) (SD1), the RR variability from heartbeat to long-term Poincaré graph (length) (SD2), short-term fluctuation of the detrended fluctuation analysis (alpha-1), long-term fluctuation of the detrended fluctuation analysis (alpha-2), and the sample entropy (SampEn), which measures the regularity and complexity of a time series.

The cortical arousal was measured by the critical flicker fusion threshold (CFFT) by a Lafayette Instrument Flicker Fusion Control Unit model 12,021 (Lafayette, IN, USA), using standards protocols previously used (Clemente-Suárez & Diaz-Manzano, 2019). Participants were familiarized with the procedure by performing practice trials before testing. The practice was before the basal sample, in line with previous studies (Aguilera et al., 2021). Three ascending trials were carried out; in each one, time was quantified as the amount of time that a participant took to detect the changes in the lights from the beginning of the test until the moment of pressing a button (Ramírez-Adrados et al., 2022). We used the critical flicker fusion threshold (CFFT) in this research since it has been widely used in different contexts, such as education, pharmacy, sports, military, and to evaluate cortical arousal and central fatigue (Clemente-Suárez & Arroyo-Toledo, 2017; Fuentes et al., 2018; Delgado-Moreno et al., 2019; Clemente-Suárez, 2021; Mendoza-Castejon et al., 2020; Redondo-Flórez et al., 2020).

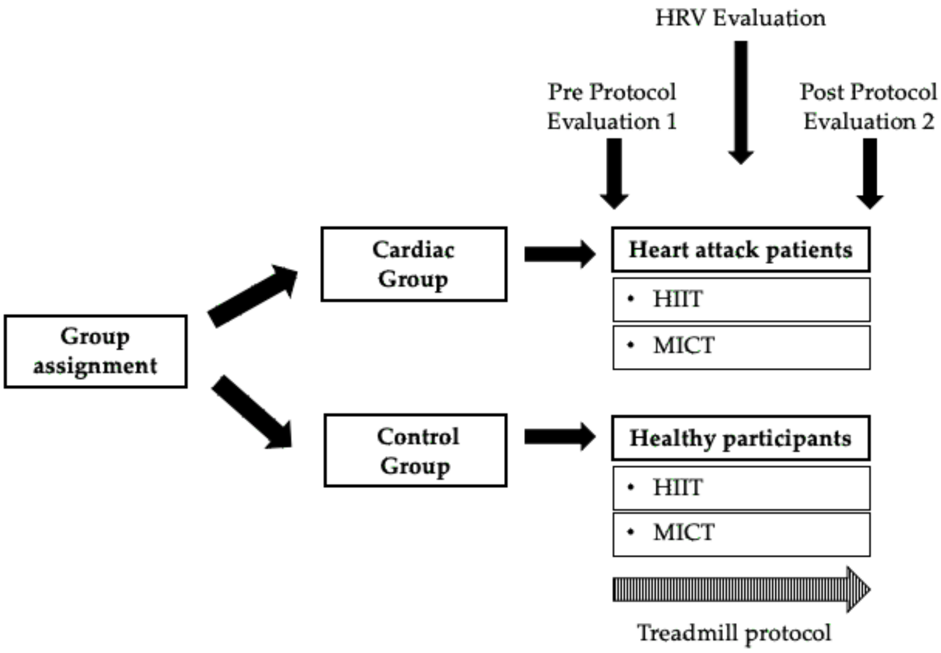
Finally, the perception of fatigue was measured by a visual analogue scale (VSA) wherein the subjective fatigue was scaled to a 0–100 scale, 0 being no fatigue and 100 being an extreme fatigue following similar VSA (Beltrán-Velasco et al., 2020).

4.2.3. Protocol and Experimental Procedures

Regarding assessment procedures, participants had to rest for 15 min prior to baseline HRV collection in a sitting position, as recommended (Catai et al., 2020; Camm et al., 1996). After 15 min at rest, 5 min of baseline was collected. Blood pressure, CNS fatigue, and cortical arousal were measured at the commencement and at the end of the session. The peripheral vascular response by thermography was collected at two different moments: pre- and post-treadmill protocols. The heart rate variability was collected: pre-, during, and post-treadmill protocols (**Figure 4.1**). Subsequently, participants performed an aleatory treadmill session of a CR program (HIIT and MICT), supervised by a physiologist.

Figure 4.1.

Summary of the present study protocol

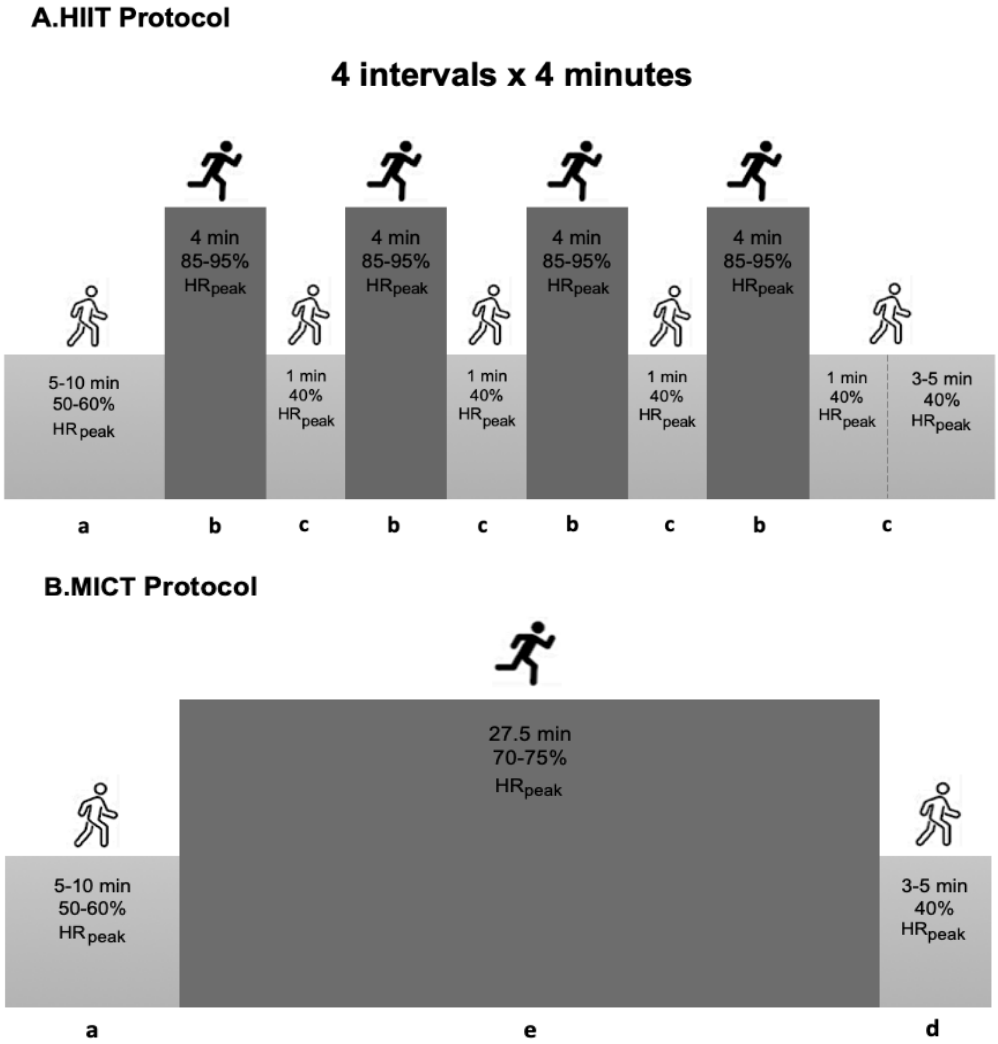


Note. HRV—Heart rate variability; HIIT—High-intensity interval training; MICT—Moderate-intensity continuous training.

The assessments and data acquisition were performed by an external agent who was trained to do so, so that the researchers were totally blinded in the management of the data. Training sessions on the treadmill were initiated with a 5–10 min warm-up at 50–60% peak Heart Rate (peakHR), and ended with 5 min of cool-down at 40% peakHR. The HIIT trial involved a total of 20 min at 85–95% peakHR, followed by a one-minute recovery interval at 40% peakHR, predicted with a supervised graded exercise test on a treadmill, using the Bruce protocol. During the high-intensity exercises, the participants were motivated to gradually increase their exercise intensity toward 15–17 on the Borg scale. The MICT protocol consisted of a continuous bout of moderate-intensity exercise to elicit 70–75% peakHR for 27.5 min, to equate the energy expenditure with the HIIT protocol (**Figure 4.2**).

Figure 4.2.

Summary of the exercise training protocol



Note. HIIT—High-intensity Interval Training; MICT—Moderate-intensity Continuous Training; a—warm-up; b—interval bout of high-intensity exercise; c—one-minute recovery interval; d—cool-down; e—continuous bout of moderate-intensity exercise; min—minutes.

As training intensity increased, the patients' heart rate, rate of perceived exertion (Borg scale), and cardiac symptoms were also taken into consideration.

4.2.4. Ethical Considerations

All work was conducted following the Declaration of Helsinki and registered at ClinicalTrials.gov (NCT03538119). Ethics approval was obtained from the University of Evora Ethics Committee (reference number: 17039). All participants signed a written informed consent before participating in this study.

4.3. Results

4.3.1. Thermography

Before starting the protocols on the treadmill, the temperature was quite similar between the HAP and healthy participants' groups. From pre- to post-protocols, there was always a decrease in temperature in all body variables evaluated in the study, except for the temperature of the right hand, where both HIIT groups increased temperature (temperature difference: 0.8±0.5ºC in HAP vs. 1.0±0ºC in control). In contrast, the MICT groups maintained the temperature from pre- to post-protocol. The same was not observed in the temperature of the left hand, which remained the same (**Table 4.2**, **Figure 4.3**).

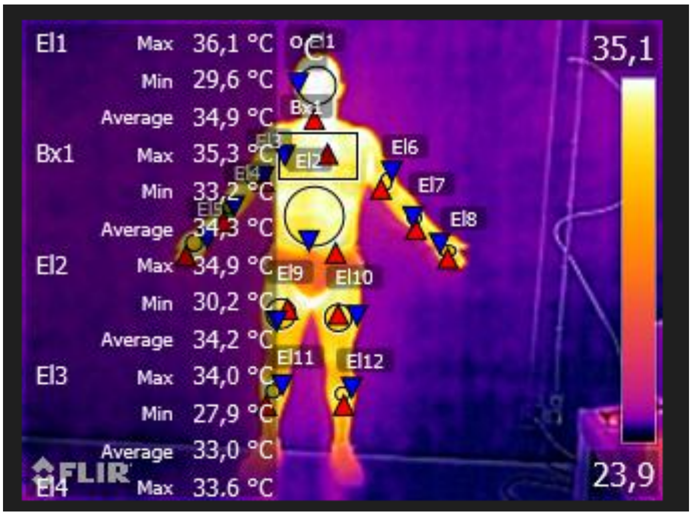
Table 4.2.

Temperature in °C by thermography analysis in heart attack patients and control in the high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT)

Variable	Group	Protocol	Pre	Post
Head (°C)	HAP	HIIT	34.1 ± 0.3	32.6 ± 0.8
		MICT	34.9 ± 1.3	33.4 ± 3.3
	Control	HIIT	34.4 ± 0.0	32.7 ± 0.0
		MICT	35.6 ± 0.0	32.8 ± 0.0
Chest (°C)	HAP	HIIT	34.6 ± 0.5	32.3 ± 1.8
		MICT	35.2 ± 1.6	32.2 ± 1.5
	Control	HIIT	34.7 ± 0.0	33,5 ± 0.0
		MICT	34.6 ± 0.0	33.6 ± 0.0
Abdomen (°C)	HAP	HIIT	34.0 ± 0.4	32.5 ± 1.6
		MICT	34.3 ± 2.5	30.6 ± 1.1
	Control	HIIT	34.3 ± 0.0	33.3 ± 0.0
		MICT	33.2 ± 0.0	30.4 ± 0.0
Right arm (°C)	HAP	HIIT	33.0 ± 0.1	31.2 ± 0.6
		MICT	34.7 ± 1.8	29.4 ± 0.4
	Control	HIIT	32.9 ± 0.0	32.2 ± 0.0
		MICT	33.5 ± 0.0	31.9 ± 0.0
Right forearm (°C)	HAP	HIIT	32.8 ± 0.4	31.1 ± 1.0
		MICT	33.8 ± 1.8	30.5 ± 0.5
	Control	HIIT	32.4 ± 0.0	32.0 ± 0.0
		MICT	34.0 ± 0.0	32.3 ± 0.0
Right hand (°C)	HAP	HIIT	31.9 ± 0.5	32.7 ± 0.5
		MICT	33.0 ± 2.0	33.2 ± 2.3
	Control	HIIT	32.3 ± 0.0	33.3 ± 0.0
		MICT	34.7 ± 0.0	34.2 ± 0.0
Left arm (°C)	HAP	HIIT	32.9 ± 0.6	30.5 ± 1.2
		MICT	34.3 ± 2.1	29.7 ± 0.8
	Control	HIIT	33.3 ± 0.0	32.2 ± 0.0
		MICT	33.5 ± 0.0	30.3 ± 0.0
Left forearm (°C)	HAP	HIIT	33.0 ± 0.8	30.5 ± 0.6
		MICT	33.6 ± 0.6	29.1 ± 0.0
	Control	HIIT	32.6 ± 0.0	32.1 ± 0.0
		MICT	33.7 ± 0.0	31.9 ± 0.0
Left hand (°C)	HAP	HIIT	32.0 ± 0.6	32.0 ± 0.7
		MICT	33.4 ± 1.1	33.1 ± 2.3
	Control	HIIT	32.8 ± 0.0	32.8 ± 0.0
		MICT	34.3 ± 0.0	34.2 ± 0.0

Figure 4.3.

Temperature modification (°C) evaluated by thermography in Heart Attack Patients (HAP) and control participants in pre- and post-treadmill protocols (HIIT vs. MICT)



The temperature difference in the chest was greater in patients with adverse cardiac events than in patients without events (temperature difference: 2.3 ± 1.2 °C in HIIT vs. 3.0 ± 1.6 °C in MICT). In the groups of healthy participants, the temperature remained practically the same. There was also a greater difference in temperature in the abdomen in the MICT group (temperature difference: 3.7 ± 1.8 °C in the HAP vs. 2.8 ± 0.0 °C in the control group) compared to the HIIT group (temperature difference: 1.5 ± 1.0 °C in the HAP vs. 1.0 ± 0.0 °C in control) (**Table 4.2**).

4.3.2. Heart Rate Variability

The stress index was higher in the HAP groups compared to the control groups. Those who did the HIIT protocol had higher Stress Index values from pre-exercise than those who did the MICT protocol, and from exercise to post-exercise, the HAP in HIIT dropped slightly, while the HAP in MICT continued to rise sharply (**Table 4.3**). In addition, there was a higher decrease in the number of RR intervals in the HIIT in both groups (HAP: 210.5 ± 112.75 ms^2 vs. control: 346 ± 0.00 ms^2) compared to the MICT groups (HAP: 120.5 ± 74.2 ms^2 vs. control: 81.7 ± 0.00 ms^2). However, no significant interaction or main effects were observed in RMSSD (**Table 4.3**).

Table 4.3.

Heart rate and heart rate variability parameters in heart attack patients (HAP) and control in high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT)

Variable	Group	Protocol	Pre	Exercise	Post
Maximum heart rate (bpm)	HAP	HIIT	65.0 ± 7.1	137.012.7	96.0 ± 9.9
		MICT	78.0 ± 4.2	123.0 ± 24.0	95.5 ± 19.1
	Control	HIIT	84 ± 0.0	170 ± 0.0	97 ± 0.0
		MICT	80 ± 0.0	138 ± 0.0	111 ± 0.0
Average heart rate (bpm)	HAP	HIIT	69.5 ± 3.5	113.0 ± 9.9	87.0 ± 7.1
		MICT	62.5 ± 7.8	104.0 ± 18.4	87.0 ± 19.0
	Control	HIIT	78 ± 0.0	133 ± 0.0	89 ± 0.0
		MICT	75 ± 0.0	112 ± 0.0	97 ± 0.0
RMSSD (ms)	HAP	HIIT	27.9 ± 12.8	8.3 ± 1.7	10.9 ± 3.3
		MICT	23.4 ± 10.0	11.5 ± 6.8	9.5 ± 3.2
	Control	HIIT	25.3 ± 0.0	10.2 ± 0.0	16.3 ± 0.0
		MICT	25 ± 0.0	5.7 ± 0.0	76.1 ± 0.0
PNN50 (ms)	HAP	HIIT	9.5 ± 12.7	0.2 ± 0.0	0.4 ± 0.5
		MICT	4.3 ± 5.4	0.5 ± 0.6	0.5 ± 0.6
	Control	HIIT	4.2 ± 0.0	0.8 ± 0.0	0.7 ± 0.0
		MICT	2.7 ± 0.0	1.9 ± 0.0	0.3 ± 0.0
Stress Index	HAP	HIIT	12.4 ± 1.9	25.3 ± 6.6	21.3 ± 6.2
		MICT	16.3 ± 2.1	19.4 ± 2.9	35.7 ± 15.4
	Control	HIIT	10.9 ± 0.0	15.3 ± 0.0	16.1 ± 0.0
		MICT	13 ± 0.0	21 ± 0.0	11.4 ± 0.0
SD1 (ms)	HAP	HIIT	19.8 ± 9.0	5.4 ± 0.5	7,7 ± 2.3
		MICT	16.5 ± 7.1	8.1 ± 4.8	6.7 ± 2.3
	Control	HIIT	18 ± 0.0	7.2 ± 0.0	11.6 ± 0.0
		MICT	17.7 ± 0.0	13.2 ± 0.0	53.6 ± 0.0
SD2 (ms)	HAP	HIIT	41.0 ± 11.7	16.9 ± 6.1	27.5 ± 9.1
		MICT	26.5 ± 3.1	10.0 ± 4.8	11.2 ± 6.6
	Control	HIIT	52.9 ± 0.0	27 ± 0.0	40.5 ± 0.0
		MICT	33.1 ± 0.0	7.4 ± 0.0	43.5 ± 0.0
ApEn	HAP	HIIT	0.9 ± 0.0	1.0 ± 0.3	1.0 ± 0.0
		MICT	0.8 ± 0.1	1.4 ± 0.1	1.0 ± 0.0
	Control	HIIT	0.9 ± 0.0	1.0 ± 0.0	0.7 ± 0.0
		MICT	1.0 ± 0.0	1.4 ± 0.0	1.0 ± 0.0
SampEn	HAP	HIIT	1.8 ± 0.0	0.8 ± 0.4	1.2 ± 0.2
		MICT	1.6 ± 0.3	1.5 ± 0.2	1.7 ± 0.0
	Control	HIIT	1.2 ± 0.0	0.9 ± 0.0	0.8 ± 0.0
		MICT	1.6 ± 0.0	1.1 ± 0.0	1.4 ± 0.0

4.3.3. Blood Pressure, Central Nervous System Fatigue, and Cortical Arousal

Analyzing the fatigue of CNS in the different protocols performed, we verified that the continuous training presented greater fatigue of CNS for the HAP than in the control. However, the blood pressure difference was greater in patients with adverse cardiac events than in participants without events, and there were no differences in cortical arousal outcomes between the groups (**Table 4.4**).

Table 4.4.

Fatigue of central nervous system, blood pressure and cortical arousal variables in heart attack patients and control in high-intensity interval training and moderate-intensity continuous training

Variable	Group	Protocol	Pre	Post
Subjective fatigue scale (0–100)	HAP	HIIT	10.0 ± 0.0	67.5 ± 3.5
		MICT	10.0 ± 0.0	85.5 ± 3.5
	Control	HIIT	10 ± 0.0	65 ± 0.0
		MICT	10 ± 0.0	40 ± 0.0
Systolic blood pressure (mmHg)	HAP	HIIT	130.0 ± 26.9	121.0 ± 12.7
		MICT	132.5 ± 19.1	124.0 ± 18.4
	Control	HIIT	120 ± 0.0	104 ± 0.0
		MICT	124 ± 0.0	138 ± 0.0
Diastolic blood pressure (mmHg)	HAP	HIIT	80.0 ± 14.1	77.0 ± 2.8
		MICT	66.5 ± 13.4	73.0 ± 1.4
	Control	HIIT	72 ± 0.0	83 ± 0.0
		MICT	81 ± 0.0	82 ± 0.0
CFFT (hz)	HAP	HIIT	36.5 ± 7.7	37.9 ± 8.0
		MICT	38.2 ± 4.1	39.4 ± 4.5
	Control	HIIT	39.7 ± 0.0	40.3 ± 0.0
		MICT	39.7 ± 0.0	41.5 ± 0.0

4.4. Discussion

This research aimed to analyze the physiological parameters of thermography, HRV, blood pressure, and cortical arousal in cardiac patients who belong to CR programs of HIIT and MICT compared to healthy participants. Analyzing the fatigue perception of the different training conducted, we found that the MICT presented a higher fatigue perception for HAP than in control participants. It seems that the short rest interval allowed the HAP to have a lower fatigue perception, a fact in line with previous studies that also found higher motivation in interval training than in continuous training (McKean et al., 2012). It is also important to note that HAP presented more than twice CNS fatigue in MICT than control participants, but HIIT had almost the same fatigue perception in HAP as control patients. We can see how MICT is more demanding for HAP, a fact that may explain the lower adherence to this training; in addition, whilst MICT is a training that is based on a traditional periodization, based on the sequencing of volume for an intensity during a certain period, which can make it less challenging, HIIT is identified more with a reverse periodization, based on an opposite paradigm—first the training intensity and then the volume (Clemente-Suarez et al., 2015)—and previous studies report that the level of adherence to reverse periodization was significantly greater than traditional training (Clemente-Suárez et al., 2021); even so, it seems that the programs where greater adherence to CR programs is being verified are those that introduce virtual reality or video games (García-Bravo et al., 2019). This result is important when practitioners have to design training for HAP since HIIT shows higher physiological adaptation (Wisløff et al., 2007); furthermore, MICT in this population produces lower fatigability, a fact that would improve adherence to programs based on HIIT. In addition, independent of the training (HIIT or MICT), a hypotension response was evaluated, in fact, in line with previous studies, although recent research showed higher adaptations after HIIT protocols (Turri-Silva et al., 2021; Moholdt et al., 2009). The same was also verified in patients with cardiac problems (Gutherie & Hammond, 2004), which coincides with the results of our study regarding the fatigability of cardiac patients in mental and physical workouts. Still, no suggestions were made on the potential value of this method for the diagnosis or prognosis of cardiac disease.

Patients with hypertension or coronary disease tend to have low values for flicker fusion frequency. However, the patients without evidence of CVD also had values of the fusion frequency, and a positive correlation between flicker fusion frequency and resting systolic blood pressure have been found previously (Gutherie & Hammond, 2004). However, the patients without evidence of CVD also had values of the fusion frequency quite comparable with those for the cardiovascular patients, except for the group with malignant hypertension, but lower than for the normal people of equal age. Many types of pathology may depress flicker fusion frequency (Truszczyński et al., 2009; Sharma et al., 2002; Balestra et al., 2018; Lecca et al., 2022).

In the same regard, the present study showed that HIIT and MICT programs decreased systolic blood pressure in pre- to post-exercise. Mounting evidence demonstrates that participating in physical activity CR programs has been recommended to cardiac patients as an effective non-pharmacological approach to improving blood pressure (Hanssen et al., 2022; Haykowsky et al., 2013; Ghadieh & Saab, 2015).

There are studies that report the importance of heart rate variability in patients who have suffered heart attacks (Arshi et al., 2022), as it seems that a reduced HRV is related to mortality after heart attack; thus, HRV can be a useful tool in risk stratification post-HAP (Huikuri & Stein, 2013; Ernst, 2017). Our findings showed that the HIIT protocol had improved the domains of HRV, including the number of RR intervals in HAP compared to MICT. In addition, some studies exposed that, compared with MICT, HIIT has good efficacy in improving cardiovascular fitness (Gonçalves et al., 2021; Wisløff et al., 2007; Moholdt et al., 2008; Shea et al., 2022). Furthermore, HIIT training appears to be a useful therapeutic intervention to improve the unbalanced autonomic function of HAP, and studies observed an increase in cardiac vagal activity after aerobic exercise programs (Benda et al., 2015; Fisher et al., 2015; Weston et al., 2014). However, our study observed no significant interaction or main effects in RMSSD. Regardless, the stress index of HRV was higher in the HAP groups compared to the control groups. The HIIT protocol had higher values from pre-exercise than those who did the MICT protocol, and from exercise to post-exercise, the HAP in HIIT dropped slightly, while the HAP in MICT continued to rise sharply. High values of stress index indicate reduced variability and high sympathetic cardiac activation. Similar exercise training programs have been provided.

Some similar training programs showed different results, although some do not describe the loads applied in training (Takeyama et al., 2000; Oya et al., 1999; Fujimoto et al., 1999; Tsai et al., 2006). Other authors report significant improvements in HRV using different training protocols (García-Bravo et al., 2020; Iellamo et al., 2000). Authors evaluated the cardiac autonomic response through HRV in women who performed a maximum incremental exercise; the results showed an abnormal autonomic modulation at rest, during, and after exercise (Upadhyay, 2015; Costa et al., 2022; Schamne et al., 2021), although other authors report that only two weeks of training with intensities above 75% can increase HRV (Gonçalves et al., 2021).

Analyzing the thermography results, our study demonstrates that the body temperature difference in the chest was greater in patients with adverse cardiac events than in patients without events. In the groups of healthy participants, the temperature remained practically the same. Many authors propose diagnostic imaging as a means of detecting the risk of suffering from CVD (Lang et al., 2022; Grundi et al., 1998; Whelton et al., 1998). Controlling inflammation in the carotid arteries may decrease the risk of CVD (Lang et al., 2022). Using imaging as a diagnosis can prevent and help determine the cause of CVD (Grundi et al., 1998). Early signs of heart disease may be associated with increased or decreased peripheral blood flow. Thermography can play a key role in this diagnosis (Whelton et al., 1998).

4.4.1. Limitations of the Study and Future Perspectives

The main limitation of the present study is the low number of participants. Due to the specificity of the disease, namely, in the recovery phases (II on an outpatient basis or in phase III after medical discharge), it is still difficult to find participants to apply high-intensity exercise stimulus; thus, we decided to carry out a case study. Another limitation was the use of indirect measures of cortical arousal; an electroencephalography would more deeply explain all cortical responses in this population group. As perspectives for the future, we believe that this methodology is safe and can be beneficial in the recovery of patients who have suffered a heart attack (mainly in phase III of recovery after medical discharge), and can be a method of education or re-education toward healthier lifestyles. Therefore, we propose that this method be used in a larger sample of patients after a heart attack.

4.5. Conclusions

Finally, we concluded that both training protocols (HIIT and MICT) produced a similar thermographic response in both heart attack patients and control participants, showing in some body segments (such as chest, abdomen, right and left arm) lower temperatures in the heart attack patients. Regarding the autonomic response, heart attack patients presented higher sympathetic modulation in both trainings, showing that HIIT had higher sympathetic modulation than MICT; however, in the post evaluation, the HRV was equal between HIIT and MICT in heart attack patients. The MICT training produced higher subjective fatigue and a greater decrease in cortical arousal in heart attack patients than HIIT, contrary to that in control participants. No differences in systolic and diastolic blood pressure were found between HIIT and MICT training in heart attack patients; however, they presented higher systolic and lower diastolic blood pressure than control participants during both trainings.

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Institutional Review Board Statement: Ethics approval was obtained from the University of Évora Ethics Committee (reference number: 17039).

Informed Consent Statement: All participants were informed about the experimental procedures, indicating the right to withdraw from the study at any time and providing written informed consent.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author, C.G., upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Abbreviations

alpha-1	Short-term fluctuation of the detrended fluctuation analysis
alpha-2	Long-term fluctuation of the detrended fluctuation analysis
CR	Cardiac rehabilitation
CVD	Cardiovascular diseases
CNS	Central nervous system
CFFT	Critical flicker fusion threshold
HAP	Heart attack patients
HRV	Heart rate variability
HR	Heart rate
HIIT	High-Intensity Interval Training
ms	Milliseconds
MICT	Moderate-intensity Continuous Training
NYHA	New York Heart Association

peakHR	Peak Heart Rate
SampEn	Sample entropy
RMSSD	Square root of differences between adjacent RR intervals
VSA	Visual analogue scale
WHO	World Health Organization

4.6. References

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CHAPTER 5

Paper 3: Effects of High-Intensity Interval Training Vs. Moderate-Intensity Continuous Training on Body Composition and Blood Biomarkers in Coronary Artery Disease Patients: A Randomized Controlled Trial

CHAPTER 5

Paper 3: Effects of High-Intensity Interval Training Vs. Moderate-Intensity Continuous Training on Body Composition and Blood Biomarkers in Coronary Artery Disease Patients: A Randomized Controlled Trial

Chapter overview

The Chapter 2 examined that HIIT has been found to be as effective, if not superior, to MICT in improving clinical outcomes for patients with CVD, including body composition, HR response to exercise, blood pressure, blood lipids, insulin dynamics, physical fitness, HRV, QoL, depression and anxiety, and with our systematic review with meta-analyses, we showed that the most effective doses of exercise intensity to optimize cardiorespiratory fitness were moderate-to-vigorous and vigorous-intensity exercises, being more effective when conducted for 6 to 12 weeks. Although the effect of HIIT has gradually proven beneficial, little is explored about the role and the validity of HIIT on CAD patients in Portugal, and the participation in CR programs in the country is less than 8%. Unfortunately, to date, there are few exercise-based CR programs in the country and the geographic distribution of these centers is poor. Notably, the absence of any CR center in the Alentejo region, where the prevalence of CVD is notably elevated, accentuates this concern.

This chapter examines a pioneering endeavor as the inaugural randomized controlled trial to systematically evaluate and differentiate the impacts of HIIT as opposed to MICT on the body composition and blood biomarkers in cardiovascular risk factors, in contrast to a control group, throughout a 6-week community-based exercise program within the Portuguese context.

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Research Article

Effects of High-Intensity Interval Training vs Moderate-Intensity Continuous Training on Body Composition and Blood Biomarkers in Coronary Artery Disease Patients: A Randomized Controlled Trial

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Abstract

Background: Cardiac rehabilitation (CR) is essential in reducing cardiovascular mortality and morbidity. High-intensity interval training (HIIT) has emerged as a promising exercise intervention for enhancing clinical outcomes in cardiac patients. This study aimed to investigate the effects of two short-term exercise-based programs employing HIIT and moderate-intensity continuous training (MICT) in comparison to a control group concerning blood pressure, body composition, and blood biomarkers in patients diagnosed with coronary artery disease (CAD).

Methods: Seventy-two CAD patients (14% women) underwent randomization into three groups: HIIT, MICT, and control. The training programs encompassed six weeks of supervised treadmill exercises, conducted thrice weekly. MICT targeted ≈70-75% of peak heart rate (HRpeak), while HIIT was tailored to ≈85-95% of HRpeak. The control group received guidance on adopting healthy lifestyles. Outcome measurements included evaluations of blood pressure, body composition, and blood biomarkers.

Results: In contrast to MICT, the HIIT exhibited superior improvements in body fat mass (Δ%HIIT: 4.5%, $p < .001$ vs. Δ%MICT: 3.2%, $p <.001$), waist circumference (Δ%HIIT: 4.1%, $p = .002$ vs. Δ%MICT: 2.5%, $p = .002$), HbA1c (Δ%HIIT: 10.4%, $p < .001$ vs. Δ%MICT: 32.3%, p < .001) and TSH (Δ%HIIT: 16.5%, $p = .007$ vs. Δ%MICT: 3.1%, $p = .201$). Both HIIT and MICT induced significant enhancements across all variables compared to the control group.

Conclusions: HIIT and MICT emerged as effective modalities for enhancing systolic and diastolic function, body composition, and blood biomarkers in CAD patients, with HIIT demonstrating incremental improvements over MICT. The absence of participation in exercise-based programs following cardiovascular events yielded less favorable outcomes. HIIT holds promise as an adjunct intervention in CR programs for CAD patients.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT03538119

Keywords: Cardiovascular Diseases • Cardiovascular Risk Factors • Clinical Trials • High-Intensity Interval Training • Randomized Controlled Trial

5.1. Introduction

Cardiovascular diseases (CVD) stands as the predominant global cause of mortality, contributing to a substantial 30% of all recorded deaths (16.7 million individuals) (Go et al., 2013). Within the ambit of CVD, coronary artery disease (CAD) emerges as the most prevalent etiology in CVD-related fatalities. Forecasts indicate a looming surge of 16.6% in CAD-related mortalities by the year 2030 (WHO, 2011). Consequently, the implementation of effective strategies to mitigate the impact of CVD assumes paramount importance. Among these strategies, comprehensive exercise-based cardiac rehabilitation (CR) has garnered worldwide acceptance as a potent secondary prevention tool for patients with various forms of CVD. A key component of a CR program is exercise training which has demonstrated its efficacy in not only reducing mortality rates but also augmenting the quality of life, ameliorating frailty, and enhancing cardiovascular fitness (defined as peak oxygen uptake [VO_2]), a parameter recognized as an autonomous predictor of hospitalizations and mortality in patients afflicted with CVD (Myers et al., 2002).

Comprehensive CR programs encompass distinct phases designed to facilitate patients' transition from acute hospital care (Phase I) to the resumption of their daily activities, spanning phases II (subacute), III (outpatient), and IV (maintenance). The World Health Organization (WHO) recognizes the multifaceted impact of exercise-based CR on patients, acknowledging its potential to influence their physical, psychological, and social well-being, enhance their overall quality of life, and mitigate the risk of potential complications (Go et al., 2013). Moreover, the implementation of safe exercise protocols, tailored to various intensity levels, exerts discernible effects on training endurance, oxygen capacity, and intervention outcomes (Smith et al., 2011). Notably, extant research has evidenced the favorable impact of exercise-based CR on a spectrum of physiological and clinical parameters, including blood pressure (WHO, 2011; Smith et al., 2011), blood lipids (WHO, 2011; Smith et al., 2011), insulin dynamics (WHO, 2011; Smith et al., 2011), physical fitness (Molino-Love et al., 2013), body composition (Lear et al., 2006; Giannuzzi et al., 2008; Pedersen et al., 2019), heart rate variability (HRV) (Gonçalves et al., 2023; Munl et al., 2010; Fiodge et al., 2018) and health-related quality of life (Piepoli et al., 2016; Francis et al., 2019).

Moderate-intensity continuous training (MICT) has historically served as a cornerstone in the prescription of aerobic-based exercise, typically consisting of 30-60 min, targeting an intensity range of 50–75% of heart rate (HR) (Piepoli et al., 2016). This approach has demonstrated both short-term and enduring clinical benefits for individuals afflicted with CVD (Gonçalves et al., 2021). Notwithstanding these advantages, a noteworthy proportion of the adult population, approximately 30%, grapples with an inability to fulfill this exercise regimen due to constraints such as time scarcity (Hallal et al., 2012). The protracted duration and intricate nature of MICT can contribute to patient attrition, rendering exercise compliance challenging (Reichert et al., 2007). Conversely, high-intensity interval training (HIIT) has recently emerged as an alternative or supplementary strategy to MICT. HIIT entails recurring bouts of relatively elevated exercise intensity, typically within the range of 85–100%, interspersed with intervals of lower-intensity recovery, totaling 20-30 min of exercise (Ito, 2019). Notably, HIIT has exhibited the capacity to yield comparable or even superior enhancements in peak oxygen uptake (VO_2) in comparison to MICT (Gonçalves et al., 2021; Hallal et al., 2012; Reichert et al., 2007; Ito, 2019; Norton et al., 2010). Indeed, HIIT has demonstrated effectiveness on par with, if not surpassing, MICT in terms of its capacity to ameliorate clinical outcomes in CVD patients, encompassing improvements in body composition (Taylor et al., 2020), HR response to exercise (Kim et al., 2015), and myocardial function (Molmen-Hanen et al., 2012). Crucially, HIIT also appears to be as safe as MICT among older individuals undergoing CR (Hannan et al., 2018; Rognnmo et al., 2012).

Despite the pronounced health enhancements associated with CR, it is disconcerting that less than 8% of survivors of various CVD are enrolled in CR programs within Portugal, and among those who do enroll, adherence rates remain notably suboptimal (Abreu et al., 2018). Regrettably, the dearth of exercise-based CR initiatives in the country exacerbates this situation, with a glaring paucity in the geographical dispersion of these facilities. Notably, the absence of any CR center in the Alentejo region, where the prevalence of CVD is notably elevated, accentuates this concern. Moreover, while the merits of HIIT have gradually emerged, there exists a notable dearth of research elucidating the role and validity of HIIT in the context of CAD patients within the country. Hence, the primary objective of the present study is to scrutinize the ramifications of two distinct six-week exercise-based regimens, namely HIIT and MICT, with regard to their impacts on body composition and cardiovascular blood biomarkers, while concurrently assessing risk factors. These outcomes will be juxtaposed against those of a control group.

5.2. Methods

This study is a single-blinded randomized controlled trial (RCT) and followed the CONSORT guidelines for RCTs (http://www.consort-statement.org).

5.2.1. Participants

Three hundred and eight patients were enrolled in the study between March 2018 and November 2021, at the cardiology unit of the Hospital do Espírito Santo de Évora, Portugal. The study included patients who had suffered a coronary event and were referred to the community-based exercise programs by their cardiologist, two months after angioplasty. Patients between the ages of 18 and 80, with a left ventricular ejection fraction ≥ 45%, and classified as New York Heart Association (NYHA) functional Class I or II were considered for inclusion. Patients who had severe exercise intolerance, uncontrolled angina pectoris, uncontrolled arrhythmia, lung or severe kidney diseases, musculoskeletal or neuromuscular conditions preventing exercise testing and training, and signs or symptoms of ischemia were excluded from the study. Recruitment ended once the required sample size for the primary outcome was reached. All patients completed a medical history and health questionnaire and provided written informed consent.

5.2.1.1. Randomization and masking

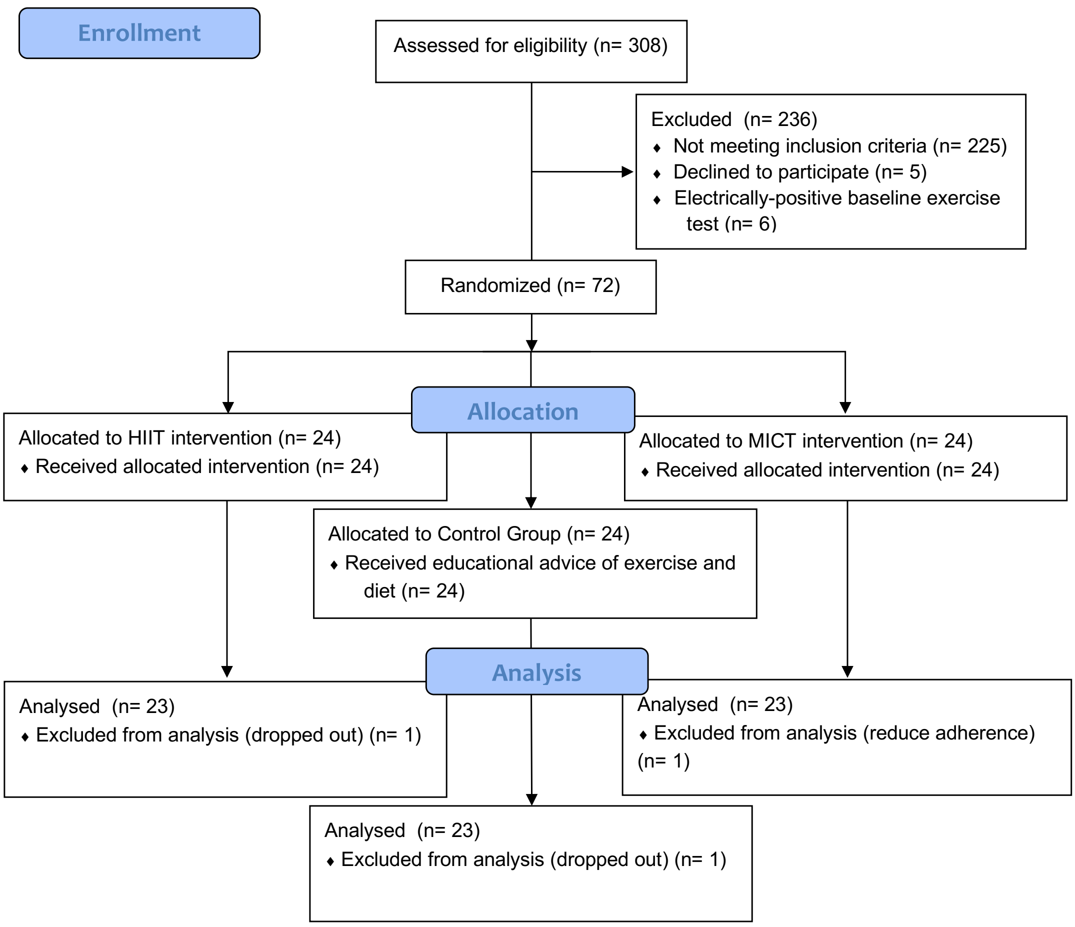
After the baseline assessment and before the start of community-based exercise programs, the 72 patients were randomly assigned in a 1:1:1 allocation ratio to one of three groups: HIIT, MICT (traditional), and control (usual medical recommendations) (**Figure 5.1**). To ensure that allocation concealment was maintained, patients belonging to each group were scheduled to be seen at specific, separate times that did not coincide with appointments for patients in the other groups. The three groups were carefully matched in terms of age, extent of coronary artery disease, coronary risk factors, type of coronary event, and left ventricular ejection fraction. While patients and physicians assigned to the intervention group were aware of their allocated category, outcome assessors and data analysts remained blinded to the allocation throughout the study.

Figure 5.1.

Diagram of the study

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



5.2.2. Outcome measures and assessments

5.2.2.1. Exercise testing

Initially, the CAD patients were submitted to a clinical evaluation performed by a cardiologist. A supervised graded exercise test to record volitional fatigue, risks or symptoms of ischemia was performed on a treadmill with the Bruce protocol (Bires et al., 2013) before the six-week intervention period. The test was done in non-fasting conditions and under medication. Electrocardiography was recorded continuously, and blood pressure was measured with an arm cuff every three minutes. Functional capacity in metabolic equivalent value (METs) was calculated. As a high proportion of patients with CAD are prescribed beta-blocker therapy, this relative method of exercise intensity takes into account the likely lower HRpeak achieved by these patients during the exercise test. To ensure training exercise intensity was reflective of medication effects, all patients were instructed to take their usual medications before the maximal exercise test.

Exercise capacity was considered as peak oxygen consumed (VO_2peak, ml-kg^{-1}-min^{-1}) that was directly measured by performing a cardiopulmonary exercise test. VO_2peak was calculated using the formula: $VO_2peak = 3.5\ ml\text{-}kg^{-1}\text{-}min^{-1} * peak$ *metabolic equivalents (METs)* (Liguori, 2020) which was determined by the standard exercise stress test (HIIT = 23; MICT = 23; Control = 23).

5.2.2.2. Blood Biomarkers

Blood samples were collected on the same day as the exercise testing, but before the exercise. The final blood samples were collected 24-48 hours after the last exercise session. Levels of various blood biomarkers such as total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), high-sensitive C-reactive protein (hsCRP), fasting blood glucose (FBG), hemoglobin A1c (HbA1c), higher free thyroxine (T4), and lower total triiodothyronine (T3), were measured. Blood samples were drawn at the beginning and at the end of the study.

5.2.2.3. Body Composition and Risk Factor Screening

On the second visit, the patients were submitted to a clinical evaluation of body composition performed by a physiologist at the laboratory of the University of Evora. Patients were asked to bring any medications that they were taking to the assessments. Initially, each patient completed a standardized questionnaire including medical history, medication use, demographic data, smoking status, and family history of CVD. Body mass index (BMI) was calculated directly by the standard formula: $weight(kg)/height(m)^2$, and waist circumference (WC) was manually measured according to standard procedures of ACSM guidelines by a trained examiner (Liguori, 2020; Thompson et al., 2013). Body composition was evaluated using dual-energy x-ray absorptiometry (DXA) scans, performed with QDR 2000 densitometers (Hologic QDR, Hologic, Inc., Bedford, MA, USA) in array beam mode. The scans took place one week prior to and following the completion of 18 exercise sessions. These scans were used to determine the total body mass, body fat mass, body lean mass, body fat percentage, and abdominal region fat percentage (defined as the area between the ribs and the pelvis by GE Healthcare systems) (Liguori, 2020; Thompson et al., 2013). Daily calibration of the scanner was made using a manufacturer-supplied calibration block to ensure accuracy and control for potential baseline drift.

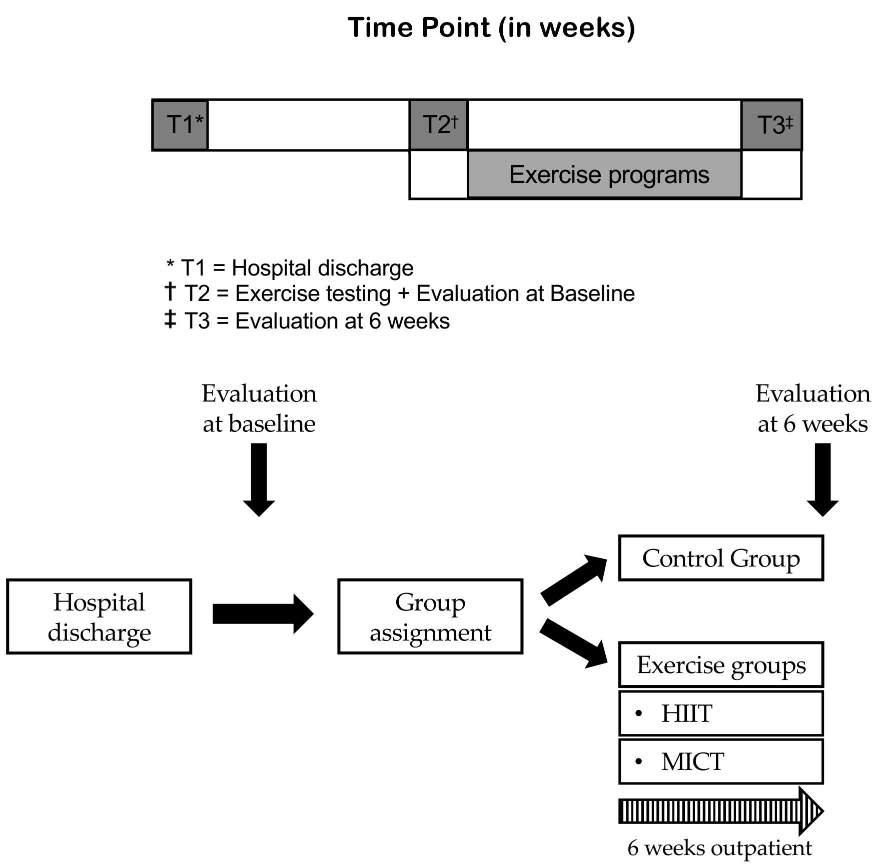
All measurements were taken at baseline and after the 6-week exercise-based programs.

5.2.3. Exercise training protocols

After hospital discharge, educational intervention, dietary advice, and psychological support were performed in all patients. The exercise programs consisted of six weeks of supervised treadmill exercise, three sessions per week (**Figure 5.2**). If a session was missed, it was made up that week or the following week. Patients performed each exercise session in a group, including a maximum of three patients per session.

Figure 5.2.

Study design and time frame

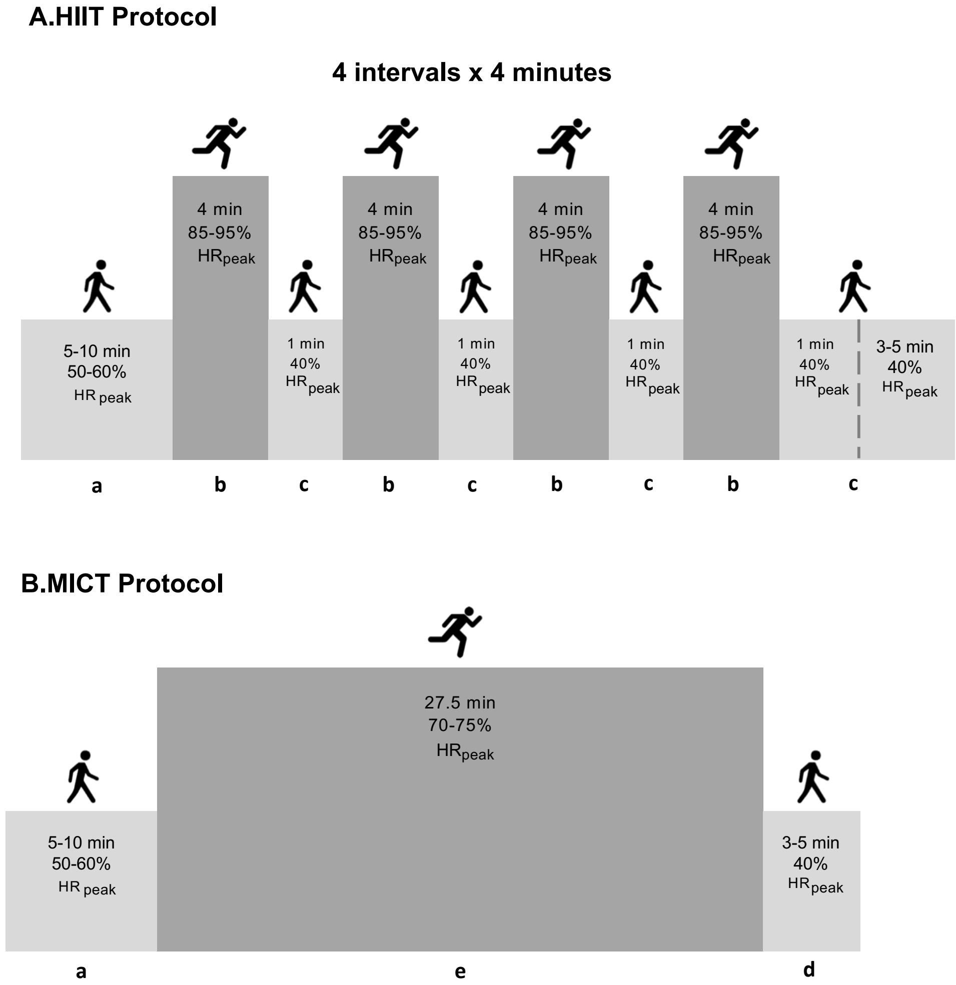


Note. Abbreviations: HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; T = time point.

The exercise intensity was calculated using the following heart rate reserve (HRR) equation: *Target HR = [(HRmax – HRrest) x %intensity desired] + HRrest* (Liguori, 2020), predicted with a supervised graded exercise test on a treadmill (Bruce protocol) (Bires et al., 2013). Training sessions were supervised by a physiologist. Blood pressure was measured at the beginning and end of each session. The patients' heart rate, rate of perceived exertion (measured using the Borg Scale) (Scherr et al., 2013), and cardiac symptoms were all taken into account as training intensity increased. Heart rates were monitored using *Polar heart rate* monitoring equipment (Polar Electro Oy in Kempele, Finland). During the exercise, patients were asked to rate their perceived effort using the 10-point Category-Ratio Borg Scale (Scherr et al., 2013), commonly known as the Rating of Perceived Exertion (RPE). This scale ranges from 0 to 10 with anchors ranging from 'No exertion at all' (0) to 'Maximal exertion' (10). Patients were required to rate their exertion before the exercise, immediately after each minute, and at the end of the exercise. Buchheit & Laursen (2013) and Levinger et al. (2004) have shown that the Borg Scale has a strong correlation with HR, ventilation, and VO_2peak in individuals with CAD. The correlation is not impacted by beta-blocker medication, which is commonly used by patients with CAD to modulate their HR (Thompson et al., 2013). During exercise, patients' heart rate was monitored minute-to-minute using a H10 chest strap manufactured by *Polar Inc.* located in Kempele, Finland.

Figure 5.3.

Summary of the exercise training protocols. Detailed description of exercise training protocol elsewhere (Gonçalves et al., 2023)



Note. Abbreviations: a = warm-up; b = interval bout of high-intensity exercise; c = one-minute recovery interval; d = cool-down; e = continuous bout of moderate-intensity exercise; HIIT = high-intensity interval training; MICT = moderate-continuous training; min = minutes.

Each exercise session was initiated with a 5–10-minute warm-up at 50-60% HRpeak and finished with 5 minutes of cool-down at 40% HRpeak. The HIIT group performed 4 × 4-minute high-intensity intervals at 85%–95% HRpeak followed by a 1-minute recovery interval at 40% HRpeak, predicted with the Bruce protocol (Bires et al., 2013). Throughout the exercise, the patients were motivated to gradually increase their exercise intensity towards 6–9 (hard to very hard) on a 0 to 10 Borg scale. The MICT group (traditional care) performed a continuous bout of moderate-intensity exercise at 70–75% HRpeak, rating of perceived exertion 3 to 5 (fairly light to somewhat hard), for

28 minutes in order to equate the energy expenditure with the HIIT group (**Figure 5.3**). The information about the mean of patients' heart rate and rate of perceived exertion (Borg scale) pre-post session throughout the six weeks of both exercise-based programs can be seen in the supplementary material (**APPENDIX 16**). The control group did not receive any additional follow-up regarding exercise beyond general advice on the importance of exercise and diet.

5.2.4. Ethical considerations

The work conducted in this study followed the guidelines of the Declaration of Helsinki and was registered at ClinicalTrials.gov (NCT03538119). Ethics approval was obtained from the University of Évora Ethics Committee (reference number 17039). All patients who participated in this study provided written informed consent beforehand.

5.2.5. Statistical analyses

The sample size was calculated using the online *G*Power software*, considering an effect size of 0.3, a predefined sample power of 0.8, a predefined sample power of 0.6, a predefined error probability defined as 0.05, and a statistical power of 95% (El Maniani et al., 2016). As a result, we determined that a minimum sample size of 66 participants (22 participants for each group) was necessary to identify significant changes.

The normality and homogeneity assumptions were tested using the Kolmogorov-Smirnov and Levene tests, respectively. Since the majority of sample variables did not conform to a normal distribution, non-parametric statistical analyses were used. Between-group comparisons were performed using the Kruskal-Wallis test, while within-group comparisons were performed using the Friedman test. Both tests were then followed by post hoc pairwise comparisons.

The means and standard deviations were calculated for all variables. The delta value (Δ: $moment_x - momentx_{-1}$) and the proportional change delta value ($\Delta\%$: $[(moment_x - momentx_{-1})/momentx_{-1}] \times 100$) were calculated for all variables to compare post-intervention values with baseline values.

The effect size (ES) was calculated using Cohen's method since the data did not follow a normal distribution (Cohen, 2013). The ES was classified based on Cohen's thresholds (defined as small: 0.10; medium: 0.30; and large: 0.50) (Cohen, 2013). The analyses were performed using SPSS (version 26.0, SPSS Inc., Chicago, IL, USA). A value of $p \leq .05$ was considered statistically significant for all analyses. To protect patients' anonymity, a code was assigned to each patient.

According to the standards for dyslipidemia, we considered an HDL-C level below 50 mg/dL (for women) or below 40 mg/dL (for men), as well as a TG level of 150 mg/dL or higher, as criteria for diagnosis (Wilson et al., 2018). A hsCRP test result of 1.0 and 10.0 milligrams per deciliter (mg/dL) is defined as moderately elevated (Pearson et al., 2003). For the diagnosis of diabetes mellitus, we utilized the American Diabetic Association criteria (Rey et al., 2022). Namely, the pre-diabetic stage was identified by HbA1c levels between 5.7 and 6.4, or impaired fasting blood glucose levels between 100 and 125 mg/dL, and diabetes mellitus was diagnosed with HbA1c ≥ 6.5 or fasting glucose levels ≥ 126 mg/dL. Impaired non-fasting glucose was defined as a glucose value of 100mg/dL or higher (Rey et al., 2022). Overweight was characterized by a BMI between 25.0 and 29.9 kg/m^2, while obesity was defined by a BMI of 30 kg/m^2 or higher (Sardinha et al., 2012). Finally, increased WC was defined as > 80 cm in women and > 94 cm in men (Sardinha et al., 2012).

5.3. Results

The baseline characteristics of participants, as presented in **Table 5.1**, exhibited no statistically significant differences among the HIIT, MICT, and control groups: age (50 ± 9 vs. 55 ± 10 vs. 57 ± 11 years respectively, $p = .180$), female (15% vs. 17% vs. 15%, $p = .211$), and VO_2peak (24.7 ± 9.0 vs. 23.4 ± 6.3 vs. ± 23.5 ± 11.0 mL/kg/min $p = .290$). Additionally, there were no significant differences in the prevalence of comorbidities or medication usage across the groups ($p > .05$).

Table 5.1.

Baseline characteristics of study participants

	Exercise-based program		No exercise-based program
	HIIT (n=23)	MICT (n=23)	Control (n=23)
Demographics			
Age (years), mean ± SD	50 ± 9	55 ± 10	57 ± 11
> 70 years, n (%)	2 (8.7)	3 (13.0)	4 (17.4)
Gender (Male/Female)	20/3	19/4	20/3
Retired, n (%)	2 (8.7)	7 (30.4)	7 (30.4)
Anterior MI, n (%)	3 (13.0)	4 (17.4)	2 (8.7)
Coronary event/intervention			
CABG, n (%)	1 (4.3)	1 (4.3)	1 (4.3)
PCI, n (%)	22 (95.7)	22 (95.7)	22 (95.7)
VO_2peak (mL/kg/min), mean ± SD	24.7 ± 9.0	23.4 ± 6.3	23.5 ± 11.0
Risk factors or comorbidities			
Diabetes mellitus, n (%)	10 (43.5)	9 (39.1)	10 (43.5)
Hypertension, n (%)	13 (56.5)	13 (56.5)	14 (60.9)
Dyslipidemia, n (%)	14 (60.9)	15 (65.2)	15 (65.2)
Body Mass index (kg/m^2), mean ± SD	28.2 ± 4.5	29.4 ± 3.9	29.4 ± 4.3
Waist Circumference (cm), mean ± SD	98.4± 14.5	101.1 ± 10.3	101.1 ± 10.8
Active smoker, n (%)	6 (26.1)	4 (17.4)	4 (17.4)
Non-smoker, but has been, n (%)	9 (39.1)	13 (56.5)	12 (52.2)
Family history of CVD, n (%)	14 (60.9)	16 (69.6)	16 (69.6)
Sedentarism, n (%)	13 (56.5)	19 (82.6)	19 (82.6)
Sleep < 5h, n (%)	6 (26.1)	9 (39.1)	11 (47.8)
Current medication			
ACE inhibitor, n (%)	21 (91.3)	23 (100)	22 (95.7)
ARBs, n (%)	16 (69.6)	7 (73.9)	11 (47.8)
Antiplatelet, n (%)	22 (95.7)	22 (95.7)	23 (100)
CCBs, n (%)	2 (8.7)	5 (21.7)	5 (21.7)
Beta-blockers, n (%)	21 (91.3)	22 (95.7)	22 (95.7)
Diuretics, n (%)	2 (8.7)	4 (17.4)	6 (26.1)
Insulin, n (%)	5 (21.7)	5 (21.7)	11 (47.8)
Statin, n (%)	22 (95.7)	22 (95.7)	23 (100)

Note. Abbreviations: ACE = angiotensin-converting enzyme inhibitor; ARBs = angiotensin II receptor blockers; CCBs = Calcium channel blockers; HIIT = high-intensity interval training; MI = Myocardial Infarction; MICT = moderate-intensity continuous training; VO_2peak = maximal oxygen consumed (measured by the cardiopulmonary exercise test).

Data are reported as Mean ± Standard deviation or number and percent population (%).

Significance is < .05.

5.3.1. Resting Heart Rate and Blood Pressures

At baseline, there were no differences across groups at rest for resting HR, SBP or DBP. After six weeks, the exercise-based groups reported a significant decrease in

SBP and DBP compared with the control (**Table 5.2**). The HIIT group reported a significant decrease in SBP (Δ HIIT: 9 mm Hg, $p < .001$) and DBP (Δ HIIT: 6 mm Hg, $p < .001$), and the MICT group reported similar results in SBP (Δ MICT: 8 mm Hg, $p < .001$) and equal results in DBP (Δ MICT: 6 mm Hg, $p < .001$). The corresponding ES in resting HR was medium between the baseline and the post-intervention periods in both exercise groups (HIIT $d = 0.56$ and MICT $d = 0.55$), and in SBP and DBP were large in both exercise groups (HIIT $d = 1.27$ and MICT $d = 0.86$; HIIT $d = 1.11$ and MICT $d = 1.19$, respectively).

Table 5.2.

Blood profile measurements of exercise groups and control group

	Baseline (A)	6-week (B)	*p*-value	ES (95% CI)	Pairwise Comparison
Resting HR (bpm)					
HIIT (n=23)	70 ± 15.4	63 ± 8.7	.061	-0.556 (-0.918; -0.194)	-
MICT (n=23)	67 ± 9.4	62 ± 4.9	.020	-0.551 (-1.060; -0.043)	-
Control (n=23)	69 ± 9.9	68 ± 8.1	.835	-0.202 (-0.459; 0.054)	-
SBP (mm Hg)					
HIIT (n=23)	135 ± 12.1	121 ± 9.5	< .001 [a]	-1.270 (-1.825; -0.715)	A > B
MICT (n=23)	135 ± 13.3	125 ± 10.9	< .001 [b]	-0.861 (-1.208; -0.514)	A > B
Control (n=23)	139 ± 6.1	136 ± 8.2	.297	-0.439 (-0.914; 0.035)	-
DBP (mm Hg)					
HIIT (n=23)	95 ± 11.6	88 ± 8.4	< .001 [a]	-1.106 (-1.624; -0.587)	A > B
MICT (n=23)	94 ± 9.6	89 ± 7.4	< .001 [b]	-1.191 (-1.659; -0.722)	A > B
Control (n=23)	95 ± 6.3	97 ± 4.9	.144	0.360 (0.092; 1.052)	-

Note. Abbreviations: DBP= diastolic blood pressure; bpm = beats per minute; HIIT = high-intensity interval training; HR = heart rate; MICT = moderate-intensity continuous training; SBP = systolic blood pressure. Values are reported as Mean ± Standard deviation.
[a] significant differences between HIIT and Control, p < .05; [b] significant differences between MICT and Control, p < .05.
</>/= indicates whether HIIT, MICT or Control achieved a more desirable outcome.

5.3.2. Body Composition measurements

At baseline, there were no differences across groups at the body composition measurements. Following six weeks of exercise, the results (**Table 5.3**) showed that the HIIT group demonstrated significant improvements comparing to MICT in body fat mass (Δ% HIIT: 4.5%, $p < .001$ vs. Δ% MICT: 3.2%, $p < .001$), and waist circumference (Δ% HIIT: 4.1%, $p = .002$ vs. Δ% MICT: 2.5%, $p = .002$). The control group had no improvements. On the other hand, all values of body composition measurements increased from baseline to post-intervention. The respective ES from baseline to six weeks were small in the HIIT group in body weight ($d = 0.20$), abdominal fat percentage ($d = 0.28$) and BMI ($d = 0.22$), and medium in waist circumference ($d = 0.34$). Moreover, in the MICT group, the effect sizes were small in body fat percentage (d = 0.22), total body fat mass (d = 0.22) and waist circumference (d = 0.22).

Table 5.3.

Body composition measurements of exercise groups and control group

	Baseline (A)	6-week (B)	*p-value*	ES (95% CI)	Pairwise Comparison
Body weight (kg)					
HIIT (n=23)	82.6 ± 14.5	79.9 ± 12.8	< .001	-0.202 (-0.331;-0.073)	-
MICT (n=23)	81.9 ± 11.7	81.1 ± 11.2	.003	-0.072 (-0.160;0.016)	-
Control (n=23)	83.1 ± 13.9	83.6 ± 14.7	.513	0.010 (-0.060;0.079)	-
BMI (kg/m^2)					
HIIT (n=23)	28.2 ± 4.5	27.2 ± 3.8	< .001	-0.221 (-0.358;-0.085)	-
MICT (n=23)	29.5 ± 3.9	29.2 ± 3.9	.005	-0.062 (-0.150;0.026)	-
Control (n=23)	29.4 ± 4.3	29.5 ± 4.4	.655	0.014 (-0.074;0.102)	-
Body fat (%)					
HIIT (n=23)	28.2 ± 5.3	27.0 ± 5.5	.002 [a]	-0.186 (-0.280;-0.092)	A > B
MICT (n=23)	32.6 ± 6.0	31.2 ± 5.6	< .001 [b]	-0.215 (-0.340;-0.089)	A > B
Control (n=23)	29.7 ± 5.0	30.0 ± 4.8	.827	0.025 (-0.063;0.114)	-
Body Fat mass (kg)					
HIIT (n=23)	23.1 ± 67.6	22.0 ± 67.3	< .001 [a,c]	-0.146 (-0.236;-0.026)	A > B
MICT (n=23)	25.7 ± 48.7	24.7 ± 42.1	< .001 [b]	-0.217 (-0.377;-0.057)	A > B
Control (n=23)	24.8 ± 60.9	25.3 ± 56.0	.061	0.089 (0.021;0.158)	-
Abdominal fat (%)					
HIIT (n=23)	36.3 ± 6.9	34.5 ± 5.9	< .001 [a]	-0.283 (-0.427;-0.138)	A > B
MICT (n=23)	37.4 ± 7.1	36.1 ± 6.4	< .001 [b]	-0.192 (-0.285;-0.099)	A > B
Control (n=23)	37.4 ± 6.0	38.4 ± 6.8	.023	0.165 (0.059;0.271)	-
Lean mass (kg)					
HIIT (n=23)	54.7 ± 14.6	55.3 ± 15.0	.144	0.041 (-0.034;0.117)	-
MICT (n=23)	55.7 ± 9.7	56.4 ± 10.0	.007	0.130 (0.025;0.235)	-
Control (n=23)	56.6 ± 12.3	56.9 ± 12.9	.835	0.021 (-0.031;0.072)	-
WC (cm)					
HIIT (n=23)	98.3 ± 14.4	93.8 ± 11.4	.002 [a,c]	-0.341 (-0.563;-0.119)	A > B
MICT (n=23)	101.0 ± 10.6	98.3 ± 9.0	.002 [b]	-0.272 (-0.456;-0.088)	A > B
Control (n=23)	101.7 ± 10.4	102.8 ± 10.5	.491	0.002 (-0.139;0.144)	-

Note. Abbreviations: BMI = body mass index; HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; WC = waist circumference.

Values are reported as Mean ± Standard deviation.

[a] significant differences between HIIT and Control, p < .05; [b] significant differences between MICT and Control, p < .05; [c] significant differences between HIIT and MICT, p < .05.
</>/= indicates whether HIIT, MICT or Control achieved a more desirable outcome.

5.3.3. Blood Biomarkers

Concerning blood biomarkers (**Table 5.4**), there were no differences across groups at baseline, but significant within-group changes between the baseline and the post-intervention were observed in both exercise protocols. The HIIT group revealed significant results comparing to MICT in HbA1c (Δ% HIIT: 10.4%, p < .001 vs. Δ% MICT: 32.3%, p < .001) and TSH (Δ% HIIT: 16.5%, p = .007 vs. Δ% MICT: 3.1%, p = .201). After the 6-week intervention, the control group had worse results, except for cholesterol variables, namely, in HDL-C (Δ% control: 15.9%, p = .002). However, it continues to be considered dyslipidemia as defined by the American College of Cardiology, although the exercise-based groups improved the lipid profile levels from baseline to post-intervention to very close to normal. The same was verified in the blood sugar and thyroid variables in the exercise-based groups but not in the control group.

The respective ES from baseline to post-intervention in the HIIT group were small in FBG (d = 0.47) and endocrine variables: T4 (d = 0.44), T3 (d = 0.47) and TSH (d = 0.41); medium in HbA1c (d = 0.65) and hsCRP (d = 0.80); and large in the cholesterol variables: TC (d = 1.35), HDL-C (d = 1.17), LDL-C (d = 1.33) and TG (d = 1.12). In the MICT group, the respective effect sizes were small in HbA1c (d = 0.37), FBG (d = 0.27), T3 (d = 0.33) and TSH (d = 0.24); medium in TC (d = 0.68), LDL-C (d = 0.66) and TG (d = 0.60); and large in hsCRP (d = 0.81) and HDL-C (d = 1.05).

Table 5.4.

Blood biomarkers of exercise groups and control group

	Baseline (A)	6-week (B)	*p-value*	ES (95% CI)	Pairwise Comparison
Total cholesterol (mmol/L)					
HIIT (n =23)	175 ± 35.2	151 ± 21.8	< .001 [a]	-1.351 (-1.198;-0.714)	A > B
MICT (n=23)	173 ± 38.5	150 ± 30.4	< .001	-0.677 (-1.023;-0.331)	-
Control (n=23)	171 ± 32.8	168 ± 38.8	.835	-0.062 (-0.436;0.312)	-
HDL-C (mmol/L)					
HIIT (n=23)	43 ± 6.7	54 ± 12.3	< .001 [a]	1.170 (0.640;1.701)	A < B
MICT (n=23)	43 ± 9.0	52 ± 9.4	< .001 [b]	1.053 (0.598;1.508)	A < B
Control (n=23)	40 ± 9.1	47 ± 12.0	.002	0.588 (0.234;0.942)	-
LDL-C (mmol/L)					
HIIT (n=23)	117 ± 38.0	85 ± 32.8	< .001 [a]	-1.330 (-1.857;-0.804)	A > B
MICT (n=23)	120 ± 45.1	92 ± 39.4	< .001 [b]	-0.659 (-0.950;0.367)	A > B
Control (n=23)	117 ± 50.4	119 ± 51.4	.144	0.039 (-0.227;0.304)	-
Triglycerides (mmol/L)					
HIIT (n=23)	200 ± 60.6	137 ± 51.2	< .001 [a]	-1.119 (-1.544;-0.693)	A > B
MICT (n=23)	187 ± 91.7	138 ± 72.1	< .001 [b]	-0.598 (-0.856;-0.341)	A > B
Control (n=23)	188 ± 78.0	187 ± 62.7	1.00	0.036 (-0.207;0.135)	-
HbA1c (%)					
HIIT (n=23)	6.1± 1.3	5.4 ± 0.8	< .001 [a,c]	-0.645 (-0.992;-0.298)	A > B
MICT (n=23)	5.8 ± 0.6	5.4 ± 0.4	< .001	-0.370 (-0.506;-0.233)	-
Control (n=23)	6.2 ± 0.9	6.2 ± 1.0	.670	0.008 (-0.227;0.227)	-
FBG (mg/dL)					
HIIT (n=23)	118 ± 28.3	106 ± 22.5	.002 [a]	-.466 (-0.776;-0.155)	A > B
MICT (n=23)	114 ± 20.2	109 ± 16.2	.007 [b]	-.271 (-0.537;-0.004)	A > B
Control (n=23)	122 ± 25.0	122 ± 29.4	.532	.003 (-0.245;0.251)	-
hsCRP (mg/L)					
HIIT (n=23)	1.5 ± 1.7	0.4 ± 0.7	< .001 [a]	-0.796 (-1.312;-0.280)	A > B
MICT (n=23)	1.1 ±1.1	0.4 ± 0.5	< .001 [b]	-0.805 (-1.280;-0.329)	A > B
Control (n=23)	1.3 ± 0.8	1.1 ± 1.0	.532	0.004 (-0.604;-0.004)	-
TSH (mU/l)					
HIIT (n=23)	1.6 ± 0.7	1.3 ± 0.9	.007 [a,c]	-0.407 (-0.830;0.016)	A > B
MICT (n=23)	1.9 ± 0.8	1.7 ± 0.7	.201	-0.242 (-0.543;0.058)	-
Control (n=23)	1.8 ± 1.4	2.4 ± 2.2	.007	0.089 (-0.109;0.760)	-
T4 (ng/dL)					
HIIT (n=23)	0.9 ± 0.2	1.0 ± 0.1	.006	0.439 (0.086;0.793)	-
MICT (n=23)	0.9 ± 0.1	1.0 ± 0.1	.007	0.089 (0.300;1.138)	-
Control (n=23)	1.0 ± 0.4	1.1 ± 0.4	.022	0.188 (0.035;0.341)	-
T3 (ng/dL)					
HIIT (n=23)	3.7 ± 0.7	3.4 ± 0.5	.002 [a]	-0.465 (-0.844;-0.085)	A > B
MICT (n=23)	3.7 ± 0.5	3.5 ± 0.5	.002 [b]	-0.327 (-0.561;-0.094)	A > B
Control (n=23)	4.4 ± 2.6	5.3 ± 3.9	.144	0.260 (-0.156;0.675)	-

Note. Abbreviations: FBG = fasting blood glucose; HDL-C = high density lipoprotein cholesterol; HIIT = high-intensity interval training; hsCRP = high-sensitive C-reactive protein; HbA1c (%) = hemoglobin A1C; LDL-C = low density lipoprotein cholesterol; MICT = moderate-intensity continuous training; SBP = systolic blood pressure; TSH = thyrotropin; T3 = triiodothyronine; T4 = thyroxine. Values are reported as Mean ± Standard deviation or number and percent population (%).

[a] significant differences between HIIT and Control, p < .05; [b] significant differences between MICT and Control, p < .05;

[c] significant differences between HIIT and MICT, p < .05.

</>/= indicates whether HIIT or MICT achieved a more desirable outcome.

5.3.4. Habitual physical activity and Diet

For habitual physical activity and dietary intake, there was no specific control. Patients just followed the ideal recommendations given by the medical specialist.

5.3.5. Adherence and Safety

Only one patient from each group discontinued the intervention, achieving 96% adherence in both groups, HIIT and MICT protocols. There were no adverse events in either protocol (HIIT and MICT) during the exercise interventions. Thus, HIIT protocols proved to be a safe, effective, and pleasant tool for low-risk patients with CAD as well.

5.4. Discussion

To our knowledge, this study represents a pioneering endeavor as the inaugural randomized controlled trial to systematically evaluate and differentiate the impacts of HIIT as opposed to MICT, in contrast to a control group, throughout a 6-week community-based exercise program within the Portuguese context. The main findings of our study are as follows: (i) in low-risk CAD patients HIIT and MICT exercise protocols promoted a significant improvement in blood pressure profile, body weight, BMI, body fat percentage, total body fat mass, abdominal fat percentage and waist circumference, compared to the control group; (ii) blood biomarkers improvement in patients undergoing HIIT protocol was slightly higher than MICT and mainly detected by hsCRP and TSH. In contrast, the control group had no significant improvements in these parameters. It is noteworthy that several variables exhibited an overall increase from baseline to the post-intervention phase, underscoring the systemic physiological responses engendered by exercise interventions. However, it is of significance to highlight that exceptions to this trend were observed in the form of reductions in total cholesterol and hsCRP levels from baseline to post-intervention .

Elevated blood pressure constitutes a prevalent health condition associated with heightened mortality and an augmented risk of CVD (Molmen-Hansen et al., 2012). Existing literature, as elucidated by Pattyn et al. (2018), underscores the favorable impact of aerobic exercise on both SBP and DBP. Specifically, Cornelissen et al. (2013) reported a reduction of 3.5 mm Hg (95% CI 2.3-4.6) and 2.5 mm Hg (95% CI 1.7-3.2) in SBP and DBP, respectively, following aerobic exercise interventions. In consonance with these findings, our study, conducted over a six-week exercise intervention period, unveiled substantial reductions in both SBP and DBP among participants in the HIIT group, with a decline of 9 mm Hg for SBP and 6 mm Hg for DBP. Similarly, the Moderate-Intensity Continuous Training (MICT) group exhibited significant reductions in SBP (8 mm Hg) and DBP (6 mm Hg). Conversely, the control group demonstrated an incremental increase in SBP (1.6 mm Hg) and DBP (1 mm Hg). Remarkably, our results align with prior investigations, such as the study by Nybo et al. (2010) which examined HIIT and MICT interventions over a 12-week period and reported notable improvements in this cardiovascular risk factor. Specifically, the HIIT group exhibited significant reductions of 8 mm Hg for SBP and 2 mm Hg for DBP, while the MICT group experienced reductions of 8 mm Hg for SBP and 5 mm Hg for DBP. Nevertheless, it is essential to acknowledge the influence of exercise intensity on blood pressure outcomes. Molmen-Hansen et al. (2012), in their study, implemented high-intensity training at 80–90% of maximum heart rate for the HIIT group (n=15) and moderate-intensity training at 50–70% of maximum heart rate for the MICT group (n=19). Notably, they reported mean decreases of 12 mm Hg in SBP and 8 mm Hg in DBP for the HIIT group, whereas the MICT group achieved non-significant reductions of 4.5 mm Hg and 3.5 mm Hg in SBP and DBP, respectively. Taken together, these findings collectively underscore the potential of both aerobic exercise modalities, namely HIIT and MICT, to effectively reduce blood pressure in patients with CAD. This demonstrates their suitability for integration into the rehabilitation regimens designed for this patient population. Moreover, the observed increase in blood pressure among subjects who did not engage in any form of exercise underscores the pivotal role of exercise in the management of blood pressure in CAD patients.

Obesity, either as an independent risk factor or in conjunction with other comorbidities, significantly heightens the susceptibility to incident CAD (Mandviwala et al., 2016). Pertinently, measures of body fat mass and percentage have established associations with an elevated risk of cardiovascular events and all-cause mortality (Jayedi et al., 2022; Despres, 2012). Additionally, higher values of BMI, increased waist circumference, and augmented waist-hip ratio have been reliably linked to a heightened risk of premature mortality (WHO, 2011; Czernichow et al., 2011; Di Angelantonio et al., 2016). Within the framework of our RCT, we discerned a conspicuous positive influence of both HIIT and MICT on the body composition of CAD patients. Contrastingly, individuals who abstained from participating in any community-based exercise program after their cardiac event displayed tendencies towards weight gain and increased fat mass. Specifically, following a six-week intervention period within the community-based exercise program, patients in the HIIT group exhibited a weight reduction of 1.9 kg more than their counterparts in the MICT group. In contrast, the control group displayed an increment of 0.5 kg. Moreover, in terms of WC, the HIIT group demonstrated a substantial decrease of −4.5 cm, while the MICT group exhibited a decrease of −2.7 cm. In stark contrast, the control group evidenced an increase of 1.1 cm. These outcomes provide compelling evidence of the favorable impact exerted by higher-intensity exercise sessions within community-based exercise programs on body composition, which corroborates findings reported by previous studies (Bires et al., 2013; Mandviwala et al., 2016; Czernichow et al., 2011; Di Angelantonio et al., 2016). In our investigation, truncal fat percentage was assessed using DXA, a measure highly correlated with abdominal fat percentage (Micklesfield et al., 2012). Our results showcased a reduction in abdominal fat percentage, translating to a decline of 1.8% in the HIIT group and 1.3% in the MICT group, signifying a 2.8% advantage over the control group after six weeks. Previous research efforts have also probed into the efficacy of HIIT in reducing abdominal fat among CAD patients. For instance, Dun et al. (2019) compared HIIT and MICT and reported that supervised HIIT engendered significant reductions in total fat mass, abdominal fat percentage, and an improved lipid profile in CAD patients. Similarly, Trapp et al. (2018) conducted a comparative analysis of HIIT and MICT, finding that the HIIT group exhibited a more pronounced decrease in abdominal fat. Slightly different were the results of the study of Zhang et al. (2017), once they demonstrated that both HIIT and MICT significantly reduced total and abdominal fat mass. It is worth noting that the study duration of six weeks in our investigation may be considered relatively short. With an extended intervention period, one could reasonably anticipate the emergence of clinically meaningful effects (Dun et al., 2019). In the context of weight control strategies for this population, aerobic programs such as walking are crucial. The distribution of exercise intensity can affect the effectiveness of these programs. Depending on whether the load is concentrated or continuous, different adaptations may occur due to varying levels of exertion (Blasco-Lafarga et al., 2020). Continuous doses can result in higher exertion for exercises with similar external intensity, while concentrating the load may lead to increased fatigue and more pronounced physiological alterations (Gonçalves et al., 2023; Blasco-Lafarga et al., 2020). For instance, a study on brisk walking in middle-aged obese females showed that both continuous and intermittent strategies were effective, but the continuous group had slightly better results in terms of weight loss and reduction of fat mass (Donnelly et al., 2000).

Considering the analysis of patient's blood biomarkers, our study results demonstrated a significant improvement in the patient s of the HIIT and MICT groups. In contrast, the control group, which did not partake in any community-based exercise program, exhibited minimal changes across these blood biomarkers, with exceptions noted in HDL-C and T4, both of which increased. When we scrutinized patients within each exercise program, we observed strikingly similar and significant reductions in all blood lipid parameters, hsCRP, T3, and blood sugar variables for both the HIIT and MICT groups. Importantly, following the six-week intervention, the control group displayed deteriorating results across all blood variables, whereas both HIIT and MICT engendered enhancements in TC, HDL-C, LDL-C, TG, hsCRP, T3 and HbA1c. These findings bear clinical significance, particularly in the context of patients with (CAD who concurrently grapple with type 2 diabetes and dyslipidemia, necessitating pharmacotherapeutic interventions. Remarkably, both exercise protocols succeeded in driving variable values back to normal levels. Our results resonate with existing literature that has juxtaposed HIIT against MICT, showcasing HIIT's potential to induce alterations in numerous physiological and health-related markers (Czernichow et al., 2011). Notably, HIIT demonstrated more pronounced improvements in total cholesterol, low-density lipoproteins, and triglycerides among CAD patients, as reported by Elmer et al. (2013) who also observed a greater reduction in triglyceride concentrations in HIIT compared to MICT. According to Ouerghi et al. (2017), short-term CR programs (≤ 10 weeks) may yield more substantial reductions in total cholesterol, LDL-C, DBP, SBP, WC, and a more substantial increase in HDL cholesterol compared to long-term CR programs. Furthermore, Pattyn et al. (2017) provided support for the beneficial impact of aerobic exercise on variables such as WC, HDL-C, LDL-C, SBP, DBP, and BMI. Moreover, a recent meta-analysis (Yamaoka & Tango, 2012) evidenced the favorable effects of lifestyle modifications on fasting blood glucose, WC, SBP and DBP, and TG, albeit with no significant impact on HDL-C.

In our study, it's noteworthy that the initial assessment revealed average levels of TSH, T3, and T4 within the normal range for all groups. Following a six-week exercise intervention, a notable trend towards further normalization of these values was observed, contrasting with a slight increase in these levels within the control group. It is crucial to underscore that subclinical hypothyroidism characterized by TSH levels exceeding 6.57 µIU/mL has been robustly linked to a significantly elevated risk of cardiovascular events and all-cause mortality (Rodondi et al., 2010). Two pertinent studies showed that high TSH levels have a protective effect on stroke severity and prognosis (Akhoundi et al., 2011; Chen et al., 2020). This observation underscores the importance of early intervention in cases of asymptomatic hypothyroidism, especially when TSH levels exceed or equal 8 µIU/mL, and particularly in individuals under the age of 65 who exhibit symptoms or possess cardiac risk factors (Jonklaas et al., 2014; Biondi et al., 2019). Moreover, Ojamaa et al. (2000) have demonstrated that low T3 syndrome also happens in an animal model of Acute Myocardial Infarction (AMI), where T3 levels decreased within a week and stayed > 40% lower than normal for 4 weeks, while T4 levels remained relatively stable. Parallelly, Olivares et al. (2007) reported noteworthy variations in thyroid hormone levels in post-AMI patients. Specifically, TSH levels demonstrated an increase, while T3 levels exhibited a decline lasting up to 8 weeks post-AMI. Meanwhile, T4 levels remained low for up to 12 weeks post-AMI, despite an initial surge in thyroid stimulation one week following the cardiac event. It is imperative to note that the "euthyroid reference range" for T4 typically spans from 10-28 pmol/L, while the "euthyroid range" for T3 generally falls within the interval of 4.6 to 9.7 pmol/L, with a median value of 6.63 pmol/L. Notably, a reduction in T3 levels has been associated with heightened stroke severity and increased mortality at the one-year mark (Alevizaki et al., 2007). Conversely, T4 levels have exhibited positive correlations with atherosclerosis in middle-aged and elderly individuals, independently of conventional cardiovascular risk factors (Xu et al., 2012). However, it is important to highlight that only a limited number of studies have undertaken the evaluation of thyroid parameters in relation to atherosclerosis in patients with CAD. Consequently, the status of thyroid function as an independent predictor of atherosclerosis in CAD patients remains an area warranting further investigation and elucidation (Akhoundi et al., 2011; Chen et al., 2020; Olivares et al., 2007).

Elevated levels of HbA1c exceeding 8.5% have been established as predictive of an increased risk of all-cause CVD (Xu et al., 2012). A normal A1C level is below 5.7%, whereas levels between 5.7% and 6.4% signify prediabetes, and levels at or above 6.5% indicate diabetes (Xu et al., 2012). Notably, individuals with higher A1C levels within the prediabetes range are at a heightened risk of progressing to type 2 diabetes. Furthermore, it's worth noting that hypothyroid patients often exhibit elevated HbA1c levels, which can be normalized through effective treatment addressing thyroid function, without significantly affecting FBG levels (Bhattacharjee et al., 2017). The normal range for FBG is typically 99 mg/dL or lower, while FBG levels between 100-125 mg/dL are indicative of prediabetes, and levels at or exceeding 126 mg/dL signify diabetes (Bhattacharjee et al., 2017). Within the context of our RCT, the initial assessment indicated that the average FBG and HbA1c levels of the study groups fell within the prediabetic range. However, following the six-week community-based exercise interventions, these levels exhibited a noteworthy trend towards normalization, whereas the control group experienced a marginal increase in their levels. The well-established effect of physical activity on glycemic control and body composition is corroborated by existing literature. Exercise training has been recognized as a frontline intervention for type 2 diabetes management, with numerous studies underscoring the efficacy of both HIIT (Fex et al., 2014; Gillen et al., 2012; Little et al., 2011) and MICT (Sigal et al., 2007; van Dijk et al., 2012) in effectively managing this condition. For instance, Mitranun et al. (2014) reported that HIIT and MICT led to similar reductions in blood glucose and body fat levels among individuals with type 2 diabetes, while HbA1c levels exhibited a significant reduction with HIIT compared to MICT ($p < .05$). Similarly, Karstoft et al. (2014) found that HIIT to significantly reduced blood glucose and body fat levels to a greater extent ($p < .05$) than MICT. Consistent with our findings, HIIT emerges as slightly more effective than MICT in reducing blood glucose levels and comparable in reducing body fat. These results hold significant clinical implications, particularly given the profound repercussions of elevated blood glucose levels and obesity in the development and progression of CVD, such as type 2 diabetes.

High-sensitive C-reactive protein is an indicator of metabolic disorders associated with an increased risk for CVD (Nathan & Ding, 2010). This heightened risk is attributed to the progression of atherosclerosis, characterized by the accumulation of cholesterol on the inner linings of blood vessels and inflammation within the vessel walls (Schaefer et al., 2000). Generally, a healthy hsCRP level falls below 0.9 milligrams per deciliter (mg/dL). When hsCRP test results range between 1.0 to 10.0 mg/dL, they are typically categorized as moderately elevated (Pearsonet al., 2003). In our study, baseline assessments revealed that all groups exhibited moderately elevated hsCRP levels.

However, following a six-week exercise intervention, both HIIT and MICT regimens succeeded in lowering hsCRP levels to within the normal range, in stark contrast to the control group, which maintained elevated values . Additionally, a substantial proportion of patients in the HIIT and MICT groups achieved hsCRP levels of less than 1 mg/L, indicative of a low risk of developing cardiovascular complications (Cardoso & Paulos, 2017). This underscores the clinical significance of the exercise's anti-inflammatory effects. Numerous studies have demonstrated that exercise regimens targeting cardiovascular health, such as HIIT or MICT, primarily induce reductions in pro-inflammatory markers, including hsCRP (Gonzalo-Encabo et al., 2021; Maturana et al., 2021; Khalafi et al., 2020). Our findings suggest that HIIT may be more efficient in reducing hsCRP levels compared to MICT, consistent with the findings of some prior studies (Khalafi et al., 2020; Rose et al., 2021). Nevertheless, it's worth noting that recent meta-analyses have not yielded conclusive evidence regarding whether HIIT consistently outperforms traditional MICT in terms of its impact on inflammatory states (Maturana et al., 2021; Leiva-Valderrama et al., 2021). Furthermore , limited research has explored the interplay between hsCRP levels and exercise programs specifically within the context of CAD patients.

Regarding the adherence of CAD patients to our programs, we report that only one patient in each group discontinued the intervention, reaching 96% adherence in both protocols (HIIT and MICT). Importantly, these exercise regimens demonstrated a commendable safety profile, with no reported adverse events during the exercise interventions. Our study boasts several notable strengths. It adhered to a randomized design, employed objective outcome measures, and featured blinded assessors to minimize bias. Additionally, the training interventions were thoughtfully individualized while maintaining consistent relative intensity in accordance with the HIIT principle. The favorable efficacy outcomes are particularly encouraging, given the substantial and clinically relevant improvements achieved within a relatively brief timeframe of six weeks, with a total of 18 sessions per patient. Collectively, these findings underscore the HIIT protocol as a safe, effective, and enjoyable tool for CAD patients, holding promise for enhancing their rehabilitation and overall well-being.

5.4.1. Study Limitations

This study entails certain limitations that should be acknowledged. Firstly, the relatively small sample size raises the possibility that only more substantial differences would attain statistical significance. Secondly, the unintended gender bias observed in the patient cohort, with only 13-17% representation of women, poses a limitation in terms of the generalizability of the findings. It is important to note that the sex distribution in the study was an unintended consequence of our clinical population composition. When considering the results of this study, due consideration must be given to potential confounding effects stemming from concurrent medications, although it is crucial to highlight that no alterations in medication dosages for lipid-lowering and heart rate control occurred throughout the study duration. Furthermore, it is noteworthy that the control group participants were not provided with diaries, thereby rendering us devoid of information regarding their physical activity patterns during the intervention period spanning from baseline to the six-week mark. The potential increase in physical activity within the control group could introduce a mitigating factor, potentially diminishing the observed differences in effects between the various groups.

5.5. Conclusions

In summary, our randomized controlled study demonstrated that both six-week HIIT and MICT programs were not only safe but also effective in eliciting favorable outcomes concerning blood pressure, body composition, and blood biomarkers in cardiac patients. Particularly noteworthy was the HIIT group's superior performance compared to the conventional community-based exercise program (MICT), displaying enhancements in SBP, reductions in total body fat mass, abdominal fat percentage, and waist circumference, as well as improvements in lipid profiles, blood glucose levels, and T3 hormone concentrations among patients with CAD. Conversely, the absence of any exercise-based intervention post-cardiac event correlated with adverse outcomes across all clinical variables. Importantly, no adverse event was reported, supporting the inclusion of HIIT as a valuable adjunct or alternative to MICT within community-based exercise programs, positioning it as a significant therapeutic strategy for managing CAD patients.

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CHAPTER 6

Paper 4: Improving health outcomes in coronary artery disease patients with short-term protocols of High-Intensity Interval Training and Moderate-Interval Continuous Training: A community-based randomized controlled trial

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Paper 4: Improving health outcomes in coronary artery disease patients with short-term protocols of High-Intensity Interval Training and Moderate-Interval Continuous Training: A community-based randomized controlled trial

Chapter overview

The previous Chapter examined the effects of two short-term exercise-based programs employing HIIT and MICT in comparison to a control group concerning blood pressure, body composition, and blood biomarkers in patients diagnosed with coronary artery disease. We conclude that HIIT and MICT are effective modalities for enhancing systolic and diastolic function, body composition, and blood biomarkers, with HIIT demonstrating incremental improvements over MICT. Plus, the absence of participation in exercise-based programs following cardiovascular events yielded less favorable outcomes. Although the benefits in that health outcomes have been verified, an additional concern regarding patients with CAD is that physical activity levels and physical fitness are critical components that are still understudied.

This Chapter examines the effects of two community-based exercise programs using two short-term protocols (HIIT and MICT) on physical fitness and physical activity levels in coronary artery disease patients.

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Research Article

Improving health outcomes in coronary artery disease patients with short-term protocols of High Intensity Interval Training and Moderate Interval Continuous Training: A community-based randomized controlled trial

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Abstract: Aerobic capacity has been shown to be inversely proportionate to cardiovascular mortality and morbidity, and there is growing evidence that high-intensity interval training (HIIT) appears to be more effective than moderate-intensity continuous training (MICT) in improving aerobic capacity within the cardiac population. The aim of this study was to investigate the effects of two community-based exercise programs using two short-term protocols (HIIT and MICT) on physical fitness and physical activity (PA) levels in coronary artery disease (CAD) patients.

Methods: In this randomized controlled trial, body composition, aerobic capacity, muscle strength, and daily PA levels were assessed before and after 6 weeks of intervention in 69 patients diagnosed with CAD. All patients were randomly (1:1:1) assigned to two exercise groups (HIIT or MICT) or a control group (no exercise). Both training programs consisted of 6 weeks of supervised treadmill exercise, three sessions per week. The MICT at ≈ 70-75% of heart rate (HR) peak and HIIT at ≈ 85-95% of HRpeak. The control group only followed the medical recommendations.

Results: HIIT could significantly improve waist circumference, body fat mass, VO_2peak, and moderate-to-vigorous PA compared to MICT. HIIT also showed more positive effects on sedentarism time with a decrease of 15% ($\Delta = -148.6 \pm 106.1$min/day) compared to 10% of MICT ($\Delta = -105.5 \pm 88.0$min/day). Moreover, the control group showed poorer results.

Conclusion: HIIT can improve health outcomes more positively than MICT and control. These findings indicate that HIIT may be an alternative and effective training method in community-based exercise programs for CAD patients.

Keywords: Cardiovascular Diseases • Cardiovascular risk factors • Clinical trials • Coronary Artery Disease • Randomized Controlled Trial

6.1. Introduction

Cardiovascular diseases (CVD) is the leading cause of death worldwide, accounting for 30% (16.7 million) of all deaths (Go et al., 2013). In Portugal, CVD signify

29.5% of all causes of death, which makes evident the importance in the public health scenario and the need to implement measures aimed at primary and secondary prevention (Andrade et al., 2018). Cardiac rehabilitation (CR) is an important tool in secondary prevention of CVD. CR programs aim to increase the aerobic capacity and muscular strength of patients with CVD (Heran et al., 2011). Aerobic capacity is recognized as a robust indicator of cardiovascular health and a well-established predictor of total and cardiovascular mortality in people with and without CVD. As a reference, improving aerobic capacity by 3.5 $mL\text{-}kg^{-1}\text{-}min^{-1}$ is associated with a ∼15% reduction in coronary heart disease/cardiovascular-related mortality (Boden et al., 2013). Fallavollita et al. (2016) studied coronary artery disease (CAD) patients who underwent a 5-week CR program and verified that CR improved aerobic capacity, while Kim et al. (2015) checked that a 6-week CR exercise program with an intensity of 60–85% heart rate reserve improved aerobic capacity in CVD patients. In addition, resistance training increases muscle strength and endurance, and positively influences cardiovascular risk factors, metabolism, and cardiovascular function in cardiac patients (Vanhees et al., 2012; Fletcher et al., 2013; Williams et al., 2017; Braith &. Beck, 2008). Previous studies have shown that exercise-based CR is also beneficial for improving blood pressure (Andrade et al., 2018; Smith et al., 2011), blood lipids (Andrade et al., 2018; Smith et al., 2011), physical fitness (Molino-Lova et al., 2013; O'Neill & Forman, 2020), body composition (Lear et al., 2006; Giannuzzi et al., 2008; Pedersen et al., 2019), and health-related quality of life (Fallavollita et al., 2016; Piepoli et al., 2016; Francis et al., 2019).

Moderate-intensity continuous training (MICT) has traditionally been a foundation of aerobic-based exercise prescription at the intensity of 50–75% heart rate (HR) (Piepoli et al., 2016), resulting in short- and long-term clinical benefits for CVD patients (Gonçalves et al., 2021). However, high-intensity interval training (HIIT) has recently emerged as an alternative or adjunct strategy to MICT. HIIT involves repeated bouts of relatively higher-intensity exercise (85–100%) interspersed with periods of lower-intensity recovery (Ito, 2019), and has been shown to result in similar or greater improvements in VO_2peak compared to MICT (Gonçalves et al., 2021; Norton et al., 2010; Taylor et al., 2020). Precisely, multiple recent meta-analyses (Gonçalves et al., 2021; McGregor et al., 2020; Mitchell et al., 2019) exploring the efficacy of HIIT within CVD patients have reported more remarkable improvement in aerobic capacity compared to MICT. Some research has shown strong evidence that HIIT is an effective method for improving strength (Adamson et al., 2014; Bruseghini et al., 2015), gait (Adamson et al., 2014; Coetsee & Terblanche, 2017) and body composition (Pedersen et al., 2019; Piepolo et al., 2016) in CAD patients. In fact, there is a trend that indicates that health indices and markers are more favorable after HIIT than after MICT (Chicharro & Campos, 2018).

Patients with CAD are encouraged to maintain an active lifestyle after the completion of exercise-based CR. However, during the observation phase after the completion of CR adherence to structured exercise remains low (Dolansky et al., 2010) and physical activity (PA) engagement decreases significantly (Ozemek et al., 2019; Chase, 2011). Major health care organizations recommend that CR patients consistently accumulate 30 to 60 minutes of moderate intensity PA per day on more than 5 days of the week and minimize the amount of time that is spent in sedentary behavior (SB) (Balady et al., 2007).

The primary objective of this randomized controlled trial (RCT) was to compare the effectiveness of 6-week supervised community-based exercise protocols, a short-duration resting HIIT, and a usual MICT, in improving health indicators among CAD patients. Specifically, this study aimed to assess the impact of these exercise protocols on physical fitness and physical activity levels of CAD patients. We chose to carry out a short-term (6-week) program based on the systems of other countries, particularly Australia, Hungary, and Austria (Chaves et al., 2020).

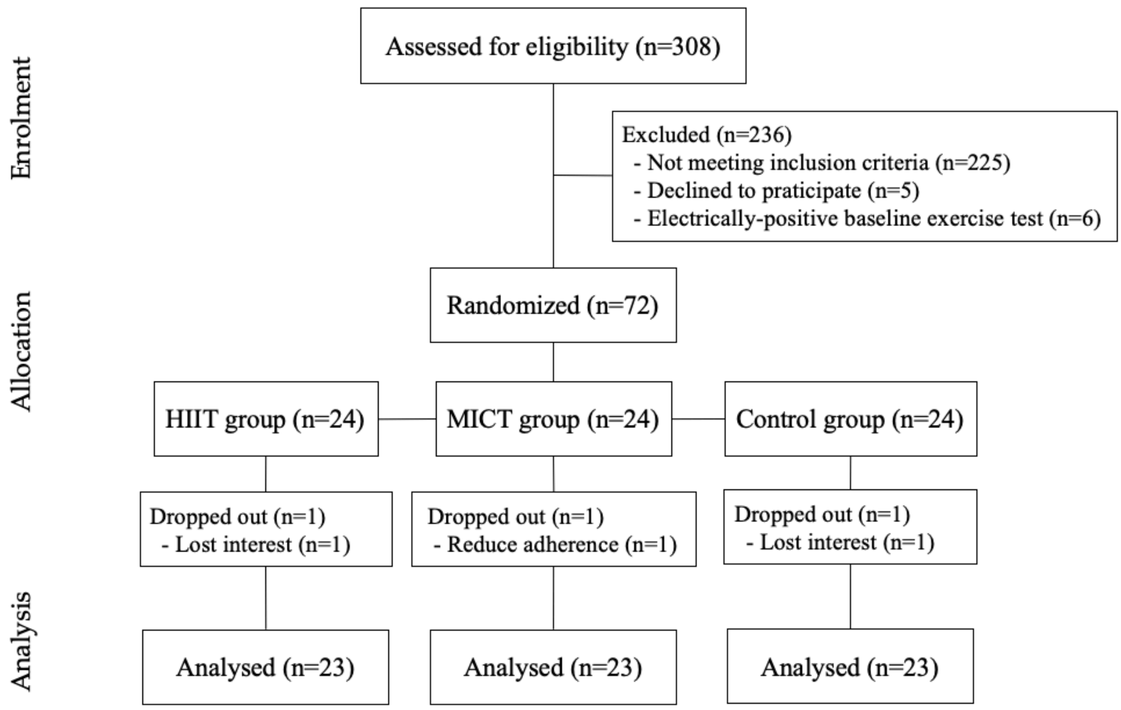
6.2. Methods

6.2.1. Participants Selection and Allocation

Seventy-two patients (men and women) were recruited between March 2018 and November 2021 within the cardiology unit of the Hospital do Espírito Santo de Évora, Portugal. All patients who had undergone a coronary event were referred by their cardiologist to the community-based exercise CR programs, 2 months after angioplasty, were evaluated for inclusion in this study. Patients were considered for inclusion in the study if they had undergone a coronary event, were aged 18 to 80 years, left ventricular ejection fraction ≥ 45%, New York Heart Association (NYHA) functional Class I or II, and were eligible to participate in the community-based exercise program. Patients were excluded from the study if they had severe exercise intolerance, uncontrolled arrhythmia, uncontrolled angina pectoris, severe kidney or lung diseases, musculoskeletal or neuromuscular conditions preventing exercise testing or training, and signs or symptoms of ischemia. Patients underwent a medically supervised cardiopulmonary exercise test (CPET) baseline testing performed on a treadmill with the Bruce protocol, before 1:1:1 randomization to either HIIT or MICT or control (no community-based exercise program). The test was done in non-fasting conditions and under medication. An electrocardiography was recorded continuously, and blood pressure was measured with an arm cuff every 3 minutes. Functional capacity in metabolic equivalent value (METs) was calculated. Patients were further excluded from the study if abnormal results identified from the baseline CPET resulted in further angiography. Blood samples were drawn on the same day as exercise testing but were collected before exercise. After completion of the informed consent process, clinical history, medication, blood sample, and echocardiogram are obtained from all patients to evaluate the eligibility criteria (**Figure 6.1**).

Figure 6.1.

Diagram of the study



After baseline testing, the patients were enrolled in the trial and given a trial-specific identification number (ID). The three groups were similar concerning age, extent of coronary artery disease, coronary risk factors, type of coronary event or left ventricular ejection fraction).

6.2.2. Health outcome measures and assessments

The patients were submitted to a clinical evaluation of physical fitness (body composition, aerobic capacity, and muscle strength), and physical activity (by accelerometry), performed by a physiologist at the University of Évora laboratory. Patients were asked to bring any medications that they were taking to the assessments. Initially, each patient completed a standardized questionnaire including demographic data, medical history, medication use, family history of CVD, and smoking status.

6.2.2.1. Physical Fitness

Body mass index (BMI) was calculated directly by the standard formula: $weight(kg)/height(m)^2$. The waist circumference was manually measured according to standard procedures of ACSM guidelines (Liguori, 2020; Thompson et al., 2013). Body composition was then assessed by dual-energy x-ray absorptiometry (DXA). DXA scans were performed with QDR 2000 densitometers (DXA, Hologic QDR, Hologic, Inc., Bedford, MA, USA), using the array beam mode. The DXA scans were performed within 1 week before starting and 1 week after the completion of 18 community-based exercise sessions. Scans were used to measure total body mass, body fat mass, body lean mass, body fat percentage, and abdominal region fat percentage (defined as the area between the ribs and the pelvis by GE Healthcare systems). The scanner was calibrated daily against a manufacturer-supplied standard calibration block to control for possible baseline drift.

In the present study, aerobic capacity was represented as peak oxygen consumed (VO_2peak, ml/kg/min). The VO_2peak was calculated from the equation $VO_2peak = 4.9486 + 0.023 * walk\ distance\ (meters)$ that was determined via using the 6-minute walking test (6MWT) as described previously (ACSM, 2013). The 6MWT was performed in a 50m pre-marked University of Évora pavilion, and instructions and encouragements were given following the test's guidelines (Guyatt et al., 1985). This test is well validated for CAD patients and has shown good reliability in this patient group (McDermott et al., 2014).

To measure the isokinetic muscle strength, we used the Isokinetic Dynamometer (Biodex®, System 3 Pro, Biodex Corp., Shirley, NY, USA). The protocol used was the concentric unilateral mode for the extensor and knee-dominant flexor muscles. Patients were tested in a seated position with hip flexion. Stabilization straps were applied to the trunk, waist, and thigh. Evaluations of peak torque (three repetitions) and fatigue resistance (20 repetitions) were carried out at angular velocities of 90°/s and 180°/s of the dominant knee. The peak torques of the knee extensor and flexor muscles were adjusted by body weight according to the following formula: *strength (Nm) × 100/body weight (kg)*, since it is well known that the peak muscle power is closely associated with body weight (Maffiuletti et al., 2007).

6.2.2.2. Physical Activity Levels

After completing all clinical evaluations, patients were asked to wear a triaxial accelerometer (ActiGraph GT3X) on their hip placed anterior to the right iliac crest for 7 consecutive days during waking and sleeping hours except when bathing or swimming. Acceleration data from the 3 planes were processed with *ActiGraph software* (ActiLife, version 6) using 15-s epochs (raw data recorded at 30 Hz) and the standard filter and were integrated into a vector magnitude count by taking the square root of the sum of squared axes (vertical, anterior–posterior, and medial–lateral). Daily averages (min/day) of accelerometer-measured PA were calculated for each patient and classified into five activity levels (sedentary time 1.00–1.99 MET, light PA 2.00–3.49 MET, and all activity ≥ 3.50 MET was classified as moderate-to-vigorous PA) using the limits set by the manufacturer (Sasaki et al., 2011). A valid day was defined as ≥ 10 hours of wear time. All activity with intensity 1 MET (1 Met = 3.5 $mL\text{-}kg^{-1}\text{-}min^{-1}$) or higher was calculated on wear time. Patients with at least four valid days (3 weekdays and 1 weekend day) were included in the analyses (monitor wear time of ≥ 600 min/day) (Prince et al., 2015).

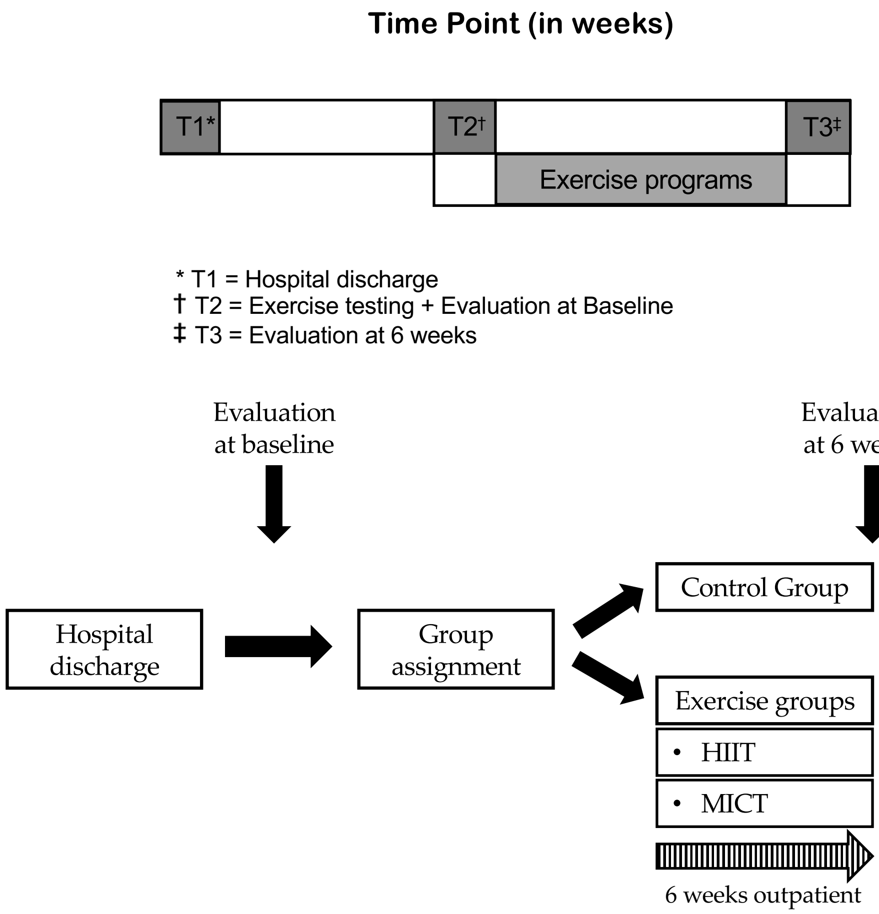
All measurements were taken at the beginning and completion of 18 sessions of community-based exercise programs. The protocols of pre- and post-intervention were the same for each patient.

6.2.3. Exercise training protocols

After hospital discharge, educational intervention, dietary advice, and psychological support were performed to all patients. The community-based exercise programs (HIIT and MICT) consisted of 6 weeks of supervised treadmill exercise, three sessions per week (**Figure 6.2**). If a session was missed, it was made up that week or the following week. Patients performed each exercise session in a group, including a maximum of three patients per session. The control group did not receive any additional follow-up regarding exercise beyond general advice on the importance of exercise.

Figure 6.2.

Study design and time frame



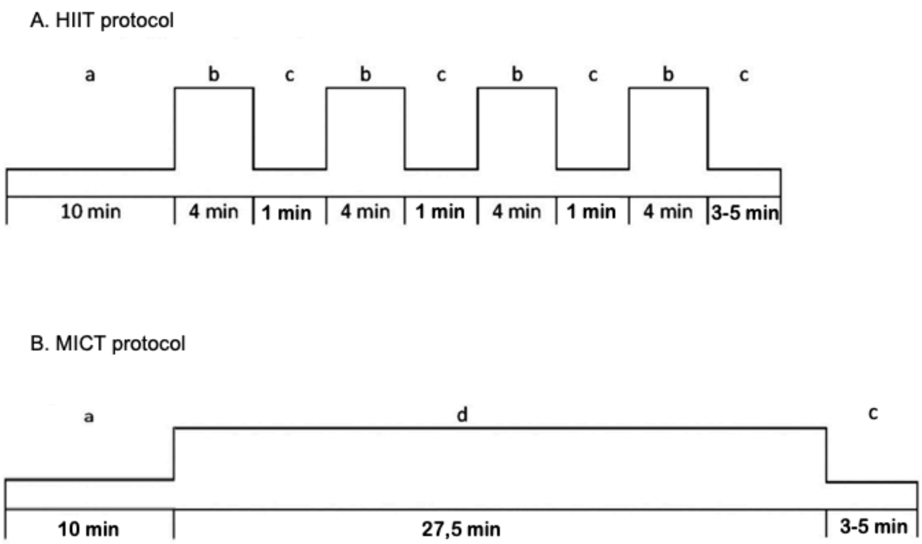
Note. Abbreviations: HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; T = time point.

Each training session was initiated with a 5–10-minute warm-up at 50-60% HRpeak and ended with 5 minutes of cool-down at 40% HRpeak. The HIIT group performed 4 × 4-minute high-intensity intervals at 85%–95% HRpeak followed by a one-minute recovery interval at 40% HRpeak, predicted with a supervised graded exercise test on a treadmill with the Bruce protocol (ACSM, 2013; Bires et al., 2013). During the exercise, the patients were motivated to gradually increase their exercise intensity towards 6–9 (hard to very hard) on a 0 to 10 Borg scale. The MICT protocol consisted of a continuous bout of moderate-intensity exercise to elicit 70–75% HRpeak, rating of perceived exertion 3 to 5 (fairly light to somewhat hard), for 27.5 minutes to equate the energy expenditure with the HIIT protocol (**Figure 6.3**). The 10-point Category-Ratio

Borg Scale (Scherr et al., 2013), also commonly referred to as the Rating of Perceived Exertion, was used to assess patients' perceived effort during exercise. The Borg Scale is a 10-point scale ranging from 0 to 10 with anchors ranging from ''No exertion at all'' (0) to ''Maximal exertion'' (10). Patients were asked to rate their exertion before (pre-exercise), minute to minute of exercise, and post-exercise. Buchheit & Laursen (2013) and Levinger et al. (2004) demonstrated that the RPE (Borg Scale) has shown a great correlation with HR, ventilation, and VO_2peak in individuals with and without CAD, and the correlation is not impacted by beta-blocker medication, a commonly used HR modulating medication by patients with CAD (McGregor et al., 2023).

Figure 6.3.

Summary of the exercise training protocol



Note. Abbreviations: HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; min = minutes;

a – warm-up; b – interval bout of high intensity exercise; c – one-minute recovery interval; d – cool-down; e – continuous bout of moderate-intensity exercise; min – minutes.

The exercise intensity was calculated using the following heart rate reserve equation: *Target HR = [(HRmax – HRrest) x %intensity desired] + HRrest* (Liguori, 2020), predicted with a supervised graded exercise test on a treadmill with the Bruce protocol (ACSM, 2013). HRR is defined as the difference between the basal rates of HR. Training sessions were supervised by a physiologist. As training intensity increased, the patient's heart rate, rate of perceived exertion (Borg scale), and cardiac symptoms were also taken into consideration. Heart rates were observed with *Polar heart rate* monitoring (Polar Electro Oy, Kempele, Finland), and blood pressure was measured at the commencement and the end of each session. Patients' heart rate was recorded using Polar heart rate monitors minute to minute of exercise.

The control group did not receive any additional follow-up regarding exercise beyond general advice on the importance of exercise and diet.

6.2.4. Ethical considerations

This RCT followed the CONSORT guidelines for RCTs (http://www.consort-statement.org) and was conducted in accordance with the Declaration of Helsinki and registered at ClinicalTrials.gov (NCT03538119). The Ethics Committee of the University of Évora (reference number: 17039) has approved the study design, protocol, and informed consent procedure. All patients signed a written informed consent before participating in this study.

6.2.5. Statistical analyses

The assumptions of normality and homogeneity were tested through the Kolmogorov-Smirnov and Levene tests, respectively. Since most of the sample variables did not follow a normal distribution, non-parametric statistical analyses were conducted. Between-group comparisons were performed using the Kruskal-Wallis test, and within-group comparisons were performed using the Friedman test; both tests were followed by post hoc pairwise comparisons. The means and standard deviations were calculated for all variables. The delta value (*Δ: momentx – momentx-1*) and the respective proportional change delta value (*Δ%: [(momentx - momentx-1)/momentx-1] × 100*) were computed for all variables: post-intervention vs. baseline. The effect size (ES) was calculated using Cohen's method since the data were not normally distributed (Fritz et al., 2012). The ES was computed and classified based on Cohen's thresholds (small: d = 0.10; medium: d = 0.30; and large: d ≥ 0.50) (Cohen, 2013). Analyses were performed using the SPSS software package (version 24.0 for Macbook, IMB Statistics). A value of $p \leq .05$ was considered statistically significant for all analyses. A code was assigned to each patient to preserve their anonymity.

6.3. Results

Patient characteristics at baseline are described in **Table 6.1**. Baseline characteristics were not different for HIIT, MICT and control groups: age (50 ± 9 vs. 55 ± 10 vs. 57 ± 11 years respectively), female (15% vs. 17% vs. 15%), BMI (28.2 ± 4.5 vs.

29.4 ± 3.9 vs. 29.4 ± 4.3 kg/m^2) and waist circumference (98.4 ± 14.5 vs. 101.1 ± 10.3 vs. 101.1 ± 10.8 cm). Most patients were hypertensive and sedentary, with dyslipidemia and a family history of CVD. The most common medications were statins, anti-platelet therapy, and β-blockers. Comorbidities and medications were also not different between groups ($p > .05$).

Table 6.1.

Baseline characteristics of study participants

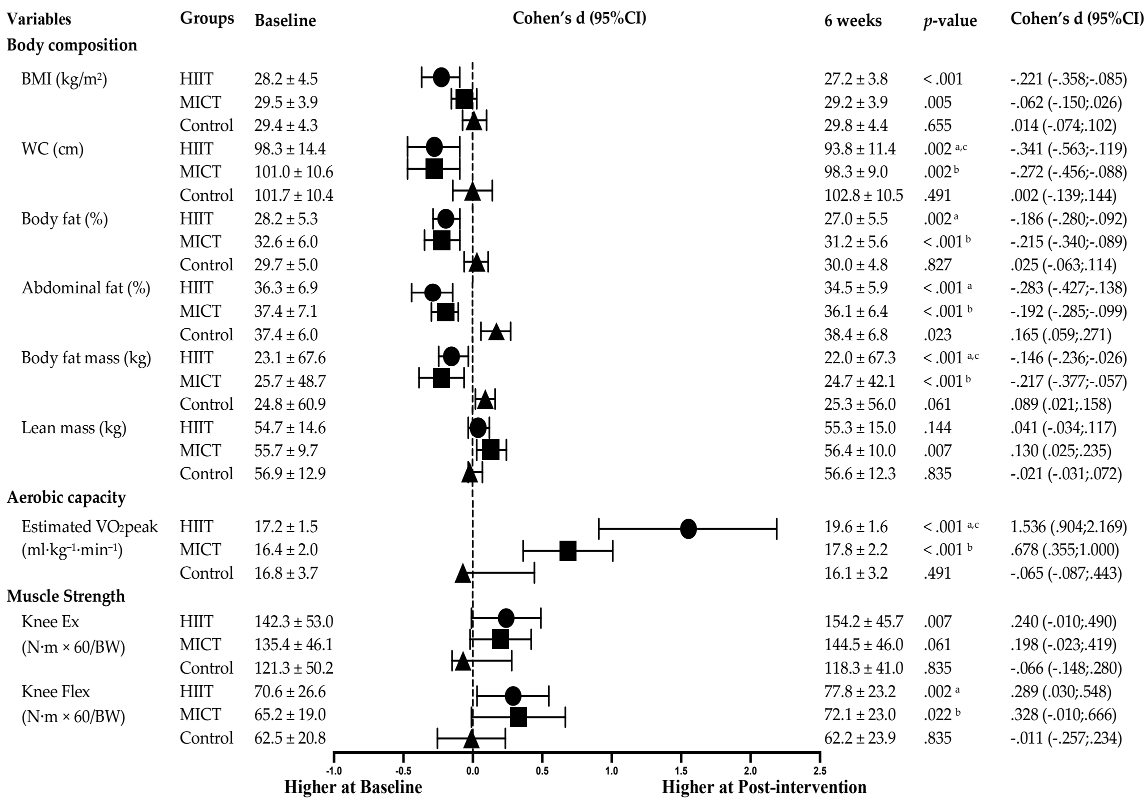
	Exercise-based program		No exercise-based program
	HIIT (n=23)	MICT (n=23)	Control (n=23)
Demographics			
Age (years), mean ± SD	50 ± 9	55 ± 10	57 ± 11
> 70 years, n (%)	2 (8.7)	3 (13.0)	4 (17.4)
Gender (Male/Female)	20/3	19/4	20/3
Retired, n (%)	2 (8.7)	7 (30.4)	7 (30.4)
Anterior MI, n (%)	3 (13.0)	4 (17.4)	2 (8.7)
Coronary event/intervention			
CABG, n (%)	1 (4.3)	1 (4.3)	1 (4.3)
PCI, n (%)	22 (95.7)	22 (95.7)	22 (95.7)
Risk factors or comorbidities			
Diabetes mellitus, n (%)	10 (43.5)	9 (39.1)	10 (43.5)
Hypertension, n (%)	13 (56.5)	13 (56.5)	14 (60.9)
Dyslipidemia, n (%)	14 (60.9)	15 (65.2)	15 (65.2)
Body Mass index (kg/m^2), mean ± SD	28.2 ± 4.5	29.4 ± 3.9	29.4 ± 4.3
Waist Circumference (cm), mean ± SD	98.4± 14.5	101.1 ± 10.3	101.1 ± 10.8
Active smoker, n (%)	6 (26.1)	4 (17.4)	4 (17.4)
Non-smoker, but has been, n (%)	9 (39.1)	13 (56.5)	12 (52.2)
Family history of CVD, n (%)	14 (60.9)	16 (69.6)	16 (69.6)
Sedentarism, n (%)	13 (56.5)	19 (82.6)	19 (82.6)
Sleep < 5h, n (%)	6 (26.1)	9 (39.1)	11 (47.8)
Current medication			
ACE inhibitor, n (%)	21 (91.3)	23 (100)	22 (95.7)
ARBs, n (%)	16 (69.6)	7 (73.9)	11 (47.8)
Antiplatelet, n (%)	22 (95.7)	22 (95.7)	23 (100)
CCBs, n (%)	2 (8.7)	5 (21.7)	5 (21.7)
Beta-blockers, n (%)	21 (91.3)	22 (95.7)	22 (95.7)
Diuretics, n (%)	2 (8.7)	4 (17.4)	6 (26.1)
Insulin, n (%)	5 (21.7)	5 (21.7)	11 (47.8)
Statin, n (%)	22 (95.7)	22 (95.7)	23 (100)

Note. Abbreviations: ACE = angiotensin-converting enzyme inhibitor; ARBs = angiotensin II receptor blockers; CCBs = Calcium channel blockers; HIIT = high-intensity interval training; MI = Myocardial Infarction; MICT = moderate-intensity continuous training; VO_2peak = maximal oxygen consumed. Data are reported as Mean ± Standard deviation or number and percent population (%). Significance is < .05.

At baseline, there were no differences across groups in the body composition measurements. Following 6 weeks of exercise, the results (**Figure 6.4**) showed that the HIIT group demonstrated significant improvements compared to MICT in waist circumference (Δ% HIIT: 4.1%, *p* = .002 vs. Δ% MICT: 2.5%, *p* = .002) and body fat mass (Δ% HIIT: 4.5%, *p* < .001 vs. Δ% MICT: 3.2%, *p* < .001). The control group had no improvements. On the other hand, all values of body composition measurements increased from baseline to post-intervention. The respective ES from baseline to 6 weeks were small in the HIIT group in body weight (*d* = .20), abdominal fat percentage (*d* = .28), and BMI (*d* = .22), and medium in waist circumference (*d* = .34). Moreover, in the MICT group, the ES were small in body fat percentage (*d* = .22), total body fat mass (*d* = .22), and waist circumference (*d* = .22).

Figure 6.4.

Physical fitness measurements of exercise groups (HIIT, n = 23 and MICT, n = 23) and control group (n = 23)



Note. Abbreviations: BMI = body mass index; Control = control group; Ext = extensors; Flex = flexors; HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; WC = waist circumference. Values are reported as Mean ± Standard deviation; 95%CI = 95% confidence interval.

[a] significant differences between HIIT and Control, *p* < .05; [b] significant differences between MICT and Control, *p* < .05; [c] significant differences between HIIT and MICT, *p* < .05.

Following the 6 weeks supervised program, VO2peak significantly increased by 14% with HIIT (Δ = 2.5 ± 1.5 ml·kg^{-1}·min^{-1}, p < .001) and 9% with MICT (Δ = 1.4 ± 1.2 ml·kg^{-1}·min^{-1}, p < .001) (**Figure 6.4**). Moreover, the control group VO2peak decreased 0.2% (Δ = −0.7 ± 1.3 ml·kg^{-1}·min^{-1}, p = .491). The respective ES from baseline to 6 weeks were large in HIIT (d = 1.54) and MICT (d = .68).

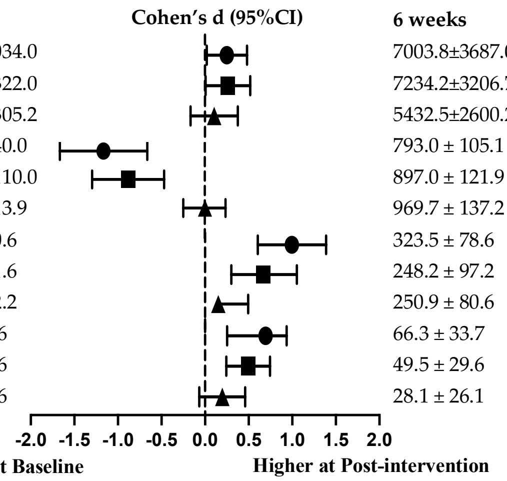
Regarding the maximal strength of the knee extensors and flexors variables (**Figure 6.4**), despite descriptive analysis demonstrating an increase of 13% at 6 weeks in the variable "Isokinetic peak torque (extension 60º)" in HIIT (Δ = 11.9 ± 27.6 N·m, p = .007) and of 10% in MICT (Δ = 9.1 ± 22.8 N·m, p = .061), the control group had a decrease of 0.4% (Δ = −3.0 ± 22.8 N·m, p = .835, d = .07). The respective ES from baseline to 6 weeks were small in HIIT (d = .24) and MICT (d = .20). A positive increase between baseline and the 6 weeks was observed in the variable "Isokinetic peak torque (flexion 60º)" in HIIT of 15% (Δ = 7.2 ± 14.2 N·m, p = .002) and MICT of 14% (Δ = 6.9 ± 16.0 N·m, p = .022). On the other hand, the control group decreased by mean 0.2% (Δ = −0.3 ± 12.8 N·m, p = .835). The respective ES from baseline to 6 weeks were small in HIIT (d = .29) and medium in MICT (d = .33).

Figure 6.5 presents the physical activity and sedentary behavior of the exercise and control groups.

Figure 6.5.

Physical Activity and Sedentary Behavior Levels of exercise groups (HIIT, n = 23 and MICT, n = 23) and control group (n = 23)

Variables	Groups	Baseline	6 weeks	*p*-value	Cohen's d (95%CI)
Daily step count	HIIT	6041.5±2034.0	7003.8±3687.0	< .001 [a]	.255 (.022;.488)
	MICT	6488.3±2322.0	7234.2±3206.7	< .001 [b]	.266 (.007;.526)
	Control	5167.0±2305.2	5432.5±2600.2	1.000	.108 (-.166;.382)
ST (min/day)	HIIT	941.6 ± 140.0	793.0 ± 105.1	< .001 [a]	-1.201 (-1.719;-.682)
	MICT	1002.5 ± 110.0	897.0 ± 121.9	< .001 [b]	-.908 (-1.336;-.481)
	Control	970.3 ± 113.9	969.7 ± 137.2	.144	-.004 (-.255;.247)
LPA (min/day)	HIIT	243.4 ± 80.6	323.5 ± 78.6	< .001 [a]	1.006 (.611;1.402)
	MICT	192.6 ± 61.6	248.2 ± 97.2	< .001 [b]	.674 (.304;1.063)
	Control	238.3 ± 82.2	250.9 ± 80.6	.532	.155 (.191;.500)
MVPA (min/day)	HIIT	29.9 ± 31.6	66.3 ± 33.7	< .001 [a,c]	.701 (.256;.946)
	MICT	26.1 ± 23.6	49.5 ± 29.6	< .001 [b]	.500 (.247;.753)
	Control	23.5 ± 18.6	28.1 ± 26.1	.033	.200 (-.066;.466)



Note. Abbreviations: HIIT = high-intensity interval training (n = 23); MICT = moderate-intensity continuous training (n = 23); Control = Control Group (n = 23); ST = Sedentary time (1.00–1.99 MET), LPA = Light physical activity (2.00–3.49 MET), MVPA = Moderate-to-vigorous physical activity (≥ 3.50 MET).

Values are reported as Mean ± Standard deviation.

[a] significant differences between HIIT and Control, $p < .05$; [b] significant differences between MICT and Control, $p < .05$; [c] significant differences between HIIT and MICT, $p < .05$

Following the 6 weeks supervised program, HIIT decreased the sedentary time (ST) of 15% (Δ = −148.6 ± 106.1 min/day, $p < .001$) and MICT decreased 10% (Δ = −105.5 ± 88.0 min/day, $p < .001$), and control decreased 0.1% (Δ = 0.559 ± 73.8 min/day, $p = .144$). Regarding the PA, HIIT increased the daily step count of 33% (Δ = 4162.3 ± 8339.7 step count, $p < .001$), MICT increased 10% (Δ = 745.9 ± 1605.4 step count, $p < .001$) and control increased 6.5% (Δ = 265.5 ± 1524.4 step count, $p = 1.000$). In LPA, HIIT increased 39% (Δ = 80.1 ± 45.2 min/day, $p < .001$), MICT increased 30% (Δ = 55.6 ± 60.3 min/day, $p < .001$), and control increased 9% (Δ = 12.6 ± 65.5 daily step count, $p = .532$). In MVPA, HIIT improved significantly 54% (Δ = 16.4 ± 14.4 min/day, $p < .001$), MICT improved 45% (Δ = 13.4 ± 12.4 min/day, $p < .001$), and control improved 19% (Δ = 4.5 ± 13.7 step count, $p = .033$). The respective ES from baseline to 6 weeks in daily step count were small in HIIT ($d = .26$) and MICT ($d = .27$), in ST were large in HIIT ($d = 1.20$) and MICT ($d = .91$), in LPA were large in HIIT ($d = 1.01$) and MICT ($d = .67$) and finally in MVPA were small in control ($d = .20$) and large in HIIT ($d = .70$) and MICT ($d = .50$).

6.4. Discussion

To our knowledge, this study is the first randomized controlled trial to characterize the effects of 6-week community-based exercise protocols in CAD patients health indicators such as physical fitness and physical activity levels. The main findings of our study are as follows: (i) Physical fitness: HIIT and MICT exercise protocols promoted a significant improvement in VO_2peak, body weight, BMI, body fat percentage, total body fat mass, abdominal fat percentage, and waist circumference, compared to the control group; (ii) the physical activity improvement in patients undergoing HIIT protocol was more positive than MICT and mainly detected by diminution of sedentarism time and increase of moderate to vigorous activity time. On the contrary, the control group decreased VO_2peak, muscle strength, and physical activity, and increased body composition variables and sedentarism time from baseline to six weeks.

Our study demonstrated that HIIT and MICT significantly decreased most body composition variables compared with patients who did not undergo exercise-based community programs. It is well documented that exercise training disproportionately reduces visceral fat compared to total body fat stores (Pattyn et al., 2014), and exercise does appear superior to dieting for inducing visceral fat loss (Cornelissen et al., 2013). The tendency for the control group was an increase in abdominal fat (+1%), body fat mass (+0.5kg), and waist circumference (+1.1cm) after six weeks. These results require attention because body fat mass and abdominal fat percentage are associated with a higher risk of cardiovascular events and all-cause mortality (Jayedi et al., 2022; Despres, 2012). On the contrary, body composition was positively affected by the HIIT intervention. Patients in the HIIT group reduced their weight by a mean 1.9 kg (−3.1%) more than patients in the MICT group (mean −0.9kg, −3%). Moreover, there was a moderate fat loss in both HIIT (mean −0.9kg, −3%) and MICT (mean −0.9kg, −3%) counteracted somewhat by a near-negligible increase in lean body mass in HIIT (mean +0.2 kg, 1.8%) and MICT (mean +0.2 kg, 0.5%). Furthermore, it is worth noting that both HIIT and MICT demonstrated a significant decrease in abdominal fat loss, with a mean reduction of 1.8% and 1.3%, respectively. This reduction is particularly important in reducing the risk of CVD. These results on body composition variables' demonstrated a beneficial effect of a higher intensity of exercise sessions in exercise-based on body composition, which is in accordance with what has been shown by others (Mandviwala et al., 2016; Czernichow et al., 2011; Di Angelantonio et al., 2016). For example, Dun et al. (2019) compared HIIT and MICT and found that supervised HIIT results in significant reductions in total fat mass and abdominal fat percentage and improved lipid profile in MI patients, compared to MICT. Trapp et al. (2008) compared HIIT and MICT and discovered the same effects. They showed that the HIIT group had a greater decrease in abdominal fat. Still, Zhang et al. (2017) demonstrated both HIIT and MICT significantly reduced total and abdominal fat mass. However, our study duration of 6 weeks was relatively short, and with an extended length of the intervention, one might expect an effect of clinical relevance.

Aerobic capacity (VO_2peak) improved by 14%, equivalent to 2.5 mL kg^{-1} min^{-1} or nearly 1 MET in the HIIT group and 9% in the MICT group (1.4 mL-kg^{-1}-min-^{1}) compared with the control group. The improvements of HIIT were almost twice as good as the MICT group ($\Delta = 2.3 \pm 1.5$ mL-kg^{-1}-min^{-1}, $p < .001$, $d = 1.54$ vs. $\Delta = 1.4 \pm 1.2$ mL kg^{-1}-min^{-1}, $p < .001$, $d = .68$, respectively). Our results indicated that training intensity is essential in improving peak aerobic capacity in CAD patients. Moreover, the mean between HIIT and MICT of 0.9 mL-kg^{-1}-min^{-1} could be considered clinically meaningful as each 1 mL-kg^{-1}-min^{-1} improvement in VO_2peak during a CR program has been associated with an ~8–17% reduction in all-cause and cardiovascular related mortality (Pedersen et al., 2019; Chicharro & Campos, 2018; Dolansky et al., 2010; Ozemek et al., 2019; Chase, 2011). Furthermore, Du et al. (2021) concluded that studies that used a non-isocaloric exercise protocol induced greater gains in VO_2peak compared to studies that used an isocaloric exercise protocol, indicating that the benefits of aerobic capacity can be determined by total caloric consumption. This is explained by the fact that we did not have greater results in this variable since we projected the same caloric expenditure between the two training intensities. Our study is in line with data from Keteyian et al. (2012), a study including 2812 cardiac patients demonstrated a cardiovascular-specific mortality risk reduction of 15% per 1 mL-kg^{-1}-min^{-1} increase in VO_2peak. Moreover, the greater efficacy of HIIT for improving VO_2peak compared with MICT during supervised training is similar to previous meta-analyses reporting group differences of 1.5 to 1.6 mL-kg^{-1}-min^{-1} (Rees et al., 2006; van Tol et al., 2006; Valkeinen et al., 2010; Pandey et al., 2015). Similarly, Rognmo et al. (2004) demonstrated that HIIT was effective to improve aerobic capacity in CAD patients. In addition, in our previous meta-analysis, we evaluated 16 studies (n = 969 patients) and concluded moderate-to-vigorous (SMD = 1.84 mL-kg^{-1}-min^{-1}; 95% CI [1.18, 2.50]) and vigorous-intensity (SMD = 1.80 mL-kg^{-1}-min^{-1}; 95% CI [0.82, 2.78]) exercise interventions were associated with larger increases in relative VO_2peak compared with moderate-intensity exercise interventions (SMD = 0.71 mL-kg^{-1}-min^{-1}; 95% CI [0.27, 1.15]) (Gonçalves et al., 2021). Sandercock et al. (2013) observed greater improvements of 5.2 mL-kg^{-1}-min^{-1} (95%CI: 4.1–6.4) in CAD patients, and Uddin et al. (2016) presented improvements of 3.3 mL-kg^{-1}-min^{-1} (95%CI: 2.6–4.0).

However, the control group who did not undergo community-based exercise programs decreased VO_2peak by −0.2% ($\Delta = -0.7 \pm 1.3$ mL-kg^{-1}-min^{-1}, $p = .491$, $d = .07$) which is alarming since it has been documented that aerobic capacity is a strong predictor of cardiovascular and all-cause mortality (Kim et al., 2018), and Martin et al. (2013) demonstrated that improvements in aerobic fitness after a 12-week exercise-based CR program was associated with an overall reduction in mortality of 13% per metabolic equivalent increase in VO_2peak and a 30% reduction in patients who entered the program with a low fitness level.

Impaired muscle strength is powerfully related to poor exercise capacity (Kamiya et al., 2014; Lang et al., 2012) and mobility disability (Manini et al., 2008) and predicts a higher rate of mortality (Guyatt et al., 1985) in CAD patients. At baseline, we found that the muscle strength of all groups was low. These results are consistent with previous studies in CAD patients before exercise-based programs (Marzolini et al., 2012; Fletcher et al., 2013). After six weeks, our study demonstrated that HIIT and MICT increased muscle strength compared with patients who did not undergo community-based exercise programs. However, HIIT increased muscle strength more than the MICT group. However, no significant increase was observed in our study, which is expectable because we only focused on aerobic training and we did not prescribe exercises for resistance training. The training effect on muscle strength in our study was similar to that demonstrated by Murabayashi et al. (2008). Yamamoto et al. (2016) reported an increased muscle volume in CAD patients, but no significant increase was observed in the study too.

In general, physical fitness (body composition, aerobic capacity, and muscle strength and) in both community-based exercise programs in 6 weeks improved, which was similar to other studies (Kida et al., 2008; Beniamini et al., 1999; Beniamini et al., 1999; Hussein, 2015; Fragnoli-Munn et al., 1998; Pierson et al., 2001). For example, Beniamini et al. (1999) demonstrated that HIIT during the 12 weeks CR program improved aerobic capacity and muscle strength and changed body composition. However, Fragnoli-Munn et al. (1998) reported an improvement in exercise capacity and muscle strength but not body composition. Pierson et al. (2001) reported mean percent strength increase 44 to 81% and significantly increased in the VO_2peak within both groups after training, but the relative improvement between groups was not different. Our results show that the control group displayed a lack of changes or even degradation of physical fitness (e.g. VO_2peak), suggesting the critical importance of referring CAD patients to a community-based exercise program.

Physical activity presents an important component of CR programs, with partial emphasis on reducing SB and increasing MVPA (Ambrosetti et al., 2021). Despite its importance, there are only a few studies that have examined the objectively measured PA and SB before enrollment to CR (Bakker et al., 2021; Freene et al., 2018; Prince et al., 2019; Prince et al., 2016; Ramadi et al., 2019; Biswas et al., 2018). Our results demonstrate high levels of SB in all three groups prior to enrollment, and their daily routine consists mainly of LPA. That is alarming since SB is an important and independent risk factor for CVD. Moreover, these results are consistent with previous findings when entering community-based exercise programs. Patients with CAD were mostly sedentary (10.5–12 h/day), followed by a longer time spent in LPA (3.5 h/day) and rarely engaged in MVPA before inclusion to CR (20–65 min/day) (Ambrosetti et al., 2021; Bakker et al., 2021; Freene et al., 2018; Prince et al., 2016; Ramadi et al., 2019). In the recent World Health Organization PA guidelines, wherein adults are advised to accumulate as much daily MVPA as possible, regardless of the single bout duration (Bull et al., 2020). After six weeks, we found a significantly higher level of daily MVPA (+36 min/day, $p < .001$) in HIIT and MICT (+23 min/day, $p < .001$) compared with the control group. However, we obtained similar results when comparing HIIT and MICT in relative daily LPA. Our findings are similar to previous findings with a MI population (Glazer et al., 2013; Wennman et al., 2016; Vasankari et al., 2018). Previously, both LPA and MVPA were associated with lower CVD risk (LaMonte et al., 2017). In our study, HIIT spent more time in MVPA and less time in sedentary compared to MICT. Based on PA guidelines, adults should spend 150min per week in MVPA (Bull et al., 2020; Piercy et al., 2018). Adherence to PA recommendations is associated with lower all-cause and cardiovascular mortality risk despite a previously inactive lifestyle (Moholdt et al., 2021). For MVPA and ST, this is partially in line with our findings, whereas patients performed slightly more MVPA and were less sedentary compared to some previous studies (Piercy et al., 2018; Diaz et al., 2017). Besides, a greater amount of daily PA at any intensity level and avoiding sedentary time are recommended.

In our study, we demonstrate a positive correlation between MVPA and aerobic capacity in patients before enrollment in community-based exercise programs. For public health, it might be most important that adults with high sedentary behavior could at least increase LPA to promote their cardiovascular health and decrease the risk of mortality. Since aerobic capacity presents a strong predictor of mortality in CAD patients (Vanhees et al., 1994). Future epidemiological and/or interventional studies should accurately assess the impact of PA and SB on clinical outcomes (mortality, re-hospitalization) and should enroll female patients to provide additional evidence on their physical fitness and physical activity levels.

To finalize, our results suggest that HIIT has a clinically significant effect in improving physical fitness and physical activity in CAD patients without adversely affecting patient safety. There were no adverse events in either protocol (HIIT and MICT) during the exercise interventions. Only one patient from each group discontinued the intervention, achieving 96% adherence in both groups, HIIT and MICT protocols. The positive efficacy findings we observed are encouraging, especially considering significant changes were induced over a relatively short duration (6 weeks) and with low training frequency (3 sessions per week; totaling ~18 sessions per patient). Chaves et al. (Chaves et al., 2020) suggest the ideal duration of community-based exercise intervention is between 12 to 36 sessions. Hence, our study demonstrated that HIIT was considered a beneficial and feasible supplementary therapy in community-based exercise program to MICT like other multiple large-scale epidemiological studies have reported the same (Kim et al., 2015; Taylor et al., 2019).

This study has some limitations that should be acknowledged. Firstly, the small sample size could mean that only greater differences would reach the significance level. Secondly, only 13-17% of the patients in this study were women, this sex bias was an unintended consequence of our clinical population but constitutes a limitation of the generalizability of the results. When considering the results of this study, the possible confounding effects of concurrent medications should be considered, although no change happened during the study period for doses of lipid-lowering and heart rate control medications. Additionally, the control group was not delivering diaries and we have no information about their physical activity habits during the intervention period from baseline to 6 weeks. A potential increase in physical activity could imply a reduced difference in effect between the groups. Another criticism of our study is the use of an isokinetic muscle test to measure changes in muscle strength. Because the training programs in our study mainly consisted of aerobic exercise, the use of an isokinetic muscle test could be argued to lack specificity. Based on this, it would have been more appropriate to complement the treadmill sessions with resistance exercises in community-based exercise programs.

6.5. Conclusions

In conclusion, this RCT showed that both 6-week HIIT and MICT programs were safe and effective to promote beneficial effects on the patient's physical fitness (body composition, aerobic capacity, and muscle strength) and physical activity. More importantly, compared to conventional exercise-based programs (MICT), the HIIT group showed further improvements in VO_2peak for reducing total body fat mass, abdominal fat percentage, waist circumference and sedentary behavior, and improving the MVPA in

CAD patients. However, not doing any type of exercise-based following a cardiac event has shown worse results in all studied clinical variables. Importantly, no adverse event was detected, so these findings support HIIT as a beneficial adjunct or alternative to MICT in community-based exercise programs and should be considered an important treatment strategy for CAD patients.

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CHAPTER 7

Paper 5: Reviving Hearts Post-Myocardial Infarction: High-Intensity Interval Training vs. Moderate-Intensity Continuous for Enhanced Quality of Life and Mental Well-being: a Randomized Controlled Trial

CHAPTER 7

Paper 5: Reviving Hearts Post-Myocardial Infarction: High-Intensity Interval Training vs. Moderate-Intensity Continuous for Enhanced Quality of Life and Mental Well-being: a Randomized Controlled Trial

Chapter overview

The previous Chapter showed HIIT could significantly improve waist circumference, body fat mass, VO_2peak, and moderate-to-vigorous PA in CAD patients compared to MICT. HIIT also showed more positive effects on sedentary time, with a decrease of 15%. The control group (no community-based exercise program) showed poorer results on physical fitness variables and physical activity levels. These findings indicate that HIIT can improve health outcomes more positively than MICT and control. However, there is a notable gap in the scientific literature regarding the comparative effects of HIIT versus MICT on the quality of life and mental health of CAD patients.

Thus, this Chapter examines the impact of two community-based exercise programs employing HIIT and MICT protocols on quality of life and mental health (anxiety and depression) in CAD patients, with a comparative analysis against a control group receiving no exercise program.

The material presented in this chapter has been peer-reviewed and and is under review in the Portuguese Journal of Public Health (Journal Impact Factor: 1.41).

Research Article

Reviving Hearts Post-Myocardial Infarction: High-Intensity Interval Training vs. Moderate-Intensity Continuous for Enhanced Quality of Life and Mental Well-being: a Randomized Controlled Trial

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Abstract: Cardiac rehabilitation (CR) has been shown to be inversely proportionate to cardiovascular mortality and morbidity and there is growing evidence that high-intensity interval training (HIIT) appears to be more effective than moderate-intensity continuous training (MICT) in improving clinical outcomes within cardiac patients. The present study aimed to investigate the effects of two exercise-based programs using two short-term (six-week) protocols: HIIT and MICT compared to the control group (no exercise program) in quality of life (QoL), anxiety and depression after myocardial infarction (MI).

Methods: In this randomized controlled trial, 72 patients with MI were individually randomized (1:1:1) into three groups: HIIT, MICT, and control. Both training programs consisted of six weeks of supervised treadmill exercise, three sessions per week. The MICT at ≈70-75% of heart rate (HR) peak and HIIT at ≈85-95% of HRpeak. The control group made the usual medical recommendations. Outcome measurements included an assessment of QoL (SF-36), anxiety and depression (HADS).

Results: In the exercise groups, six out of the eight SF-36 dimensions exhibited significant improvement after six weeks, in contrast to the control group. The HIIT group demonstrated noteworthy enhancements in physical functioning and general health compared with the MICT group. Baseline anxiety scores, albeit modestly elevated, substantially decreased following the six-week exercise interventions in both exercise groups, exhibiting statistical significance in comparison to the control group ($p < .05$).

Conclusion: Both exercise programs were equally effective in enhancing QoL and mental health among patients with MI, with the HIIT group showing additional improvements compared to the MICT group. Importantly, our findings emphasize that abstaining from exercise-based post-MI programs correlates with lower QoL, anxiety, and depression scores. This underscores the significance of implementing exercise-based rehabilitation strategies to optimize the recovery and well-being of patients with MI.

Keywords: Cardiovascular Diseases • Health-Related Quality of Life • High-Intensity Interval Training • Mental Health • Randomized Controlled Trial

7.1. Introduction

Coronary artery disease (CAD), the leading global cause of death affecting nearly 200 million people in 2019, often manifests as myocardial infarction (MI), with roughly one in three cases being repeat events (Roth et al., 2019; Deloite et al., 2011). In Portugal, CAD is the main cause of mortality, with MI accounting for 6.1% of total disability-adjusted life years (Wilkins et al., 2017). The chronic nature of CAD negatively impacts patients' Quality of Life (QoL), with increasing recognition of the association of depressive symptoms' association with higher morbidity and mortality rates in cardiovascular diseases (CVD) (Schopfer & Forman, 2016). Comparative research by Unsar et al. (2007) has demonstrated that individuals with CAD experience lower QoL across multiple domains, including mobility, hearing, breathing, elimination, usual activities, mental function, discomfort, symptoms, vitality, sexual activity, and overall score when compared to those without the disease, underscoring the imperative for medical and lifestyle interventions aimed at enhancing QoL, preserving physical and psychosocial independence, and reducing long-term healthcare and social care utilization.

Physical exercise is therefore essential to maximize physical, psychological, and social well-being by promoting the development of motor learning skills and cognitive function, which influence QoL (Ståhle & Cider, 2018). Cardiac rehabilitation (CR), which is crucial for reducing morbidity and mortality and enhancing the Quality of Life (QoL) of patients with MI (Woodruffe et al., 2014; Stewart et al., 2017; Piepoli et al., 2014; Balady et al., 2007), is linked to various positive outcomes including reductions in waist circumference (Bakker et al., 2021), body mass index (BMI) (Baker et al., 2021; Savage & Ades, 2008), blood glucose and triglyceride levels (Bäck et al., 2013; Prince et al., 2016), depression and anxiety (Smith et al., 2017) and health-related QoL (Hurdus et al., 2020). A Cochrane review published in 2016 revealed that exercise-based CR decreased the risk of cardiovascular mortality, enhanced QoL, and resulted in short-term reductions in hospital admissions when compared to a no-exercise control group (Anderson et al., 2016). Given that the restoration and preservation of QoL constitute primary objectives of CR (Magalhaes et al., 2013) it is imperative to investigate its influence on QoL, anxiety, and depression.

Moderate-intensity continuous training (MICT) has traditionally been a foundation of aerobic-based exercise prescription at the intensity of 50–75% heart rate (HR) (Piepoli et al., 2016) resulting in short- and long-term clinical benefits for CAD patients (Gonçalves et al., 2021). However, High-intensity interval training (HIIT) has recently emerged as an alternative or adjunct strategy to MICT. HIIT involves repeated bouts of relatively higher-intensity exercise (85–100%) interspersed with periods of lower-intensity recovery (Ito, 2019) and has been shown to result in similar or greater improvements in VO_2peak (Gonçalves et al., 2021; Norton et al., 2010), body composition (Taylor et al., 2020), heart rate response to exercise (Kim et al., 2015), and myocardial function (Molmen-Hansen et al., 2012) compared to MICT. However, there is a notable gap in the scientific literature regarding the comparative effects of HIIT versus MICT on the QoL and mental health of MI patients. Thus, the primary objective of this study is to investigate the impact of two community-based exercise programs employing HIIT and MICT protocols on QoL and mental health (anxiety and depression) in MI patients, with a comparative analysis against a control group receiving no exercise program.

7.2. Methods

This study is a single-blinded randomized controlled trial (RCT) and followed the CONSORT guidelines for RCTs (http://www.consort-statement.org).

7.2.1. Participants

Seventy-two MI patients were recruited from those entering the cardiology unit at the Hospital of Evora, Portugal between March 2018 and November 2021. The sample size was calculated using the online *G*Power software*, considering an effect size of 0.3, a predefined sample power of 0.8, a predefined error probability defined as 0.05, and statistical power of 95% (Faul et al., 2007). Hence, a minimum sample size of 66 participants was determined (22 participants for each group) to identify significant changes. The number of participants was increased to cover an expectable dropout rate. The inclusion criteria were age 18–80 years, left ventricular ejection fraction ≥ 45%, and New York Heart Association (NYHA) functional Class I or II. Patients were excluded from the study if the following criteria were met: severe exercise intolerance; uncontrolled arrhythmia; uncontrolled angina pectoris; severe kidney or lung diseases; musculoskeletal or neuromuscular conditions preventing exercise testing or training; and signs or symptoms of ischemia. Recruitment ended when the sample size for the primary outcome was attained. All patients completed a medical history and health questionnaire and provided written informed consent.

7.2.1.1. Randomization and masking

After the baseline assessment and before the start of exercise programs, the 72 patients were randomly assigned in a 1:1:1 allocation ratio to one of three groups: HIIT, MICT (traditional), and control (usual medical recommendations) (**Figure 7.1**). To ensure allocation concealment, patients in each group were seen at a specific, prescheduled time, and appointments for each group did not coincide with appointments for any patients in either of the other groups. The three groups were similar regarding age, the extent of coronary artery disease, coronary risk factors, type of coronary event or left ventricular ejection fraction).

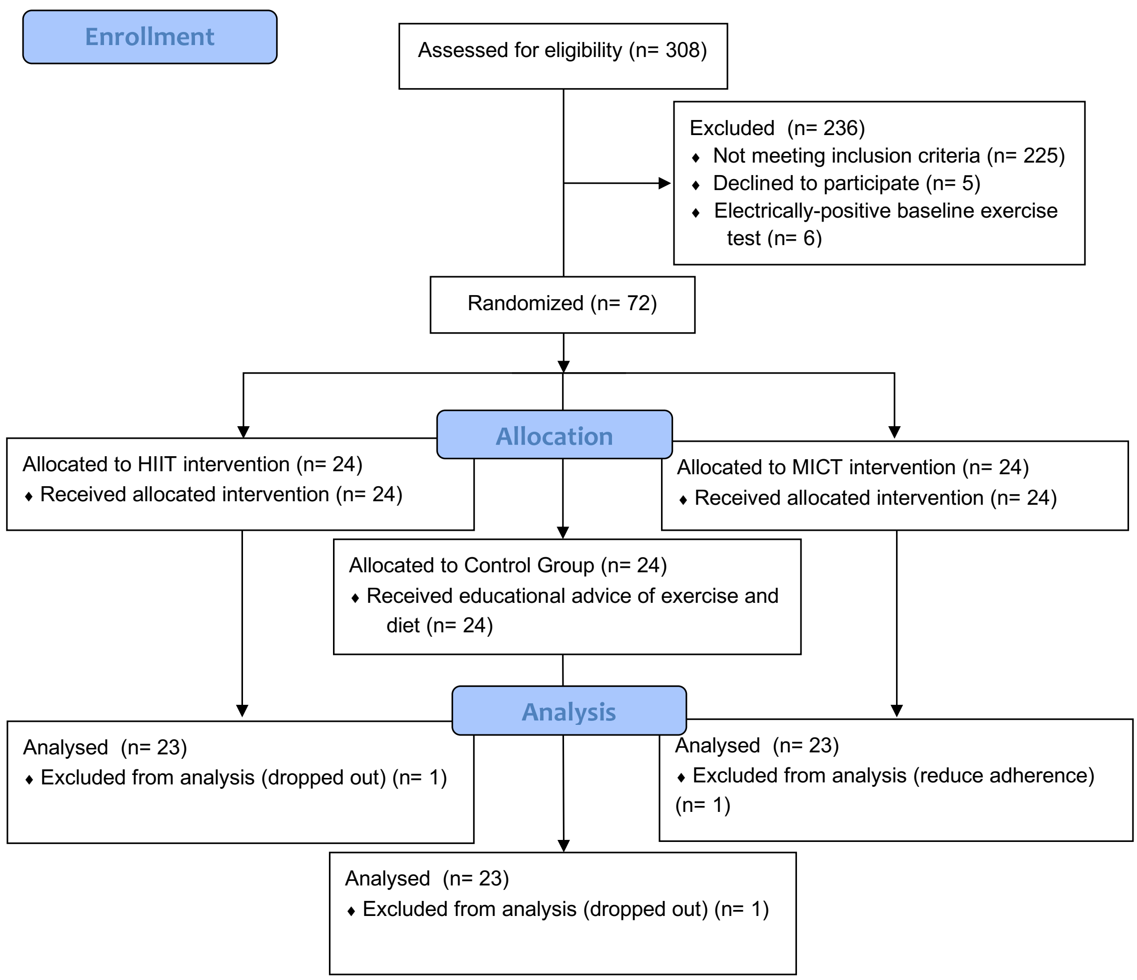
Figure 7.1.

Diagram of the study

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



7.2.2. Outcome measures and assessments

7.2.2.1. Exercise testing

Initially, the patients were submitted to a clinical evaluation performed by a cardiologist. A supervised graded exercise test to record volitional fatigue, risks or symptoms of ischemia was performed on a treadmill with the Bruce protocol (Bires et al., 2013) before the 6-week intervention period. The test was done in non-fasting conditions and under medication. Electrocardiography was recorded continuously, and blood pressure was measured with an arm cuff every 3 minutes. Functional capacity in metabolic equivalent value (METs) was calculated. As a high proportion of patients with MI are prescribed beta-blocker therapy, this relative method of exercise intensity considers the likely lower HRpeak achieved by these patients during the exercise test. To ensure training exercise intensity was reflective of medication effects, all patients were instructed to take their usual medications before the maximal exercise test.

7.2.2.2. Blood Biomarkers

Blood samples were drawn on the same day as exercise testing but were collected before exercise. All final blood samples were obtained 24-48 hours after completion of the last exercise session. Levels of blood biomarkers: fasting blood glucose, hemoglobin A1c, total cholesterol, low- and high-density lipoprotein cholesterol and triglycerides were collected to a clinical evaluation.

7.2.2.3. Body composition and Risk Factor Screening

On the second visit, the patient's blood pressure, height, weight and waist circumference were recorded by a physiologist at the laboratory of the University of Evora. Patients were asked to bring any medications that they were taking to the assessments. Initially, each patient completed a standardized questionnaire including demographic data, medical history, medication use, family history of CVD, and smoking status. Body mass index (BMI) was calculated directly by the standard formula: $weight(kg)/height(m)^2$ and the waist circumference was manually measured according to standard procedures of ACSM guidelines (Liguori, 2020; Thompson et al., 2013).

7.2.2.4. Quality of Life, Anxiety and Depression questionnaires

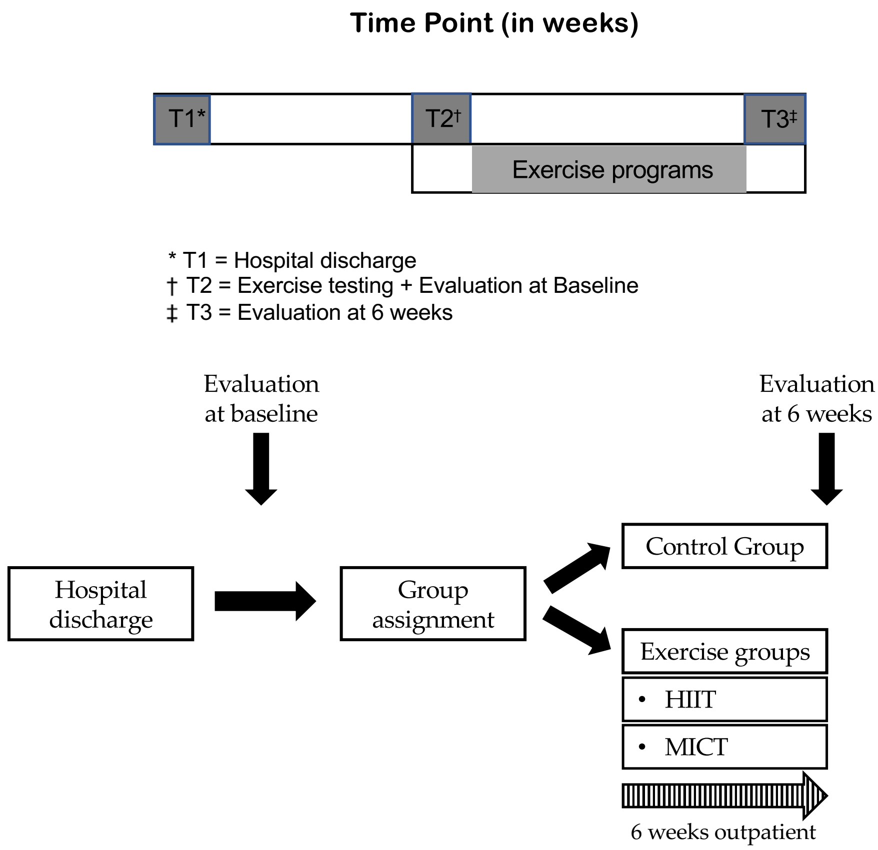
After that, they completed the patient-reported QoL questionnaire and the Hospital Anxiety and Depression Scale (HADS). The QoL questionnaire consisted of the rating scale, Short Form 36 (SF-36; Quality Metric, Lincoln, Rhode Island, USA), with eight domains: physical functioning, role-physical, role-emotional, social functioning, mental health, vitality, bodily pain and general health (Wave et al., 1993; Jenkinson et al., 1996). For all reported QoL instruments, higher scores correspond to better QoL as perceived by the patient (Thompson et al., 2013). The HADS questionnaire has been widely used to screen anxiety and depression among cardiac patients in the hospitals. The HADS questionnaire has two subscales including anxiety and depression, each of which comprised of items rated on four-point Likert scales (Herrero et al., 2003). The total HADS score ranged between 0-42 with 0-14 being considered as low, 15-28 considered as moderate, and 29-42 being considered as high. For each subscale (anxiety and depression subscales), the scores ranged between 0 to 21, where 0-7 was considered low, 8-14 being moderate, while 15-21 was considered high (Spinhoven et al., 1997; Snaith, 2003). The questionnaires were taken at the beginning and completion of 18 sessions of community-based exercise programs.

7.2.3. Exercise training protocols

After hospital discharge, educational intervention, dietary advice, and psychological support were performed in all patients. The exercise programs consisted of 6 weeks of supervised treadmill exercise, three sessions per week (**Figure 7.2**). If a session was missed, it was made up that week or the following week. Patients performed each exercise session in a group, including a maximum of three patients per session.

Figure 7.2.

Study design and time frame

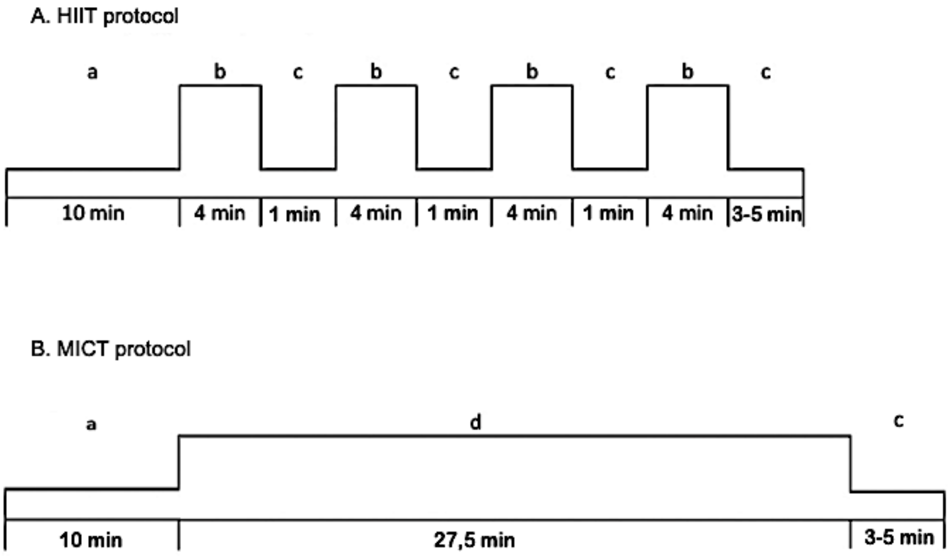


Note. Abbreviations: HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; T = time point.

Each training session was initiated with a 5–10-minute warm-up at 50-60% HRpeak and ended with 5 minutes of cool-down at 40% HRpeak. The HIIT group performed 4 × 4-minute high-intensity intervals at 85%–95% HRpeak followed by a one-minute recovery interval at 40% HRpeak, predicted with a supervised graded exercise test on a treadmill with the Bruce protocol (Bires et al., 2013). During the exercise, the patients were motivated to gradually increase their exercise intensity towards 6–9 (hard to very hard) on a 0 to 10 Borg scale. The MICT protocol (usual care) consisted of a continuous bout of moderate-intensity exercise to elicit 70–75% HRpeak, rating of perceived exertion 3 to 5 (fairly light to somewhat hard), for 27.5 minutes to equate the energy expenditure with the HIIT protocol (**Figure 7.3**).

Figure 7.3.

Summary of the exercise training protocol



Note. Abbreviations: HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; a = warm-up; b = interval bout of high intensity exercise; c = one-minute recovery interval; d = cool-down; e = continuous bout of moderate intensity exercise; min = minutes.

Training sessions were supervised by a physiologist. As training intensity increased, the patient's heart rate, rate of perceived exertion (Borg scale), and cardiac symptoms were also taken into consideration. Heart rates were observed with *Polar heart rate* monitoring (Polar Electro Oy, Kempele, Finland), and blood pressure was measured at the commencement and the end of each session.

The 10-point Category-Ratio Borg Scale (Scherr et al., 2013), also commonly referred to as the Rating of Perceived Exertion, was used to assess patient's perceived effort during exercise. The Borg Scale is a 10-point scale ranging from 0 to 10 with anchors ranging from ‘‘No exertion at all’’ (0) to ‘‘Maximal exertion’’ (10). Patients were asked to rate their exertion before (pre-exercise), immediately post minute to minute and post-exercise. Buchheit & Laursen (2013) and Levinger et al. (2004) demonstrated that the RPE (Borg Scale) has shown a great correlation with HR, ventilation, and VO_2 in individuals with and without CAD, and the correlation is not impacted by beta-blocker medication, a commonly used HR modulating medication by patients with CAD. Patient's heart rate was recorded using Polar heart rate monitors minute to minute of exercise. The control group did not receive any additional follow-up regarding exercise beyond general advice on the importance of exercise and diet.

7.2.4. Ethical considerations

All work was conducted following the Declaration of Helsinki and registered at ClinicalTrials.gov (NCT03538119). Ethics approval was obtained from the University of Evora Ethics Committee (reference number: 17039). All patients signed a written informed consent before participating in this study.

7.2.5. Statistical analyses

The assumptions of normality and homogeneity were tested through the Kolmogorov-Smirnov and Levene tests, respectively. Since most of the sample variables did not follow a normal distribution, non-parametric statistical analyses were conducted. Between-group comparisons were performed using the Kruskal-Wallis test, and within-group comparisons were performed using the Friedman test; both tests were followed by post hoc pairwise comparisons. The means and standard deviations were calculated for all variables. The delta value *(Δ: momentx – momentx-1)* and the respective proportional change delta value *(Δ%: [(momentx - momentx-1)/momentx-1] × 100)* were computed for all variables: post-intervention vs. baseline. The effect size (ES) was calculated using Cohen's method since the data were not normally distributed (Fritz et al., 2012). The ES was classified based on Cohen's thresholds (small: 0.10; medium: 0.30; and large: 0.50) (Cohen, 1988, 2013). Analyses were performed using the SPSS software package (version 24.0 for Macbook, IMB Statistics). A value of $p \leq .05$ was considered statistically significant for all analyses. A code was assigned to each patient to preserve their anonymity.

7.3. Results

Demographics and clinical characteristics are summarized in **Table 7.1**. Baseline characteristics were not different for HIIT, MICT and control groups: age (50 ± 9 vs. 55 ± 10 vs. 57 ± 11 years respectively, $p = .180$), female (15% vs. 17% vs. 15%, $p = .211$), BMI (28.2 ± 4.5 vs. 29.4 ± 3.9 vs. 29.4 ± 4.3 kg/m^2, $p = .659$), waist circumference (98.4 ± 14.5 vs. 101.1 ± 10.3 vs. 101.1 ± 10.8 cm, $p = .218$) and VO_2max (34.7 ± 9.0 vs. 30.4 ± 6.3 vs. ± 23.5 ± 11.0 mL/kg/min $p = .290$). Comorbidities and medications were also not different between groups ($p > .05$).

Table 7.1.

Patient characteristics at baseline

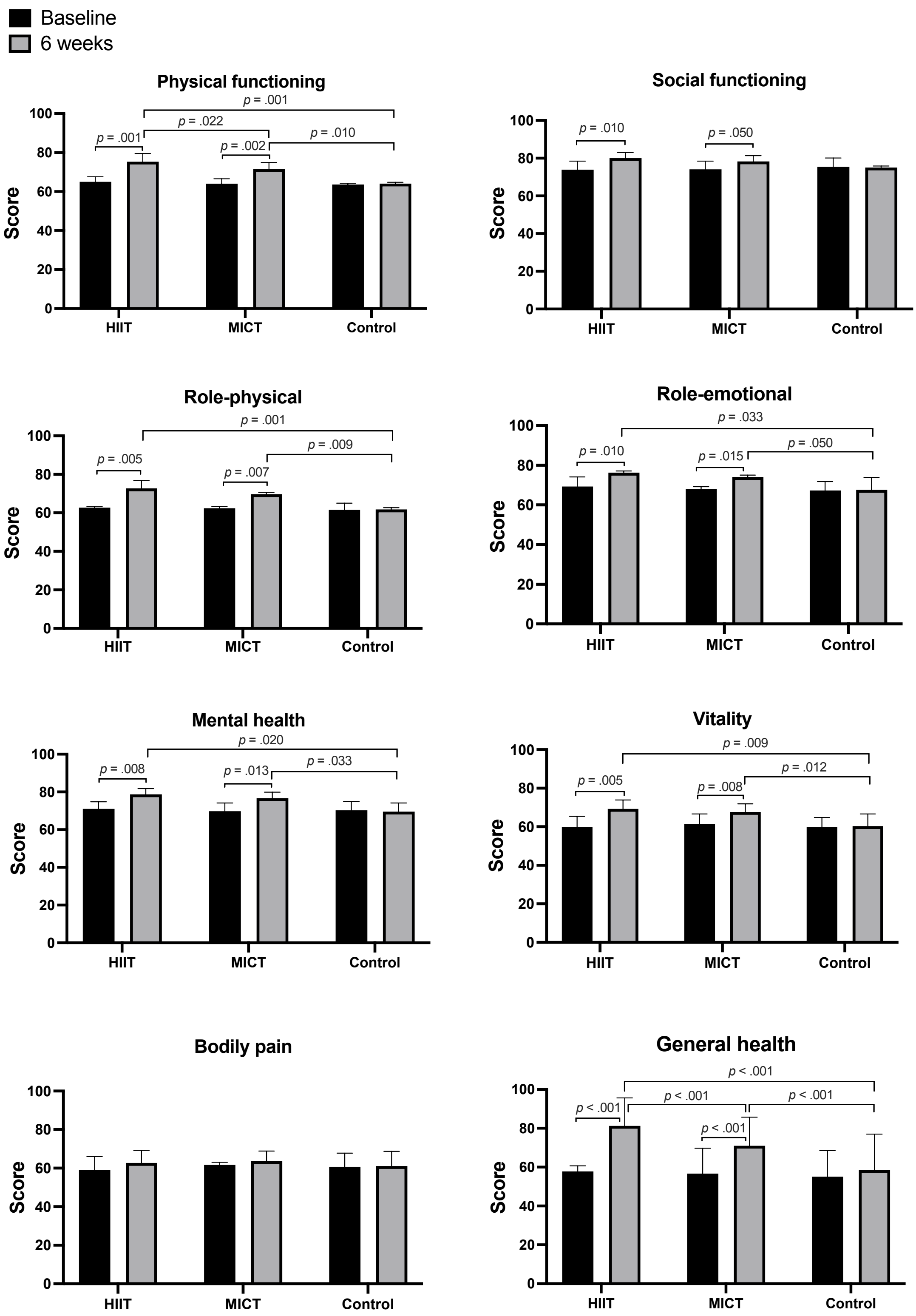
	HIIT (n=23)	MICT (n=23)	Control (n=23)
Demographics			
Age (years), mean ± SD	50 ± 9	55 ± 10	57 ± 11
> 70 years, n (%)	2 (8.7)	3 (13.0)	4 (17.4)
Gender (Male/Female)	20/3	20/4	20/3
Retired, n (%)	2 (8.7)	7 (30.4)	7 (30.4)
Anterior MI, n (%)	3 (13.0)	4 (17.4)	2 (8.7)
VO_2peak (mL/kg/min), mean ± SD	24.7 ± 9.0	23.4 ± 6.3	23.5 ± 11.0
Risk factors or comorbidities			
Diabetes mellitus, n (%)	10 (43.5)	9 (39.1)	10 (43.5)
Hypertension, n (%)	13 (56.5)	13 (56.5)	14 (60.9)
Dyslipidemia, n (%)	14 (60.9)	15 (65.2)	15 (65.2)
Body Mass index (kg/m^2), mean ± SD	28.2 ± 4.5	29.4 ± 3.9	29.4 ± 4.3
Waist Circumference (cm), mean ± SD	98.4 ± 14.5	101.1 ± 10.3	101.1 ± 10.8
Active smoker, n (%)	6 (26.1)	4 (17.4)	4 (17.4)
Non-smoker, but has been, n (%)	9 (39.1)	13 (56.5)	12 (52.2)
Family history of CVD, n (%)	14 (60.9)	16 (69.6)	16 (69.6)
Sedentarism, n (%)	13 (56.5)	19 (82.6)	19 (82.6)
Sleep < 5h, n (%)	6 (26.1)	9 (39.1)	11 (47.8)
Current medication			
ACE inhibitor, n (%)	21 (91.3)	23 (100)	22 (95.7)
ARBs, n (%)	16 (69.6)	7 (73.9)	11 (47.8)
Antiplatelet, n (%)	22 (95.7)	22 (95.7)	23 (100)
CCBs, n (%)	2 (8.7)	5 (21.7)	5 (21.7)
Beta-blockers, n (%)	21 (91.3)	22 (95.7)	22 (95.7)
Diuretics, n (%)	2 (8.7)	4 (17.4)	6 (26.1)
Insulin, n (%)	5 (21.7)	5 (21.7)	11 (47.8)
Statin, n (%)	22 (95.7)	22 (95.7)	23 (100)

Note. ACEIs: indicates angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; BMI: body mass index; CCBs: Calcium channel blockers; CVD: Cardiovascular Diseases; HIIT: high-intensity interval training; MI: Myocardial Infarction; MICT: moderate-intensity continuous training; VO_2peak: maximal oxygen consumed. Data are reported as Mean ± Standard deviation or number and percent population (%).

In the exercise groups, 6 of the 8 SF-36 dimensions improved significantly after 6 weeks of the community-based exercise program in comparison to the control group. These dimensions encompassed physical functioning, role-physical, role-emotional, mental health, vitality, and general health (**Figure 7.4**). In contrast to the control group, HIIT and MICT participants reported superior QoL outcomes at all assessment time points, except for the baseline measurement. Furthermore, within the community-based exercise programs, participants engaged in the HIIT regimen exhibited statistically significant temporal enhancements in physical functioning (p = .022) when juxtaposed with their counterparts in the MICT group, as depicted in **Figure 7.4**.

Figure 7.4.

Changes in scores of individual SF-36 dimensions both before and after 6 weeks of community-based exercise programs and control

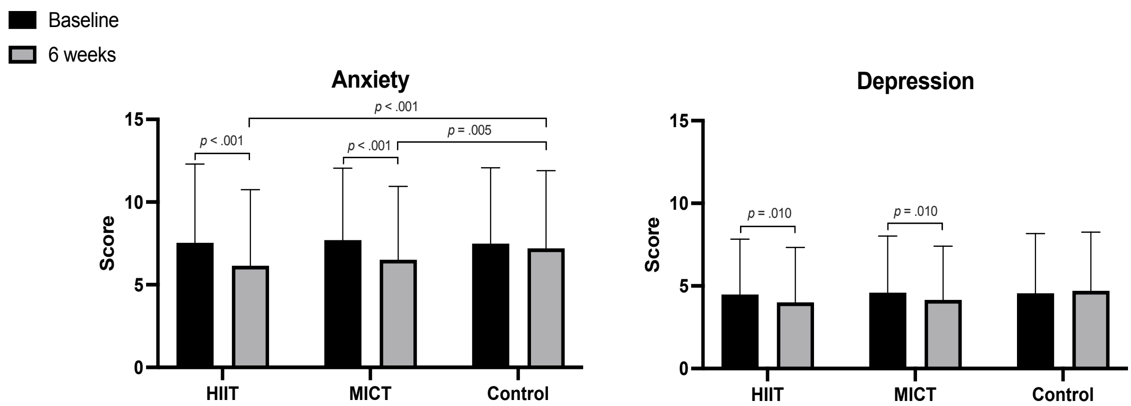


Note. Significant differences between baseline and 6 weeks (p < .05). Abbreviations: Control = Control group (n=23); HIIT = high-interval intensity training (n=23); MICT = moderate-intensity continuous training (n=23).

The ES calculated for changes from baseline to the 6-week mark revealed that, in the HIIT group, ES values were categorized as small for bodily pain (*d* = 0.2), medium for social functioning (*d* = 0.4), and large for physical functioning (*d* = 2.9), role-physical (*d* = 2.7), role-emotional (*d* = 1.6), mental health (*d* = 2.3), vitality (*d* = 1.9), and general health scores (*d* = 1.7). In contrast, within the MICT group, the ES were identified as small for bodily pain (*d* = 0.1), medium for social functioning (*d* = 0.3), and large for physical functioning (*d* = 2.5), role-physical (*d* = 1.7), role-emotional (*d* = 1.3), mental health (*d* = 1.8), vitality (*d* = 1.3), and general health scores (*d* = 1.0).

Figure 7.5.

Changes in scores of individual HADS dimensions before and after 6 weeks of community-based exercise programs and control



Note. Significant differences between baseline and 6 weeks ($p < .05$). Abbreviations: Control = Control group (n=23); HIIT = high-interval intensity training (n=23); MICT = moderate-intensity continuous training (n=23).

Anxiety scores were modestly elevated at baseline (mean HIIT = 7.5 ± 4.8, mean MICT = 7.7 ± 4.4 and mean control = 7.5 ± 4.6), demonstrating a subsequent decline following participation in the 6-week community-based exercise program within the exercise groups (mean HIIT = 6.2 ± 4.6 and mean MICT = 6.5 ± 4.4). Correspondingly, mirroring the trends observed for depression scores, a large subset of patients exhibited clinically elevated levels of depression scores at baseline (mean HIIT = 4.5 ± 3.4, mean MICT = 4.6 ± 3.4, and mean control = 4.6 ± 3.6), as illustrated in **Figure 7.5**. The frequency of clinically-elevated depression scores dropped following the completion of the 6-week community-based exercise program within the exercise groups (mean HIIT = 4.0 ± 3.3 and mean MICT = 4.2 ± 3.3). In contrast, the control group experienced an increase in depression scores (mean HIIT = 4.7 ± 3.6). The ES computed for the interval spanning from baseline to 6-week mark unveiled medium ES in depression scores (d = 0.4) and large ES in anxiety scores (d = 1.0) within the HIIT group. Similarly, the MICT group exhibited medium ES in depression scores (d = 0.4) and large ES in anxiety scores (d = 0.9) during this time frame.

7.3.1. Adherence and Safety

Only one patient from each group discontinued the intervention, achieving 96% adherence in both groups, HIIT and MICT protocols. There were no adverse events in either protocol (HIIT and MICT) during the exercise interventions. Thus, HIIT protocols proved to be a safe, effective, and pleasant tool for low-risk patients with CAD as well.

7.4. Discussion

In pursuit of our primary objective, this study examined the effects of community-based HIIT and MICT exercise protocols on the QoL and mental health, specifically anxiety and depression, among individuals who had experienced MI. Our comparative analysis, including a control group receiving no exercise program, uncovered substantial enhancements in QoL dimensions, with notable improvements in physical functioning, mental health, vitality, and general health within the HIIT and MICT groups. Moreover, both exercise groups exhibited significant reductions in anxiety and depression levels, highlighting the beneficial impact of structured exercise-based cardiac rehabilitation on psychosocial well-being and reinforcing the importance of these interventions in post-MI patient care.

Exercise's positive impact on post-MI mortality dates back to the 1950s, but its potential to enhance QoL has only recently gained recognition (Antonakoudis et al., 2006; Anderson et al., 2016; Munyombwe et al., 2020). While CR has shown QoL improvements in post-MI patients (Antonakoudis et al., 2006), most studies are limited by small sample sizes, cross-sectional designs, or a lack of longitudinal QoL assessments (Mollon & Bhattacharjee, 2017; Staniūtė & Brožaitienė, 2010; Bahall & Khan, 2018). This study, the first randomized controlled trial of its kind in Portugal, compares the effects of HIIT and MICT during a 6-week community-based exercise program with a control group following standard medical recommendations, shedding light on the potential benefits of these exercise modalities.

CVD significantly impacts an individual's QoL by increasing functional dependence (Cuerda et al., 2012). Our findings align with existing literature, reaffirming that exercise-based CR post-MI induces positive effects in QoL and all-cause mortality (Adams et al., 2017; Elshazly et al., 2018; Mora & Valencia, 2018). Multiple studies support the effectiveness of exercise-based CR in improving QoL and exercise capacity (Franklin et al., 2013; Korzeniowska-Kubacka et al., 2015; Tessitore et al., 2017). Lovlien et al. (2017) demonstrate that even low-intensity exercise-based CR can notably enhance health-related QoL in acute MI patients. Most previous systematic reviews have deemed QoL data for exercise-based CR to be insufficient or unsuitable for meta-analysis because of the significant heterogeneity (Anderson et al., 2016; Candelaria et al., 2020; Zheng et al., 2019; Worcester et al., 1993). In 2015, a systematic review of RCTs revealed QoL improvements in 14 out of 20 studies for MI patients undergoing exercise-based CR compared to usual care (Anderson et al., 2016). A 2018 meta-analysis (41 RCTs, N=11 747), spanning studies from 1975 to 2017, indicated a modest positive effect of exercise-based CR on QoL. However, it favored 'psychosocial management' as more effective overall (Francis et al., 2019). Subsequently, a 2019 systematic review of 14 RCTs, encompassing 1739 individuals with post-acute coronary syndrome, reported clinically significant positive effects on SF-36 domains at 6 months (role physical and general health) and one domain at 12 months (physical function) (Candelaria et al., 2020). Furthermore, a 2019 meta-analysis highlighted the effectiveness of exercise in reducing anxiety and depression following MI (Zheng et al., 2019). Comparatively, a study found that the QoL improvement from 11 weeks of low-intensity MICT paralleled that of HIIT during the early stages of acute MI (Worcester et al., 1993). In a RCT involving MI patients, both aerobic interval training and usual care rehabilitation improved serum adiponectin, endothelial function, and QoL, and reduced resting heart rate and serum ferritin. However, only aerobic interval training elevated high-density lipoprotein cholesterol, which holds potential benefits (Moholdt et al., 2912). Lastly, in a cohort study, 37 MI patients (mean age, 66 years) who underwent a 5-week CR program demonstrated improvements in QoL, exercise capacity, and autonomic modulation (Fallavollita et al., 2016).

Anxious and depressive symptoms have been associated with a greater risk of subsequent cardiac events (Huffman et al., 2013; Barth et al., 2004; Nicholson et al., 2006; Celano et al, 2015; Emdin et al., 2016; Gan et al., 2014). It was already established that an exercise-based CR program contributes to diminished levels of anxiety and depression (Freitas et al., 2011; Lavie & Milani, 2004). Our study's HIIT and MICT groups demonstrated significant improvements in anxiety and depression symptoms, with no discernible difference between the two training modalities. Conversely, both exercise protocols markedly ameliorated anxiety in comparison to the control group, which experienced an increase in mental health scores post-intervention, emphasizing the potential detriment of forgoing community-based exercise programs post-MI. These findings underscore the significant role of exercise-based programs, coupled with multidisciplinary support, in enhancing anxiety and depression levels among CR patients. Notably, Bakker et al (2021) noted that anxiety correlated with higher self-reported sedentary behavior in CVD patients, suggesting a need for further investigation into the interplay between depression, anxiety, and sedentary behavior in CR. Previous studies have consistently demonstrated that exercise-based CR improves psychosocial functioning (Lavie et al., 2016; Lavie & Milani, 2006) and QoL (Anderson et al., 2016). Furthermore, meta-analysis and systematic reviews have reported that structured exercise-based CR programs are associated with small-to-moderate reductions in depressive symptoms (Celano et al, 2015; Emdin et al., 2016; Gan et al., 2014; Kachur et al., 2016).

Regarding patient adherence, it's notable that only one patient in each group discontinued the intervention, resulting in a remarkable adherence rate of 96% for both the HIIT and MICT protocols. In terms of patient safety, there were no adverse events in either protocol (HIIT and MICT) during the exercise interventions. Thus, our study underscores that HIIT protocols are not only safe but also effective and well-received by MI patients. Our study's strengths lie in its randomized design, use of objective outcome measures, and blinded assessors. Furthermore, the individualized training intervention, maintaining consistent relative intensity following the HIIT principle, adds value. Importantly, our study's positive efficacy findings are encouraging, particularly given the significant improvements achieved within a relatively short six-week duration, involving three sessions per week, totaling 18 sessions per patient.

7.4.1. Study Limitations

Several limitations warrant acknowledgment in this study. Firstly, the small sample size could mean that only greater differences would reach the significance level. Secondly, only 13-17% of the patients in this study were women. This sex bias was an unintended consequence of our clinical population but constitutes a limitation of the generalizability of the results. When considering the results of this study, the possible confounding effects of concurrent medications should be considered although no change happened during the study period for doses of lipid-lowering and heart rate control medications. Additionally, the control group did not provide activity diaries, making it impossible to assess their physical activity levels during the 6-week intervention period from baseline, which could have influenced the observed effects.

7.5. Conclusions

In summary, our randomized controlled study demonstrated the safety and effectiveness of both 6-week HIIT and MICT programs in improving patients' health-related quality of life and reducing anxiety and depression following myocardial infarction. Conversely, individuals who did not engage in a community-based exercise program post-MI did not exhibit similar improvements in these variables. Notably, the absence of adverse events underscores HIIT as a valuable adjunct or alternative to MICT in community-based exercise programs, serving as a crucial treatment strategy for post-MI patients. Our data emphasize the vital role of community-based exercise programs in enhancing the quality of life and supporting mental health recovery post-MI.

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CHAPTER 8

Paper 6: Comparing High-Intensity versus Moderate-Intensity Exercise Training in Coronary Artery Disease Patients: a Randomized Controlled Trial with 6- and 12-Month Follow-up

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Paper 6: Comparing High-Intensity versus Moderate-Intensity Exercise Training in Coronary Artery Disease Patients: a Randomized Controlled Trial with 6- and 12-Month Follow-up

Chapter overview

The previous Chapter showed that both exercise programs proved equally effective in enhancing the quality of life and mental health among CAD patients, with the HIIT group showing additional improvements relative to MICT. Importantly, our findings emphasize that abstaining from exercise-based programs post-CAD correlates with inferior outcomes in QoL, anxiety, and depression scores.

However, despite the demonstrable favorable outcomes in the previous Chapter and Chapters 5 and 6 of both MICT and HIIT within community-based exercise CR programs, many individuals fail to sustain their exercise regimens upon CR completion. The maintenance of PA is a critical facet that remains understudied, particularly in the prolonged context of CAD patients. It is plausible that any potential benefits accrued during CR participation might dissipate among patients who relinquish their established exercise routines.

This new Chapter examines the long-term effects of two exercise-based CR programs on physical activity, sedentary behavior, physical fitness, quality of life, and mental health in CAD patients.

The material presented in this Chapter has been peer-reviewed and is under review in the Journal of Public Health (Journal Impact Factor: 4.4).

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Research Article

Comparing High-Intensity versus Moderate-Intensity Exercise Training in Coronary Artery Disease Patients: a Randomized Controlled Trial with 6- and 12-Month Follow-up

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Abstract: *Aim:* This study aimed to investigate the long-term effects of two exercise-based CR programs on physical activity (PA), sedentary behavior (SB), physical fitness, quality of life (QoL), and mental health in coronary artery disease (CAD) patients.

Subject and Methods: Seventy-two CAD participants were randomized (1:1:1) into three groups: HIIT, MICT, and control group. Both training programs spanned 6 weeks with three supervised treadmill exercise sessions per week. MICT targeted ≈70-75% of peak heart rate (HR), while HIIT aimed for ≈85-95% of peak HR. The control group adhered to standard medical recommendations. Assessments at 6- and 12-months post-intervention included body composition, aerobic capacity, muscle strength, PA, SB, QoL, anxiety, and depression.

Results: Over the 6- and 12-month follow-up periods, both exercise groups maintained higher levels of aerobic capacity, QoL, and PA compared to baseline (p<.001). Body composition parameters, SB, and symptoms of anxiety and depression remained lower than baseline (p<.001). The HIIT group exhibited superior maintenance of post-intervention results compared to MICT. In contrast, the control group experienced deteriorations in body composition, SB, symptoms of anxiety and depression, along with a decline in aerobic capacity over time.

Conclusion: Encouraging CAD patients to maintain elevated PA levels can promote cardiovascular and mental health. Both CR exercise programs effectively reduced cardiovascular risk factors and induced favorable lifestyle changes. Notably, HIIT demonstrated sustained improvements surpassing those of MICT. These findings underscore the importance of structured exercise-based CR programs in optimizing long-term outcomes for CAD patients.

Keywords: Cardiovascular Diseases • Cardiovascular Risk Factors • Clinical Trials • High-Intensity Interval Training • Randomized Controlled Trial

8.1. Introduction

Coronary artery disease (CAD) is the main cause of death worldwide (Roth et al., 2019). Cardiac rehabilitation (CR) emerges as a pivotal constituent in the amelioration of morbidity and mortality rates associated with CAD (Stewart et al., 2017). The escalating incidence of cardiovascular diseases (CVD) and CR's essential role in cardiac event convalescence contribute to an increasing demand for CR programs (Turk-Adawi et al., 2019). Regrettably, global CR participation remains notably suboptimal, primarily attributed to restricted accessibility issues (Mamataz et al., 2021). In Portugal, less than 8% of survivors of any CAD enrolled in CR programs, and adherence is relatively poor among patients who do enroll in CR settings (Andrade et al., 2018).

Physical inactivity represents an autonomous risk factor in individuals afflicted with CAD (Stewart et al., 2017). Consequently, CR programs advocate adherence to public health guidelines for physical activity (PA) to enhance health outcomes, specifically targeting the attainment of a minimum of 150 minutes of moderate-to-vigorous intensity physical activity (MVPA) per week (Woodruffe et al., 2015). The nexus between PA, sedentary behavior (SB), cardiovascular risk factors, and health-related quality of life (QoL) within the ambit of CR remains enigmatic. Scarce studies have explored the correlation between PA, SB, and cardiovascular risk factors among CAD patients engaged in CR. Researchers who have gauged SB and PA have discerned that elevated SB levels correlate with diminished high-density lipoprotein (HDL) levels, reduced exercise capacity, and augmented triglyceride levels, body mass index (BMI), waist circumference, and anxiety (Bäck et al., 2013; Piepoli et al., 2014). Conversely, heightened PA levels are associated with reductions in triglyceride levels, blood glucose, BMI, waist circumference, depression, anxiety, and increases in HDL levels and QoL (Bäck et al., 2013; Piepoli et al., 2014; Hurdus et al., 2020). In a recent systematic review appraising PA and SB in the secondary prevention of CAD, augmented PA levels resulted in improved 6-minute walk test (6MWT) outcomes, enhanced QoL, and favorable blood glucose and lipid profiles (Vasankari et al., 2021). Moderate-intensity continuous training (MICT) has conventionally constituted the cornerstone of aerobic exercise prescription, targeting an intensity level within the range of 50–75% of heart rate (HR) (Piepoli et al., 2016). This approach yields both short- and long-term clinical benefits for CAD patients (Gonçalves et al., 2021). Nevertheless, approximately 30% of adults fail to comply due to time constraints, protracted duration and intricacy of these exercise regimens contribute to patient attrition (Hallal et al., 2012). Nonetheless, high-intensity interval training (HIIT) has recently emerged as an alternative or adjunct strategy to MICT. HIIT involves repeated bouts of higher intensity exercise (85–100%) interspersed with periods of lower-intensity recovery (Ito, 2019), and has been shown to be as effective, if not superior, to MICT in terms of enhancing clinical outcomes for CAD patients, encompassing improvements in body composition, VO_2peak, HR response to exercise, and myocardial function (Gonçalves et al., 2021; Taylor et al., 2020; Gonçalves et al., 2023). Importantly, HIIT also appears to offer a comparable level of safety to MICT, even for older participants in CR programs (Hannan et al., 2018; Rognmo et al., 2012).

Despite the demonstrable favorable outcomes of both MICT and HIIT within community-based exercise CR programs, a considerable proportion of individuals fail to sustain their exercise regimens upon CR completion, with merely one-third of patients adhering to regular PA at the 6-month post-CR evaluation (Bock et al., 2003). Maintenance of PA is a critical facet that remains understudied, particularly in the prolonged context of CAD patients. It is plausible that any potential benefits accrued during CR participation might dissipate among patients who relinquish their established exercise routines. The current investigation was undertaken to scrutinize the effects of two distinct six-week community-based exercise CR protocols, namely HIIT and MICT, on physical fitness, QoL, and psychological well-being. Additionally, this study aimed to juxtapose the exercise cohorts with a control group devoid of any interventions and to evaluate the long-term dynamics of lifestyle alterations and cardiovascular risk factors among patients.

8.2. Methods

This study is a single-blinded randomized controlled trial (RCT) and followed the CONSORT guidelines for RCTs (http://www.consort-statement.org).

8.2.1. Participants

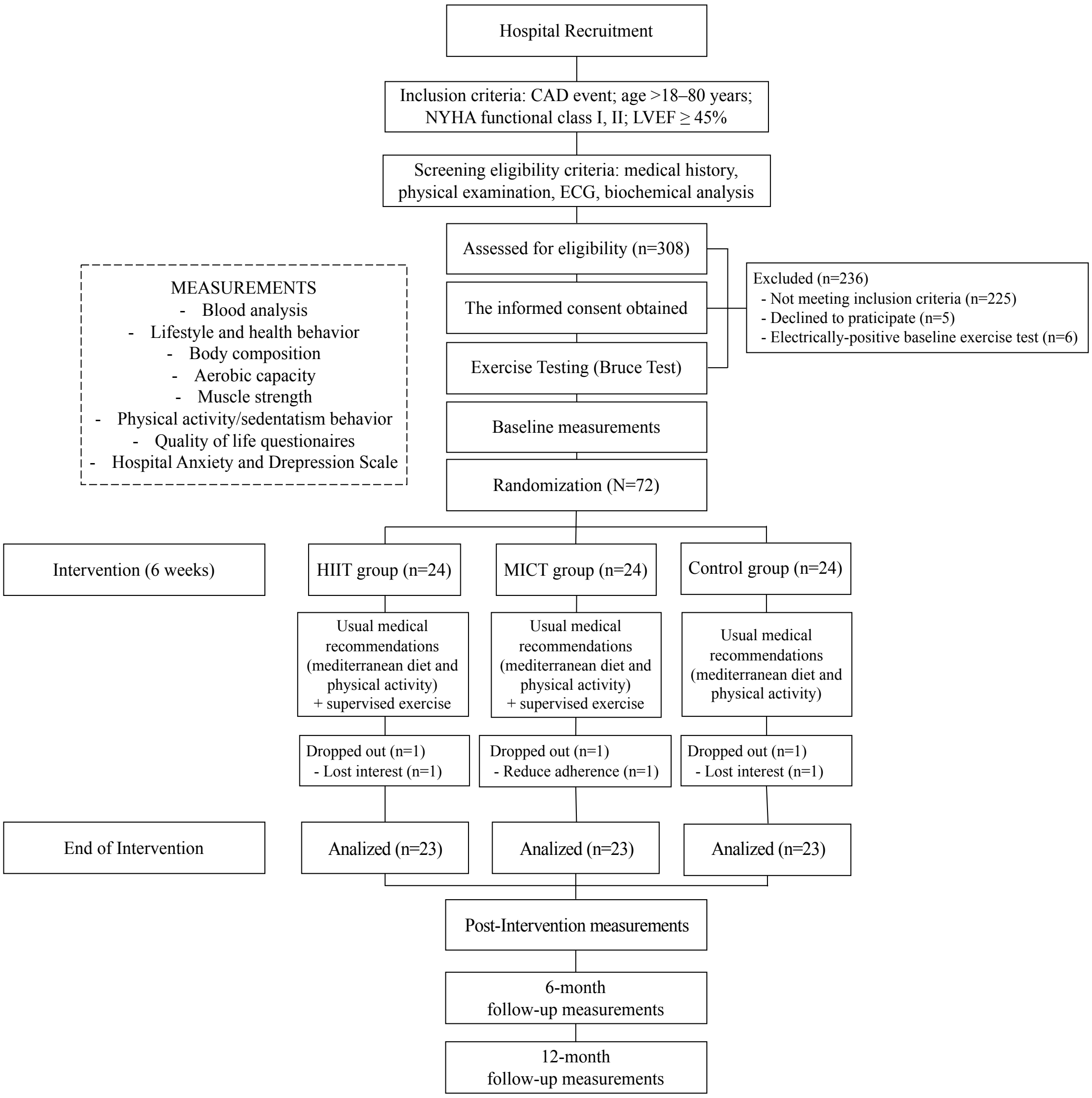
Participants were recruited between March 2018 and November 2021 within the cardiology unit of the Hospital do Espírito Santo de Évora, Portugal. All patients who had undergone a coronary event and were referred by their cardiologist to the community-based exercise CR programs, 2 months after angioplasty, were evaluated for inclusion in this study. The inclusion criteria were age 18–80 years, left ventricular ejection fraction ≥ 45%, and New York Heart Association (NYHA) functional Class I or II. Patients were excluded from the study if the following criteria were met: severe exercise intolerance; uncontrolled arrhythmia; uncontrolled angina pectoris; severe kidney or lung diseases; musculoskeletal or neuromuscular conditions preventing exercise testing or training; and signs or symptoms of ischemia. Recruitment ended when the sample size for the primary outcome was attained. All participants completed a medical history and health questionnaire and provided written informed consent.

8.2.1.1. Randomization and masking

The sample size was calculated using the online *G*Power software*, considering an effect size of 0.3, a predefined sample power of 0.8, a predefined error probability defined as 0.05, and statistical power of 95% (El Maniani et al., 2016). Hence, a minimum sample size of 66 participants was determined (22 participants for each group) to identify significant changes. The number of participants was increased to cover an expectable dropout rate. After the baseline assessment and before the start of training protocols, the 72 participants were randomly assigned in a 1:1:1 allocation ratio to one of three groups: HIIT, MICT (traditional), and control (usual medical recommendations) (**Figure 8.1**). To ensure allocation concealment, participants in each group were seen at a specific, prescheduled time, and appointments for each group did not coincide with appointments for any participants in either of the other groups. The three groups were similar regarding age, the extent of coronary artery disease, coronary risk factors, type of coronary event or left ventricular ejection fraction). Whereas patients and physicians allocated to the intervention group were aware of the allocated arm, outcome assessors and data analysts were kept blinded to the allocation.

Figure 8.1.

Diagram of the study



Note. HIIT = high-intensity interval training; LVEF = left ventricular ejection fraction; MICT = moderate-intensity continuous training; NYHA = New York Heart Association.

Following health screening, 72 cardiac participants were enrolled in the study and allocated to one of three groups: (1) HIIT; (2) MICT, who did participate in formal exercise training and (3) control, who did not participate in any exercise program training.

8.2.2. Outcome measures and assessments

8.2.2.1. Exercise testing

Initially, the participants were submitted to a clinical evaluation performed by a cardiologist. A supervised graded exercise test to record volitional fatigue, risks or symptoms of ischemia was performed on a treadmill with the Bruce protocol before the six-week intervention period. The test was done in non-fasting conditions and under medication. Electrocardiography was recorded continuously, and blood pressure was measured with an arm cuff every 3 minutes. Functional capacity in metabolic equivalent value (METs) was calculated. As a high proportion of participants with CAD are prescribed beta-blocker therapy, this relative method of exercise intensity considers the likely lower HRpeak achieved by these participants during the exercise test. To ensure training exercise intensity was reflective of medication effects, all participants were instructed to take their usual medications before the maximal exercise test.

8.2.2.2. Blood Biomarkers

Blood samples were drawn on the same day as exercise testing but were collected before exercise. All final blood samples were obtained 24-48 hours after completion of the last exercise session. Levels of biomarkers: high-sensitive C-reactive protein (hsCRP), fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol, low- and high-density lipoprotein cholesterol (LDL-C and HDL-C) and triglycerides (TG) were collected. Blood samples were collected at baseline and at the end of the study.

8.2.2.3. Risk Factor Screening

On the second visit, the participants were submitted to a clinical evaluation of resting heart rate, blood pressure, medical history, body composition, aerobic capacity, muscle strength, PA and SB, QoL, anxiety and depression tests, performed by a physiologist at the laboratory of the University of Évora. Participants were asked to bring any medications that they were taking to the assessments. Initially, each participant completed a standardized questionnaire including demographic data, medical history, medication use, family history of CVD, and smoking status. They also completed the patient-reported QoL questionnaire and the Hospital Anxiety and Depression Scale (HADS). The QoL questionnaire consisted of the rating scale, Short Form 36 (SF-36; Quality Metric, Lincoln, Rhode Island, USA). As physical functioning, role functioning limitations due to physical problems, bodily pain, and general health domains of the SF-36 instrument are the most relevant for describing the health status of patients with CVD, the present analysis was restricted to these four domains. For all reported QoL instruments, higher scores correspond to better QoL as perceived by the patient (Ware & Sherbourne, 1992). The HADS questionnaire has been widely used to screen depression among cardiac patients in the hospitals. The HADS questionnaire has 2 subscales including anxiety and depression, each of which comprised of items rated on 4-point Likert scales (Herrero et al., 2003). The total HADS score ranged between 0-42 with 0-14 being considered as low, 15-28 considered as moderate, and 29-42 being considered as high. For each subscale (anxiety and depression subscales), the scores ranged between 0 to 21, where 0-7 was considered low, 8-14 being moderate, while 15-21 was considered high. After completing the health questionnaires, the participant's blood pressure, height, weight, and waist circumference were recorded.

The participants' height (to nearest 0.5 cm) and weight (to nearest 0.1 kg) were measured. Body mass index (BMI) was calculated directly by the standard formula: $weight(kg)/height(m)^2$. The waist circumference (WC) (to nearest 0.5 cm) was measured three times on the midpoint of the lowest rib and the iliac crest, and the mean of measurements was used in analyses (Liguori 2020). Body composition was then assessed by dual-energy x-ray absorptiometry (DXA). DXA scans were performed with QDR 2000 densitometers (DXA, Hologic QDR, Hologic, Inc., Bedford, MA, USA), using the array beam mode. The DXA scans were performed within 1 week before starting and 1 week after the completion of 18 community-based exercise CR sessions. Scans were used to measure total body mass, body fat mass, body lean mass, body fat percentage, and abdominal region fat percentage (defined as the area between the ribs and the pelvis by GE Healthcare systems). Percentages of the total were calculated accordingly. The scanner was calibrated daily against a manufacturer-supplied standard calibration block to control for possible baseline drift.

Aerobic capacity was represented as peak oxygen consumed (VO_2peak, $mL\text{-}kg^{-1}\text{-}min^{-1}$) that was calculated from the equation $VO_2peak = 4.9486 + 0.023 * walk\ distance\ (meters)$ that was determined via using 6-minute walking test (6MWT) as described previously (ACSM, 2013). The 6MWT was performed in a 50m pre-marked University of Evora pavilion, and instructions and encouragements were given following the test's guidelines (Guyatt et al., 1985). This test is well validated for CAD patients and has shown good reliability in this patient group (McDermott et al., 2014).

To measure the isokinetic muscle strength, we used the Isokinetic Dynamometer (Biodex®, System 3 Pro, Biodex Corp., Shirley, NY, USA). The protocol used was the concentric unilateral mode for the extensor and knee-dominant flexor muscles. Patients were tested in a seated position with hip flexion. Stabilization straps were applied to the trunk, waist, and thigh. Evaluations of peak torque (three repetitions) and fatigue resistance (20 repetitions) were carried out at angular velocities of 90°/s and 180°/s of the dominant knee. The peak torques of the knee extensor and flexor muscles were adjusted by body weight according to the following formula: *strength (Nm) × 100/body weight (kg)*, since it is well known that the peak muscle power is closely associated with body weight (Maffiuletti et al., 2007).

After completing all clinical evaluations, patients were asked to wear a triaxial accelerometer (ActiGraph GT3X) on their hip placed anterior to the right iliac crest for seven consecutive days during waking and sleeping hours except when bathing or swimming. Acceleration data from the three planes were processed with ActiGraph software (ActiLife, version 6) using 15-s epochs (raw data recorded at 30 Hz) and the standard filter and were integrated into a vector magnitude count by taking the square root of the sum of squared axes (vertical, anterior–posterior, and medial–lateral). Daily averages (min/day) of accelerometer-measured PA were calculated for each patient and classified into five activity levels (sedentary time 1.00–1.99 MET, light PA 2.00–3.49 MET, and all activity ≥ 3.50 MET was classified as moderate-to-vigorous PA) using the limits set by the manufacturer. A valid day was defined as ≥ 10 hours of wear time. All activity with intensities 1 MET (1 Met = 3,5 ml-kg^{-1}-min^{-1}) or higher was calculated on wear time. Patients with at least four valid days (3 weekdays and 1 weekend day) were included in the analyses (monitor wear time of ≥ 600 min/day) (Prince et al., 2015).

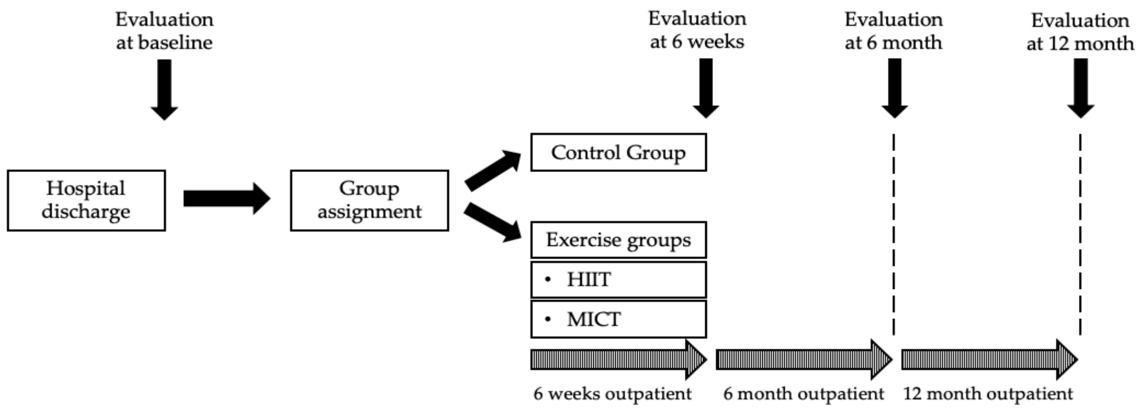
All measurements were taken at the beginning and completion of 18 sessions of community-based exercise CR programs. The protocols of pre- and post-intervention were the same for each patient. Compliance and adherence to exercise training was determined by recording the number of sessions attended.

8.2.3. Exercise training protocols

After hospital discharge, educational intervention, dietary advice, and psychological support were performed in all participants. The exercise programs consisted of 6 weeks of supervised treadmill exercise, three sessions per week (**Figure 8.2**). If a session was missed, it was made up that week or the following week. Participants performed each exercise session in a group, including a maximum of three participants per session.

Figure 8.2.

Study design and time frame



Note. HIIT = high-intensity interval training; MICT = moderate-intensity continuous training.

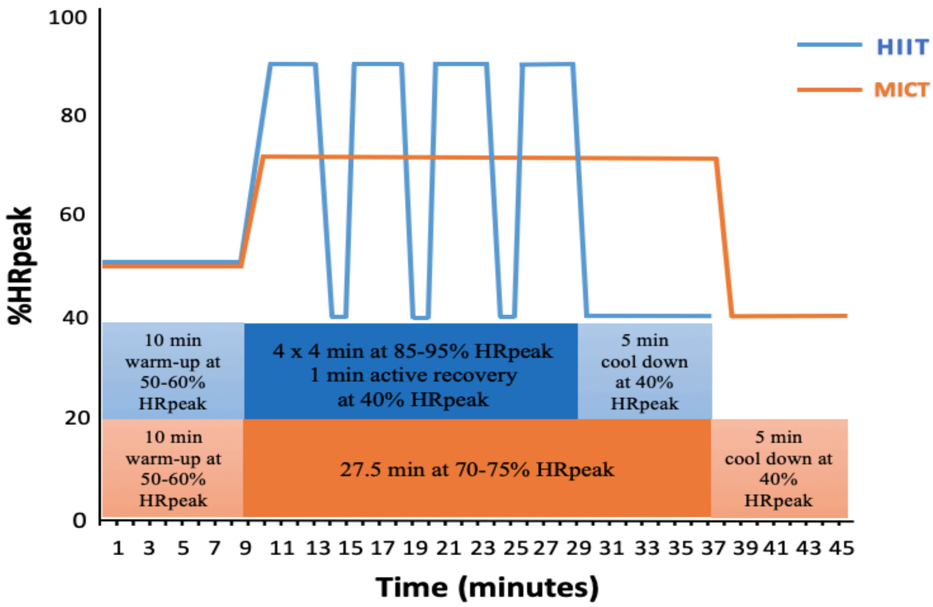
Training sessions were supervised by a physiologist. As training intensity increased, the participant's heart rate, rate of perceived exertion (Borg scale), and cardiac symptoms were also taken into consideration. Heart rates were observed with *Polar heart rate* monitoring (Polar Electro Oy, Kempele, Finland), and blood pressure was measured at the commencement and the end of each session.

The 10-point Category-Ratio Borg Scale (Scherr et al., 2013), also commonly referred to as the Rating of Perceived Exertion, was used to assess participants' perceived effort during exercise. The Borg Scale is a 10-point scale ranging from 0 to 10 with anchors ranging from ''No exertion at all'' (0) to ''Maximal exertion'' (10). Participants were asked to rate their exertion before (pre-exercise), immediately post minute to minute and post-exercise. Buchheit & Laursen (2013) demonstrated that the RPE (Borg Scale) has shown a great correlation with HR, ventilation, and VO_2 in individuals with and without CAD, and the correlation is not impacted by beta-blocker medication, a commonly used HR modulating medication by patients with CAD. Participants' heart rate was recorded using Polar heart rate monitors minute to minute of exercise. The control group did not receive any additional follow-up regarding exercise beyond general advice on the importance of exercise and diet.

Each training session was initiated with a 5–10-minute warm-up at 50-60% HRpeak and ended with 5 minutes of cool-down at 40% HRpeak. The HIIT group performed 4 × 4-minute high-intensity intervals at 85%–95% HRpeak followed by a 1-minute recovery interval at 40% HRpeak, predicted with a supervised graded exercise test on a treadmill with the Bruce protocol (Bires et al., 2013). During the exercise, the participants were motivated to gradually increase their exercise intensity towards 6–9 (hard to very hard) on a 0 to 10 Borg scale. The MICT protocol (usual care) consisted of a continuous bout of moderate-intensity exercise to elicit 70–75% HRpeak, rating of perceived exertion 3 to 5 (fairly light to somewhat hard), for 27.5 minutes to equate the energy expenditure with the HIIT protocol (**Figure 8.3**).

Figure 8.3.

Summary of the exercise training protocol



Note. HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; min = minutes; HRpeak = peak heart rate.

8.2.4. Ethical considerations

All work was conducted following the Declaration of Helsinki and registered at ClinicalTrials.gov (NCT03538119) on May 25, 2018. Ethics approval was obtained from the University of Evora Ethics Committee (reference number: 17039). All participants signed a written informed consent before participating in this study.

8.2.5. Statistical analyses

According to the Shapiro–Wilk and the Levene test results, repeated measures ANOVA assumptions were not met. Thus, non-parametric statistics were performed. The Friedman test was used for within-group comparisons, and the Kruskal–Wallis test was used for between-group comparisons. Pairwise post hoc tests were also carried out when significant differences were found. Lastly, the Wilcoxon test was performed to compare paired fall data between the baseline and the post-intervention. The means and standard deviations were calculated for all variables. The variation value was calculated between the baseline, post-intervention, and follow-up evaluations as Δ: *moment* $_{x}$ – *moment* $_{x-1}$. For significant differences between the evaluation moments, the respective delta percentage was also computed by the following formula: *(Δ%: [(moment* $_{x}$ *– moment* $_{x-1}$*) / moment* $_{x-1}$*] × 100)*. The effect size (ES) was calculated using Cohen's method since the data were not normally distributed (Cohen, 2013). The ES was computed and classified based on Cohen's thresholds (small: $d = 0.10$; medium: $d = 0.30$; and large: $d \geq 0.50$) (Cohen, 2013). Analyses were performed using the SPSS software package (version 24.0 for Macbook, IMB Statistics). A value of $p \leq .05$ was considered statistically significant for all analyses. A code was assigned to each participant to preserve their anonymity.

Based on guidelines, dyslipidemia was defined as an HDL-C level < 50 mg/dL in women or < 40 mg/dL in men and a TG level ≥ 150 mg/dL (Wilson et al., 2019). The cutoff for elevated hsCRP was ≥ 3.0 mg/L, according to national guidelines (Pearson et al., 2003). Criteria of diabetes mellitus diagnosis was defined according to the American Diabetic Association's diagnostic criteria (Rey & Hawks, 2022): pre-diabetic stage [HbA1c 5.7–6.4 / impaired fasting blood glucose (100–125 mg/dL)] and diabetes mellitus (HbA1c ≥ 6.5 /fasting glucose ≥ 126 mg/dL). Impaired non-fasting glucose was defined as a glucose value ≥ 100 mg/dL, based on the American Diabetes Association (2003) expert recommendations. Overweight was defined as a BMI 25.0 to 29.9 kg/m^2, and obesity was defined as a BMI ≥ 30 kg/m^2 (Liguori, 2020). WC was measured by a trained examiner using a standard protocol. In this study, increased WC was defined as > 80 cm in women and > 94 cm in men (Sardinha et al., 2012).

8.3. Results

Baseline characteristics (**Table 8.1**) were not different for HIIT, MICT and control groups: age (50 ± 9 vs. 55 ± 10 vs. 57 ± 11 years respectively, $p = .180$), female (15% vs. 17% vs. 15%, $p = .211$), BMI (28.2 ± 4.5 vs. 29.4 ± 3.9 vs. 29.4 ± 4.3 kg/m^2, $p = .659$), waist circumference (98.4 ± 14.5 vs. 101.1 ± 10.3 vs. 101.1 ± 10.8 cm, $p = .218$) and VO_2max (34.7 ± 9.0 vs. 30.4 ± 6.3 vs. ± 23.5 ± 11.0 mL/kg/min $p = .290$). Comorbidities and medications were also not different between groups ($p > .05$).

Table 8.1.

Participant characteristics at baseline

	Community-based program		No community-based program
	HIIT (n=23)	MICT (n=23)	Control (n=23)
Demographics			
Age (years), mean ± SD	50 ± 9	55 ± 10	57 ± 11
> 70 years, n (%)	2 (8.7)	3 (13.0)	4 (17.4)
Gender (Male/Female)	20/3	19/4	20/3
Retired, n (%)	2 (8.7)	7 (30.4)	7 (30.4)
Anterior MI, n (%)	3 (13.0)	4 (17.4)	2 (8.7)
Coronary event/intervention			
CABG, n (%)	1 (4.3)	1 (4.3)	1 (4.3)
PCI, n (%)	22 (95.7)	22 (95.7)	22 (95.7)
Blood biomarkers, mean ± SD			
Total cholesterol (mmol/L)	175 ± 35.2	173 ± 38.5	171 ± 32.8
HDL-C (mmol/L)	43 ± 6.7	43 ± 9.0	40 ± 9.1
LDL-C (mmol/L)	117 ± 38.0	120 ± 45.1	117 ± 50.4
Triglycerides (mmol/L)	200 ± 60.6	187 ± 91.7	188 ± 78.0
FBG (mg/dL)	118 ± 28.3	114 ± 20.2	122 ± 25.0
HbA1c (%)	6.1± 1.3	5.8 ± 0.6	6.2 ± 0.9
hsCRP (mg/L)	1.5 ± 1.7	1.1 ±1.1	1.3 ± 0.8
Risk factors or comorbidities			
Diabetes mellitus, n (%)	10 (43.5)	9 (39.1)	10 (43.5)
Hypertension, n (%)	13 (56.5)	13 (56.5)	14 (60.9)
Dyslipidemia, n (%)	14 (60.9)	15 (65.2)	15 (65.2)
Body Mass index (kg/m^2), mean ± SD	28.2 ± 4.5	29.4 ± 3.9	29.4 ± 4.3
Waist Circumference (cm), mean ± SD	98.4± 14.5	101.1 ± 10.3	101.1 ± 10.8
SBP (mm Hg), mean ± SD	135 ± 12.1	135 ± 13.3	139 ± 6.1
DBP (mm Hg), mean ± SD	95 ± 11.6	94 ± 9.6	95 ± 6.3
Active smoker, n (%)	6 (26.1)	4 (17.4)	4 (17.4)
Non-smoker, but has been, n (%)	9 (39.1)	13 (56.5)	12 (52.2)
Family history of CVD, n (%)	14 (60.9)	16 (69.6)	16 (69.6)
Sedentarism, n (%)	13 (56.5)	19 (82.6)	19 (82.6)
Sleep < 5h, n (%)	6 (26.1)	9 (39.1)	11 (47.8)
Current medication			
ACE inhibitor, n (%)	21 (91.3)	23 (100)	22 (95.7)
ARBs, n (%)	16 (69.6)	7 (73.9)	11 (47.8)
Antiplatelet, n (%)	22 (95.7)	22 (95.7)	23 (100)
CCBs, n (%)	2 (8.7)	5 (21.7)	5 (21.7)
Beta-blockers, n (%)	21 (91.3)	22 (95.7)	22 (95.7)
Diuretics, n (%)	2 (8.7)	4 (17.4)	6 (26.1)
Insulin, n (%)	5 (21.7)	5 (21.7)	11 (47.8)
Statin, n (%)	22 (95.7)	22 (95.7)	23 (100)

Note. ACEIs = Indicates angiotensin-converting enzyme inhibitors; ARBs = Angiotensin II receptor blockers; BMI = body mass index; CABG = Coronary artery bypass grafting; CCBs = Calcium channel blockers; CVD = Cardiovascular diseases; HIIT = High-intensity interval training; MI = Myocardial Infarction; MICT = Moderate-intensity continuous training; PCI = Percutaneous coronary intervention; VO_2peak = Maximal oxygen consumed. Data are reported as Mean ± Standard deviation or number and percent population (%).

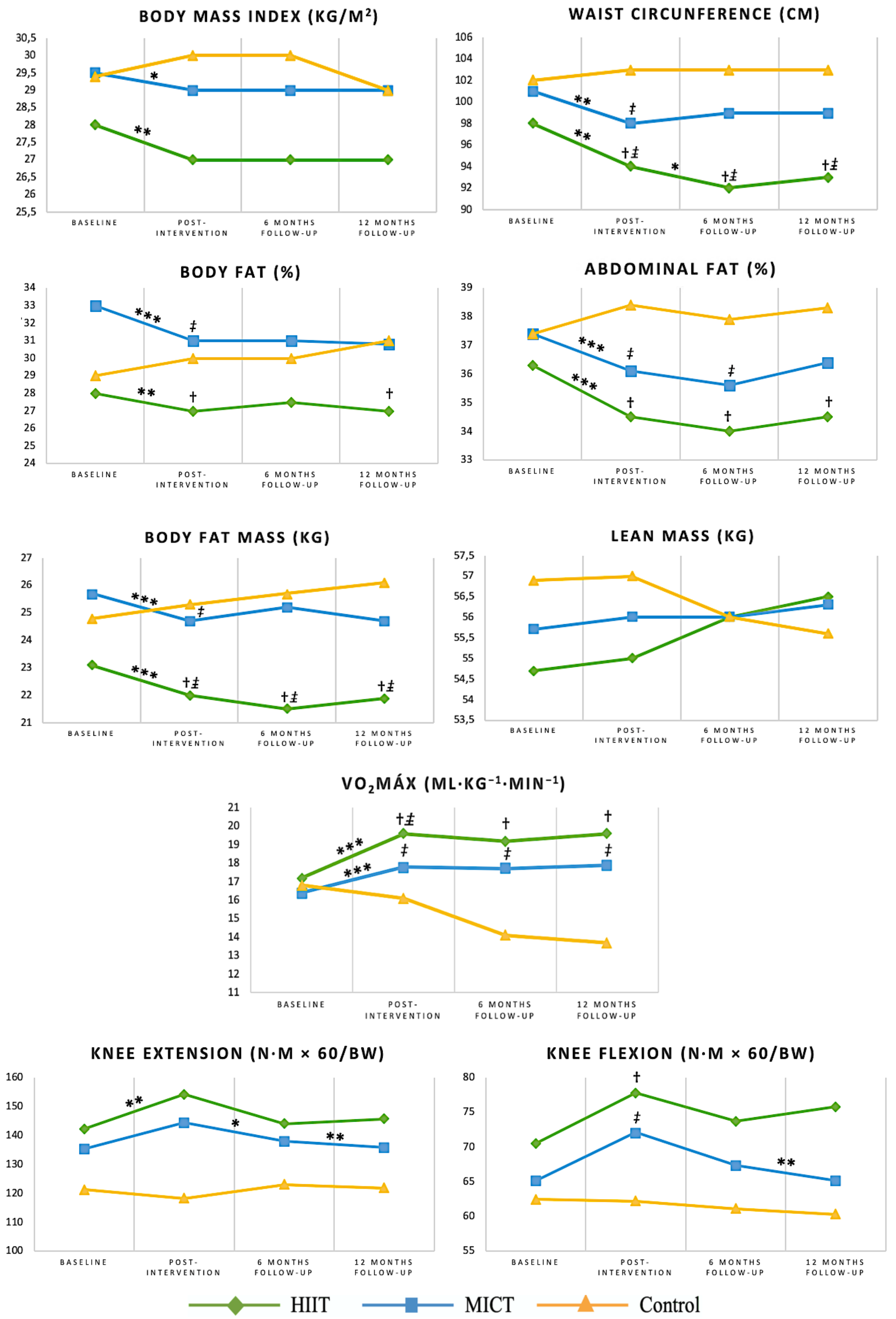
8.3.1. Physical fitness (body composition, aerobic capacity, and muscle strength)

Longitudinal changes in physical fitness levels are shown in **Figure 8.4**. At baseline, there were no differences across groups at the body composition measurements. Following 6 weeks of exercise, the results showed that the HIIT group demonstrated greater improvements compared to MICT in waist circumference ($\Delta_{m2-m1\%}$ HIIT: 4.1%, $p = .002$ vs. $\Delta_{m2-m1\%}$ MICT: 2.5%, $p = .002$) and body fat mass ($\Delta_{m2-m1\%}$ HIIT: 4.5%, $p < .001$ vs. $\Delta_{m2-m1\%}$ MICT: 3.2%, $p < .001$). The Control group had no improvements, on the other hand, all values of body composition measurements increased over time. These results were only maintained at 6 months of follow-up in HIIT group, which demonstrated a significant decreasing trend in waist circumference ($\Delta_{m3-m2\%}$: −2cm, $p = .033$) compared to MICT ($p = .016$) and Control ($p = .001$), and maintained at 12 months of follow-up with significant differences to MICT ($p = .018$) and Control ($p = .001$). There were also significant differences in body fat at 6 months in the HIIT group compared to the MICT ($p = .05$) and Control ($p = .047$) groups, as well as at 12 months compared to MICT ($p = .048$) and Control ($p = .028$) groups. The respective ES from baseline to 6 weeks were small in the HIIT group in body weight ($d = 0.20$), abdominal fat percentage ($d = 0.28$) and BMI ($d = 0.22$), and medium in waist circumference (d = 0.34). Moreover, in the MICT group, the ES were small in body fat percentage ($d = 0.22$), total body fat mass ($d = 0.22$) and waist circumference ($d = 0.22$). The ES between post-intervention and the 6- and 12-months follow-up were small in HIIT in lean mass ($d = 0.14$ and $d = 0.15$, respectively), and in MICT in body fat mass ($d = 0.11$ and $d = 0.10$, respectively).

Following the 6 weeks of the supervised program, aerobic capacity significantly increased by 14% with HIIT (Δ_{m2-m1}: 2.5 ± 1.5 $ml \cdot kg^{-1} \cdot min^{-1}$, $p < .001$) and 9% with MICT (Δ_{m2-m1}: 1.4 ± 1.2 $ml \cdot kg^{-1} \cdot min^{-1}$, $p < .001$) (**Figure 8.4**). There were significant differences between the HIIT group and the MICT group at the end of the intervention, at 6 months and 12 months of follow-up. Moreover, the control group decreased the VO_2peak from the baseline to the end of the program ($p = .003$) and continued to decrease at 6 months ($p = .008$) and at 12 months ($p = .016$), with significant differences between the exercise groups at all evaluations ($p < .001$). The respective ES from baseline to 6 weeks were large in HIIT ($d = 1.54$) and MICT ($d = 0.68$), whereas those between post-intervention and the follow-up in HIIT were small at 6 months ($d = 0.25$) and medium at 12 months ($d = 0.34$).

Figure 8.4.

Impact of the community-based exercise CR programs on physical fitness indicators



Note. Control = Control group; HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; min = minutes; * *p*-value <.05, ** *p*-value <.01, *** *p*-value <.001; † significant differences between HIIT and Control, $p < .05$; ‡ significant differences between MICT and Control, $p < .05$; ‡significant differences between HIIT and MICT, $p < .05$.

The maximal strength of the knee extensors and flexors indicators can be seen in **Figure 8.4**. Descriptive analysis demonstrates an increase of 13% at 6 weeks in the knee extension peak torque in the HIIT group (Δ_{m2-m1}: 11.9 ± 27.6 N·m, $p = .007$) and 10% in the MICT group (Δ_{m2-m1}: 9.1 ± 22.8 N·m, $p = .061$). These results were only not maintained at follow-up evaluations in the MICT group, which demonstrated a significant decrease trend at 6 months (Δ_{m3-m2}: − 6.5 ± 17.8 N·m, $p = .022$), and at 12 months (Δ_{m4-m2}: − 8.6 ± 12.9 N·m, $p = .002$). The control group had a decrease of 0.4% (Δ_{m2-m1}: − 3.0 ± 22.8 N·m, $p = .835$) from the baseline to the end of the program and this trend was maintained throughout the follow-up evaluations. A positive increase between baseline and the 6 weeks was observed in the knee flexion peak torque of 15% in HIIT (Δ_{m2-m1}: 7.2 ± 14.2 N·m, $p = .002$) and 14% in MICT (Δ_{m2-m1}: 6.9 ± 16.0 N·m, $p = .022$). These results were again not maintained at follow-up assessments in the MICT group, which demonstrated a significant downward trend at 6 and 12 months (Δ_{m4-m2}: − 6.8 ± 11.0 N·m, $p = .007$) in this indicator. The control group decreased by a mean of 0.2% (Δ_{m2-m1}: − 0.3 ± 12.8 N·m, $p = .835$) from the baseline to the end of the program and maintained the tendency of decreasing in the follow-up evaluations. Significant differences were observed between the HIIT group and the control group in the knee extension peak torque after the intervention ($p = .025$), and in the knee flexion peak torque after the intervention ($p = .031$) and at 12 months of follow-up ($p = .028$). The respective ES in the knee extension peak torque (from baseline to 6 weeks were small in HIIT ($d = 0.24$) and MICT ($d = 0.20$), from post-intervention to 6-month follow-up the ES were small in HIIT ($d = 0.21$) and in MICT ($d = 0.15$), and from post-intervention to 12-month follow-up the ES were small in HIIT ($d = 0.19$) and in MICT ($d = 0.20$). The knee extension peak torque had a small ES from baseline to 6 weeks small in HIIT ($d = 0.29$) and medium in MICT ($d = 0.33$), from post-intervention to 6-month follow-up the ES were small in HIIT ($d = 0.18$) and medium in MICT ($d = 0.22$), and from post-intervention to 12-month follow-up the ES were medium in MICT only ($d = 0.35$).

8.3.2. Physical activity and Sedentary Behavior

Figure 8.5 presents the PA and SB of exercise and control groups. Following the 6 weeks supervised program, HIIT decreased the sedentary time of 15% (Δ_{m2-m1}: −148.6 ± 106.1 min/day, $p < .001$), MICT decreased 10% (Δ_{m2-m1}: −105.5 ± 88.0 min/day, $p <$

.001), and control decreased 0.1% (Δ_{m2-m1}: 0.559 ± 73.8 min/day, *p* = .144). The control group spent 176 min more sedentary time than HIIT (p < .001) and 72 min than MICT (*p* < .001). Regarding the PA, HIIT increased the daily step count of 33% (Δ_{m2-m1}: 4162.3 ± 8339.7 step count, *p* < .001), MICT increased 10% (Δ_{m2-m1}: 745.9 ± 1605.4 step count, *p* < .001) and control increased 6.5% (Δ_{m2-m1}: 265.5 ± 1524.4 step count, *p* = 1.000). In LPA, HIIT increased 39% (Δ_{m2-m1}: 80.1 ± 45.2 min/day, *p* < .001), MICT increased 30% (Δ_{m2-m1}: 55.6 ± 60.3 min/day, *p* < .001), and control increased 9% (Δ_{m2-m1}: 12.6 ± 65.5 daily step count, *p* = .532). In MVPA, HIIT improved significantly 54% (Δ_{m2-m1}: 16.4 ± 14.4 min/day, *p* < .001), MICT improved 45% (Δ_{m2-m1}: 13.4 ± 12.4 min/day, *p* < .001), and control improved 19% (Δ_{m2-m1}: 4.5 ± 13.7 step count, *p* = .033). Although, the control group had the amount of LPA 72.6 min lower than HIIT (*p* = .003), and the amount of MVPA was 38 min lower than HIIT (*p* < .001) and 17 min than MICT (*p* < .001).

Figure 8.5.

Impact of the community-based exercise CR programs on physical activity levels and sedentary behavior

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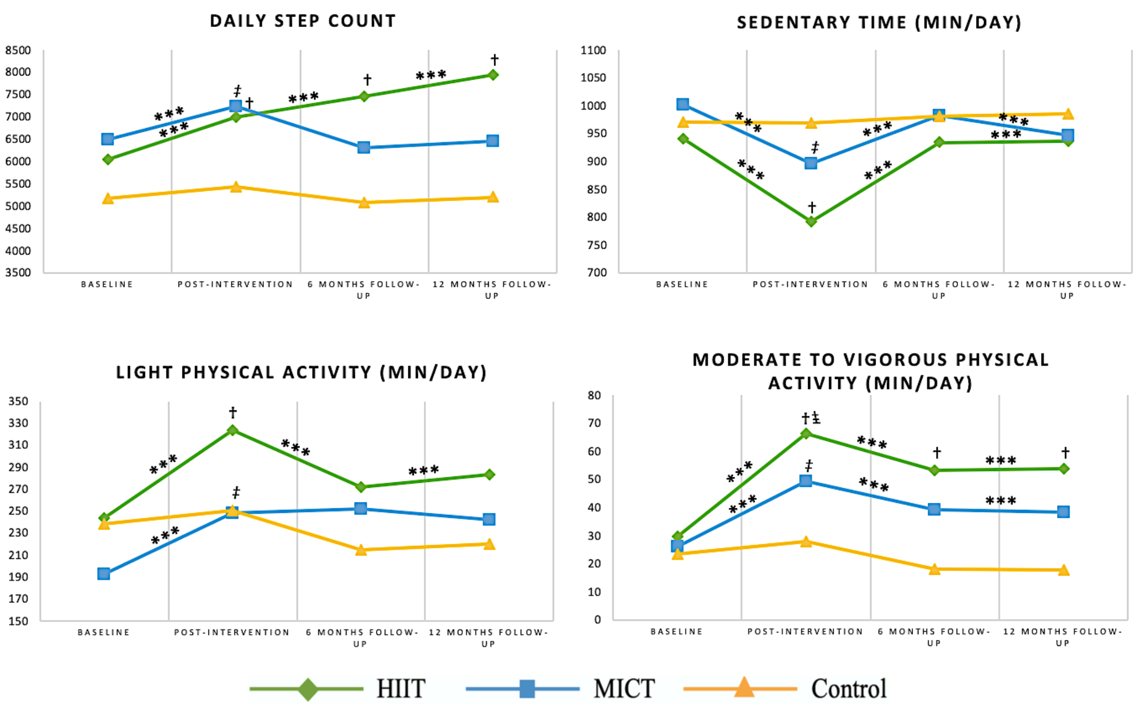


Note. Control = Control group; HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; min = minutes; * *p*-value <.05, ** *p*-value <.01, *** *p*-value <.001; † significant differences between HIIT and Control, p < .05; ‡ significant differences between MICT and Control, p < .05; significant differences between HIIT and MICT, p < .05.

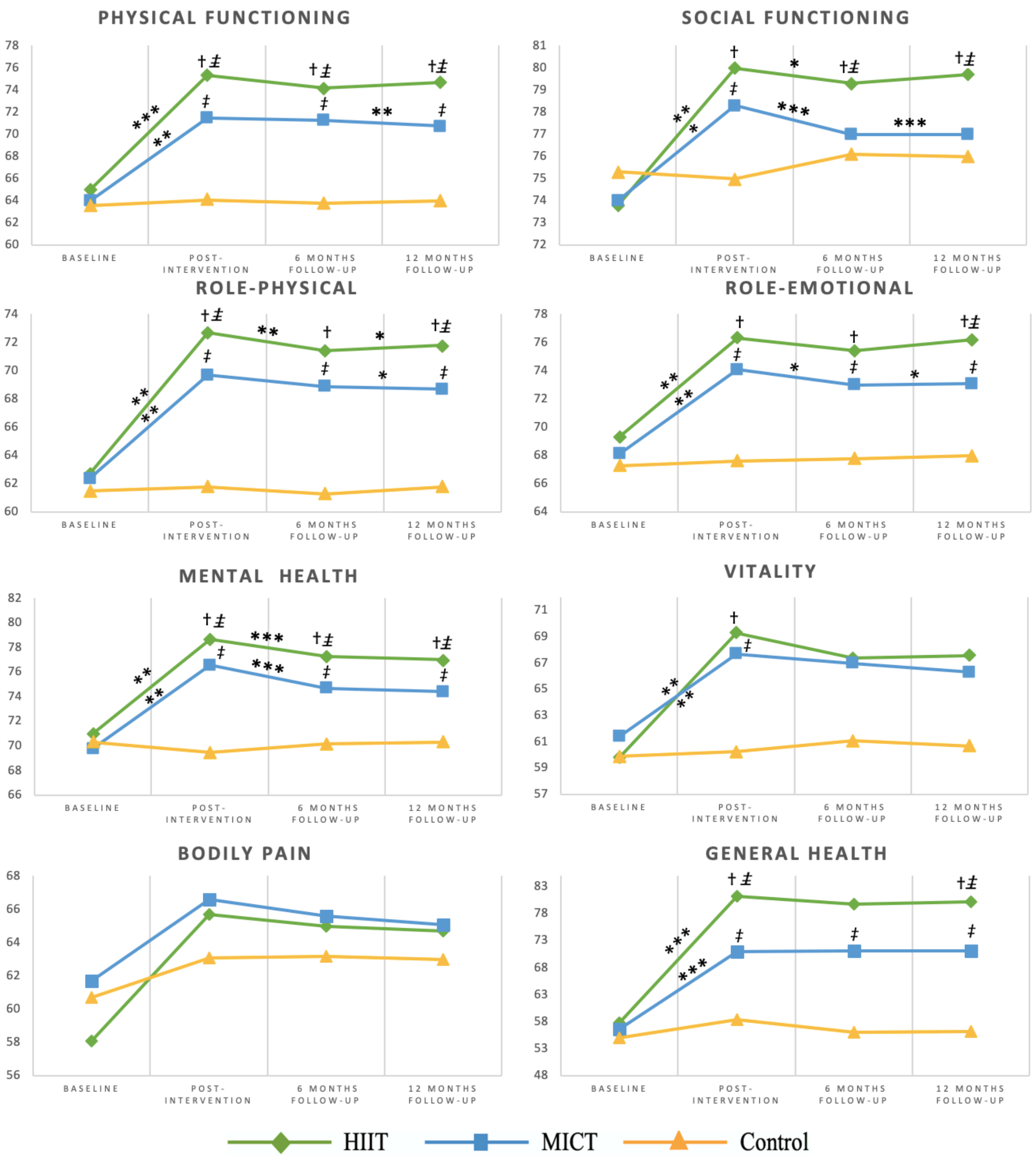
These results were not maintained at the follow-up evaluations in the exercise groups, which demonstrated a significant increasing trend in sedentary time at 6 months (Δ_{m3-m2} HIIT: 141.4 ± 127.9 min/day, $p < .001$ and Δ_{m3-m2} MICT: 86.0 ± 75.6 min/day, $p < .001$) and also at 12 months (Δ_{m4-m2} HIIT: 144 ± 151.6 min/day, $p < .001$ and Δ_{m3-m2} MICT: 50.0 ± 88.0 min/day, $p < .001$), but this results remaining lower than prior to participating in community-based exercise CR programs. In PA levels at 6 and 12 months, MICT maintained the amount of LPA from post intervention, but MVPA decreased significantly. The same was observed in the HIIT group with a decreasing trend in LPA and MVPA. The control group had a decrease in all PA indicators at 6 and 12 months of follow-up evaluations (**Figure 8.5**). Significant differences were observed between the exercise groups and the control group in sedentary time, MVPA and number of steps ($p < .001$) over time. The respective ES from baseline to 6 weeks in daily step count were small in HIIT (d = 0.26) and MICT (d = 0.27), in sedentary time were large in HIIT (d = 1.20) and MICT (d = 0.91), in LPA were large in HIIT (d = 1.01) and MICT (d = 0.67) and finally in MVPA were small in control (d = 0.20) and large in HIIT (d = 0.70) and MICT (d = 0.50).

8.3.3. Quality of Life

The control group reported a lower QoL compared to both the HIIT and MICT groups at all assessed time points, except for the baseline measurement. Within the exercise cohorts, there was a statistically significant enhancement observed in seven out of the eight SF-36 dimensions following six weeks of engagement in the community-based exercise CR programs, as compared to the control group. These improved dimensions encompassed physical functioning, role-physical, role-emotional, mental health, vitality, and general health. Furthermore, individuals who participated in community-based exercise CR programs, particularly in the HIIT group, exhibited noteworthy temporal ameliorations in physical functioning (p = .022) when juxtaposed with their counterparts in the MICT group, as illustrated in **Figure 8.6**.

Figure 8.6.

Impact of the community-based exercise CR programs on quality of life indicators



Note. Control = Control group; HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; min = minutes; * *p*-value <.05, ** *p*-value <.01, *** *p*-value <.001; † significant differences between HIIT and Control, p < .05; ‡ significant differences between MICT and Control, p < .05; significant differences between HIIT and MICT, p < .05.

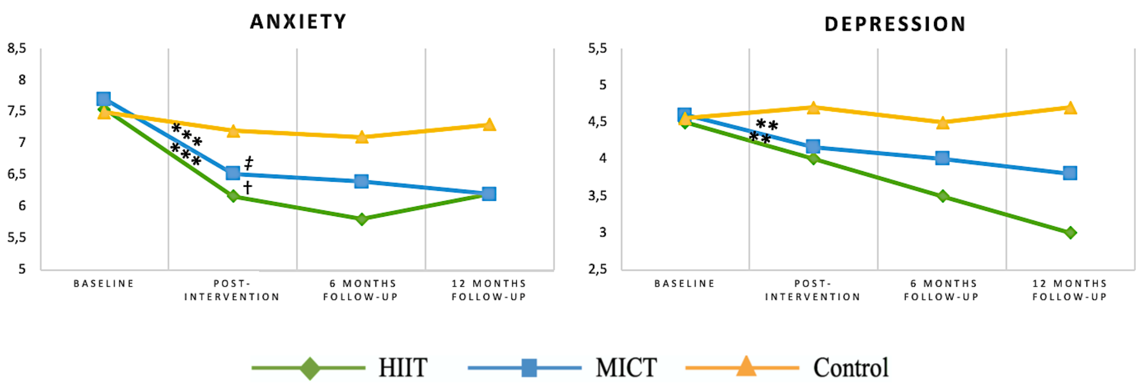
Following 6 and 12 months of intervention, both exercise groups exhibited significant intragroup improvements. Specifically, in the MICT group, noteworthy enhancements were observed at the 6 months follow-up in social functioning, role-emotional, and mental health dimensions, as well as at the 12 months follow-up in physical functioning, social functioning, role-physical, and role-emotional dimensions. A parallel pattern was evident in the HIIT group, with significant within-group improvements seen in social functioning, role-physical, and mental health dimensions. Furthermore, at the 12 months follow-up, significant progress was observed in the role-physical dimension. In contrast, significant disparities were observed between the exercise groups and the control group across QoL indicators ($p < .001$), except for the bodily pain. Additionally, within the exercise groups, there were differences between the HIIT and MICT groups. These differences were evident in the "physical functioning" indicator after the intervention ($p = .002$), at 6 months ($p = .023$), and at the 12 months of follow-up ($p = .003$). In the "role-physical" indicator, differences were observed after the intervention ($p = .025$) and at the 12 months of follow-up ($p = .017$). Furthermore, distinctions were noted in the "role-emotional" indicator at the 12 months follow-up ($p = .014$). In the "social functioning" indicator disparities were evident at 6 months ($p = .010$) and at the 12 months of follow-up ($p = .004$). For the "mental health" indicator, differences were observed after the intervention ($p = .030$), at 6 months ($p = .015$), and at the 12 months of follow-up ($p = .020$). Lastly, differences were apparent in the "general health" indicator after the intervention ($p = .016$) and at the 12 months of follow-up ($p = .034$). The ES from baseline to 6 weeks in the HIIT group were small in bodily pain ($d = 0.21$), medium in social functioning ($d = 0.44$), and large in physical functioning ($d = 2.89$), role-physical ($d = 2.71$), role-emotional ($d = 1.57$), mental health ($d = 2.28$), vitality ($d = 1.93$), and general health scores ($d = 1.72$). In the MICT group, the ES was small in bodily pain ($d = 0.11$), medium in social functioning ($d = 0.33$), and large in physical functioning ($d = 2.50$), role-physical ($d = 1.71$), role-emotional ($d = 1.30$), mental health ($d = 1.84$), vitality ($d = 1.29$), and general health scores ($d = 1.03$).

8.3.4. Anxiety and Depression

At the outset of the study, anxiety scores were modestly elevated at baseline (mean HIIT = 7.5 ± 4.8, mean MICT = 7.7 ± 4.4, and mean control = 7.5 ± 4.6), decreasing after the community-based exercise CR program in the exercise groups (mean HIIT = 6.2 ± 4.6 and mean MICT = 6.5 ± 4.4). Similarly, the initial assessment of depression scores revealed a significant portion of patients with clinically elevated depression levels at baseline (mean HIIT = 4.5 ± 3.4, mean MICT = 4.6 ± 3.4, and mean control = 4.6 ± 3.6). Notably, upon completion of the six-week community-based exercise program in the exercise groups, a reduction in the frequency of clinically elevated depression scores was observed, resulting in mean values of 4.0 ± 3.3 for HIIT and 4.2 ± 3.3 for MICT. Conversely, the control group witnessed an increase in depression scores, with a mean value of 4.7 ± 3.6, as depicted in **Figure 8.7**. The ES from baseline to six weeks in the HIIT group were medium in depression scores ($d = 0.40$) and large in anxiety scores ($d = 1.00$). In the MICT group, the ES were medium in depression scores ($d = 0.40$) and large in anxiety scores ($d = 0.90$).

Figure 8.7.

Impact of the community-based exercise CR programs on anxiety and depression indicators



Note. Control = Control group; HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; min = minutes; * p-value <.05, ** p-value <.01, *** p-value <.001.

8.3.5. Adherence and Safety

Only one participant from each group discontinued the intervention, achieving 96% adherence in both exercise groups. There were no adverse events in either program (HIIT and MICT) during the exercise interventions. Thus, HIIT protocols proved to be a safe, effective, and pleasant tool for low-risk patients with CAD as well.

8.4. Discussion

This study represents a pioneering endeavor as the first RCT to systematically investigate the impact of community-based exercise CR programs on various health-related parameters, lifestyle modifications, and the evolution of cardiovascular risk factors at both the 6- and 12-month post-intervention time points. The study's outcomes have revealed noteworthy insights. Low-risk CAD patients who engaged in HIIT and MICT interventions demonstrated substantial enhancements in a multitude of physical fitness parameters. These encompassed reductions in BMI, body fat percentage, total body fat mass, abdominal fat percentage, WC, and an elevation in VO_2peak. Furthermore, the HIIT group displayed commendable improvements in knee extensor strength.

Critically, these favorable changes exhibited a tendency to endure over the long term, underscoring the enduring advantages of exercise-based cardiac rehabilitation, especially concerning cardiovascular risk factors. Conversely, the control group, devoid of any exercise regimen, exhibited diminishing trends in physical fitness metrics. Regarding PA and SB, both exercise groups demonstrated heightened levels of physical activity compared to the control group. This was characterized by reductions in sedentary time and an increase in daily step count, LPA, and MVPA. Nevertheless, the preservation of these enhancements in physical activity presented a challenge during the 6- and 12-month follow-up assessments, with particular difficulty encountered in curtailing SB and augmenting MVPA. In the realm of QoL, both the HIIT and MICT programs engendered substantial ameliorations across various dimensions, encompassing physical functioning, emotional role, mental health, and general health when juxtaposed with the control group. Notably, these enhancements exhibited sustained continuity throughout the study, emphasizing the pivotal role of exercise-based cardiac rehabilitation in enhancing the QoL of CAD patients. In what concerns to anxiety and depression, both exercise cohorts experienced marked reductions in anxiety levels compared to the control group. In contrast, the control group displayed an exacerbation in depression scores following the intervention, signifying the potentially deleterious consequences of refraining from participation in cardiac rehabilitation post-cardiac event. Crucially, the exercise groups managed to preserve lower levels of anxiety and depression during the 6- and 12-month follow-up evaluations.

Among patients with low-risk CAD, both HIIT and MICT exercise programs led to significant enhancements in BMI, body fat percentage, total body fat mass, percentage of abdominal fat, WC, and VO_2peak. The HIIT group additionally exhibited a substantial improvement in maximal knee extensor strength. Importantly, following the culmination of the community-based exercise CR program, these improvements were largely sustained over time, with only two significant variations observed: a reduction in WC after 6 months in the HIIT group and a significant decline in maximal knee flexor strength in the MICT group after 12 months. Conversely, the control group, devoid of any exercise program, experienced a decline in VO_2peak, muscle strength, and PA, alongside unfavorable shifts in body composition and increased sedentary time from baseline to six weeks. This trend persisted at the 6 and 12-month follow-up assessments. These findings merit particular attention due to the well-established associations between body fat mass, abdominal fat, higher BMI, greater waist circumference, and waist-hip ratio with an elevated risk of cardiovascular events, all-cause mortality, and premature mortality (Di Angelantonio et al., 2016). It is noteworthy that exercise training disproportionately targets visceral fat reduction in comparison to overall body fat reserves, with exercise proving more effective than dietary interventions in inducing visceral fat loss (Pattyn et al., 2014). Within our RCT, both HIIT and MICT demonstrated substantial positive effects on body composition in CAD patients. In contrast, CAD patients who did not engage in any form of community-based exercise CR program following a cardiac event exhibited trends towards increased BMI, fat mass, and waist circumference. Notably, the HIIT intervention appeared to exert a more pronounced influence on body composition compared to MICT, a trend supported by prior research (Marzolini et al., 2012; Fletcher et al., 2013; Kida et al., 2008; Yamoto et al., 2016; Ambrosetti et al., 2021; Bakker et al., 2021; Prince et al., 2019). For instance, Dun et al. (2019) included 120 patients who completed 36 CR sessions and compared HIIT (involving 4 to 8 alternating intervals of 30-60 seconds at a rating of 15-17 of RPE) and MICT (performed for 20 to 45 minutes at an RPE of 12 to 14), revealing that supervised HIIT led to significant reductions in total fat mass and abdominal fat percentage. Similarly, Trapp et al. (2008) compared HIIT and MICT, highlighting that the HIIT group experienced a more pronounced decrease in abdominal fat. In contrast, Zhang et al. (2017) demonstrated that both HIIT and MICT significantly reduced total and abdominal fat mass, with no discernible differences across groups.

Aerobic capacity (VO_2peak) improved by 14%, equivalent to 2.5 mL-kg^{-1}-min^{-1} or nearly 1 MET in the HIIT group and 9% in the MICT group and these results were maintained in the exercise groups at the follow-up evaluations. These results indicated that training intensity is essential in improving VO_2peak in CAD patients since the improvements of HIIT were almost twice as good as the MICT group. The mean difference of 0.9 mL-kg^{-1}-min^{-1} between HIIT and MICT holds clinical significance, as each 1 mL-kg^{-1}-min^{-1} enhancement in VO_2peak during a CR program is associated with an approximately ~8–17% reduction in all-cause and cardiovascular-related mortality (Davidson et al., 2018). These findings align with data from Keteyian et al. (2012), whose study involving 2812 cardiac patients demonstrated a 15% reduction in cardiovascular-specific mortality risk per 1 mL-kg^{-1}-min^{-1} VO_2peak increment. Moreover, the superior efficacy of HIIT in elevating VO_2peak compared to MICT during supervised training is similar to previous meta-analyses reporting group disparities of 1.5 to 1.6 mL-kg^{-1}-min^{-1} (Valkeinen et al., 2010; Pandey et al., 2015). Similarly, Rognmo et al. (2004) affirmed HIIT's effectiveness in augmenting aerobic capacity in CAD patients. In addition, our prior systematic review with meta-analysis, encompassing 16 studies with 969 patients, revealed that both moderate-to-vigorous intensity (SMD = 1.84 mL-kg^{-1}-min^{-1}; 95% CI [1.18, 2.50]) and vigorous-intensity (SMD = 1.80 mL-kg^{-1}-min^{-1}; 95% CI [0.82, 2.78]) programs were linked to more substantial increases in relative VO_2peak in contrast to moderate intensity interventions (SMD = 0.71 mL-kg^{-1}-min^{-1}; 95% CI [0.27, 1.15]) (Gonçalves et al., 2021). Furthermore, Sandercock et al. (2013) reported greater improvements of 5.2 mL-kg^{-1}-min^{-1} (95%CI: 4.1–6.4), while Uddin et al. (2016) presented enhancements of 3.3 mL-kg^{-1}-min^{-1} (95%CI: 2.6–4.0). Nevertheless, in our investigation, the control group witnessed a decline in VO_2peak from baseline, with this decline persisting at 6 and 12 months. This trend is disconcerting, as aerobic capacity is a robust predictor of both cardiovascular and all-cause mortality (Davidson et al., 2018). Martin et al. (2013) demonstrated that an increase in aerobic capacity post a 12-week exercise-based CR program correlated with a 13% reduction in overall mortality per metabolic equivalent elevation in VO_2peak, with a 30% reduction among patients commencing the program with low fitness levels.

Muscle strength plays a crucial role in exercise capacity, and survival rates among CAD patients (Kamiya et al., 2014). At baseline, all groups exhibited low muscle strength levels, consistent with prior studies involving CAD patients pre-exercise programs (Marzolini et al., 2012; Fletcher et al., 2013). Following six weeks of intervention, our investigation revealed that both HIIT and MICT led to increased muscle strength in comparison to patients who did not participate in a community-based exercise CR program. Notably, HIIT induced more substantial gains in muscle strength compared to MICT, although these differences did not attain statistical significance, which aligns with our focus on aerobic training. Our study's observed impact on muscle strength closely resembled the findings of Murabayashi et al. (2008). In contrast, despite Yamamoto et al. (2016) report of increased muscle volume in CAD patients, our study did not yield significant increases. Importantly, at follow-up assessments, the maintenance of these results was evident exclusively in the HIIT group.

The PA levels in the exercise groups significantly exceeded those in the control group, manifesting as a substantial reduction in sedentary time and increased daily step count, LPA, and MVPA. Notably, cardiac patients frequently exhibit low MVPA levels, which is a crucial component of CR programs. These programs emphasize reducing SB while promoting MVPA (Ambrosetti et al., 2021). Despite its significance, information concerning SB in patients with CVD patients remains scarce. Objective assessments of PA and SB have been scarcely explored (Bakker et al., 2021). Our results unveiled elevated SB levels across all three groups before enrollment, with daily routines predominantly characterized by LPA. This is concerning since SB independently heightens CVD risk (Stewart et al., 2017), our findings align with prior research indicating that CAD patients are predominantly sedentary (10.5–12 h/day), followed by extended periods of LPA (3.5 h/day) and minimal engagement in MVPA (20–65 min/day) (Prince et al. 2019; Biswas et al. 2018). As per PA guidelines, adults should accumulate 150 min per week in MVPA (Woodruffe et al., 2015) a criterion met by the exercise groups in our study. Six weeks post-intervention, we observed a significant surge in daily MVPA (+ 36 min/day, $p < .001$) in the HIIT group and (+ 23 min/day, $p < .001$) in the MICT group compared to the control. However, when comparing HIIT to MICT, similar daily LPA levels were noted. Previously, both LPA and MVPA have been associated with reduced CVD risk (LaMonte et al., 2017), aligning partially with our findings, where HIIT and MICT patients engaged slightly more in MVPA and exhibited reduced SB compared to previous studies (Diaz et al. 2017; Wennman et al., 2016; Vasankari et al., 2018). However, CR-induced increases in MVPA tend to be transient, with many patients reverting to inactive lifestyles within months (Bock et al., 2003). Our study confirmed this trend as, after the intervention, the exercise groups exhibited a significant trend towards increased SB and decreased MVPA at the 6- and 12-month follow-up assessments. This might be attributed to the brief intervention duration, particularly the intensive nature of HIIT, which led to a greater increase in SB. It aligns with the findings of Milkman et al. (2021), emphasizing the limited long-term behavior change associated with short-term, intensive health interventions. This observation is consistent with reports by Guiraud et al. (2012) and Dolansky et al. (2010), where only around 40% of patients sustained physical activity one year after CR, highlighting the challenge of maintaining long-term health behavior change.

Both the HIIT and MICT programs yielded significant enhancements in various of QoL, including physical functioning, physical role, emotional role, mental health, vitality, and general health when compared to the control group. Notably, within the exercise groups, significant differences were observed only in the indicators of physical functioning and general health in patients undergoing the HIIT protocol compared to MICT. These improvements persisted through the 6 and 12-month follow-up assessments in both exercise groups. In contrast, the group that did not undergo any exercise intervention did not experience significant improvements in QoL. These results show that community-based exercise CR programs, even at moderate intensity, can play an important role in improving QoL. This is especially significant given the influence of CAD on an individual's QoL, often associated with increased functional dependence (Cuerda et al., 2012). Our RCT aligns with existing literature supporting the notion that exercise-based CR programs consistently generate positive effects on QoL (Lovlien et al., 2017; Anderson et al., 2016; Francis et al., 2019; Candelaria et al., 2020). For instance, Lovlien et al. (2017) observed QoL improvements in 142 women diagnosed with CAD following participation in exercise-based CR programs. A 2015 systematic review of RCTs comparing exercise-based CR programs to traditional care programs reported QoL enhancements in 14 out of 20 studies involving CAD patients (Anderson et al., 2016). Likewise, a 2018 meta-analysis encompassing 41 RCTs (N = 11.747) investigating CR measures and interventions revealed that exercise-based CR programs had a positive impact on QoL (Francis et al., 2019). A 2019 systematic review (14 RCTs, N = 1739) that documented clinically positive effects in two domains of the SF-36 at 6 months (physical role and general health) and one domain at 12 months (physical functioning) following exercise-based CR programs (Candelaria et al., 2020). Another study that closely aligns with our findings is that of Worcester et al. (1993), who observed that the QoL improvement provided by 11 weeks of MICT in 224 CAD patients was comparable to that achieved with HIIT. Additionally, in an RCT involving CAD patients, both HIIT training and traditional MICT were found to enhance QoL (Moholdt et al., 2012). Lastly, a cohort study involving 37 CAD patients who completed a 5-week exercise-based CR program revealed significant QoL improvements (Fallavollita et al., 2016).

Both exercise groups demonstrated significant reductions in anxiety levels when compared to the control group. The control group exhibited an increase in depression scores from baseline to post-intervention, underscoring the potential harm of not engaging in a community-based exercise CR program after a cardiac event. Furthermore, at the 6 and 12-month marks post-intervention, the HIIT and MICT groups continued to experience decreases in both anxiety and depression scores, while the control group maintained the previous upward trend. These findings hold substantial clinical relevance, as anxiety and depressive symptoms are associated with an elevated risk of subsequent cardiac events (Baker et al., 2021; Celano et al., 2015; Emdin et al., 2014), and exercise-based CR programs have demonstrated their efficacy in reducing levels of anxiety and depression (Freitas et al., 2011; Lavie & Milani, 2004). Additionally, Bakker et al. (2021) identified an association between anxiety in CAD patients and higher levels of self-reported SB. Furthermore, our study revealed no significant differences in anxiety and depression reductions between the HIIT and MICT groups, suggesting that training intensity did not significantly impact these symptoms. These outcomes are consistent with those of several other authors, affirming the efficiency of exercise-based CR programs in mitigating symptoms of anxiety and depression (Lavie et al., 2016; Zheng et al., 2019; Smith et al., 2017; Kachur et al., 2016). Lavie et al. (2016) demonstrated the enhancement of psychosocial functioning through exercise-based CR programs. Notably, a recent meta-analysis highlighted the effectiveness of exercise in reducing anxiety and depression in CAD patient (Zheng et al., 2019). Additionally, Smith et al. (2017) found that higher levels of PA following CR were associated with lower depressive and anxiety symptoms. Finally, Kachur et al. (2016) in a comprehensive meta-analysis and systematic review, studied 1.150 CAD patients who completed a formal CR program, and they reported a low incidence of depression post-CR (6.8%), with a corresponding reduction in mortality (20.8%).

In summary, accumulating research indicates that HIIT has the potential, when compared to MICT, to induce changes in numerous physiologic and health-related markers, including greater improvement in body composition, aerobic capacity, PA, SB, quality of life, anxiety, and depression in CAD patients. Importantly, our study's positive efficacy outcomes are promising, especially considering the relatively short intervention duration (6 weeks) and frequency (3 sessions per week, totaling 18 sessions per participant). Encouraging patients to maintain higher PA levels may contribute to long-term enhancements in both physical and mental health. Additionally, this study underscores the necessity for strategies aimed at promoting PA adherence following a cardiac event and sustaining PA after participation in a community-based CR exercise program. Perhaps a better understanding of physical and psychological obstacles hindering PA adherence could facilitate the maintenance of PA levels over time. We advocate for more vigilant post-CR exercise program monitoring of cardiac patients.

8.4.1. Study Limitations

This study has some limitations that should be acknowledged. Firstly, most of our subjects were men, which is a frequently encountered referral bias in CR (Cottin et al., 2004). Secondly, there was no specific control for habitual dietary intake, participants just followed the ideal dietary recommendations given by the medical specialist. Plus, when considering the results of this study, the possible confounding effects of concurrent medications should be considered although no change happened during the study period for doses of lipid-lowering and heart rate control medications. Additionally, the control group was not delivering diaries and we have no information about their PA habits during the intervention period from baseline to 6 weeks. A potential increase in PA could imply a reduced difference in effect between the groups. However, our study duration of 6 weeks was relatively short and with an extended duration of the intervention, one might expect an effect of clinical relevance.

8.5. Conclusions

This RCT demonstrates that participation in a community-based exercise CR program is strongly linked to improved aerobic capacity, PA, QoL, reduced WC, lower fat mass, decreased SB, and reduced anxiety and depressive symptoms among cardiac patients. Both exercise-based CR programs proved to be effective in mitigating cardiovascular risk factors and positively influencing these cardiac patients' lifestyle. The HIIT group exhibited superior long-term improvements compared to the MICT group. Conversely it is crucial to motivate patients to sustain higher levels of physical activity to enhance both cardiovascular and psychological well-being.

Abbreviations and Acronyms: ACSM = American College of Sports Medicine; BMI = body mass index; CAD = coronary artery disease; CPET = cardiopulmonary exercise test; CR = cardiac rehabilitation; DBP = diastolic blood pressure; DXA = dual-energy x-ray absorptiometry; HDL-C = high-density lipoprotein cholesterol; HIIT = high-intensity interval training; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; MET = metabolic equivalent; MI = myocardial infarction; MICT = moderate-intensity continuous training; RPE = rating of perceived exertion; SB = Sedentary Behavior; SBP = systolic blood pressure.

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CHAPTER 9

Discussion and Conclusions

CHAPTER 9 – Discussion and Conclusions

Chapter overview

This multi-study thesis includes six peer-reviewed papers that, report on the results of research studies that aimed to:

1) identify, through RCTs of exercise-based CR, the most effective exercise intensity and intervention length to optimize VO_2peak in patients with CVD;
2) analyze the physiological parameters of thermography, heart rate variability, blood pressure, and cortical arousal in CAD patients who belong to CR programs of HIIT and MICT, compared to healthy participants;
3) investigate the effects of two different six-week community-based exercise programs, HIIT and MICT, on the body composition and cardiovascular biomarkers risk factors and compare them with a control group;
4) compare the effectiveness of six-week supervised community-based exercise programs, a short-duration resting HIIT, and a usual MICT, in improving health indicators (physical fitness and activity levels) vs. a control group among CAD patients;
5) investigate the impact of two community-based exercise programs employing HIIT and MICT protocols on QoL and mental health (anxiety and depression); with a comparative analysis against a control group receiving no exercise program;
6) assess whether there are changes in the patients' lifestyle and the association with long-term cardiovascular risk factors (6- and 12-month follow-up).

This chapter presents a summary of key findings in this thesis and provides a critical discussion of these findings within the context of currently available literature. This chapter also highlights the contributions to knowledge the thesis makes, outlines implications for practice, considers limitations, presents considerations for future research, and provides recommendations for community-based CR service planning, implementation, and research. This chapter acknowledges that community-based CR is not only a complex intervention that is dynamic with interactive parts, but one that is also situated in a broader health care and societal system.

9.1. Main findings

- **Prescription methodology to meet the needs of CAD survivors**

Our systematic review with meta-analyses of randomized controlled trials has sought to examine the impact of different intensity and length training regimes on aerobic capacity. Moderate-to-vigorous and vigorous-intensity training have shown to be more effective than moderate-intensity training in CVD patients in improving exercise capacity. Additionally, we observed that studies employing 6-12 weeks length of exercise training appear more effective than shorter durations of training to increase aerobic capacity. In this regard, our study confirmed the results of previous systematic reviews, pointing out that moderate-to-vigorous- and vigorous-intensity interventions improved aerobic fitness to a more significant extent than moderate-intensity (Mitchell et al., 2019; Hannan et al., 2018; Pattyn et al., 2018).

After studying the optimal intensity and duration of exercise intervention, our case study aimed to investigate the physiological response of people with CAD during two different CR programs (HIIT and MICT) compared to healthy individuals without CVD. We found that individuals with CVD who underwent MICT experienced over two times the amount of CNS fatigue when compared to healthy individuals who followed the same protocol, a fact in line with previous studies that also found higher motivation in interval training than in continuous training (McKean et al., 2012). We can see how MICT is more demanding for CVD patients, which may explain the lower adherence to this training (McKean et al., 2012). However, participants with and without CVD who underwent HIIT had almost similar levels of CNS fatigue. Additionally, during exercise, individuals with CVD in the HIIT and MICT groups had higher chest temperatures compared to their healthy counterparts. The initial indications of heart disease could be linked to either high or low blood flow in the peripheral areas. Several authors suggest that diagnostic imaging could help identify the likelihood of developing CVD (Alcantara et al., 2023; Al-Absi et al., 2022.; Oloumi et al., 2014). Our case study found that the HIIT protocol improved HRV parameters, such as the number of RR intervals, in patients who had experienced heart attacks compared to MICT. Furthermore, other studies have shown that HIIT is more effective than MICT in enhancing aerobic fitness (Okamura et al., 2023; Pattyn et al., 2018; Mitchell et al., 2019; Gomes-Neto et al., 2018). HIIT training can also be beneficial to improving the unbalanced autonomic function of HAP, as studies have shown an increase in cardiac vagal activity after aerobic exercise programs (Benda et al., 2015; Fisher et al., 2015; Weston et al., 2014). In addition, both HIIT and MICT led to a decrease in systolic blood pressure from before to after the exercise. Research suggests that physical activity CR programs can be a helpful non-pharmacological approach for improving blood pressure in cardiac patients (Hanssen et al., 2022; Haykowsky et al., 2013; Ghadieh & Saab, 2015). All these results are important information for specialists who design training programs for CAD because HIIT has been shown to produce higher physiological adaptation.

- **Physical and psychological problems after cardiac event**

Studies 3, 4, and 5 successfully involved a predicted relative number of participants with CAD in Évora, coming from various areas of the Alentejo region, with baseline characteristics that, for the most part, are similar to contemporary epidemiologic and observational registry studies of such individuals (Timóteo & Mimoso, 2019; Santos et al., 2009; Townsend et al., 2016). We found with these studies that CAD survivors reported multiple comorbidities (such as overweight, hypertension, dyslipidemia), low aerobic fitness, muscle strength, PA levels and QoL, smoking habits, high levels of sedentarism, anxiety, and depression problems. These are the common problems in CAD survivors, as others verified (Lavie et al., 2019; Lee et al., 2020); plus, within Study 6, we realized with the control group that this trend continues over time, as Peterson et al. (2014), Moholdt et al. (2009) and Taylor et al. (2020) shown in their studies. These data underscore the continued pressing need to implement and find community-based exercise programs for patients with CAD (Clark et al., 2015).

- **Developing and testing interventions to meet the needs of CAD survivors**

Originally we titled ‘cardiac rehabilitation programs’ to allow the broadest inclusion of interventions but exclude medically-based post-resuscitation interventions. However, we were directed to use “community-based exercise rehabilitation” as this is more widely understood by the mainly clinical readership. As exercise is a modifiable health behavior, offering cardiac rehabilitation exercise sessions in a community setting may help reframe exercise as a lifestyle modification, as opposed to an isolated hospital treatment, and thereby facilitate exercise maintenance post-program (Bethell & Mullee, 1990). This highlights the tension created by variation in terminology used in post-CAD literature because community-based CR is increasingly utilized for patients at low to moderate risk who are in earlier recovery (4-6 weeks after a cardiac event) (Blake et al., 2009), and community programs have demonstrated effectiveness similar to that of hospital-based programs in improving CVD risk factors (Clark et al., 2015). We chose to carry out a short-term (6-week) program based on the systems of other countries, particularly Australia, Hungary, and Austria (Chaves et al., 2020), and the positive efficacy findings we observed are encouraging, especially considering significant changes were induced over a relatively short duration and with three sessions per week, totaling 18 sessions per patient. Chaves et al. (2020) suggest the ideal length of community-based exercise intervention is between 12 to 36 sessions.

The magnitude of the observed improvement in Studies 3, 4, and 5 in health measurements and the decreased cardiovascular risk factors following community-based exercise CR and that the level of exercise intensity is a key driver of this improvement is in line with previous studies in CAD patients (Anderson et al., 2016; Elbourne et al., 2002; Rivera-Brown & Frontera, 2012; Ghroubi et al., 2012; Blumenthal et al., 2005; Sandercock et al., 2013), where HIIT demonstrated to be more effective than MICT as other studies have shown (Sultana et al., 2019; Reed et al., 2018; Villelabeitia-Jaureguizar et al., 2017; Cornish et al., 2010).

Studies 3, 4, 5, and 6 found both exercise interventions were feasible with a high retention rate (96%), high participant/clinician satisfaction, and the potential to improve intervention outcomes. The adherence to exercise training prescriptions in HIIT vs. MICT in CAD patients has only been assessed in two studies, with comparable outcomes (Quindry et al., 2019; Spiteri et al., 2019).

There were no adverse events in either protocol (HIIT and MICT) during the exercise interventions. Thus, HIIT protocols proved to be a safe, effective, and a pleasant tool for low-risk patients with CAD as well. Confirming what is written in the existing literature. In a study covering 25 420 CVD patients, 20 severe cardiac events were reported, of which 5 were related to exercise testing and 15 to exercise training (Pavy et al., 2006). The event rate was 1 per 8484 exercise stress tests and 1 per 49 565 patient-hours of exercise training, and the cardiac arrest rate was 1.3 per 1 000 000 patient training hours (Pavy et al., 2006). This data clearly indicates that the current CR is very safe.

- **Physical fitness, levels of physical activity and sedentary behavior**

Markers of success of our investigation were outcomes such as losing body weight, increasing physical activity, preventing sedentary behavior, and improving physical fitness compared to the no-exercise control group (Studies 3 and 4). Over the course of six weeks, the control group exhibited an unfavorable trend characterized by increased abdominal fat, body fat mass, and waist circumference, all of which carry elevated risks of cardiovascular events and all-cause mortality. On the other hand, community-based exercise programs improved physical fitness, mainly HIIT, which was similar to other studies. Namely, Fragnoli-Munn et al. (1998) were the first to report an improvement in aerobic capacity and muscle strength and a slight decrease in body weight, fat mass, and maintenance of lean body mass in a 12-week CR program. After that, Beniamini et al. (1999) demonstrated that HIIT during the 12-week CR program improved aerobic capacity and muscle strength and changed body composition. Pierson et al. (2001) reported a mean percent strength increase of 44 to 81% and a significant increase in the VO_2peak within both HIIT and MICT after training, but the relative improvement between groups was not different. Warburton & Bredin (2017), with a systematic review of current systematic reviews, concluded that the relationships between PA and health outcomes are generally curvilinear such that marked health benefits are observed with relatively minor volumes of PA. Lastly, den Ujil et al. (2023) studied the effects of two 6- to 12-week CR programs on physical activity, sedentary behavior, and physical fitness. Patients allocated to more intensive CR showed more significant weight loss (mean change −3.6 vs. −1.8 kg) and a more considerable improvement in physical activity (mean change +880 vs. +481 steps per day) than patients randomized to standard CR (mainly weight-bearing activities such as walking, jogging, sports).

The positive efficacy findings we observed are encouraging, especially considering significant changes were induced over a relatively short duration (6 weeks) and with low training frequency (3 sessions per week, totaling ∼18 sessions per patient). Hence, our study demonstrated that HIIT was considered a beneficial and feasible supplementary therapy in community-based exercise programs compared to MICT, like other multiple large-scale epidemiological studies have reported the same (Way et al., 2020; Reeds et al., 2018; Kim et al., 2015; Taylor et al., 2019).

- **Health-related Quality of Life and Mental Health**

Study 5 demonstrated that exercise protocols promoted a significant improvement in HRQOL, anxiety, and depression compared to the control group. These results are in line with previous studies that have demonstrated that CR improves mental health (Lavie et al., 2016) and quality of life (Anderson et al., 2016). Meta-analyse studies and systematic reviews have reported that participation in a structured exercise-based CR program is associated with small-to-moderate improvements in depressive symptoms (Rutledge et al., 2013; Reed et al., 2019) and HRQOL (Yu et al., 2023; Gomes-Neto et al., 2018). Our results (Study 5) demonstrated that HIIT and MICT exercise protocols promote the QoL dimensions, i.e., physical functioning, role-physical, role-emotional, mental health, vitality, and general health. General health improvement in patients undergoing HIIT protocol was significantly higher than in MICT. Both exercise groups improved anxiety and depression levels, with no discernible difference between the two training modalities.

For many survivors, their HRQOL may continue to change (Ørbo et al., 2016), and a longer-term assessment of HRQOL is recommended (Haywood et al., 2018; Moulaert et al., 2015). Our Study 6 showed that these improvements persisted through the 6- and 12-month follow-up assessments in both exercise groups. In contrast, the group that did not undergo any exercise intervention did not experience significant improvements in HRQoL. These results show that community-based exercise CR programs, even at moderate intensity, can play an important role in improving HRQOL and mental health. This is especially significant given the influence of CAD on an individual's HRQOL, which is often associated with increased functional dependence (Cuerda et al., 2012).

- **High-intensity interval training vs. Moderate-intensity continuous training**

In the last decade, it has been intensely discussed whether HIIT specifically outperforms MICT with regard to improvements in aerobic fitness, cardiovascular risk factors, cardiac and vascular function, and QoL in CVD patients. In our Study 2, there is a fundamental physiological difference between exercising at a HIIT vs. MICT. We observed that MICT in this population causes more CNS fatigue, showing how MICT is more demanding for CVD patients. This may explain the lower adherence usually to this training and could improve adherence to programs based on HIIT (McKean et al., 2012).

Our randomized controlled trial of Study 4 found community-based exercise rehabilitation programs to significantly improve aerobic capacity compared to no exercise control, and that the magnitude of this improvement to be almost twice in HIIT compared to MICT in CAD patients. However, in the subgroup of exercise intensity programs reporting VO_2peak, the mean increase in aerobic capacity following HIIT training was higher by 3.5 mL-kg^{-1}-min^{-1} (=1.0 MET) compared to control. This corresponding to a 14% increase compared to the mean pooled VO_2max at baseline. On the other hand, MICT training was higher by 1.7 mL-kg^{-1}-min^{-1} compared to control, corresponded to a 9% increase. The improvements of HIIT were almost twice as good as the MICT group (Δ = 2.3 ± 1.5 mL-kg^{-1}-min^{-1}, p < .001 vs. Δ = 1.4 ± 1.2 mL-kg^{-1}-min^{-1}, p < .001, respectively). These results are in line with our previous systematic review with meta-analyses (Study 1), indicating that training intensity is essential in improving peak aerobic capacity in CAD patients. A comparison of the mean effects between intensity classifications showed significant improvements with moderate-to-vigorous-intensity interventions providing the greatest improvements in VO_2peak, which the differences were considered clinically significant (p = .03), and the retro transformation of the SMD suggested that the difference between the intensities was 3.92 mL-kg^{-1}-min^{-1}. In this regard, both our studies confirmed the results of previous systematic reviews, pointing out that moderate-to-vigorous- and vigorous-intensity interventions improved aerobic fitness to a larger extent than moderate-intensity (Mitchell et al., 2019).

Moreover, the mean difference between HIIT and MICT of 0.9 mL-kg^{-1}-min^{-1} could be considered clinically meaningful as each 1 mL-kg^{-1}-min^{-1} improvement in VO_2peak during a community-based exercise program has been associated with an ~8–17% reduction in all-cause and cardiovascular-related mortality (Davidson et al., 2018; Keteyian et al., 2012; Valkeinen et al., 2010; Pandey et al., 2015). These results are in line again with our Study 1, where the difference between moderate-to-vigorous- and vigorous-intensity in our Study 1 was 0.4 mL-kg^{-1}-min^{-1}, and the difference between moderate- and moderate-to-vigorous-intensity was more significant (1.13 mL-kg^{-1}-min^{-1}). Even so, the differences were not considered clinically significant once the retro transformation of the SMD suggested that the differences between the intensities were, at most, only 1.67 mL-kg^{-1}-min^{-1}. Additionally, across intensities, the mean aerobic capacity following community-based exercise rehabilitation in HIIT was 1.5 standard deviation units higher than with control and 0.7 standard deviation units in MICT. This corresponds to a 'large' and 'medium' effect size (where Cohen defines a standardized effect of 0.2 means a 'small' effect size, 0.5 represents a 'medium' effect size, and 0.8 or more be a 'large' effect size), respectively (ACSM, 2017). Equally, our study is in line with data from the meta-analysis by Pattyn et al. (2018) in CAD patients that found more significant improvements in VO_2peak after HIIT compared with MICT (mean difference of 0.9 mL-kg^{-1}-min^{-1}). These findings are supported by Mitchell et al. (2019) who verified that moderate- and moderate-to-vigorous-intensity interventions were associated with a moderate increase in relative VO_2peak (SMD ± 95% CI = 0.94 ± 0.30 mL-kg^{-1}-min-^{1} and 0.93 ± 0.17 mL-kg^{-1}-min-^{1}, respectively), and vigorous-intensity exercise with a large increase (SMD ± 95% CI = 1.10 ± 0.25 mL-kg^{-1}-min-^{1}), and moderate- and vigorous-intensity interventions were associated with moderate improvements in absolute VO_2peak (SMD ± 95% CI = 0.63 ± 0.34 mL-kg^{-1}-min-^{1} and SMD ± 95% CI = 0.93 ± 0.20 mL-kg^{-1}-min-^{1}, respectively), whereas moderate-to-vigorous-intensity interventions elicited a large effect (SMD ± 95% CI = 1.27 ± 0.75 mL-kg^{-1}-min-^{1}). Similarly, Keteyian et al. (2008), a study including 2812 CAD patients, demonstrated a greater efficacy of HIIT for improving VO_2peak compared with MICT during supervised training is similar to previous meta-analyses reporting group differences of 1.5 to 1.6 mL-kg^{-1}-min-^{1} (Wen et al., 2011; Gebel et al., 2015; Wang et al., 2021). Furthermore, Rognmo et al. (Lee et al., 2003) demonstrated that HIIT was effective in improving aerobic capacity in CAD patients.

Other markers of success of our investigation were outcomes such as losing body weight, increasing physical activity, preventing sedentary behavior, and improving physical fitness compared to the no-exercise control group (Studies 3 and 4). Over the course of six weeks, the control group exhibited an unfavorable trend characterized by increased abdominal fat, body fat mass, and waist circumference, all of which carry elevated risks of cardiovascular events and all-cause mortality. On the other hand, exercise programs, mainly HIIT exhibited a positive influence on body composition. Weight loss in the HIIT group averaged –1.9 kg (–3.1%) more than the MICT group (mean –0.9 kg, –3%), with both groups experiencing moderate fat loss (HIIT: mean –0.9 kg, –3%; MICT: mean –0.9 kg, –3%), slightly offset by negligible lean body mass increases (HIIT: mean +0.2 kg, 1.8%; MICT: mean +0.2 kg, 0.5%). Additionally, abdominal fat decreased in both the HIIT (mean –0.2 kg, 1.8%) and MICT (mean –0.2 kg, 1.3%) groups. These outcomes underscore the benefits of higher-intensity exercise sessions on body composition, consistent with previous studies (Mandviwala et al., 2018; Czernichow et al., 2011; Di Angelantonio et al., 2016). Since obesity is a risk factor for cardiac disease, losing excessive body weight is of the utmost importance. In patients with CAD, weight loss is associated with symptom reduction (Milson et al., 2014). Studies showed that a weight loss of 5-10% is associated with a cardiovascular risk reduction, but is often not achieved during CR (Brown et al., 2016; Milson et al., 2014). Furthermore, Du et al. (2021) concluded that studies that used a non-isocaloric exercise protocol induced more significant effects compared to studies that used an isocaloric exercise protocol, indicating that benefits can be determined by total caloric consumption. This is explained by the fact that we did not have greater results in this variable since we projected the same caloric expenditure between the two training intensities.

Although we have not focused on muscular resistance training, low improvements in muscular strength have been reported with both training interventions in our Study 4, with no significant differences between groups. In addition, loss of muscle strength was observed in patients with CAD in the control group. Our data is in line with other studies (Hollings et al., 2017, Gomes-Neto et al., 2019). These results are relevant, given that muscle weakness is a strong predictor of premature death in CAD patients (Kamiya et al., 2015), maximizing muscle strength is of paramount importance. Moreover, following cardiac surgery, significant muscle wasting is observed, warranting interventions to regain muscle mass and strength (Boujemaa et al., 2020; Hansen et al., 2015). According to meta-analysis, the addition of resistance training on top of aerobic training leads to greater increments in physical fitness and muscle strength in CVD patients (Hollings et al., 2017). In addition, resistance training favorably affects bone health (Gómez-Cabello et al., 2012), glycemic control, blood pressure, and lipid profile (Hansen et al., 2018). In our Study 3, before the intervention, all groups had high levels of blood pressure and inflammatory biomarkers, but after the intervention, these values decreased.

Study 4 shows before the intervention, all three groups had high levels of SB and mainly engaged in LPA. This is concerning because SB is known to increase the risk of CVD (Stewart et al., 2017). Our findings are consistent with previous studies that have shown that patients with CAD are predominantly sedentary for about 10.5 to 12 hours a day, engage in LPA for 3.5 hours a day, and have minimal MVPA of 20 to 65 minutes a day (Prince et al., 2016, 2019; Biswas et al., 2018). After the intervention, the exercise groups showed significantly higher levels of PA compared to the control group. This was reflected in a decrease in sedentary time and an increase in daily step count, LPA, and MVPA. It is worth noting that patients with heart conditions often have low MVPA levels, and according to the guidelines for PA, adults should engage in at least 150 minutes of MVPA per week (Piepoli et al., 2014; Woodruff et al., 2015; Baladyet al., 2007). The exercise groups in our study met this criterion after six weeks of the intervention. However, when comparing HIIT to MICT, we observed a significant increase of +36 minutes/day ($p < .001$) in daily MVPA in the HIIT group and +23 minutes/day ($p < .001$) in the MICT group compared to the control group. These results are relevant since regular PA in patients with CAD is associated with a lower risk of recurrent cardiovascular events and a 25% mortality risk reduction (LaMonte et al., 2017), whereas HIIT and MICT patients engaged slightly more in MVPA and exhibited reduced sedentary behavior compared to previous studies (Diaz et al., 2017; Wennman et al., 2016; Vasankari et al., 2018). Additionally, a regular PA was demonstrated in Study 3 to be beneficial in regulating blood pressure, lipid profile, thyroid function, and blood glucose; in Study 4, in increasing physical fitness (reducing body weight, waist circumference, and body fat, improving aerobic capacity, and muscle strength); and in Study 5, in increasing the quality of life and mental health in CAD patients.

Our results demonstrated that HIIT and MICT exercise protocols promote the QoL dimensions, i.e., physical functioning, role-physical, role-emotional, mental health, vitality, and general health. General health improvement in patients undergoing HIIT protocol was significantly higher than in MICT. Both exercise groups improved anxiety and depression levels, with no discernible difference between the two training modalities. Our Study 6 showed that these improvements persisted through the 6- and 12-month follow-up assessments in both exercise groups. Therefore, it seems that HIIT could be a more time-efficient manner to improve VO_2peak and other health outcomes when compared with MICT.

- **Comparison of Community-based exercise CR programs vs. Control**

Both exercise protocols of community-based CR markedly ameliorated aerobic capacity, PA, QoL, reduced WC, lower fat mass, decreased SB and reduced anxiety and depressive symptoms in comparison to the control group. On the opposite, the control group experienced an increase in mental health scores post-intervention (Study 5), body composition variables (Studies 3 and 4), blood biomarkers (Study 3), sedentary time (Study 4), a decrease in cardiorespiratory fitness (Study 4) and MVPA (Study 4), emphasizing the potential detriment of forgoing community-based exercise programs post-CAD. Both exercise-based CR programs proved to be effective in mitigating cardiovascular risk factors and positively influencing these cardiac patients' lifestyles. Conversely, individuals who did not engage in a community-based exercise program post-CAD did not exhibit similar improvements in these variables.

Furthermore, at the 6- and 12-month marks post-intervention, the exercise groups continued to maintain health values below baseline values, while the control group maintained the previous upward trend (Study 6). These findings underscore the significant role of exercise-based programs, coupled with multidisciplinary support, in enhancing health outcomes among CR patients.

Our data emphasize the vital role of community-based exercise programs in enhancing health outcomes and recovery post-CAD, which is in line with other studies (Anderson et al., 2016; Candelaria et al., 2020; Zheng et al., 2019).

- **Changes in the patients' lifestyle and the association with long-term cardiovascular risk factors (6- and 12-month follow-up)**

Study 6 suggests that the short-term effects of HIIT and MICT on VO_2peak, PA, QoL, and mental health were sustained after six months and one year of follow-up in CAD patients. Therefore, it seems that HIIT could be a more time-efficient manner to improve VO_2peak and other health outcomes when compared with MICT. Our findings also demonstrate that greater PA levels are associated with less anxious and depressive symptoms in longer-term follow-ups of CAD individuals who completed a 6-week program of exercise-based CR. PA levels 6 and 12 months after participating in community-based exercise CR were higher than pre-CR levels. However, a substantial number of CAD patients fell below MVPA, representing a decrease in PA from the levels exhibited after completing community-based exercise programs. This decline in PA levels aligns with previous studies that suggest the long-term maintenance of PA levels among CR participants is low, with only 30-60% of patients continuing to exercise after six months of completing CR (Hellman, 1997; Bock et al., 2003; Barth et al., 2004; Huffman et al., 2013). Depressive and anxious symptoms also were lower compared to baseline levels, and participants with higher levels of PA showed the lowest levels of depressive and anxious symptomatology. In addition, patients randomly assigned to control with elevated anxiety symptoms at baseline tended to show maintained anxiety symptoms following community-based exercise programs and after 6 and 12 months.

As far as we know, only three studies have investigated long-term outcomes of HIIT compared with MICT in patients with CAD at 6 months (Moholdt et al., 2009) and 12 months (Taylor et al., 2020; Pattyn et al., 2016) and the results are similar to ours. Moholdt et al. (2009) found a superior effect of HIIT compared with MICT on the improvement of VO_2peak and HR recovery at 6 months in patients with CABG, but similar improvements in QoL. At 12 months, the studies found similar improvements between HIIT and MICT in patients with CAD for VO_2peak and other exercise variables, CVD risk factors, QoL, body composition, and MVPA (Taylor et al., 2020, 2021; Pattyn et al., 2016).

- **Delivery of community-based exercise CR programs**

Our results provide program providers with further evidence supporting and encouraging them to consider CR sessions as standard hospital-based or community-based exercise program offerings. Although our results cannot affirm that community-based exercise programs should be offered as usual care for all cardiac patients (e.g., high-risk patients who require close monitoring), these findings align with those of other studies demonstrating the utility of hybrid CR delivery models for eligible patients (Suskin et al., 2019; Clark et al., 2015).

This study also serves as a comprehensive analysis of community patients and is strengthened by including all eligible records since the inception of the Alentejo-based community CR program. Further, this study is the first to describe the characteristics and cardiac conditions of community-based exercise programs in that region and bridging participants in this high-intensity cardiac rehabilitation program. Study findings illustrate that patients of diverse ages and low-risk patients with CAD may opt for community or bridging program types when provided the choice. However, the most optimal HIIT protocol for CVD patients still remains to be defined, taking into account the variations in the patients' phenotype and preferences, as well as the stage of the CR program (e.g. early, after a few weeks, after several months of participation) (Gayda et al., 2016). As a result, it is important to decide with the patient what exercise intensities will be applied in a shared decision-making process. This will assist in long-term adherence to the prescribed exercises.

9.2. Limitations

Several limitations warrant acknowledgment in this study. Firstly, the small sample size could mean that only greater differences would reach the significance level. Secondly, only 13-17% of the patients in this study were women. This sex bias was an unintended consequence of our clinical population but constitutes a limitation of the generalizability of the results. When considering the results of this study, the possible confounding effects of concurrent medications should be considered although no change happened during the study period for doses of lipid-lowering and heart rate control medications. Additionally, the control group did not provide activity diaries, making it impossible to assess their physical activity levels during the 6-week intervention period from baseline, which could have influenced the observed effects.

On March 2020, the Portuguese Society of Cardiology and the Coordination of the Study Group on Effort Pathophysiology and Cardiac Rehabilitation suspended all Cardiac Rehabilitation Programs at a national level to prevent the spread of the new coronavirus (SARS-CoV-2) due to the high risk of contagion in a cardiac population with multiple risk factors. During the study, we faced challenges and obstacles due to global measures that resulted in home confinement. Unfortunately, we had to interrupt the study several times and experienced withdrawals from some participants in participating in the study.

9.3. Conclusions

In summary, considering the impact of community-based exercise CR and the lack of Portugal/Alentejo-based investigation of CR programs this thesis demonstrated the safety and effectiveness of both 6-week HIIT and MICT programs in improving patients' aerobic capacity, PA, QoL, reduced WC, lower fat mass, decreased SB, and reduced anxiety and depressive symptoms. Both exercise-based CR programs proved to be effective in mitigating cardiovascular risk factors and positively influencing these cardiac patients' lifestyles. The HIIT group exhibited superior long-term improvements compared to the MICT group. Conversely, it is crucial to motivate patients to sustain higher levels of PA to enhance both cardiovascular and psychological well-being. Conversely, individuals who did not engage in a community-based exercise CR post-CAD did not exhibit similar improvements in these variables. Notably, the absence of adverse events underscores HIIT as a valuable adjunct or alternative to MICT in community-based exercise programs, serving as a crucial treatment strategy for post-CAD patients.

9.4. Clinical implications

This thesis particularly highlights the importance of rehabilitating CAD patients into community-based exercise programs, providing information on the physical and psychological consequences of CAD and how these consequences can be long-standing. Early screening for problems and referral to rehabilitation may prevent problems from becoming chronic (Studies 3, 4, and 5). Screening should be followed by referral to appropriate CR programs, regarding that problems can remain in the long term (Study 6).

For community-based exercise program pathways to be successful, we need to share research knowledge with clinicians, physiologists, nurses, etc., on post-CAD problems, how they may persist in the long term, and how CAD patients may benefit from CR interventions. These knowledge-sharing activities should include critical care staff, physiologists, general practitioners, and those in rehabilitation services that CAD patients may be referred to CR.

9.5. Future Recommendations

The present findings of this thesis therefore suggest that future intervention studies could use community-based exercise programs to reduce or prevent cardiovascular risk factors and improve physical fitness, physical activity levels, QoL, and mental health.

We have listed some questions that we believe are still pertinent and require further answers:

- Why different exercise intensities matter
- How to build in progression in exercise intensities during CR
- How to personalize this approach based on the patients' abilities and preferences by shared-decision making

Despite research examining the delivery of exercise rehab care to CAD patients and the effectiveness of those community-based programs in different intensities in improving health outcomes to reduce cardiovascular risk factors, no work has evaluated the value of multidisciplinary teams in these CR programs and in improving those long-term outcomes. How it could be important, especially when the patient is young and the cardiac event is unexpected. Plus, qualitative research to explore facilitators and barriers for screening patient survivors for post-CAD problems and strategies for educating all healthcare individuals involved in CR programs.

This statement is intended for healthcare professionals who specialize in exercise for patients with CVD, including cardiologists, physiotherapists, clinical exercise physiologists, and nurses.

We also suggest exploring new programs to reach patients unable to attend rehabilitation cardiac centres, such as home-based, telehealth, and other community-based programs (e.g. with resistance training), which may help mitigate traditional centre-based limitations and additionally, take into account patient preferences.

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APPENDICES

APPENDIX 1. Ethical approval

Document number: 17039

Ethics Committee for Research in the Areas of Human Health and Well-Being University of Évora

The Ethics Committee for Research in the Areas of Human Health and Well-Being hereby informs that its members, Professor Doctor Carlos Silva, Professor Doctor Jorge Fernandes and Professor Doctor Felismina Mendes, decided to give, at the meeting of the 30th of June of 2017, the Favorable Opinion for carrying out the Project "Phase III Cardiac Rehabilitation in Coronary Patients: High-intensity Interval Training or Moderate-intensity Continuous Training?" researchers Catarina Joaquim Gonçalves, Nuno Batalha, Jorge Duarte dos Santos Bravo, Rui Soares and Armando Raimundo.

Vice President of the Ethics Committee

(Professor Doctor Felismina Mendes)

APPENDIX 2. ClinicalTrials.gov registration

ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: October 14, 2023

ClinicalTrials.gov ID: NCT03538119

Study Identification

Unique Protocol ID: CR_UEvora

Brief Title: Comparison Between HIIT and MICT on the Phase III of Cardiac Rehabilitation

Official Title: Phase III Cardiac Rehabilitation in Coronary Patients: High-intensity Interval Training or Moderate-intensity Continuous Training?

Secondary IDs:

Study Status

Record Verification: October 2023

Overall Status: Completed

Study Start: December 19, 2018 [Actual]

Primary Completion: October 30, 2022 [Actual]

Study Completion: June 30, 2023 [Actual]

Sponsor/Collaborators

Sponsor: University of Évora

Responsible Party: Principal Investigator
Investigator: Catarina Joaquim Gonçalves [cgoncalves]
Official Title: Principal Investigator
Affiliation: University of Évora

Collaborators:

Oversight

U.S. FDA-regulated Drug: No

U.S. FDA-regulated Device: No

U.S. FDA IND/IDE: No

Human Subjects Review: Board Status: Approved
Approval Number: 17039
Board Name: Ethics Commission
Board Affiliation: Health and Well Being of University of Evora
Phone: 00351266760220
Email: uevora@uevora.pt
Address:

Largo dos Colegiais 2, 7000-Évora

Data Monitoring:	No
FDA Regulated Intervention:	No

Study Description

Brief Summary: The increase in the prevalence of cardiovascular diseases (CVD), directly associated with the aging of the population, is a concern for public health in Portugal. Given the high prevalence of risk factors and the increasing number of cases of CD throughout Alentejo, where there is no cardiac rehabilitation (CR) coverage, there is an urgent need for the implementation of a CR program.

CR has evolved over the past decades to multidisciplinary approaches focused on education, individualized training, modification of risk factors, and overall well-being of cardiac patients. Studies suggest that high intensity interval training (HIIT) allows greater patient benefits compared to moderate continuous training (MCT), reversal of DC and increased aerobic capacity in CR patients. This study intends to compare HIIT and MCT interventions investigating direct and indirect associations between informally performed physical activity (AF), sedentary behavior, cardiovascular fitness and quality of life (QoL) among patients enrolled in RC programs in phase III.

Detailed Description: According to WHO (1) cardiovascular diseases (CVD) are the number 1 cause of death globally: an estimated 17.5 million people died from CVD in 2012, representing 31% of all global deaths. In 2013 there were 1.9 million deaths resulting from CVD of the circulatory system in the EU-28, which was correspondent to 37.5 % of all deaths considerably higher than the second most prevalent cause of death, cancer.

In Portugal, cardiovascular diseases lead to morbidity and mortality rates, which makes evident the importance in the Public Health scenario and the need to implement measures aimed at primary and secondary prevention. In 2004, cardiovascular diseases signify 39% of all causes of death, since then a reduction in these values has been recorded and, according to more recent data (2013), the values are around 29.5%.

As these pathologies are associated, among other causes, with aging, the Alentejo emerges as one of the regions where the prevalence of these pathologies is greater. In fact, since Alentejo is the oldest region, it becomes an authentic Living Lab. In this way, this study intends to study the effects of different types of cardiac rehabilitation (CR) programs, emphasizing in particular the use of a high intensity interval program that we will compare with a traditional program.

For the program will be recruited patients who have been admitted in the Cardiology Services at Espírito Santo Hospital in Évora. Participants of both sexes will be included, between 18 and 80 years of age, meeting the criteria for low or moderate risk, class B for participation and exercise supervision, absence of signs/symptoms after cardiac surgery, with a left ventricular ejection fraction greater than 40%, according to the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation.

Those who meet the inclusion criteria will be evaluated in a clinical context in order to determine the capacity to integrate phase III of CR. This phase will last about 6 weeks, will be held at the Nursing School located at the Espírito Santo Hospital.

The sessions will be supervised and will take place on a cycloergometer and treadmill, 3 times a week for 6 consecutive weeks. If a session is lost, it will be recovered that week or the following week. Each session will be limited to three participants.

The HIIT protocol will consist of four four-minute intervals at high intensity, stimulating 85-95% of peak-FC followed by active recovery at 70% peak-FC for a total of 20 minutes. The MCT protocol consists of continuously exerting moderate intensity, causing a peak-FC 70-75% for 27.5 minutes to equal the energy expenditure of the HIIT protocol. Both protocols will include a warm-up of 10 minutes at low moderate intensity (50-70% of peak-FC) and a 3 to 5 minute calm return period was performed at 50% of peak-FC.

During the intervention, the workload, FC and the subjective effort perception scale (EPE - Borg) will be recorded throughout each session, every minute for the HIIT training and all other minutes for the MTC. During the intervention the load will be adjusted to obtain the target FC.

After the exercise session, participants will complete 1 of 18 items of the Physical Activity and Pleasure Scale (PACES) on a weekly basis in which subjects rate their appreciation for the exercise of that week on a seven-point scale.

In the same period, the usual medical recommendations for cardiac rehabilitation through exercise will be provided to the Control Groups (phase III).

When subjects complete phase III CR, they will be given guidelines on exercise and nutrition. The intention is that participants after the program have adopted a healthy lifestyle, where the practice of physical exercise is a reality. The intention is also to verify if participation in one of the different exercise programs that have been implemented, in phase III of CR, can possibly provide better results both in maintaining good life habits and also in reducing the time in the sedentary activities, the "Active Couch Potato" phenomenon. More than solving a health problem at a certain stage of a subject's life, it is intended to consolidate healthy habits of life.

In order to verify which type of program allows to modify the habits of life towards the increase of the practice of physical activity, as well as the maintenance of these habits, we will carry out a follow-up at 6 months and one year after the beginning of the intervention.

Conditions

Conditions:	Patients With Coronary Artery Disease
Keywords:	Cardiac Rehabilitation High Intensity Interval Training Moderate Intensity Continuous Training Secondary prevention Cardiovascular Risk Factors Exercise-based Rehabilitation

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	N/A
Interventional Study Model:	Parallel Assignment
Number of Arms:	3
Masking:	None (Open Label)
Allocation:	Randomized

Enrollment: 69 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: High Intensity Interval Training Program Three sessions of exercises will be performed weekly with duration of 30 min to 45 min, divided into warm up, aerobic exercise (4x4 high-intensity intervals at 85%-95%) and recovery.	High Intensity Interval Training Program The HIIT group performed 4 × 4-minute high-intensity intervals at 85%-95% HRpeak followed by a 1-minute recovery interval at 40% HRpeak, predicted with a supervised graded exercise test on a treadmill with the Bruce protocol. The protocol will include a warm-up of 10 minutes at low moderate intensity (50-70% of HRpeak) and a 3 to 5 minute calm return period at 50% of the HRpeak. The supervised sessions will take place on treadmill, 3 times a week for 6 consecutive weeks. If a session is lost, it will be recovered that week or the following week. Each session will be limited to three participants. Other Names: • HIIT
Experimental: Moderate Intensity Continuous Training Program Three sessions of exercises will be performed weekly with duration of 45 min to 60 min, divided into warm up, aerobic exercise (continuous intensity at 70-75%HRpeak) and recovery.	Moderate Intensity Continuous Training Program The MICT protocol (usual care) consisted of a continuous bout of moderate-intensity exercise to elicit 70-75% HRpeak, rating of perceived exertion 3 to 5 (fairly light to somewhat hard), for 27.5 minutes to equate the energy expenditure with the HIIT protocol. The protocol will include a warm-up of 10 minutes at low moderate intensity (50-70% of HRpeak) and a 3 to 5 minute calm return period at 50% of the HRpeak. The supervised sessions will take place on treadmill, 3 times a week for 6 consecutive weeks. If a session is lost, it will be recovered that week or the following week. Each session will be limited to three participants. Other Names: • MICT
No Intervention: Control Group Usual care. The patients will receive nutritional counseling as well as physical activity.	

Outcome Measures

Primary Outcome Measure:

1. Change from Baseline between and within groups comparison in Blood Pressure Profile
   Systolic and diastolic blood pressure, in mmHg, and Basal Heart Rate, in heart beats per minute, to assess blood pressure profile.

   [Time Frame: 0 weeks, 6 weeks, 6 months and 12 months]
2. Change from Baseline between and within groups comparison in Lipid Profile
   Evaluated with blood tests to assess fasting triglyceride levels (mg/dL), total cholesterol (mg/dL), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL), insulin (mg/dL) and glucose (mg/dL)

   [Time Frame: 0 weeks, 6 weeks, 6 months and 12 months]
3. Change from Baseline between and within groups comparison in Body Composition
   Evaluated with the Dual-energy X-ray Absorptiometry to assess body fat mass (%) and body lean mass (%)

[Time Frame: 0 weeks, 6 weeks, 6 months and 12 months]

4. Change from Baseline between and within groups comparison in Aerobic Capacity
   Evaluated with the 6 Minute Walking Test, in meters, to assess aerobic capacity

   [Time Frame: 0 weeks, 6 weeks, 6 months and 12 months]

5. Change from Baseline between and within groups comparison in Muscle Strength
   Evaluated with the Biodex (Peak Torque) to assess lower body muscle strength

   [Time Frame: 0 weeks, 6 weeks, 6 months and 12 months]

6. Change from Baseline between and within groups comparison in Physical Activity Levels
   Patients were asked to wear a triaxial accelerometer (ActiGraph GT3X) on their hip placed anterior to the right iliac crest for 7 consecutive days during waking except when bathing or swimming. Acceleration data from the 3 planes were processed with ActiGraph software (ActiLife, version 6) using 15#s epochs (raw data recorded at 30 Hz) and the standard filter and were integrated into a vector magnitude count by taking the square root of the sum of squared axes (vertical, anterior–posterior, and medial–lateral).

   [Time Frame: 0 weeks, 6 weeks, 6 months and 12 months]

Secondary Outcome Measure:

7. Change from Baseline between and within groups comparison in Health-related Quality of Life
   Evaluated with the Short Form Health Survey 36 (SF-36V2) questionnaire, total score, to assess health-related quality of life. The questionnaire consisted of the rating scale, Short Form 36 (SF-36 Quality Metric, Lincoln, Rhode Island, USA), with eight domains: physical functioning, role-physical, role-emotional, social functioning, mental health, vitality, bodily pain and general health. This instrument addresses health concepts from the patient's perspective and the scores range from 0 (worst) to 100 (best).

   [Time Frame: 0 weeks, 6 weeks, 6 months and 12 months]

8. Change from Baseline between and within groups comparison in Anxiety and Depression
   Evaluated with the Hospital Anxiety and Depression Scale (HADS) questionnaire, total score, to assess health-related anxiety and depression levels. The total HADS score ranged between 0-42 with 0-14 being considered as low, 15-28 considered as moderate, and 29-42 being considered as high. For each subscale (anxiety and depression subscales), the scores ranged between 0 to 21, where 0-7 was considered low, 8-14 being moderate, while 15-21 was considered high.

   [Time Frame: 0 weeks, 6 weeks, 6 months and 12 months]

9. Change from Baseline between and within groups comparison in Bone Composition
   Evaluated with Dual-energy X-ray Absorptiometry to assess bone mineral density (g/cm2)

   [Time Frame: 0 weeks, 6 weeks, 6 months and 12 months]

10. Change from Baseline between and within groups comparison in Sleep Quality
    Evaluated with the Actigraph accelerometers, in Actigraph wGT3X-BT, during 7 days of a normal week, covering 5 days weeks and 2 days of weekend to analyze sleep quality. patients were asked to wear a triaxial accelerometer (ActiGraph GT3X) on their hip placed anterior to the right iliac crest for 7 consecutive days during sleeping hours. Acceleration data from the 3 planes were processed with ActiGraph software (ActiLife, version 6) using 15#s epochs (raw data recorded at 30 Hz) and the standard filter and were integrated into a vector magnitude count by taking the square root of the sum of squared axes (vertical, anterior–posterior, and medial–lateral).

    [Time Frame: 0 weeks, 6 weeks, 6 months and 12 months]

Other Pre-specified Outcome Measures:

11. Change from Baseline between and within groups comparison in Aerobic Capacity
    Evaluated with the Balke treadmill protocol to assess aerobic capacity response (ml.kg 1.min 1)

    [Time Frame: 0 weeks, 6 weeks, 6 months and 12 months]

12. Change from Baseline between and within groups comparison in the Perceived Exertion during intervention
    The Borg Scale is a 10-point scale ranging from 0 to 10 with anchors ranging from "No exertion at all" (0) to "Maximal exertion". Patients were asked to rate their exertion before (pre-exercise), minute to minute of exercise, and post-exercise.

[Time Frame: 0 weeks, 6 weeks, 6 months and 12 months]

Eligibility

Minimum Age: 18 Years

Maximum Age: 80 Years

Sex: All

Gender Based: No

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- low-moderate risk for physical exercise, with the following pathologies / conditions:
  - stable coronary disease;
  - after acute myocardial infarction;
  - after coronary angioplasty;
  - after cardiac surgery (coronary revascularization or valve surgery);
- stable chronic heart failure in class I-II of the New York Heart Association;
- acceptance of the informed consent assumptions of CR programs;
- must not have participated in physical exercise programs in the 3 months preceding the referral;
- should not have more than one hour of vigorous physical activity per week according to the International Physical Activity Questionnaire.

Exclusion Criteria:

- presenting symptoms of heart failure of class III and IV according to the New York Heart Association (or documented signs and symptoms of chronic heart failure with ejection fraction >45%);
- uncontrolled arrhythmias;
- severe chronic obstructive pulmonary disease;
- uncontrolled hypertension;
- symptomatic peripheral arterial disease; unstable angina;
- uncontrolled diabetes;
- inability to perform a maximum VO2 test;
- locomotion exclusively dependent on mechanical means.

Contacts/Locations

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Principal Investigator: Catarina Gonçalves, MSc

Principal Investigator: Armando Raimundo, Ph.D.
Principal Investigator: Jorge Bravo, Ph.D.

IPDSharing

Plan to Share IPD: No

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Citations:

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World Health Organisation. Global recommendations on physical activity for health. 2010

Links:

APPENDIX 3. Table S1: Complete search strategy for MEDLINE

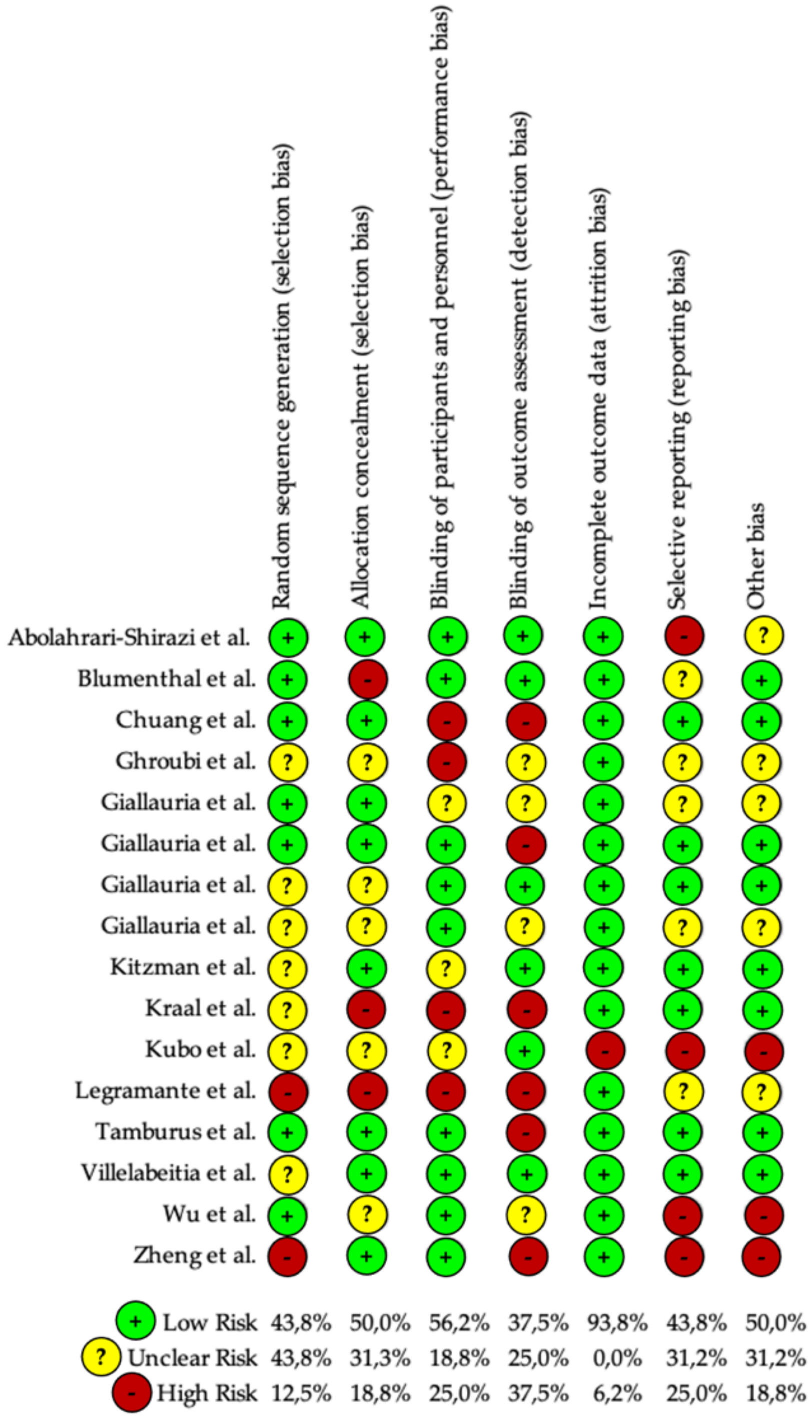
Key concepts	**Concept 1-** Patient, Population **Patients with cardiac diseases (OR)**		**Concept 2 -** Intervention (or Exposure) **Exercise in Cardiac Rehabilitation (OR)**		**Concept 3 -** Comparison (or Control) if appropriate **Exercise intensity/Programs (OR)**		**Concept 4 -** Outcome **Aerobic capacity (OR)**
Free text terms / natural language terms	Myocard* near/5 isch*mi* Isch*mi* near/5 heart Myocard* near/5 infarct* Heart near/5 infarct* Angina Coronary near/5 disease* or bypass or thrombo* or angioplast* (Percutaneous next coronary near/2 interven* or revascular* Angioplast* coronary or arterial near/4 dilat* Endoluminal next repair* Stent* Pci or ptca Atherectom* Acute next coronary next syndrom*	AND	Rehabilitat* Physical* near/5 fit* or train* or therap* or activit* train* near/5 strength* or aerobic* or exercise* exercise* or fitness near/3 treatment or intervent* or program* Kinesiotherap* patient* near/5 educat* lifestyle or life-style near/5 interven* or program* or treatment* self near/5 manag* or care or motivate* Psychotherap* Psycholog* near/5 intervent* counselling or counseling behavior* or behaviour* near/5 modify or modificat* or therap* or change psycho-educat* or psychoeducat* motivat* near/5 (intervention or interv* health near/5 educat* psychosocial or psycho-social cognitive near/2 behav*	AND	Exercise Test/methods* High-Intensity Interval Training* HIIT HIIT or HIT Exercise intensit* Exercise next intensit* Exercise near/5 intensit* Exercise Intensity Program* intensit* near/5 interven* or program* or treatment* intensity* near/5 interven* or program* or treatment* intensit* near/5 method* intensit* near/5 exercise* intensit* near/5 program* Moderate continuous training Moderate-intensity continuous training moderate near/4 training MCT moderate continuous training near/5 methods* moderate continuous training near/5 standards* *rehabilitation near/5 exercise* *rehabilitation near/5 program* Home-based Home-based near/5 methods* Home-based near/5 satandards* Aerobic Exercises Anaerobic Exercises No exercise	AND	Heart Failure next mortality Heart Failure near/5 mortality Cardiovascular Capacity* Oxygen Consumption/physiology*
Controlled vocabulary terms / Subject terms	Intervention (MeSH) Coronary Artery Bypass (MeSH) Percutaneous Coronary Intervention (MeSH) Angioplasty (MeSH) Stents (MeSH) Atherectomy (MeSH)		Exercise Therapy (MeSH) Sports (MeSH) Physical Exertion (MeSH) Exercise (MeSH) Rehabilitation (MeSH) Physical Education and Training (MeSH) Patient Education as Topic (MeSH) Self Care (MeSH) Psychotherapy (MeSH) Counseling (MESH) Health Education (MeSH)		Exercise Tolerance (MeSH) High Intensity Interval Training/methods (MeSH) High Intensity Interval Training/standards (MeSH) Telerehabilitation (MeSH) Telerehabilitation/methods (MeSH) Telerehabilitation/standards (MeSH) Cardiac Rehabilitation/methods (MeSH) Cardiac Rehabilitation/standards (MeSH) High Intensity Interval Training/standards (MeSH)		Surveys and Questionnaires (MeSH) Cardiovascular Diseases/epidemiology (MeSH) Cardiovascular Diseases/mortality (MeSH) Morbidity/trends (MeSH) Motor Activity/physiology*(MeSH) Prevalence (MeSH) Risk Factors (MeSH) Sedentary Lifestyle (MeSH) Oxygen Consumption/physiology (MeSH) Predictive Value of Tests (MeSH) Reproducibility of Results (MeSH) Recovery of Function (MeSH)

APPENDIX 4. Table S2: Summary of study characteristics

		Participant characteristics			Rehabilitation protocols										Primary Outcome	
Study	**Year**	**n (men)**	**Age**	**Conditions**	**Length**	**Freq.**	**Exercise duration**	**Intensity**	**Mode**	**Type**	**Sup.**	**Prog.**	**Res.**	**Comp.**	**ΔVO2R**	**ΔVO2AT**
Abolahrari-Shirazi et al.	2018	25 (NS)	56.76 (8.71)	PCI	7	3	W:5; A:30; C:5	40-70%VO2p	CY+AE+TM+RES	Cont	CL/H	Y	Y	Y	8.2	
		25 (NS)	57.64 (7.85)	PCI	7	3	W:5; A:45; C:5	40-70%VO2p	CY+AE+TM	Cont	CL/H	Y	N	Y	9.4	
		25 (NS)	57.32 (9.41)	PCI								N	N	Y	1.8	
Blumenthal et al.	2005	48 (31)	62 ± 11	IHD EMI	16	3	W:10; A:35; C:10	70-85%HRR	WK	Cont	CL	N	N	N	1.9	
		44 (29)	63 ± 12	IHD EMI	16	1			STM		CL	N	N	N	0.3	
		42 (32)	63 ± 9	IHD EMI								N	N	N	-0.3	
Chuang et al.	2005	17 (15)	64 ± 8	CABG	12	2	A:30	70-80%HRp, 60-70%VO2p, RPE 11-15	TM	Cont	CL	N	N	N	4.76	
		15 (13)	69 ± 12	CABG								N	N	N	1.72	
Ghroubi et al.	2013	16 (NS)	59 ± 6	CABG	8	3	W:10; A:20; C:10	70%HRR	CE	Cont	CL	N	N	N	1.70	
		16 (NS)	59 ± 2	CABG	8	3	W:5; A:20;	70%HRR (20-30% Peak torque)	RES	Cont/Int	CL	N	Y	N	4.00	
Giallauria et al.	2006	22 (16)	55 ± 8	MI	12	3	W:5; A:30; C:5	60-85%VO2p	CE+CY	Cont	CL/H	Y	N	N	4.2	
		22 (17)	54 ± 10	MI	12	3	W:5; A:30; C:5	60%VO2p	CE	Cont	CL	Y	N	N	3.8	
Giallauria et al.	2009	26 (2)	58 ± 8	MI	12	3	W:5; A:30; C:5	60-70%VO2p	CE	Cont	CL	N	N	N	4.3	2.3
		26 (2)	57 ± 10	MI								N	N	N	-2	-1.7
Giallauria et al.	2011	37 (28)	61 ± 7	MI	26	3	W:5; A:30; C:5	60-70%VO2p	CE	Cont	CL	N	N	Y	4	
		26 (23)	52 ± 10	MI	26							N	N	N	1	
Giallauria et al.	2013	25 (22)	54 ± 7	MI	26	3	W:5; A:30; C:5	60-70%VO2p	CE	Cont	CL	N	N	N	4.00	
		21 (18)	54 ± 9	MI								N	N	N	1.00	
Kitzman et al.	2013	32 (NS)	70 ± 7	FMD CAS	16	3	W:10; A:20(WK)+20(E); C:10	40/50-70%HRR	WK, AE, CE	Cont	CL	Y	N	N	1.6	
		31 (NS)	70 ± 7	FMD CAS	16	2						N	N	N	-0.2	
Kraal et al.	2013	25 (21)	56 ± 9	PCI CABG	12	2	A:45-60	70-85%HRp	TM, CE	Cont	CL	N	N	N	2.40	
		25 (22)	61 ± 8	PCI CABG	12	2	A:45-60	70-85%HRp	TM, CE	Cont	CL/H	N	N	N	3.20	
Kubo et al.	2004	24 (21)	59 ± 12	MI	12	3	A:320	60-70%HRp	TM, CE	Cont	CL	N	N	N	2.9	
		24 (17)	62 ± 12	MI	12							N	N	N	-0.3	
Legramante et al.	2017	43 (NS)	60 ± 9	CABG	2	6x2	A:30	75-85% HRp	WK, CAL, CE	Cont	CL	Y	Y	N	2.6	
		39 (NS)	58 ± 8	CABG	2	6x2	A:30	75-85% HRp	WK, CAL	Cont		Y	N	N	0.9	
Tamburus et al.	2016	15 (NS)	57 ± 7	CAD	16	3	W:10; A: 30-40; C:10	70-110% VO2VAT	CE	Int	CL	Y	N	N	1.51	
		17 (NS)			16							N	N	N	-1.86	
		15 (NS)	57 ± 7	None	16	3	W:10; A: 30-40; C:10	70-110% VO2VAT	CE	Int	CL	Y	N	N	1.95	
		17 (NS)		None	16							N	N	N	-1.43	
Villelabeitia et al.	2017	37 (29)	58 ± 11	CAD	8	3	W:5-12; A:15-30; C:5-13	104.5% ± 22.2% VO2p (1ºmonth) and 134.5% ± 29.7% VO2p (2ºmonth)	CE	Int	CL	Y	N	N	4.5	
		36 (33)	58 ± 11	CAD	8	3	W:5-12; A:15-30; C:5-13	64.2% ± 8.5% VO2p (1ºmonth) and 69.5% ± 8.7% VO2p (2ºmonth)	CE	Cont	CL	Y	N	N	2.46	
Wu et al.	2006	18 (NS)	63 ± 7	CABG	12	3	W:10; A:30-60; C:10	60-85 %HRp	TM, CE	Cont	CL	N	N	N	8.50	
		18 (NS)	61 ± 8	CABG	12	3	W:10; A:30-60; C:10	60-85 %HRp, RPE 11-13	WK	Cont	H	N	N	N	6.50	
		18 (NS)	62 ± 10	CABG								N	N	N	3.50	
Zheng et al.	2008	27 (NS)	NS	MI	26	3	W:15; A:30; C:15	100% AT	CE	Cont	CL	N	N	N	3.10	
		30 (NS)	NS	MI	26							N	N	N	0.3	

Note. NS, not stated/missing. n(men) presented as the sample size (number of men). Age presented as mean ± SD years. Conditions: MI, myocardial infarction. CABG, coronary artery bypass graft. PCI, percutaneous coronary intervention. CAD, coronary artery disease. IHD, ischemic heart disease. EMI, exercise-induced myocardial ischemia. FMD, endothelial-dependent flow-mediated arterial dilation. CAS: carotid artery stiffness. Rehabilitation protocols: Length presented as no. of weeks. Frequency (Freq.) presented as sessions per week. Exercise Duration: presented as minutes per session: W, warm-up. A: aerobic component (interval programs presented as interval x duration). C, cool-down. SMT: stress management training. R, recovery. wk, week. Intensity: %HRp, % peak heart rate. %HRR, % heart rate reserve. $\%VO_2peak$, % peak oxygen uptake. %AT/VT, % of anaerobic/ventilatory threshold. RPE, rating of perceived exertion. Mode: TM, treadmill. CE, cycle ergometer. AE, arm ergometer. RES, resistance training protocol. WK, walking/jogging. CY, cycling, training. CAL: Calisthenics. Type: Cont, continuous training. Int, interval. Supervision (Sup.), level of monitoring/supervision: CL, clinic-based. H, home-based. Progressive (Prog.), whether aerobic exercise intensity was re-evaluated during the program: Y, yes. N, no. Resistance exercises (Res.): Y, yes. N, no. Comprehensive rehabilitation (Comp.), exercise training plus education and risk factor management: Y, yes; N, No. Outcomes: $\Delta\dot{V}O_2R$, change in relative VO_2peak (presented as $mL{\cdot}kg^{-1}{\cdot}min^{-1}$).

APPENDIX 5. Figure S3: Outcome of the risk of bias assessment



APPENDIX 6. Systematic Review Registration

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Exercise intensity in cardiac rehabilitation: systematic review

Citation

Catarina Goncalves. Exercise intensity in cardiac rehabilitation: systematic review. PROSPERO 2018 CRD42018097319 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018097319

Review question

Exercise intensity in cardiac rehabilitation – Systematic Review

Searches

We will updated searches from the previous Cochrane review, by searching Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 6, 2014) from April 2018 to July 2018. We also searched MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCO) and Science Citation Index Expanded (April 2018 to July 2018). Additional linked searches will be performed in the references for the studies found.

Types of study to be included

We will include RCT to compare aerobic capacity changes resulting from exercise interventions in cardiac rehabilitation, focusing in the exercise intensity.

Condition or domain being studied

Experimental randomised controlled trials (RCT) of exercise based interventions, with a control group, with exercise group (or groups), which describe exercise intensities, including data for risk ratio and confidence intervals.

Participants/population

Participants of all ages who have stable coronary heart disease, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty or another transcatheter procedure, or have had a myocardial infarction.

Intervention(s), exposure(s)

We will include RCT that report at least one of the following exposures: cardiorespiratory fitness (VO2 peak or VO2 at anaerobic threshold), mortality, morbidity, myocardial infarction, revascularizations, hospitalisation related to cardiac disease.

Comparator(s)/control

Effectiveness of different exercise intensities in patients with cardiac diseases.

Main outcome(s)

Cardiorespiratory fitness (VO2 peak or VO2 at anaerobic threshold).

Timing and effect measures.

VO2 max testing before and after the exercise intervention

Additional outcome(s)

Mortality (total and cardiovascular), recurrences of myocardial infarction (fatal and non-fatal), revascularizations (CABG, PCI), hospitalisations and health-related quality of life assessed using validated instruments (e.g. SF-36, EQ-5D) in patients with cardiac diseases.

Data extraction (selection and coding)

The following terms will be used initially: cardiac rehabilitation, cardiorespiratory fitness. (MeSH terms: interval training, exercise, intensity, physical therapy, cardiovascular disease, exercise therapy).

Firstly we will include a detailed assessment of the titles and abstracts to determine those meeting the requirements for inclusion. In case of doubts, full texts will be assessed to decide whether it meets these criteria. All records will be doubly evaluated, by two blinded reviewers.

Afterwards, all the references identified as potentially eligible will be evaluated in parallel by two blinded reviewers. A third expert, not involved in previous processes, will be consulted in case of any discrepancies that might arise.

Statistical estimates will either be extracted directly from included studies or calculated from reported 2x2 data.

For each RCT, the author, year of publication, patient characteristics (e.g. age, sex, cardiac disease diagnosis) and details of the intervention (including mode of exercise, duration, frequency, intensity and pre- and post-VO2 peak values, and change in VO2 peak/VO2 at anaerobic threshold).

If will be there multiple reports of the same study, we will assess the duplicate publications for additional data. We will contact study authors if necessary in order to provide additional information.

Risk of bias (quality) assessment

The reviewers will use the checklist included in the application RevMan 5.3 (RevMan 2014), for assessing the quality of the intervention studies. In addition, reviewers will use Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) to resolve those cases where doubts may arise regarding the diagnostic validation studies.

Studies results will be inserted in RevMan 5.3 (RevMan 2014) application including clinical characteristics, context items and details of the intervention.

Also will be included on this form will be the RevMan 5.3 (RevMan 2014) check-list items for assessing the quality of diagnostic studies and, if applicable, those arising from the QUADAS-2 regulations for publication

Strategy for data synthesis

The Systematic Review will be performed depending on the degree of heterogeneity and comparability of studies. Using RevMan 5.3 (RevMan 2014), the sensitivity, specificity and positive and negative predictive, positive and negative likelihood ratios should be reported. In case of excessive heterogeneity, no meta-analysis will be carried out and a narrative review of the different studies will be performed.

Heterogeneity will be explored with visual inspection of the forest plot diagrams for sensitivity and specificity and the likelihood ratio test for these two dimensions and performing χ^2 test. Inconsistency will be also quantified using I^2 test. The heterogeneity will be stratified into three levels, following the criteria of Higgins et al. (2003).

In case of non-excessive heterogeneity, the data will be analysed using a meta-analysis based on random effects and standardised mean difference. If standard deviations are not published, RevMan 5.3 software will be used for p values entrance. If no p values or standard deviations are published, the highest standard deviation will be used from similar studies to ensure results are conservative.

We will stratify systematic review of each outcome according to the length of trial duration i.e. 'short-term' follow up (6 to 12 months); 'medium-term' follow-up (13 to 36 months), and 'long- term' follow-up (more than 36 months).

Analysis of subgroups or subsets

Studies will be grouped by exercise intensities in cardiac rehabilitation according to the duration of the intervention (up to 6 weeks, 7–12 weeks, and more than 12 weeks).

Contact details for further information

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Organisational affiliation of the review

University of Evora

Review team members and their organisational affiliations

Miss Catarina Goncalves. University of Evora

Collaborators

Dr Armando Raimundo. University of Evora

Dr Jorge Bravo. University of Evora

Type and method of review

Epidemiologic, Intervention, Meta-analysis, Methodology, Prevention, Qualitative synthesis, Systematic review

Anticipated or actual start date

03 April 2018

Anticipated completion date

03 July 2019

Funding sources/sponsors

None

Conflicts of interest

Language

English

Country

Portugal

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Cardiac Rehabilitation; Exercise Therapy; Heart Diseases; Humans

Date of registration in PROSPERO

12 June 2018

Date of first submission

22 May 2018

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

12 June 2018

APPENDIX 7. Clinical Assessments

Projeto Reabilitação Cardíaca Fase III HESE-UÉ Hospital Espírito Santo E.P.E.

Paciente nº ___ **Data:** ___/___/_____

Grupo 6 – Variáveis Clínicas *(a preencher pelo profissional de saúde)*

PAS (mmHg): ________ PAD (mmHg): ________

Frequência Cardíaca Basal: ______________

Radioisótopos FEVE (%): __________ Radioisótopos FEVD (%): __________

DDVE (cm) no ecocardiograma: __________ NYHA, I/II/III/IV (%): __________

*FEVE, fração de ejeção de ventrículo esquerdo; FEVD, fração de ejeção de ventrículo direito; DDVE, diâmetro diastólico de ventrículo esquerdo; N.Y.H.A., New York Heart Association.

Triglicéridos: ________ Colesterol total: ________ HDL: ________ LDL: ________

Sódio: ________ Cortisol: ________ Nível de glicose: ________ Insulina: ________

Grupo 7 – Medicação e Condições Médicas

Medicação: ____

Dosagem cardíacas: ____

Condições médicas: ____

____

Grupo 8 – Composição Corporal *(a preencher pelo fisiologista do exercício)*

Peso: ____kg Altura: ____m IMC: ____kg/m² Classificação IMC: ______________

%MG: ________ % Peso MG: ________ kg Densidade mineral óssea: __________

Circunferência do abdómen: _______ cm Circunferência do quadril: _______ cm

Relação W/h: ______________ Medida de Pregas Cutâneas: ________________ %

Grupo 9 – VO_2Máximo

Teste 6 minutos a caminhar:

Resultado: _______________________ metros **Número de voltas:** ______________

Teste de Balke:

Resultado: _______________________

Projeto Reabilitação Cardíaca Fase III HESE-UÉ Hospital Espírito Santo E.P.E.

Grupo 10 – Força Muscular (Biodex)

Pico de Torque 60º/s extensão: ______________ N-M

Pico de Torque 60º/s flexão: ______________ N-M

Pico de Torque BW 60º/s extensão: ______________ N-M

Pico de Torque BW 60º/s flexão: ______________ N-M

Fadiga de trabalho 180º/s extensão: ______________ %

Fadiga de trabalho 180º/s flexão: ______________ %

Coeficiente de Variação 60º/s extensão: ______________ %

Coeficiente de Variação 60º/s flexão: ______________ %

Rácio agonista-antagonista extensão: ______________ %

Grupo 11 – Atividade Física por Acelerometria

Número do Acelerómetro: _______ Data de Entrega: ___/___/_____

Código Acelerómetro: _______________ Data de Recolha: ___/___/_____

Data de Início: ___/___/_____ Data de Fim: ___/___/_____

Resultados:

Sedentário: _______________________ %

Atividade Leve: _______________________ %

Atividade Moderada a Vigorosa: _______________________ %

Grupo 12 – Questionários

Comportamento do sono

Resultado: _______________________

Questionário SF-36

Resultado: _______________________

Questionário EQ-5D

Resultado: _______________________

Questionário do Nível de Ansiedade e Depressão (escala de ansiedade e depressão hospitalar)

Resultado: _______________________

APPENDIX 8. Flyer of the study

APPENDIX 9. Informed Consent

Informed Consent

Project Title: Phase III Cardiac Rehabilitation in Coronary Patients: High Intensity Interval Training or Moderate Intensity Continuous Training?

We would like to invite you to participate, voluntarily, in a study on changes in several indicators associated with physical exercise in Cardiac Rehabilitation in phase III. Please read carefully the entire content of this document. Do not hesitate to request more information from the responsible investigator if you are not completely clear. Check that all information is correct. If you understand that everything is in order and if you agree with the proposal being made to you, then sign this document.

1. I was informed that the program aims at the prevention and control of cardiovascular risk factors through a Cardiac Rehabilitation intervention in phase III integrated in physical exercise, clinical and psychological aspects.

2. Under the Cardiac Rehabilitation program in phase III in exercise, my participation in a research study was requested.

3. This study aims to analyze changes in body composition, physical fitness, muscle strength, quality of life, psychophysical parameters, biochemical indicators, among other clinical factors associated with physical exercise in Cardiac Rehabilitation in Phase III, after 6 months and 12 months involving intensive lifestyle modification.

4. My participation will include taking the following exams:

- Objective assessment of physical activity and sedentary lifestyle by accelerometry;

- Assessment of functional physical fitness through a specific battery of physical tests for this purpose;

- Determination of the maximum aerobic capacity through the Balke VO2max test and the 6-minute walk test;

- Estimation of fat mass, muscle mass and bone mass by whole-body X-ray densitometry;

- Evaluation of the peak-torque in the extension and flexion of the lower limbs, as well as evaluation of the agonist/antagonist ratio, using an isokinetic dynamometer;

- Personal clinical characterization (cardiac medication and dosage, medical conditions, systolic and diastolic blood pressure, baseline heart rate);

- Assessment of health-related quality of life using the SF-36 questionnaires;

- Assessment of the level of anxiety and depression through the hospital anxiety and depression questionnaire;

- Evaluation of several biochemical indicators: complete blood count, glycated hemoglobin, C-reactive protein, TSH, total T3, free T4, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, sodium, potassium, glucose and insulin.

5. The research study is free and involves the use of accelerometers, as well as the performance of all the tests indicated in point three of this informed consent.

6. I undertake to attend the evaluation times indicated in point four of this informed consent.

7. The risks of my participation in the research study are those associated with participation in a clinically supervised cardiac rehabilitation program.

8. The research study is not responsible for damages or injuries caused by non-compliance, or different compliance with the instructions and/or recommendations of the experts involved in it.

9. None of the specifications of this informed consent should be interpreted or considered as a promise or guarantee of progress and/or results by the subject.

10. I understand that through my participation I will be contributing to the evolution of scientific knowledge in this area and that it is also possible that, in the longer term, the results of this study will contribute to the implementation of effective Cardiac Rehabilitation programs.

11. I understand that the information about me and my health collected for this study will be used for the purposes of the study and for associated additional scientific research. The information will be filed in paper and electronic format, with a code number to protect my privacy. Thus, even if the results of the study are published, your identity will remain confidential.

12. I understand that the regulatory authorities and the members of the ethics committee may have access to the archived information and examine the records made within the scope of the study, being subject to a duty of secrecy regarding them. By signing this form, I authorize direct access to these records, under the terms described herein.

13. I know that, through the principal investigator, I will be able to access all the information collected about me, as well as request the rectification of any inaccuracies that I detect. This access to my information can be postponed, in case it can delay the continuation of the study, but it cannot be denied.

14. I have been informed that I will not be compensated monetarily for my participation in the research study.

15. I understand that I have the possibility to approach those responsible for the research study whenever I feel that my student has been put at risk.

16. I have read all of the above information. The nature, risks and benefits of the research study were explained to me. I assume the risks involved and understand that I can withdraw my consent and stop his participation at any time, without this affecting the follow-up he will receive and without this implying the loss of any benefits he would be entitled to if he had taken another option. By signing this consent, I am not waiving any legal rights, claims, medication or treatment. A copy of this form will be provided to me

____

Participant's full name

________________________________ ______________

Participant's signature | Date

I certify that I have explained to the participant in this research study the nature, purpose, potential benefits and risks associated with participating in the same. I provided a copy of this form to the study participant.

________________________________ ______________

Signature of the researcher who obtained consent | Date

APPENDIX 10. G*Power calculation

[7] -- Thursday, March 02, 2017 -- 10:43:06
F tests - ANOVA: Repeated measures, between factors

Analysis:	A priori: Compute required sample size		
Input:	Effect size f	=	0,3
	α err prob	=	0,05
	Power (1-β err prob)	=	0,8
	Number of groups	=	3
	Number of measurements	=	4
	Corr among rep measures	=	0,5
Output:	Noncentrality parameter λ	=	10,3680000
	Critical F	=	3,1296440
	Numerator df	=	2,0000000
	Denominator df	=	69,0000000
	Total sample size	=	66
	Actual power	=	0,8123011

APPENDIX 11. Patients' standardized questionnaire

Projeto Reabilitação Cardíaca Fase III HESE-UÉ

1.Paciente nº ______ **2.Data:** ___/___/_____

Grupo 1 – Informações Gerais

3.Nome: ____________________________ **4.Género:** F ☐ M ☐ **5.Idade** ______

6.Raça: Caucasiano ☐ Negro ☐ Amarelo ☐ **7.Data de Nascimento:**___/___/_____

8.Nacionalidade: ____________________ **9.Estado Civil** ______________________

10.Situação Profissional: Ativo ☐ Desempregado ☐ Reformado ☐

11.Contacto(s): ____

Grupo 2 – Doença Cardíaca e Atividade Ambulatória

12.a Doença(s) cardíaca(s): ____

12.b Tempo de diagnóstico da doença cardíaca: ____________________________

13.Tem história familiar de doença cardíaca? Sim ☐ Não ☐

14. Tem história familiar de ataques cardíacos? Sim ☐ Não ☐

15. Tem história familiar de morte por doença(s) cardíaca(s)? Sim ☐ Não ☐

16.a Já esteve internado por doença cardíaca? Sim ☐ Não ☐

16.b Se sim, quantas vezes? _______________

16.c Se sim, quanto tempo passou desde o último internamento? _______________

Grupo 3 – Outras Doenças

17.a Tem alguma outra doença? Sim ☐ Não ☐
17.b Se sim, qual/quais a(s) doença(s)? ____________________________________
17.c Se sim, há quantos anos tem? __________________
18.a Tem colesterol elevado? Sim ☐ Não ☐ Não sei ☐
18.b Sem sim, há quanto tempo? _____________
19.a Tem diabetes tipo 1 ou 2? Sim ☐ Não ☐ Não sei ☐
19.b Sem sim, há quanto tempo? _____________
20.a Tem hipertensão? Sim ☐ Não ☐ **20.b Se sim, há quanto tempo?** _______
21.a Tem dislipidémia? Sim ☐ Não ☐ **21.b Se sim, há quanto tempo?** _______
22.a Toma algum medicamento há mais de 6 meses? Sim ☐ Não ☐
22.b Se sim, para que fim? ____
22.c Se sim, há quanto tempo? ______________
23.a É fumador? Sim ☐ Não ☐ Não, já fui ☐
23.b Caso seja/tenha sido fumador, há/durante quanto tempo? __________
23.c Caso seja/tenha sido fumador, quantos cigarros fuma/fumava por dia? ___________
24.a Tem alguma dependência (álcool, droga, etc)? Sim ☐ Não ☐
24.b Caso tenha, qual é/quais são? ____

Projeto Reabilitação Cardíaca Fase III HESE-UÉ

Grupo 4 – Atividade Física

25.a Nos seus tempos de lazer, costuma praticar algum tipo de exercício ou desporto de forma programada e regular? Sim ☐ Não ☐
25.b Se sim, qual o tipo de exercício ou desporto? ____________________
25.c Se sim, qual a frequência semanal? ____________________
25.d Se sim, qual o nº de minutos por semana? ____________________
25.e Se sim, indique, quais são as principais motivos que o levam a praticar exercício ou desporto? ____
26.a Se já praticou exercício ou desporto e não pratica atualmente, há quanto tempo está sem praticar? ____________________
26.b Indique, por favor, quais são as principais barreiras que o impedem de praticar exercício ou desporto? ____

Grupo 5 – Active Couch Potato

27.a Quantas horas diárias de sono costuma fazer em média (2ª a 6ª feira)? ______
27.b Quantas horas diárias de sono costuma fazer em média (sábado a domingo)? _________
28.a No seu local de trabalho, quantas horas e minutos despende sentado? (se for reformado passe para a próxima questão)? _________
28.b Quantas horas e minutos despende diariamente a ver televisão enquanto sentado? _________
28.c Quantas horas e minutos despende diariamente a realizar tarefas no telemóvel ou tablet, enquanto sentado? _________
28.d Quantas horas e minutos despende diariamente no computador ou a jogar uma consola, enquanto sentado? _________
28.e Quantas horas e minutos despende diariamente a ler sentado (ex. livro ou jornal)? _________
28.f Quantas horas e minutos despende diariamente em transportes (ex. carro, autocarro ou comboio)? _________
29. Durante o dia, costuma estar sentado muito tempo seguido ou interrompe frequentemente?
Várias horas sem interromper ☐ Interrompo a cada hora ☐ Interrompo muitas vezes ☐

Muito Obrigado!

APPENDIX 12. SF-36 questionnaire

QUESTIONÁRIO DE ESTADO DE SAÚDE (SF-36V2)

INSTRUÇÕES: As questões que se seguem pedem-lhe opinião sobre a sua saúde, a forma como se sente e sobre a sua capacidade de desempenhar as actividades habituais.

Pedimos que leia com atenção cada pergunta e responda o mais honestamente possível. se não tiver a certeza sobre a resposta a dar, dê-nos a que achar mais apropriada e, se quiser, escreva um comentário a seguir à pergunta.

Para as perguntas 1 e 2, por favor coloque um círculo no número que melhor descreve a sua saúde.

1. Em geral, diria que a sua saúde é:

Óptima	Muito boa	Boa	Razoável	Fraca
1	2	3	4	5

2. Comparando com o que acontecia há um ano, como descreve o seu estado geral actual:

Muito melhor	Com algumas melhoras	Aproximadamente igual	Um pouco pior	Muito pior
1	2	3	4	5

3. As perguntas que se seguem são sobre actividades que executa no seu dia-a-dia.
Será que a sua saúde o/a limita nestas actividades? Se sim, quanto?

(Por favor assinale com um círculo um número em cada linha)

	Sim, muito limitado/a	Sim, um pouco limitado/a	Não, nada limitado/a
a. **Actividades violentas**, tais como correr, levantar pesos, participar em desportos extenuantes…….	1	2	3
b. **Actividades moderadas**, tais como deslocar uma mesa ou aspirar a casa………………………………………	1	2	3
c. Levantar ou pegar nas compras da mercearia…..	1	2	3
d. Subir **vários** lanços de escadas…………………………	1	2	3
e. Subir **um** lanço de escadas………………………………..	1	2	3
f. Inclinar-se, ajoelhar-se ou baixar-se…………………	1	2	3
g. Andar **mais de 1 Km**………………………………………..	1	2	3
h. Andas **várias** centenas de metros……………………	1	2	3
i. Andar **uma** centena de metros……………………….	1	2	3
j. Tomar banho ou vestir-se sozinho/a………………	1	2	3

4. Durante as últimas 4 semanas teve, no seu trabalho ou actividades diárias, algum dos problemas apresentados a seguir como consequência do seu estado de saúde físico?

Quanto tempo, nas **últimas quatro semanas...**	**Sempre**	**A maior parte do tempo**	**Algum tempo**	**Pouco tempo**	**Nunca**
a. Diminuiu o **tempo gasto** a trabalhar ou outras actividades	1	2	3	4	5
b. Fez **menos** do que queria?...	1	2	3	4	5
c. Sentiu-se limitado/a no tipo de trabalho ou outras actividades	1	2	3	4	5
d. Teve **dificuldade** em executar o seu trabalho ou outras actividades (por exemplo, foi preciso mais esforço).......	1	2	3	4	5

5. Durante as últimas 4 semanas, teve com o seu trabalho ou com as suas actividades diárias, algum dos problemas apresentados a seguir devido a quaisquer problemas emocionais (tal como sentir-se deprimido/a ou ansioso/a)?

Quanto tempo, nas **últimas quatro semanas...**	**Sempre**	**A maior parte do tempo**	**Algum tempo**	**Pouco tempo**	**Nunca**
a. Diminuiu o **tempo gasto** a trabalhar ou outras actividades	1	2	3	4	5
b. Fez **menos** do que queria?...	1	2	3	4	5
c. Executou o seu trabalho ou outras actividades **menos** cuidadosamente do que era costume.......................................	1	2	3	4	5

Para cada uma das perguntas 6, 7 e 8, por favor ponha um círculo no número que melhor descreve a sua saúde.

6. Durante as últimas 4 semanas, em que medida é que a sua saúde física ou problemas emocionais interferiram no seu relacionamento social normal com a família, amigos, vizinhos ou outras pessoas?

Absolutamente nada	**Pouco**	**Moderadamente**	**Bastante**	**Imenso**
1	2	3	4	5

7. Durante as últimas 4 semanas teve dores?

Nenhumas	Muito fracas	Ligeiras	Moderadas	Fortes	Muito fortes
1	2	3	4	5	6

8. Durante as últimas 4 semanas, de que forma é que a dor interferiu com o seu trabalho normal (tanto o trabalho fora de casa como o trabalho doméstico)?

Absolutamente nada	Pouco	Moderadamente	Bastante	Imenso
1	2	3	4	5

9. As perguntas que se seguem pretendem avaliar a forma como se sentiu e como lhe correram as coisas nas últimas quatro semanas.
Para cada pergunta, coloque por favor um círculo à volta do número que melhor descreve a forma como se sentiu.
Certifique-se que coloca um círculo em cada linha.

Quanto tempo, nas **últimas quatro semanas...**	**Sempre**	**A maior parte do tempo**	**Algum tempo**	**Pouco tempo**	**Nunca**
a. Se sentiu cheio/a de vitalidade?.............	1	2	3	4	5
b. Se sentiu muito nervoso/a?....................	1	2	3	4	5
c. Se sentiu tão deprimido/a que nada o/a animava?..	1	2	3	4	5
d. Se sentiu calmo/a e tranquilo/a?..........	1	2	3	4	5
e. Se sentiu com muita energia?...............	1	2	3	4	5
f. Se sentiu deprimido/a?.........................	1	2	3	4	5
g. Se sentiu estafado/a?...........................	1	2	3	4	5
h. Se sentiu feliz?......................................	1	2	3	4	5
i. Se sentiu cansado/a?............................	1	2	3	4	5

10. Durante as últimas quatro semanas, até que ponto é que a sua saúde física ou problemas emocionais limitaram a sua actividade social (tal como visitar amigos ou familiares próximos)?

Sempre	A maior parte do tempo	Algum tempo	Pouco tempo	Nunca
1	2	3	4	5

11. Por favor, diga em que medida são verdadeiras ou falsas as seguintes afirmações. Ponha um círculo para cada linha.

	Absolutamente verdade	Verdade	Não sei	Falso	Absolutamente falso
a. Parece que adoeço mais facilmente do que os outros……………………………	1	2	3	4	5
b. Sou tão saudável como qualquer outra pessoa…………………………………..	1	2	3	4	5
c. Estou convencido/a que a minha saúde vai piorar……………………………..	1	2	3	4	5
d. A minha saúde é óptima……………….	1	2	3	4	5

MUITO OBRIGADO

APPENDIX 13. Hospital anxiety and depression scale (HADS) questionnaire

ESCALA HAD - AVALIAÇAO DO NIVEL DE ANSIEDADE E DEPRESSÃO

DADOS PESSOAIS			
NOME			
ORIENTAÇÕES PARA REALIZAÇÃO DO TESTE			
Assinale com "X" a alternativa que melhor descreve sua resposta a cada questão.			
1. Sinto-me tenso(a):			
( ) a maior parte do tempo [3]	( ) boa parte do tempo [2]	( ) de vez em quando [1]	( ) nunca [0]
2. Eu ainda sinto que gosto das mesmas coisas como antigamente:			
( ) sim do mesmo modo como antigamente [0]	( ) não tanto quanto antigamente [1]	( ) só um pouco [2]	( ) já não consigo ter prazer em nada [3]
3. Eu sinto uma sensação de medo, como se alguma coisa má fosse acontecer:			
( ) sim, uma sensação muito forte [3]	( ) sim, mas não tão forte [2]	( ) um pouco, mas isso não me preocupa [1]	( ) não sinto nada disso [0]
4. Rio-me e divirto-me quando vejo coisas engraçadas:			
( ) do mesmo jeito que antes [0]	( ) atualmente um pouco menos [1]	( ) atualmente bem menos [2]	( ) já não consigo [3]
5. Ando com a cabeça cheia de preocupações:			
( ) a maior parte do tempo [3]	( ) boa parte do tempo [2]	( ) de vez em quando [1]	( ) raramente [0]
6. Sinto-me alegre:			
( ) nunca [3]	( ) poucas vezes [2]	( ) muitas vezes [1]	( ) a maior parte do tempo [0]
7. Consigo ficar sentado à vontade e sentir-me relaxado:			
( ) sim, quase sempre [0]	( ) muitas vezes [1]	( ) poucas vezes [2]	( ) nunca [3]
8. Sinto-me lento(a) para pensar e fazer coisas:			
( ) quase sempre [3]	( ) muitas vezes [2]	( ) poucas vezes [1]	( ) nunca [0]
9. Tenho uma sensação má, um frio na barriga ou um aperto no estômago:			
( ) nunca [0]	( ) de vez em quando [1]	( ) muitas vezes [2]	( ) quase sempre [3]
10. Eu perdi o interesse em cuidar da minha aparência:			
( ) completamente [3]	( ) já não me cuido como deveria [2]	( ) talvez não tanto quanto antigamente [1]	( ) me cuido do mesmo jeito que antes [0]
11. Sinto-me inquieto(a), como se eu não pudesse ficar parado(a) em nenhum lugar:			
( ) sim, demais [3]	( ) bastante [2]	( ) um pouco[1]	( ) não me sinto assim[0]
12. Fico animado(a) e espero animado(a) pelas coisas boas que estão por vir:			
( ) do mesmo modo que antes [0]	( ) um pouco menos que antes [1]	( ) muito menos que antes[2]	( ) quase nunca [3]
13. De repente, tenho a sensação de entrar em pânico:			
( ) a quase todo momento[3]	( ) várias vezes [2]	( ) De vez em quando [1]	( ) não senti isso [0]
14. Consigo sentir prazer quando assisto a um bom programa de televisão, de rádio ou quando leio alguma coisa:			
( ) quase sempre[0]	( ) várias vezes[1]	( ) poucas vezes[2]	( ) quase nunca [3]
RESULTADO DO TESTE			
OBSERV AÇÕES:			
Ansiedade: [ ] questões (1,3,5,7,9,11,13) **Depressão: [ ] questões (2,4,6,8,10,12 e 14)**		**Score:** **0 – 7 pontos: improvável** **8 – 11 pontos: possível – (questionável ou duvidosa)** **12 – 21 pontos: provável**	
NOME RESPONSÁVEL PELA APLICAÇÃO DO TESTE			
DATA			

Botega, N. J., Bio, M.R., Zomignani, M. A., Garcia, J. R. C., & Pereira, W. A. B. (1995). Transtornos do humor em enfermaria de clínica médica e validação de escala de medida (HAD) de ansiedade e depressão. *Revista de Saúde Pública*, 29(5), 355-63.
Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*. 67, 361 -370.

APPENDIX 14. Perceived Exertion (Borg Rating of Perceived Exertion Scale)

Source: https://horadotreino.com.br/escala-de-borg-e-a-percepcao-do-esforco/

APPENDIX 15. Patients' exercise record

Figure S4.

HIIT intervention

Projeto Reabilitação Cardíaca - HESE/UÉ

Nome: **ID:** **Contacto:** **Data de nascimento:** **Idade:** **Fcmáx:** **Percentagens:** **60%:_____** **70%:____** **75%:_____** **85%: _____** **95%:_____**

Semana 1

	Data:___/___/______					
	Minutos	**Carga**	**FC**	**Borg**	**VO2**	**METs**
Aquecimento (50-60%)	0					
	1					
	2					
	3					
	4					
	6					
	7					
	8					
	9					
	10					
HIIT (85-95%)	11					
	12					
	13					
	14					
Recuperação (60%)	15					
	16					
	17					
	18					
HIIT (85-95%)	19					
	20					
	21					
	22					
Recuperação (60%)	23					
	24					
	25					
	26					
HIIT (85-95%)	27					
	28					
	29					
	30					
Recuperação (60%)	31					
	32					
	33					
	34					
HIIT (85-95%)	35					
	36					
	37					
	38					
Recuperação (60%)	39					
	40					
	41					
	42					
Retorno à calma (3-5' 50%)	43					
	44					
	45					
	46					
	47					
					Calorias:	
PAS início:			PAS fim:			
PAD início:			PAD fim:			
Fcrepouso:			Fcrepouso:			
NOTAS: ____________________						

	Data:___/___/______					
	Minutos	**Carga**	**FC**	**Borg**	**VO2**	**METs**
Aquecimento (50-60%)	0					
	1					
	2					
	3					
	4					
	6					
	7					
	8					
	9					
	10					
HIIT (85-95%)	11					
	12					
	13					
	14					
Recuperação (60%)	15					
	16					
	17					
	18					
HIIT (85-95%)	19					
	20					
	21					
	22					
Recuperação (60%)	23					
	24					
	25					
	26					
HIIT (85-95%)	27					
	28					
	29					
	30					
Recuperação (60%)	31					
	32					
	33					
	34					
HIIT (85-95%)	35					
	36					
	37					
	38					
Recuperação (60%)	39					
	40					
	41					
	42					
Retorno à calma (3-5' 50%)	43					
	44					
	45					
	46					
	47					
					Calorias:	
PAS início:			PAS fim:			
PAD início:			PAD fim:			
Fcrepouso:			Fcrepouso:			
NOTAS: ____________________						

	Data:___/___/______					
	Minutos	**Carga**	**FC**	**Borg**	**VO2**	**METs**
Aquecimento (50-60%)	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
HIIT (85-95%)	11					
	12					
	13					
	14					
Recuperação (60%)	15					
HIIT (85-95%)	16					
	17					
	18					
	19					
Recuperação (60%)	20					
HIIT (85-95%)	21					
	22					
	23					
	24					
Recuperação (60%)	25					
HIIT (85-95%)	26					
	27					
	28					
	29					
Recuperação (60%)	30					
Retorno à calma (3-5' 50%)	31					
	32					
	33					
	34					
	35					
					Calorias:	
PAS início:			PAS fim:			
PAD início:			PAD fim:			
Fcrepouso:			Fcrepouso:			
NOTAS: ____________________						

	Data:___/___/______					
	Minutos	**Carga**	**FC**	**Borg**	**VO2**	**METs**
Aquecimento (50-60%)	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
HIIT (85-95%)	11					
	12					
	13					
	14					
Recuperação (60%)	15					
HIIT (85-95%)	16					
	17					
	18					
	19					
Recuperação (60%)	20					
HIIT (85-95%)	21					
	22					
	23					
	24					
Recuperação (60%)	25					
HIIT (85-95%)	26					
	27					
	28					
	29					
Recuperação (60%)	30					
Retorno à calma (3-5' 50%)	31					
	32					
	33					
	34					
	35					
					Calorias:	
PAS início:			PAS fim:			
PAD início:			PAD fim:			
Fcrepouso:			Fcrepouso:			
NOTAS: ____________________						

Semana 2

	Data:___/___/______					
	Minutos	**Carga**	**FC**	**Borg**	**VO2**	**METs**
Aquecimento (50-60%)	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
HIIT (85-95%)	11					
	12					
	13					
	14					
Recuperação (60%)	15					
HIIT (85-95%)	16					
	17					
	18					
	19					
Recuperação (60%)	20					
HIIT (85-95%)	21					
	22					
	23					
	24					
Recuperação (60%)	25					
HIIT (85-95%)	26					
	27					
	28					
	29					
Recuperação (60%)	30					
Retorno à calma (3-5' 50%)	31					
	32					
	33					
	34					
	35					
					Calorias:	
PAS início:			PAS fim:			
PAD início:			PAD fim:			
Fcrepouso:			Fcrepouso:			
NOTAS: ____________________						

Figure S5.

MICT intervention

Projeto Reabilitação Cardíaca - HESE/UÉ

Nome: **ID:** **Contacto:** **Data de nascimento:** **Idade:** **Fcmáx:** **Percentagens:** **50%:_____** **60%:_____** **70%:____** **75%:_____**

Semana 1

Data:___/___/______

	Minutos	Carga	FC	Borg	VO2	METs
Aquecimento (50-60%)	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
TCM (70% a 75%)	11					
	12					
	13					
	14					
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22					
	23					
	24					
	25					
	26					
	27					
	28					
	29					
	30					
	31					
	32					
	33					
	34					
	35					
	36					
	37					
	38					
Retorno à calma (3-5' 50%)	39					
	40					
	41					
	42					
	43					
					Calorias:	
PAS início:			PAS fim:			
PAD início:			PAD fim:			
Fcrepouso:			Fcrepouso:			

NOTAS: ______________________________

Data:___/___/______

	Minutos	Carga	FC	Borg	VO2	METs
Aquecimento (50-60%)	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
TCM (70% a 75%)	11					
	12					
	13					
	14					
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22					
	23					
	24					
	25					
	26					
	27					
	28					
	29					
	30					
	31					
	32					
	33					
	34					
	35					
	36					
	37					
	38					
Retorno à calma (3-5' 50%)	39					
	40					
	41					
	42					
	43					
					Calorias:	
PAS início:			PAS fim:			
PAD início:			PAD fim:			
Fcrepouso:			Fcrepouso:			

NOTAS: ______________________________

Data:___/___/______

	Minutos	Carga	FC	Borg	VO2	METs
Aquecimento (50-60%)	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
TCM (70% a 75%)	11					
	12					
	13					
	14					
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22					
	23					
	24					
	25					
	26					
	27					
	28					
	29					
	30					
	31					
	32					
	33					
	34					
	35					
	36					
	37					
	38					
Retorno à calma (3-5' 50%)	39					
	40					
	41					
	42					
	43					
					Calorias:	
PAS início:			PAS fim:			
PAD início:			PAD fim:			
Fcrepouso:			Fcrepouso:			

NOTAS: ______________________________

Semana 2

31/05/21

	Minutos	Carga	FC	Borg	VO2	METs
Aquecimento (50-60%)	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
TCM (70% a 75%)	11					
	12					
	13					
	14					
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22					
	23					
	24					
	25					
	26					
	27					
	28					
	29					
	30					
	31					
	32					
	33					
	34					
	35					
	36					
	37					
	38					
Retorno à calma (3-5' 50%)	39					
	40					
	41					
	42					
	43					
					Calorias:	
PAS início:			PAS fim:			
PAD início:			PAD fim:			
Fcrepouso:			Fcrepouso:			

NOTAS: ______________________________

01/06/21

	Minutos	Carga	FC	Borg	VO2	METs
Aquecimento (50-60%)	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
TCM (70% a 75%)	11					
	12					
	13					
	14					
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22					
	23					
	24					
	25					
	26					
	27					
	28					
	29					
	30					
	31					
	32					
	33					
	34					
	35					
	36					
	37					
	38					
Retorno à calma (3-5' 50%)	39					
	40					
	41					
	42					
	43					
					Calorias:	
PAS início:			PAS fim:			
PAD início:			PAD fim:			
Fcrepouso:			Fcrepouso:			

NOTAS: ______________________________

APPENDIX 16. Table S4: Patients' heart rate and rate of perceived exertion (Borg scale) averaged across sessions and weeks for HIIT and MICT

Table S6.

Means (standard errors) of patients' heart rate and rate of perceived exertion (Borg scale) averaged across sessions and weeks for high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT).

	HIIT						MICT					
	1	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
HR	146 (3)	138 (1)	138 (2)	136 (2)	137 (3)	134 (1)	127 (3)	124 (2)	124 (3)	120 (1)	123 (2)	119 (2)
RPE	7 (0.4)	6 (0.4)	7 (0.2)	6 (0.3)	6 (0.3)	5 (0.2)	6 (0.4)	6 (0.3)	6 (0.3)	6 (0.2)	5 (0.4)	5 (0.3)

Note. HR = Heart rate (beats per minute); RPE = Rating of perceived exertion (Borg scale 0–10).