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"ENVIRONMENTAL SUSTAINABILITY AND WELLBEING"

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Behavioral sustainability: An interdisciplinary challenge for the wellbeing of older cardiac patients

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An ounce of prevention

is worth a pound of cure

Benjamin Franklin

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Abbreviations

1km-TWT = one-km treadmill walking test

6MWT = six-minute walking test

ACE = angiotensin-converting enzyme

ACS = acute coronary syndrome

AMI = acute myocardial infarction

ANOVA = analysis of variance

ARBs = angiotensin receptor blockers

Ca-ant = calcium channel antagonists

CABG = coronary artery bypass grafting

CBA = cost-benefit analysis

CHD = chronic heart disease

CI = confidence intervals

CPX = cardiopulmonary exercise testing

CR = cardiovascular rehabilitation

CRF = cardiorespiratory fitness

cTn = cardiac troponin

CVD = cardiovascular disease

DALY = disability adjusted life years

DAPT = dual antiplatelet therapy

DRG = diagnoses related group

ECG = electrocardiogram

HBCR = home-based cardiac rehabilitation

HDL = high-density lipoprotein

IQR = interquartile range

ISTAT = istituto nazionale di statistica

LDL = low-density lipoprotein

LTPA = leisure time physical activity

MET = metabolic equivalent

NSTEMI = non-ST-segment elevation myocardial infarction

NYHA = New York heart association

OEP = Otago exercise program

OMT = optimal medical therapy

PA = physical activity

PCI = percutaneous coronary intervention

PRISMA = preferred reporting items for systematic reviews and meta-analyses

QOL = quality of life

RCT = randomized controlled trial

RER = respiratory exchange ratio

SP = secondary prevention

SPPB = short physical performance battery

STEMI = ST-segment elevation myocardial infarction

USD = United States dollar

VCO2 = carbon dioxide output

VE = ventilation

VO2 = oxygen uptake

WHO = World Health Organization

WS = walking speed

Chapter 1

General introduction

This chapter provides a general overview about cardiovascular disease, with reference to the management of myocardial infarction. It includes epidemiological and clinical information about the disease, along with an analysis of the literature, examining the role of physical activity and motivational aspects within cardiac rehabilitation and secondary prevention programs. Recent studies, conducted on patients with myocardial infarction, underscore the critical need for effective exercise-based interventions to address this persistent health challenge.

It is widely recognized that engaging in regular physical activity plays a fundamental role in reducing the risk of all-cause hospitalization and mortality in cardiac patients. Consequently, promoting exercise in cardiac rehabilitation and secondary prevention programs is strongly recommended by international guidelines, and it has emerged as a cornerstone in public health strategies worldwide.

Despite the well-documented advantages of physical activity in this context, a significant portion of these patients remain inactive. This negative trend is particularly evident in older patients, who would benefit the most from this intervention, considering that most of the individuals diagnosed with myocardial infarction are aged ≥ 65 years. Hence, there is the need for a deeper investigation of existing models of intervention, to develop more accessible and effective approaches.

1.1 Acute myocardial infarction

1.1.1 Definition and diagnosis

Acute myocardial infarction (AMI) is a clinical condition characterized by myocardial necrosis caused by an unstable ischemic syndrome.[1] The usual initiating mechanism is

the rupture, or the erosion of a vulnerable, atherosclerotic coronary plaque followed by platelet aggregation, thrombus formation, and subsequent partial or complete occlusion of the coronary vessels.[2] Symptoms may vary based on the extension and location of the obstruction. Typically, patients report ischemic-type pain that includes various combinations of chest, upper extremity, mandibular, or epigastric pain or discomfort, sometimes accompanied by dyspnea, nausea, unexplained weakness, or a combination of these symptoms.[1,3] Based on the electrocardiogram analysis (ECG), AMI can be classified as non-ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI). NSTEMI involves necrosis restricted to specific layers of the ventricular wall without extending throughout its full thickness. In contrast, STEMI is the most severe form of infarction, caused by complete occlusion of the epicardial coronary vessel. This results in a sudden reduction of coronary blood flow to a portion of the myocardium, affecting the entire thickness of the heart muscle.

Diagnosis of AMI is mainly based on the patient's history, blood samples, specific biomarkers and on the 12-lead ECG analysis.[1] The ECG is a core part of the diagnostic process and should be acquired and interpreted promptly (i.e., within 10 minutes) after clinical presentation.[4] Changes in the ST-T waveforms and Q waves, when present, potentially allow the clinician to time the event, identify the infarct-related artery, estimate the amount of myocardium at risk and prognosis, and determine therapeutic strategy.[1] As regards biomarkers, cardiac troponin (cTn) has high myocardial tissue specificity and clinical sensitivity and plays an important role in the diagnosis.[5] Cardiac troponin should be measured at baseline and three to six hours after the onset of ischemic symptoms. An increased cTn concentration is defined as a value exceeding the 99th percentile of a normal reference population (upper reference limit).[6,7]

1.1.2 Clinical and economic burden

Cardiovascular disease (CVD) comprises a variety of clinical conditions that affect cardiac and cerebrovascular system.[8] It is the second leading cause of disability adjusted life years (DALY), which is the sum of years of life lost due to premature mortality and years lived in less-than-optimal health or with disability. Thus, it is still considered a major public health problem.[8,9] According to the Global Burden of Disease, in Italy, over 9.6 million people are affected by CVD (54% women), of which nearly 80% are over 60

years old,[9] while newly diagnosed cases are approximately 880,000 each year. The 70% of these cases occur between the ages of 55 and 85, a statistic that could indicate diagnostic delays, especially in women. The onset differs by gender: usually, men begin to manifest the disease around the age of 40, while in women, considering their longer life expectancy, the incidence is lower before menopause and increases after the age of 60, with a further acceleration after 70. Furthermore, CVD is responsible for over 30% of deaths among older individuals and entail about 40% of years of life lost due to illness, disability, or mortality in the same age group.[9] Data from the "Istituto nazionale di statistica" (ISTAT) in Italy recorded 220,993 deaths due to cardiocirculatory diseases in 2019, nearly 35% of the total deaths, showing significant regional and local variations, and highlighting a growing increase in the mortality rate between North and South.[10,11]

Among CVD, myocardial infarction remains the leading cause of morbidity and mortality,[12] accounting for about 110,000 deaths yearly in the United States.[13] As regards Europe, recent statistics show that between the years 2012 and 2020 1,732,386 deaths were attributed to AMI, but the trend is declining showing a similar pattern for males and females.[14] This is partly due to the better recognition of the disease and the capacity to manage patients with improved treatments, including pharmacological and non-pharmacological interventions as well as percutaneous techniques.[15] Moreover, the reduction of risk factors, as well as the promotion of primary and secondary preventive programs play an important role in this trend.[16–18]

Regarding financial aspects, CVD produces a huge economic burden. According to the Medical Expenditure Panel Survey, the annual direct and indirect cost of CVD in the United States is an estimated USD 378.0 billion, of which 60% includes direct costs, such as treatment, medications, and hospital services. The remaining part is linked to the loss of future productivity (indirect costs) attributed to premature CVD mortality.[13,19] In addition, it has been calculated that the yearly medical costs of CVD are estimated to increase to USD 918 billion in 2030.[20] In Europe, the latest statistics reported that costs for CVD are estimated at €282 billion annually, equaling 11% of European Union health expenditure.[21,22] Total cost per citizen varies across countries and regions and has been estimated at around €630, where 55% is related to health and long-term care (including

hospital care, residential nursing, and medications), in addition to productivity losses due to illness, disability, and premature death.[21]

1.1.3 Risk factors

Non-modifiable factors

Non-modifiable risk factors can be managed through screening activities and secondary prevention strategies.

- **Age**. The risk of developing CVD is linked to age. Each decade of life has been approximately associated with a doubled risk of developing the disease: 51-60 years at 3.5%, 61-70 years at 7.15%, 71-80 years at 13%, 81-90 years at 22.3%, and 91-100 years at 32.5%.[23] Thus, as people get older, the risk of developing CVD increases due to both physiological and pathological aging. In men, the risk of mortality emerges between 40 and 50 years and then progresses exponentially. In contrast, in women, this phenomenon occurs around 50-60 years, about 10 years later, and increases rapidly.
- **Sex**. As regards sex, an increased risk of ischemic disease is associated with males, even though in women, the likelihood is higher after menopause. This is partly explained by endogenous estrogen activity during premenopause, which provides a protective effect against disease development. Female hormones have a reducing effect on total cholesterol and low-density lipoprotein (LDL) levels, lipoprotein A, and homocysteine, in addition to improving postprandial lipid metabolism and high-density lipoprotein (HDL) levels. Moreover, gender comparisons also reveal differences in psychosocial and behavioral coronary risk factors, favoring women to be more cardioprotective due to how they deal with stressful events.[24]
- **Genetics**. In addition to age and gender, family history and genetics are also predisposing factors for CVD, especially for young individuals who have two or more first-degree relatives such as a parent or sibling who have experienced or suffered from heart conditions prematurely, i.e., before the age of 55 (men) and 65 (women) years. In this case, several studies assert that the risk significantly increases by three times before the age of 50.[23] Family history is a key element in medical history as it is strongly associated with various aspects of health. It is considered an additional modifier of risk which can be effectively assessed with a yes/no question: "*Has*

anyone among your parents, siblings, or children ever been diagnosed with a heart attack, angina, or stroke?".[25] Studies conducted on thousands of patients with a positive family history for ischemic CVD have led to the identification of some genetic variants associated with an increased risk.[26,27]

Modifiable factors

Modifiable risk factors can be subdivided into behavioral (sedentary lifestyle, diet, smoking, alcohol consumption), metabolic (hypercholesterolemia, hypertension, diabetes), and relational factors (psychosocial factors). These are preventable and treatable through the adoption of healthy lifestyles, such as proper nutrition and regular physical activity.

- **Hypertension**. It is defined as persistently elevated blood pressure, with values above the normal range: 140 mmHg of systolic and 90 mmHg of diastolic pressure.[28] Both the duration and the severity of hypertension are strong predictors of cardiovascular events.[29,30] In a recent study conducted in the United States, 3,667 young adults who attended six visits over fifteen years were analyzed. The purpose was to verify the association between cumulative blood pressure in young adults and the risk of cardiovascular events compared to the prognostic value of a single moment's blood pressure and its longitudinal changes. Results demonstrated that cumulative blood pressure in young adults was directly associated with the risk of heart failure, coronary artery disease, stroke, or other heart diseases. Additionally, cumulative blood pressure provides incremental prognostic value and better reclassification of CVD risk compared to single assessments of blood pressure or changes in pressure over time.[31] In Italy, 19.3% of the adult population (18-69 years old) reports a diagnosis of hypertension. The prevalence increases with age: from less than 3% before the age of 35 to 36% among those aged 50-69. This condition is more frequent in men, especially among economically and socially disadvantaged individuals.[32]
- **Hypercholesterolemia.** It is defined as a lipid disorder characterized by high levels of LDL in the blood.[33] The causal role of LDL in the development of CVD has been widely demonstrated,[34] with a proportional inverse association between CVD risk and LDL reduction.[35] In Europe, its prevalence exceeds 50%.[36] In Italy, 18.7% of the adult population (18-69 years old) has been diagnosed with hypercholesterolemia.[32] The

prevalence increases with age: from less than 5% among 18-34 years old to 31% among 50-69 years old. The treatment of this risk factor is one of the fundamental elements in primary and secondary prevention, considering that atherosclerotic disease is preventable and caused by cholesterol accumulation in the arteries. According to the new recommendations from the American College of Cardiology and the American Heart Association, statin treatment should be extended to all subjects with LDL cholesterol levels ≥70 mg/dL (1.81 mmol/L), with diabetes or a 10-year cardiovascular risk ≥7.5%.[37] Additionally, in the current guidelines for the management of dyslipidemia, the European Society of Cardiology and the European Atherosclerosis Society recommend a reduction in LDL cholesterol levels ≥50% compared to baseline values and achieving a threshold <1.4 mmol/L (<55 mg/dL) after a recent acute coronary syndrome (Class I recommendation, Level of evidence A).[33,38] However, only a low percentage of patients are treated with the recommended lipid-lowering therapy, resulting in only a minority of individuals achieving the recommended lipid targets.

- **Diabetes mellitus**. It is a chronic disease characterized by elevated blood glucose levels, which damages the endothelium and increases the risk of CVD. This is due to a lack (Type 1) or deficiency (Type 2) of insulin production.[39] According to the World Health Organization (WHO), this condition is one of the most critical public health issues globally, with its prevalence constantly increasing over the years: approximately 422 million people suffer from diabetes mellitus, resulting in 1.5 million deaths annually.[39] In Italy, according to recent statistics, 5.8% of the population (6.2% males and 5.5% females) are affected by Diabetes.[32] Diagnosis of Type 2 Diabetes represents about 90% of total cases and it is strongly linked to overweight, physical inactivity, and socioeconomic status. Furthermore, Diabetes is a major risk factor for cardiovascular diseases, generally associated with stroke, vascular complications, and AMI, as reported in the literature. The INTERHEART case-control study, conducted in 52 countries, confirmed a higher risk of AMI in patients with diabetes.[40] Another study conducted on approximately 90,000 Danish patients stratified considering the presence or absence of diabetes and coronary artery disease demonstrated that the group with both factors had a higher risk for all-cause

and cardiovascular mortality, along with a higher incidence of AMI compared to the other groups.[41]

- **Cigarette smoking**. It is another major risk factor for CVD. It causes alterations to the vascular endothelium causing inflammation and increased permeability, with consequent platelet aggregation and hypertension. This could favor the onset of atherosclerotic processes, increasing the risk of stroke and heart attacks. A multitude of epidemiological investigations have consistently reported a positive correlation between the incidence of CVD and the quantity of cigarettes smoked per day, and a documented reduction with smoking cessation.[32] Research underscores the higher risk of AMI for heavy smokers (twenty or more cigarettes daily) compared to non-smokers.[42] However, encouragingly, complete smoking cessation for a minimum of one year reduces of a 50% the probability of recurrent heart attacks.[43] It is important to underline that achieving complete cessation is complex and necessitates a comprehensive multidisciplinary intervention. Key strategies to help smokers include both psychological and pharmaceutical strategies. The main interventions aim to encourage attempts to give up the habit through counseling and monitoring activities, as patients usually suffer from depression. Some studies show that the prevalence of depressive symptoms among smokers hospitalized for CVD is between 22-24% and that these individuals with depressive symptoms are more likely to return to smoking after hospital discharge compared to non-smokers.[44] As regards pharmacological therapy, the main treatment includes the use of nicotine doses in the form of gum, nasal spray, inhaler, sublingual tablet, or a transdermal patch. In addition, this can be associated with bupropion and varenicline.[45]
- **Diet**. Poor diet has been recognized as a main risk factor in the pathophysiology of several chronic non-communicable diseases. Hence, a long-term healthy diet appears to be essential to prevent and manage CVD and positively influence human well-being. A better diet is associated with a 14-29% lower risk of CVD and a CVD-free survival time greater than 0.5-2.2 years.[46] Current research indicates that the best dietary pattern seems to be the Mediterranean diet, rich in fruits and vegetables, which has a cardioprotective role due to its high concentration of bioactive compounds such as unsaturated fatty acids, polyphenols, fibers, and phytosterols.[47] In 2013 in Spain, 7,747 people with higher CVD risk were involved in a program based on

Mediterranean diet.. Diets were randomly assigned with different supplements: with extra virgin olive oil, or with mixed nuts. After approximately 5 years of follow-up, the study demonstrated that this type of diet is effective in reducing the incidence of cardiovascular events, but it has not been tested in patients who already had the disease.[48]

- **Sleep disorders**. Defined as conditions that affect the quality, timing and amount of sleep, they have been linked to higher risk of CVD.[49] Most common disorders include insomnia, apnea, narcolepsy, and restless leg syndrome.[50] According to the literature, various adverse cardiovascular outcomes, ranging from acute events to chronic conditions, have been linked to disrupted sleep patterns. A growing body of research highlighted how irregular or insufficient sleep can negatively impact on lifestyle causing major risk factors, such as obesity, hypertension, and diabetes.[51,52] This is also related to an augmented risk of depression and other mental issues. Statistics report that on average, 1 in 3 adults do not get adequate rest on a regular basis.[49] A recent systematic review aimed to investigate the association between sleep disorders and CVD. It concluded that there is the need for early identification and comprehensive management of sleep disorders to mitigate their potential adverse effects on cardiovascular health.[53] Therefore, international guidelines highlight the importance of a healthy sleep as a key strategy for maintaining cardiovascular health, by providing specific notions and tips, including sleep hygiene and modifications in bedtime routine.[54]
- **Physical inactivity**. It has been defined as an important modifiable and independent risk factor, responsible for the development of most chronic non-communicable diseases, such as CVD, type 2 diabetes, and cancer.[55,56] Reduced physical performance and low cardiorespiratory fitness levels have been designated as the most powerful predictors of cardiovascular mortality in both male and female populations. For this reason, over the years, regular physical activity has increasingly acquired a central role in modifying the lifestyle of patients with CVD and in rehabilitation after a cardiac event. Physical activity has a protective action and acts as a control for mental health and cardiovascular risk factors.[56–61] In particular, physical training improves contractility and endothelial functions thanks to the release of nitric oxide, which promotes coronary blood flow and angiogenesis of new capillaries.[62] As

regards coronary artery disease, studies carried out on different populations demonstrated that the correlation between the amount of physical activity and mortality is not linear: even small increases in physical activity in sedentary participants were associated with a significant mortality rate reduction. However, in people who used to perform higher levels of exercise, this relationship was progressively mitigated.[63,64] Therefore, regular physical exercise, even if of a moderate degree, must be included in everyday life and associated with a healthy lifestyle. This will lead to an improved state of psycho-physical health and a reduced risk for all-cause hospitalization and mortality.[40]

1.2 Common treatment of acute myocardial infarction

1.2.1 Interventional procedures

This type of treatment is necessary when the revascularization of one or more coronary vessels is indicated. It comprises non-surgical percutaneous coronary intervention (PCI), or surgical intervention through coronary artery bypass grafting (CABG). Rapid coronary reperfusion is essential in patients with STEMI diagnosis to preserve as much myocardial tissue as possible from necrosis. For this reason, the emergency system is structured to allow STEMI patients to reach the nearest procedural area to reopen the lesion within a maximum time of 90 minutes between access to the hospital and the intervention. This technique involves inserting a catheter into the radial artery, as it guarantees fewer complications compared to femoral access,[65] and once the responsible lesion has been overcome, a "balloon" is inflated to dilate the coronary restriction or occlusion. Subsequently, a drug-eluting stent (a cylindrical metal structure coated with drugs), can be implanted. If other obstructive coronary lesions are identified, they could be considered eligible for a preventive angioplasty.[66] When the intervention cannot be performed quickly, the immediate administration of systemic fibrinolytic therapy within 30 minutes is indicated before PCI, to reduce the impact of the time between the onset of symptoms and the intervention.[67] CABG is a frequently performed cardiothoracic surgical procedure, recommended in the presence of multiple stenoses or those non-treatable with PCI. Several trials have demonstrated that the use of this technique in high

and medium-risk patients, as opposed to pharmacological therapy, leads to a significant reduction in mortality.[68] This interventional technique requires the surgeon to connect healthy blood vessels bypassing the narrowed or obstructed vascular segment and allowing blood to circulate the blockage. Typically, this surgery is performed using the great or small saphenous vein, the mammary artery, the internal thoracic artery, or the radial artery. This is especially indicated in patients with a high-risk profile, identified based on clinical characteristics, electrocardiographic presentation, or risk stratification scores. CABG procedure can also be useful when PCI has not yielded a favorable result, is not technically feasible, or in the presence of structural complications.[68,69]

1.2.2 Optimal Medical therapy

The purpose of the optimal medical therapy (OMT) is to reduce anginal symptoms, decrease exercise-induced ischemia, and prevent cardiovascular events. It should be tailored to each patient based on the individual's characteristics and managed through different phases along the continuum of care. The ideal treatment should effectively control symptoms and prevent cardiac events with minimal side effects and maximum patient adherence. Optimal cardiovascular medical therapy has been extensively validated and reviewed. As indicated in the guidelines, it consists of various types of medications that can be combined based on the therapeutic strategy used.[70,71]

- **Anti-ischemic drugs**. they represent a cornerstone of therapy for patients with ischemic heart disease as they prevent and treat anginal symptoms. They can be classified as short-acting drugs, to alleviate symptoms during an acute event, and long-acting drugs used for the management of long-term angina symptoms.
- **Beta-blockers**. Medications for the control of angina pectoris or equivalent symptoms. They inhibit the effects of circulating catecholamines on the heart and blood vessels by blocking beta-adrenergic receptors in response to both physiological and pathological stress factors.[72] This results in a reduced heart rate, systemic blood pressure, and myocardial contractility, leading to a decrease in myocardial oxygen demand. Additionally, it has been demonstrated the role of Beta-blockers in slowing cardiac remodeling and preventing ventricular arrhythmias in patients with AMI.[73] The most common beta-blockers are Metoprolol, Bisoprolol, Atenolol, and Carvedilol. Early administration of these drugs is advisable in the presence of

tachycardia, high blood pressure, opioid-resistant pain, ventricular and supraventricular arrhythmias, and signs of sympathetic hyperactivity.

- **Calcium channel antagonists (Ca-ant)**. Primarily act on vasodilation and reduce peripheral resistance through voltage-dependent L-type channel inhibition. They can be divided into dihydropyridine drugs (such as amlodipine, manidipine, and lercanidipine) and nondihydropyridine drugs (verapamil and diltiazem).[74] As regards antiplatelets, the most common medication is aspirin (salicylic acid) commonly administered for thrombotic event prevention.
- **Antiplatelets.** Aspirin is recommended for all older patients in the absence of contraindications and is typically administered at a daily dose ranging from 75 to 150 mg. Another type of antiplatelet are P2Y12 receptor inhibitors (clopidogrel and ticagrelor) that inhibit platelet ADP receptors. In patients with acute coronary syndrome (ACS), dual antiplatelet therapy (DAPT, association of aspirin with P2Y12 inhibitors) is recommended for 12 months, as well as for patients undergoing PCI.[75] Prolonging the therapy offers benefits but also an increased risk of bleeding.[76]
- **Angiotensin-converting enzyme (ACE)**. inhibitors aim to inhibit the enzyme responsible for converting angiotensin and are mainly implied in the management of hypertension. They are administered to patients with ischemic heart disease as they reduce the risk of cardiac remodeling and improve endothelial dysfunction. Studies confirm that their use reduces the risk of mortality, AMI, and hospitalization for stable angina by approximately 28% in post-ACS patients.[77] If this therapy is not tolerated, angiotensin II receptor antagonists (ARBs) are a valuable alternative.

Currently, during the first year after the event, this type of therapy is prescribed for the majority of patients. According to the results of the EUROASPIRE V survey, conducted in 27 countries for a total of 8,261 patients, on a median of 1.1 years after the event, cardioprotective medication was composed by: anti-platelets 93%, beta-blockers 81%, ACE/ARBs 75% and statins 80%.[78]

1.3 Cardiovascular rehabilitation and secondary prevention

1.3.1 Definition

WHO has defined cardiac rehabilitation (CR) as: "*the sum of activities required to influence favorably the underlying cause of the disease, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their efforts, preserve or resume a place in the community"*.[79] Therefore, the main objectives of CR are to prevent disability, especially in older individuals, to reduce the risk of subsequent cardiovascular events, hospitalizations, and cardiovascular death, and to improve the quality of life. Traditional cardiac rehabilitation usually consists of three phases.[80,81] The inpatient phase, also known as Phase I, begins during the patient's hospital stay. The purpose is to gradually mobilize stable cardiac patients to the degree of activity required for basic home duties and social activities. As modern cardiology guidelines recommend shorter hospital stays, inpatient cardiac rehabilitation programs are largely concerned with early mobilization to enable self-care following discharge. They also involve brief counseling on the nature of the condition, treatment options, risk factor management, and follow-up care planning. Phase II (secondary prevention, SP) consists of outpatient visits to the cardiac rehabilitation facility where individuals go through a planned and monitored exercise program. The program's length varies based on the country and national guidelines indications. It typically starts 2-4 weeks after the discharge and the length ranges from 12 to 36 weeks, with 2-3 sessions per week. SP goal is to improve the individual's psychosocial wellness and to define strategies for reducing associated risks of CVD through risk factor control and physical exercise prescription.[82–84] Finally, Phase III is defined as a long-lasting maintenance phase in which physical training and stable risk factor control are emphasized. It comprises home- or center-based exercise to maintain established healthy behavior modifications.[81] Cardiac rehabilitation – secondary prevention (CR/SP) programs are widely recognized as the standard of care for the comprehensive treatment of post-acute or chronic heart disease, and their utilization is strongly recommended in current guidelines (Class IA).[85]

1.3.2 The role of physical activity

A major component of CR/SP is physical activity (PA).[85,86] As previously reported, according to the literature, regular PA offers a broad range of health benefits. PA has a positive impact on all major risk factors, and significantly reduces the risk of adverse outcomes, both for all-cause and disease-specific causes of hospitalization and mortality.[87] International guidelines indicate that people should practice PA at least three

to five times a week, ideally daily. The minimum recommendation is to achieve at least 30 minutes of moderate-intensity PA per day (150 minutes per week), 15 minutes of vigorous-intensity PA per day (75 minutes per week), or a combination of both.[61] Shorter exercise sessions, particularly for sedentary or deconditioned individuals, may also be suitable.[88–90] Physical activity sessions should comprehend several phases, including warm-up, conditioning (aerobic, muscle strength, and neuromotor exercises), cool-down, and stretching exercises.[88]

An important factor associated with a more physically active lifestyle is the increase and maintenance of higher exercise capacity, identified by cardiorespiratory fitness (CRF). It is defined as maximal oxygen uptake (VO_{2max}), that is the ability of the circulatory and respiratory systems to supply oxygen to the skeletal muscle during exercise. Cardiorespiratory fitness is associated with the ability to perform activities that necessitate the prolonged activation of aerobic mechanisms,[91] and depends on different factors such as lung ventilation and diffusion, cardiocirculatory function, and the ability of the muscles to utilize oxygen.[92] It can be reported as an absolute value in liters of oxygen per minute (l/min) or expressed in milliliters of oxygen per kilogram of body weight (ml/kg/min). This can be directly measured through the determination of maximum oxygen consumption or indirectly using submaximal tests and the calculation of a VO_{2peak} (i.e., the highest VO_2 achieved during the test). Moreover, it is frequently expressed in metabolic equivalents (METs), with 1 MET representing the resting energy expenditure (3.5 ml/kg/min). This is a standardized unit, that can be applied to people with different characteristics and compare a variety of activities.[93] According with the current American College of Sports Medicine Guidelines on Exercise Testing and Prescription,[94] the intensity of physical activity is classified as: light intensity (< 3 METs); moderate intensity (from 3 to 6 METs: i.e., walking at a speed of 3-5 km/h or cycling at a speed of up to 15km/h); vigorous intensity (> 6 METs: i.e., practicing activities that require higher levels of effort).

As reported in the literature, CRF is a significant and independent predictor of hospitalization and mortality among healthy individuals and in patients with CVD.[85,95,96] For this reason, it has been proposed as an additional "vital sign", as robust measure of cardiovascular health.[92] It is partly influenced by genetic heredity and correlated with an individual's age and gender.[97] Additionally, literature describes a decline in PA patterns

along with increased obesity and sedentary lifestyle, that contribute to negatively affect CRF levels among the general population.[97], However, despite the amount of evidence, CRF is the only major risk factor that is not routinely assessed in the general or specialized clinical setting.[98] Therefore, the inclusion of CRF assessment in clinical practice may provide healthcare professionals with an important opportunity to improve patient management and individualized exercise prescription.[99]

1.3.3 Strengths and limitations of traditional models of intervention

The beneficial cardioprotective effects of exercise have been widely demonstrated. In 2013 American Heart Association stated that: *"Exercise can be viewed as a preventive medical treatment, like a "pill" that should be taken on an almost daily basis"*.[100] The efficacy of exercise-based CR/SP programs is well established. A systematic review and meta-analysis of 63 randomized controlled trials showed that exercise-based CR programs are associated with a reduction in cardiovascular mortality (relative risk: 0.74; 95% confidence interval: 0.64 to 0.86) a reduction in the risk of hospital admissions (relative risk: 0.82; 95% confidence interval: 0.70 to 0.96), and improved quality of life.[84] Despite the great importance of this intervention, the uptake remains low, with documented participation rates of about 40%,[78] and this percentage tends to decline as patients get older.[101] Traditional CR/SP programs appear to be unsustainable and present a variety of barriers.[102,103] These include socioeconomic and behavioral factors, along with physical, cognitive, or logistic limitations.[104–107] Moreover, many clinicians and patients do not consider CR/SP a high priority and people often decline to follow the program. Furthermore, most patients do not meet SP long-term targets,[78] while many patients are able to change their lifestyles, but relapse into old behaviors once they begin to feel better after returning to their regular lives. According to the literature, motivation in lifestyle changing tends to decline after about 3 months from the event.[108] Therefore, as the effectiveness of PA depends on how carefully patients adhere to the recommended program of intervention,[83] alternative long-term strategies have been advocated.[109]

1.3.4 Functional evaluation in the clinical setting

The assessment of functional capacity in the clinical setting provides important diagnostic and prognostic information.[91] In the context of CVD management, functional evaluation involves a comprehensive assessment of a patient's physical capacity, cardiac function,

and overall well-being. Typically, patients are monitored while performing incremental or constant-load exercises on a treadmill or cycle ergometer, according to standardized protocols and procedures.[91] The purpose is to obtain a physiological response to a maximal or submaximal physical exertion to determine exercise capacity and evaluate both qualitative and quantitative limit values. The selection of an adequate exercise test methodology for determining functional capacity is crucial, especially when estimating aerobic capacity from exercise time or peak work rate.[91]

Cardiorespiratory fitness: direct assessment

The gold standard assessment method of CRF is directly measured VO_{2peak}, determined during maximum incremental cardiopulmonary exercise testing (CPX).[91] It combines conventional exercise testing procedures with ventilatory expired gas analysis, providing valuable diagnostic and prognostic information regarding cardiovascular and pulmonary diseases.[110] More in detail, CPX systems allow for the breath-by-breath measurement of oxygen uptake (VO_2), CO_2 output (VCO_2) and ventilation (VE) at rest, during exercise, and during recovery.[110] These data are integrated with adjunctive imaging modalities along with clinical and functional parameters including blood pressure, heart rate, ECG and symptoms, providing a comprehensive assessment of exercise tolerance and exercise responses.[110] The evaluation of exercise capacity is typically performed on a treadmill or a stationary cycle ergometer.[110] Incremental load protocols are the most frequently used in clinical practice.[94,111–114] Exercise protocols with large stage-to-stage increments in energy expenditure generally present a weaker relationship between VO_2 and work rate. Hence, tests such as the Bruce,[111] Balke and Ware,[112] Naughton,[113] and other individualized ramp protocols,[94] characterized by progressive and modest increases in work rate, are more recommended for this reason.[110] All incremental protocols include the calculation of exercise thresholds and an analysis of ventilation and exhaled gases, including the relationship between ventilatory equivalents (VE/VO_2 and VE/VCO_2), as well as an objective determination of the effort reflected by the peak respiratory exchange ratio (RER), given by the VCO_2 divided by the VO_2 during the same time interval.[92] A peak RER $\geq$1.10 is generally considered the "gold standard" indicator of maximal effort.[100,110,115] Regardless of the specific protocol chosen, it should be tailored to the patient to provide a fatigue-limited exercise duration between 8 and 12 minutes.[91] Patients perform the CPX until individual exhaustion or until the appearance of specific signals or

complications, including exertional chest pain, dyspnea, signs of poor perfusion (eg, dizziness or near syncope), ST-segment elevation (+ 1.0 mm) or depression (≥2.0 mm occurring in ≥2 leads), sustained supraventricular or ventricular tachyarrhythmia, heart block, or desire of participant to stop.[110] Finally, patients should be encouraged to use minimally (or not use at all) the handrail support during the exercise testing, as it reduces the work performed at any given level influencing the relationship between VO_2 and work rate.[110] Its application in the clinical setting has several indications: to assess exercise capacity; to evaluate the severity and the prognosis of disease; to estimate the likelihood of perioperative morbidity and mortality and contribute to preoperative risk assessment and guide perioperative care; to identify previously unsuspected pathology of gas exchange disturbances and cardiocirculatory function; to guide and evaluate the efficacy of training programs; to evaluate the effects of drug treatment.[116,117] However, economic, and practical issues such as the necessity of space, time, and trained personnel make this method less feasible. Therefore, submaximal exercise testing can be considered a feasible alternative.[118]

Cardiorespiratory fitness: indirect methods

Submaximal tests are considered a preferable choice over CPX in several situations.[92] These include functional evaluations in people who may be at higher risk for cardiovascular events, or when there is the necessity to test larger groups of patients during everyday practice. Typically, these tests rely on an extrapolation from the work rate (i.e., submaximal heart rate), subsequently associated with an algorithm (that considers both demographic and clinical parameters) for the estimation of the exercise capacity.

Over the years, the need for an indirect exercise capacity assessment using population-specific equations has led to the development of several submaximal field and laboratory protocols, mainly based on walking activity.[119–125] Although these tests are classified as submaximal, they are characterized by several significant aspects. First, they have been primarily validated on healthy participants by excluding people with known disease. Second, they require walking as quickly as possible *("Each subject performed a minimum of two, one-mile track walks as fast as possible"*,[119] *"symptom-free volitional maximum",*[125]) over a specified distance or covering as much ground as possible within a

set time frame. This can impact their adaptability in the evaluation of individuals with greater physical limitations, therefore potentially increasing the risk of bias.

Among all the walking tests, one of the most valuable and commonly used is the six-minute walk test (6MWT). It was originally derived from a longer 12-min walk/run test developed by Cooper et al. in 1986 for the evaluation of the level of physical fitness in healthy individuals.[126] Reasons for this adaptation were the need to create a more feasible test, better tolerated by patients with respiratory disease, and more reflective of daily living activities.[127,128] The 6MWT measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. It is a practical simple test that do not requires exercise equipment or advanced training, and aims to evaluate the global and integrated responses of all the systems involved during exercise.[129] In the last decades, it has been validated to estimate exercise capacity and degree of autonomy, as well as predict incidence, morbidity and mortality in various populations from children to older people with major chronic diseases.[122,130–134] The test presents some limitations: it does not provide insight into the specific mechanisms of exercise limitation, and results can be influenced by various factors such as age, gender, and weight, which may limit its accuracy as a standalone assessment. Furthermore, as the test requires to *"walk as far as possible for 6 minutes"* it may not be suitable for individuals with certain health conditions, and its interpretation can be challenging in some frail patient populations.[129,135] Another limitation is related to a learning effect, where the patient's performance may improve with repeated testing due to increased familiarity with the procedure. This can lead to overestimation of the patient's functional capacity and may not accurately reflect their true exercise tolerance.[136] Finally, more research is needed to develop exercise prescription techniques from 6MWT results in both cardiac and pulmonary populations.[137]

To address these limits and to improve the exercise testing and prescription in patients with stable cardiovascular disease, the one-km treadmill walking test (1km-TWT) has been validated.[138,139] This test appears to be more feasible for the clinical setting as it has some relevant features: treadmill protocols are easy to administer; walking activity is one of the most common forms of exercise especially among older adults; the test provides the opportunity to educate the patient to maintain the proper exercise intensity, and

individualized exercise prescription can be based on the results of the test. A detailed description of the test and its clinical usefulness are described in Chapter 4.

1.4 Time to rebrand: a comprehensive approach to the disease

As highlighted in previous paragraphs, traditional CR/SP programs and functional evaluations often present several drawbacks. One of the core components of these programs should be the focus on the individualized needs of the single patient. This is mainly based on the biopsychosocial model,[140] where health is seen as a scientific construct and a social phenomenon that involves a multidisciplinary approach, which aims to investigate psychological and social factors that affect the patient.[141,142] It directly contrasts the more traditional biomedical model characterized by a reductionist approach, in which illness is attributed to a single cause located within the body.[141] In more recent times this concept has been taken up by the lifestyle medicine and translated into lifestyle modification programs.[143] They represents a new approach to major chronic disease risk reduction, that aim to introduce a feasible and cost-effective approach into existing clinical practice of secondary prevention.[143–145]

Moreover, according to the literature, many authors have investigated the perceptions and experiences of cardiac patients in relation to the management of symptoms and the stable modification of their lifestyle,[146] or their engagement in CR/SP programs.[147] Most of the studies described experiences of fear, uncertainty, and disconnection after the acute event,[146] as well as a variety of barriers that limit a stable change and reduce the quality of life, such as psychological distress,[148] lack of time, loss of interest physical discomfort or other comorbidities.[146] Moreover, for most patients achieving control of their own health is seen as a struggle, including dealing with the management of daily problems.[149] Finally, the feelings of independence and long-term change can be influenced by the behavior of the caregiver or family members, with episodes of excessive protection after the event which could reduce independence and the maintenance of a long-term change.[108,150]

These aspects have been properly investigated. However, several research focused on a sample of younger participants (mean age <65 years old),[108,150,151] while others considered

patients in an early stage after the acute event (within 6-8 weeks from the event),[108,152] or those who undergone traditional models of intervention.[153] Hence, there is a gap in knowledge about the long-term efficacy of these strategies especially on older patients, who often report unique needs and are less likely to participate in traditional programs due to various and daunting barriers.[154–157]

Based on these assumptions, CR/SP strategies should consider a comprehensive approach to the disease. The value of a person-centered intervention must be emphasized, along with a more tailored assessment and communication, to enhance adherence and lifestyle change.

1.5 The concept of behavioral sustainability in secondary prevention and health promotion

Sustainability is an open concept that lends itself to numerous interpretations and context-specific usage.[158] It can be utilized to indicate the ability to maintain or support a process over time, preventing the depletion of natural or physical resources, so they will remain available for the long term.[159] It is becoming a fundamental pillar of modern society, and it is increasingly gaining recognition even in the healthcare sector. In this context, the application of sustainability is multifaceted and involves the convergence of environmental, social, and economic dimensions. About social aspects, intervention should guarantee the centrality of the person by developing a multidisciplinary approach considering physical, cognitive, and behavioural aspects. Moreover, the model needs to be low-cost and accessible to a broad number of people given a limited requirement of personnel and instrumentation, this will reflect on an overall environmental impact reduction.

Within this framework, behavioral sciences play a fundamental role in promoting behavioral change by providing insights into human actions, motivations, and barriers.[160] The purpose is to improve the implementation of evidence-based practice and public health based on behavioral change. These models of intervention can be defined as coordinated sets of activities designed to change specified behavior patterns. They should

address individual needs, preferences, and challenges, increasing the likelihood of long-term adherence to recommended health practices.[161]

In this scenario is it possible to introduce the innovative concept of behavioral sustainability, referring to the ability to maintain changes in behavior over time and ensuring that positive habits are consistently practiced within a sustainable model of intervention. A sustainable change in behavior is crucial as it allows individuals to achieve long-term health outcomes, especially in contexts like secondary prevention where adherence to an active lifestyle is vital for improving cardiovascular health and overall well-being.

Chapter 2

Efficacy of home-based intervention compared to usual care

Given the variety of limitations that affect traditional rehabilitation programs, there is the need for the development of new valuable and practical strategies. Among available options, home-based cardiac rehabilitation (HBCR) is one of the most promising treatments in terms of effectiveness and feasibility.

HBCR is defined as a structured program that includes exercise training, scheduled follow-up visits, or alternative monitoring strategies such as telephone calls or self-monitoring diaries.[162] It can include either supervised and unsupervised elements as well as increasing the use of technology or "telehealth" interventions to support exercise and behavior change.[163,164] Moreover, several reviews and meta-analyses carried out in recent decades demonstrated how HBCR is safe,[165] and comparable with traditional center-based intervention in terms of mortality and hospitalization reduction, along with the improvement of exercise capacity and health-related quality of life.[166] The review conducted by Claes et al. compared HBCR with both usual care and center-based CR, demonstrating that HBCR is slightly more effective than center-based CR in terms of maintaining exercise capacity, while no significant differences were found with usual care.[167] Although the review provides robust evidence on HBCR and on its effectiveness compared to other programs, the comparison has been made including patients of all ages, without a focus on a specific age group. However, older patients with chronic heart disease report less participation rates in traditional CR programs compared to younger patients. Hence, there is very limited data about older patients in CR programs, and comparisons between HBCR should be made mainly with usual care.

Therefore, this systematic review aimed to provide an updated overview of the published literature about effectiveness of HBCR on older patients with CVD.

2.1 Methods

The systematic review has been developed following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) amendment to the quality of reporting of meta-analyses statement.[168,169] A systematic literature search was conducted in March 2023 on Medline (via PubMed), Scopus, Web of Science, and Cochrane CENTRAL for randomized controlled trials (RCTs) online database. A combination of terms related to the type of disease, the rehabilitation, and physical activity: ("myocardial infarction" OR "acute coronary syndrome" OR "coronary heart disease" OR “coronary artery disease” OR “coronary disease” OR "cardiac rehabilitation" OR "secondary prevention") AND ("physical activity" OR "physical exercise") have been entered in the search fields. The search strategy was adapted for each database, as necessary. A detailed description of the search strategy is reported in **Table 1**. Only papers published in English, in peer-reviewed journals, and related to human trials were included in the analysis. The inclusion criteria were: (1) randomized controlled trials on adults aged 65 or older, with a diagnosis of chronic heart disease (CHD); (2) home-based exercise intervention strategy; (3) a detailed description of the exercise-based intervention (4) comparison with a usual care control group. Regarding the disease, studies were included with people who had a myocardial infarction or underwent a PCI, or CABG. Trials with patients that presented additional underlying diseases, such as valve surgery or cardiomyopathy, were not excluded. As type of intervention, any form of home-based exercise prescription and training was considered. Clear and detailed instructions about the exercise intervention protocol and information about regular follow-up assessments (in-hospital sessions, home visits, phone calls, diary, or logbook) were required. Regarding the control group, we considered usual care as standard medical care without any form of structured exercise. The exclusion criteria were: (1) inappropriate study design (case report, cross-sectional, study protocol, reviews, or meta-analysis); (2) lack of data on the outcome of interest. The inclusion of studies was not restricted based on the type of measured outcome. Two researchers analyzed the records. A third independent reviewer was involved to discuss in case of disagreement and to take the final decision. All the authors agreed on the final number and type of studies included. Data extraction was based on a database including data about authors, journals, year of publication, population characteristics, type of intervention, and

outcomes of interest. The primary outcome was the effect of HBCR programs on adherence and mortality rates, and secondary outcomes were improvement of exercise capacity and quality of life, compared with usual care.

2.2 Search results and study characteristics

A total of 7260 records were identified through database searching. After duplicates removal 5890 records were screened. Of these, 13 articles were assessed for eligibility. 2 studies were excluded as they were not RCTs, and 5 articles were removed as the mean age was lower than 65 years. Therefore 5 studies were included in the review.[170–174] The study selection procedure is reported in **Figure 1**. Of the five RCTs included one was conducted in Canada,[170] one was held in Denmark,[171] one in Spain,[172] one in Italy,[173] and one in the Netherlands.[174] Characteristics of the studies included in the review are described in **Table 2**. They include a total of 883 patients with CHD diagnosis, respectively allocated into intervention group (441 patients; 335 males and 96 females) or control group (442 patients; 327 males and 104 females). The mean age for the intervention arm was 73.3 ± 1.8 years old, while for controls it was 73.2 ± 2.4 years old. All the studies reported a 12-month follow-up. The quality of studies and risk of bias were assessed using the Revise Cochrane risk-of-bias tool for randomized trials (RoB 2).[175] The tool includes five domains of bias risk: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. A critical assessment of the risk of bias level (high, low, some concerns) was made for each item. It is reported in **Figure 2**.

2.2.1 Type of intervention

Home-based interventions slightly differ among the studies. One study analyzed the efficacy of a home-based exercise program after 16 weeks of supervised sessions. Each participant had to report information on an exercise, diet, and medication logbook, and patients were periodically contacted via telephone for follow-up counseling, in addition to counseling sessions at 6 and 9 months.[170] Another study proposed an individualized home-based training program regularly discussed with a physiotherapist twice a week within a 6-week interval, accompanied by regular phone calls. The individualized

exercise program was generally composed of 5-10 minutes of warm-up (i.e., slow walking), 30 minutes of exercise and 10 minutes of cool down, for 6 days/week.[171] In one research, people at baseline received recommendations to improve their lifestyle and maintain physical function. Additionally, they attended physician appointments every three months to assess clinical conditions and reinforce initial suggestions. The physical activity goal was 30 minutes per day of exercise at a moderate intensity at least 3 days per week (≥6 MET/hours-week).[172] One study included four supervised sessions followed by home-based exercise programs individualized after each visit based on clinical and functional results. Patients received continuous motivational support along with individualized exercise prescription of aerobic physical activity (i.e., walking and cycling) for at least 20 min on 5 days/week, accompanied by a selection of calisthenic exercises.[173] Finally, one study reported a 6-month HBCR with telemonitoring and coaching based on motivational interviewing to stimulate patients to reach their exercise goals. Patients were equipped with smartphones and heart rate belts and instructed to exercise at moderate intensity for at least 30 minutes/day, 5 days per week.[174] In all the studies control patients were treated following specific usual care guidelines and they did not receive any form of CR throughout the study period.

2.2.2 Adherence and mortality

All the studies included in the analysis reported a description of adherence and mortality rates. Overall, the median percentage of adherence was 89.0% (82%-96%) for the intervention group and 90.0% (83%-96%) for the control arm, while drop-outs varied from 2 to 15 and from 1 to 12 in the intervention and control groups, respectively. As regards mortality, the median of all-cause death ranged from 1 (0-4) in the intervention to 3 (0-4) in the control group. Only two studies reported deaths for cardiovascular reasons.[173,174] In the study conducted by Lear et al., 302 patients were enrolled and 278 completed all the assessments (92.1%), while three people in the control group died.[170] Oerkild et al. reported that 36 out of 40 patients (90.0%) were included in the analysis at 12 months during which one decease occurred.[171] Marcos-Forniol et al. presented 127 eligible participants, of which 106 (83.5%) completed the evaluations and four participants per group died.[172] In the analysis of Campo et al. 235 patients were eligible for the study. After the 12-month intervention nine people (3.8%) declined to participate and four (1.7%) died, with a significant difference between intervention and control group

(1 vs 3).[173] Finally, Snoek at al. reported that 179 participants were randomized, and 151 (84.4%) were included, while one death was registered.[174]

2.2.3 Physical activity levels and exercise capacity

Physical activity levels were assessed by four studies with different questionnaires and scales (Physical Activity Questionnaire;[174] Minnesota Leisure Time Physical Activity Questionnaire;[170] Saltin-Grimby Physical Activity Level Scale;[171] 7-day Physical Activity Recall[173]), or objectively measured by wearing an accelerometer.[173] Two studies assessed physical performance reporting results of the Short Physical Performance Battery (SPPB),[172,173] handgrip test,[173] and gait speed.[173] One study did not find significant changes in physical activity levels between groups.[170] Another study described an initial significant change from inactive to active lifestyle in the intervention arm compared to the usual care group with a difference of 33%. However, the proportion of active patients in the home group declined after 12 months.[171] One study reported a significant and progressive increase in the time engaged in physical activity, associated with an improvement of SPPB values in the intervention, with no observed changes in the control group. Similar findings were described regarding grip strength and gait speed.[173] Finally, one research showed a change in the amount of self-reported physical activity in the intervention compared to the control group (mean absolute difference, 0.7 [95% CI, 0.1-1.3]).[174] Exercise capacity was assessed directly through CPX,[170,174] or indirectly by performing submaximal tests such as the 6MWT,[171] or the 1km-TWT.[173] One study did not evaluate exercise capacity.[172] An overall improvement has been evidenced in almost all the analyses. As regards the two studies which reported a direct assessment of the peak oxygen uptake, the first one did not register any significant change in VO_2 levels compared to the control group,[170] while in the second one the authors described a valuable improvement in the intervention arm both at 6 (1.2 [95% CI, 0.2 to 2.1] ml/kg/min) and 12 months (0.9 [95% CI, 0.05 to 1.8] ml/kg/min).[174] Other research conducted using indirect methods reported similar results. More in detail, one study described a significative increase in the VO_{2peak} levels estimated through the 1-km treadmill walking test (4.6 ml/kg/min). As a limitation, these data were not extracted from the main paper,[176] and the test was performed only by participants in the experimental group. Finally, one study analyzed changes in Six-minute walk test, describing a significant decline in

walking distance (-55.2m [95% CI 18.7 to 91.7]) at 12 months follow-up but there were no significant differences compared to the usual care group.[171]

2.2.4 Quality of life

The quality of life, along with the presence of anxiety and depression symptoms was assessed in all the studies by administrating validated scales and questionnaires (Perceived Stress Scale and Illness Intrusive Rating;[170] Hospital Anxiety and Depression Scale;[171] Older Americans' Resources and Services Activities of Daily Living;[172] Short Form-12;[171] Short Form-36;[172,174] General Anxiety Disorder Questionnaire;[174] Patient Health Questionnaire;[174] EuroQol-Visual Analogue Scale and EuroQol-5 Domains[173]). These instruments cover a range of characteristics, including social interactions, physical and mental health, and environmental factors. Additionally, these tools often assess functional aspects like mobility, self-care, and daily activities, along with emotional states such as happiness, life satisfaction, anxiety, and depression. As regards the studies included in the review, four articles out of five did not report any significant change between the intervention and the usual care group. In the study conducted by Campo et al., exercise capacity was associated with a significative improvement in the quality of life (80 vs 70 at 6 months, 75 vs 65 at 12 months, as measured by EuroQol-visual analogue scale) and with a reduced perception of anxiety and depression (21% vs 42% at 6 moths, 32% vs 47% at 12 months).[173]

2.3 Discussion

This systematic review examined the effectiveness of home-based cardiac rehabilitation for the management of older patients with CHD, compared to usual care. The purpose was to provide an updated and detailed description of existing studies and extend the body of evidence. The analysis of the five studies included in the review suggests that home-based intervention can provide important benefits for older patients affected by CHD. As regards physical activity, all the studies described how patients were able to achieve and maintain a more active lifestyle despite the differences between the methods of intervention. This is relevant, considering that participation in supervised CR programs does not necessarily lead to a long-lasting improvement in physical activity levels.[97,177,178]

Moreover, this leads to a significant improvement of exercise capacity and physical performance. Regarding adherence to the program, HBCR is confirmed to be safe and feasible even for older patients, who are usually characterized by high drop-out rates due to loss of interest, elevated mobility limitation and typical sedentary behavior.[86,101] The intervention seems to be effective even on mortality, even though such finding needs to be interpreted with caution given the small number of studies and the lack of specific information about the cause of death. Finally, the absence of quality-of-life improvement was detected using different measures, suggesting that the lack of difference between groups could not be an artifact due to limitations of a single measurement tool.[170–172,174] This could be related to the perception of the common clinical and functional status of these patients, inducing similar responses. However, given the limited number of studies, this hypothesis should be confirmed by further investigation.

The present systematic review has several limitations. First, due to exclusion criteria, it considered a small number of articles. Second, computing a meta-analysis was not possible given the differences between factors assessed in the available studies. This heterogeneity was previously evidenced by other research that claimed how CR programs present varying doses of exercise, delivery settings, and type of intervention strategy.[166] Future research should aim to address these limitations by expanding upon the literature on this topic and conducting more targeted investigations about home-based programs for older patients.

2.3.1 Conclusions

To conclude, this research supports the assumption that home-based CR/SP programs are feasible and effective for the maintenance of a more active lifestyle even in older patients. As HBCR is frequently the preferred choice of many patients, these findings aim to provide detailed information about the variety of alternative available strategies, addressing the need of more feasible and less expensive models of intervention.

Chapter 3

Thesis overview

3.1 Rationale and purpose of the study

The insufficient level of physical activity is a powerful and independent risk factor for survival.[56,60] Despite this, one in four adults worldwide does not meet the physical activity recommendations of 150 minutes of moderate to vigorous intensity per week.[61] Latest statistics showed that the median prevalence of insufficient PA across Europe was 30.8% (with a prevalence of 41.4% in Italy).[179] Moreover, literature describes a discrepancy between self-reported and objectively measured PA. British Heart Foundation statistics showed a difference of about 40% in meeting PA recommendations. Based on accelerometry data, only 10% of people met the recommended level, in comparison to the self-reported levels of 50%, suggesting that PA levels are often over-reported.[180] This has been confirmed by several studies.[181–183] In particular, one research analyzed data about 2,998 participants highlighting a direct association between ageing and the overestimation of self-reported PA levels.[183] These growing body of evidence has led national and international health organizations around the world to make PA promotion part of health care policy goals.[61,184]

This negative trend is noticeable even in the context of CR/SP. Sedentary behavior and low adherence to traditional programs of intervention are still a major problem of public health, particularly among older cardiac patients, that do not reach the minimum recommended dose of exercise.[185,186] Traditional programs are effective and characterized by multifactorial and specifically designed interventions. Unfortunately, these complex programs are time consuming, expensive, and require a rigorous goal-oriented collaboration between different healthcare figures.[187–191] Thus, there is the need for developing more feasible intervention models, to achieve a stable clinical and behavioral change among patients. The decision to engage in health-oriented intervention strategies is personal and the healthcare system cannot force individual choices. Nevertheless, it is

evident that opting for participation in such interventions can have implications for public health. In this context, healthcare professionals should effectively motivate and facilitate behavioral changes. This has the potential to positively impact on the individual's health and, consequently, contribute to the overall improvement of public health. Additionally, the possibility of integrating all the elements of lifestyle intervention into relatively few sessions could be advantageous to patients and institutions, because results can be achieved without increasing costs or time.[143] Moreover, HBCR programs are welcomed by patients, economically convenient and represent a bridge toward introducing exercise into everyday routine.[143]

Given these premises, the purpose of this research was to develop an innovative exercise- and patient-based model of intervention composed by a low number of supervised sessions. It includes clinical and behavioral aspects along with exercise prescription, with an expected improvement on physical performance and long-term health outcomes, including physical and mental conditions.

3.2 Study design

The current study is a secondary observational analysis from the "*Effectiveness of an early, tailored, Physical activity Intervention in ELderly patients with myocardial INfarction (PIpELINe)*" randomized clinical trial (NCT03021044), that aims to evaluate the effectiveness of an early, tailored, physical activity intervention in older patients with myocardial infarction. The study protocol was approved by the institutional ethics committee (376/2019/AOUFe) and was conducted in accordance with the principles of the Declaration of Helsinki. Patients were informed that their participation was voluntary, and all of them gave written informed consent. All data collected were treated confidentially and anonymized.

3.2.1 Outcomes

Primary outcome is the promotion of a sustainable change in behavior. Adopting healthy lifestyle is expected to be associated with improved survival and reduced rate and costs of hospitalization, but behavioral change is challenging. Behavioral and motivational

factors are typically overlooked in traditional CR and exercise prescription, despite their increasingly documented importance in achieving a stable lifestyle change. A sustainable model of intervention should therefore aim at improving patients' health and wellbeing, reducing the drop-out rate and the risk of hospitalization and mortality. Moreover, it should contribute to achieve socioeconomic benefits demonstrating its efficacy in reducing future healthcare costs. Other outcomes include: (i) the improvement of exercise capacity (estimated VO_{2peak}, average and maximum walking speed); (ii) the stable maintenance of higher physical activity levels; (iii) the analysis of the adherence rate after one year from the event; (iv) a qualitative evaluation of patients' perceptions and experiences after the event; (v) an economic evaluation of the intervention model.

3.3 Study population

All patients aged 65 years old with diagnosis of AMI were screened for eligibility. The moment of discharge coincided with T0. During this phase the short physical performance battery (SPPB) tool was performed: patients with a score between 4 and 9 were scheduled for a second visit after one month (T1) at Cona University Hospital (Ferrara, Italy). Patients with values below 4 were excluded considering the worse physical performance and poorer probabilities of recovery and improvement, while values over 9 reflects higher physical performance, good quality of life and very low mortality risk. SPPB was re-evaluated and if the score was confirmed between 4 and 9, patients were randomized to the intervention group or to the usual care (control group) with a 2:1 allocation. Randomization was stratified by sex, SPPB value, clinical presentation, and center by using a proper tool (REDCap, version 10.6.11 - © 2022 Vanderbilt University). Inclusion criteria were age ≥65 years; AMI (STE or NSTEMI) with indication to invasive management; SPPB 4-9 1-month after hospital discharge; providing written informed consent. Exclusion criteria were multivessel coronary artery disease or left main coronary artery disease candidate to surgical revascularization; planned staged PCI; life expectancy < 1 year or any factor precluding 1-year follow-up; severe aortic or mitral valvular pathology; ejection fraction <30%; chronic heart failure NYHA III-IV; severe cognitive or physical impairment.[192] Between June 2020 and December 2023 160 patients were enrolled in the intervention group. Of these, 92 completed the 12-month follow-up and

therefore were included in the present analysis. Study flowchart is reported in **Figure 3**. Demographic and clinical characteristics of the patients are shown in **Table 3**. All patients randomized to the usual care group were managed according to current guidelines, receiving clinical guidance and general indications about healthy lifestyle. In addition to the common instructions for both groups, participants enrolled in the intervention group were involved in an exercise-based secondary prevention program. The first assessment was taken at T1 in the hospital 30 days after T0. Subsequently, patients participated in five consecutive supervised sessions at the Center for Exercise Science and Sport (at 60, 90, 180, 270, and 360 days after T0). Study timeline is reported in **Figure 4.** Details about the structure of each visit will be discussed in Chapter 4. As the usual care group did not perform any functional evaluation nor received exercise prescription, only parameters related to the intervention arm were analyzed in this thesis.

Chapter 4

Physical exercise intervention

4.1 Methods

4.1.1 Physical exercise intervention

During each center-based session, patients performed a submaximal, moderate, and perceptually regulated one-km treadmill walking test (1km-TWT).[138] Specifically, patients started the test at a walking speed (WS) of 2.0 km/h, with a progressive increase of 0.3 km/h every 30 seconds up to a WS corresponding to a perceived exercise intensity (RPE) of 11-13/20 on the Borg scale (6-20). The walking speed reached during this phase was maintained relatively constant for 1000m. During the test, WS could be adjusted to maintain a constant level of perceived effort allowing the patient to complete the test (**Figure 5**). Furthermore, approximately every two minutes, the Borg scale was administered to assess any changes in perceived effort, and WS adjusted according with. Heart rate was monitored continuously using a Polar RS100 heart rate monitor (Polar Electro, Kempele, Finland). During the test, the time taken to complete the 1000m, along with heart rate and average and maximum WS were recorded. VO_{2peak} was estimated using a specific equation considering time to complete the distance, height, weight, and age, and specifically adapted for individuals who take beta-blockers. Patients unable to complete the test at a WS ≥3.0 km/h performed a validated "short form" over 500m or 200m.[193–195] Based on the results of the 1km-TWT, patients were encouraged to replicate similar walking sessions at home. In addition, a selection of supervised calisthenics exercises, derived from the Otago exercise program (OEP), was performed, with the recommendation to be replicated at home.[196] This protocol have been developed to improve limb strength, balance, gait posture and control in older people reducing the risk of falls.[197] Self-reported weekly leisure-time physical activity (LTPA) was assessed from the 7-day physical activity recall questionnaire and reported as MET/h-week.[198]

As regards exercise prescription, during each visit patients received an educational intervention with the purpose to reinforce the idea of being physically active. Based on the concept that "*every move count toward better health*" (WHO 2020), the proposed approach was not an imposition but rather a recommendation. Walking was the most advised activity as it is more feasible and easier to perform,[199,200] but patients were free to decide what type of exercise could be the best for them based on their habits. Nonetheless, walking appeared to be the most popular form of exercise (**Figure 6**).

4.1.2 Motivational approach

The approach was mainly based on a continuous motivational counseling and the importance of patients' perception, along with a specific strategy of exercise testing.[201] It involved a motivational interview between the patient, the exercise specialist, and the physician. It underscored the significance of maintaining an active lifestyle, with a focus on enhancing quality of life, promoting independence, and reducing the need for caregiver assistance. Patients were encouraged to bring their partner or a significant family member to increase social support and involve them in decision-making. Patient's individualized goals (i.e., achievement of the recommended level of Leisure Time Physical Activity) were discussed and used as a basis for tailoring the exercise prescription. Patients who reported significant improvements were encouraged to maintain their level of commitment. Patients who failed to achieve their target goals received support to overcome barriers. Limiting factors to complete the home program were discussed and solutions were proposed, even during the 1km-TWT, which functioned as an informal problem-solving activity integrated within the testing session. In fact, as the test plays an important educational role, not only it was useful for exercise capacity assessment, but patients could also experience the proper intensity and duration of walking in such a way to reach a certain learning effect. The program was repeatedly adjusted during subsequent follow-up visits, and at the end of the protocol, patients could voluntarily continue to attend the exercise-based program. A detailed description of the program is displayed in **Figure 7**.

4.1.3 Statistical analysis

Normal distribution was verified through a Kolmogorov-Smirnov test. Values are expressed as number and percentages, mean (standard deviation), or median [IQR,

interquartile range]. At each time point, changes in the functional variables were assessed by computing the repeated-measures analyses of variance (ANOVA). The Bonferroni method was used for post-hoc tests. All tests were two sided, and the statistical significance was defined as $p<0.05$. All statistical analyses were performed using the statistical software Stata 17 (StataCorp LP) and MedCalc® Statistical Software version 22.016 (MedCalc Software Ltd, Ostend, Belgium).

4.2 Results

The adherence rate to the program ranged from 100% at baseline to 68.7% after 12 months (**Table 5**). The analysis of the drop-out percentages revealed that the highest risk occurred between the first and second visit, (from 100% to 89.6%) considered as a "transition phase" from the hospital to the facility, while drop-out diminished in subsequent sessions (**Figure 8**). Reasons for the incomplete cycle of sessions were progressively recorded by asking the patients or caregivers. They include physical, psychological, and logistical limitations, schematized in **Table 6**. During the follow-up there were seven deaths, mainly attributable to cardiovascular reasons or cancer.

Considering LTPA, it increased from a median 6.0 [IQR 3.0-9.0] MET/h-week at baseline to 12.0 [IQR 6.0-18.0] MET/h-week at 12 months (p for trend <0.0001) (**Table 7**), and the percentage of patients meeting the minimal recommended dose (≥ 7.5 METs-h/week) was progressively higher. Outdoor walking was the preferred exercise choice, followed by indoor or outdoor cycling. Observing the trend derived from the values in **Figure 9**, there was a progressive increase in home-based physical activity levels, particularly between T1 and T3, followed by a plateau phase between T3 and T6.

As regards functional parameters, a significant and gradual increase was observed between T1 and T6 (**Table 7**). Average walking speed progressively increased throughout the sessions, from 3.1 km/h at baseline to 4.5 km/h at 12 months (p for trend <0.0001) (**Figure 10**). Similar responses were found for VO_{2peak} estimated through the 1km-TWT, with an observed improvement from 17.4 [IQR 13.7-20.6] ml/kg/min at baseline to 21.9 [IQR 18.2-24.8] ml/kg/min at 12 months (p for trend <0.0001) (**Figure 11**). These results were obtained at the same average hear rate during the test ranging from 94.9 ± 14.8 at

baseline to 96.5 ± 13.5. Moreover, examining the trends of these variables in male and female participants a progressive and comparable improvement can be seen in both groups (**Figures 12-14**).

Considering differences between sexes, is noticeable that women progressively increased their level of LTPA, reaching values comparable to men (**Figure 12**). Women at baseline had a lower average WS and VO_{2peak} compared to men (2.1 km/h and 14.1 ml/kg/min, respectively). This difference could be related to demographic factors and a lower quantity of MET/h-week compared to males at baseline (2.7 MET/h-week vs 8.8 MET/h-week). At the end of the follow-up, LTPA increased from 2.7 and 8.8 to 10.4 and 14.8, respectively, indicating an increase of 7.7 MET/h-week (74% in women) and 6.0 MET/h-week (40% in men). Both genders increased average WS and VO_{2peak} (**Figures 13, 14**), which, however, remained significantly different between the two sexes ($p<0.001$). Finally, patients were able to cover a progressively longer standardized walking distance, even considering that some patients were limited by osteoarthritis or vascular comorbidities and were not able to perform a higher distance. Percentages of patients categorized by length of walk are reported in **Table 8**.

4.3 Discussion

The first major finding of this research was the high adherence rate observed after one year, which stands at about 69%. This proves to be relevant, considering that, as previously described, adherence to CR/SP programs in older patients are documented to be very low.[105] The higher risk of dropout in the early stages of the program could be mostly attributable to logistical difficulties and low interest about the proposed intervention. These data are consistent with the literature.[202] Consequently, the motivational approach during the initial phase appears of great importance to reduce the risk of dropout. During follow-up, reasons for withdrawal are more often related to physical and cognitive issues. Several patients had to suspend the program due to unfavorable osteoarticular prognoses (resulting in limited mobility), cardiovascular issues, or other comorbidities, as well as family problems related to caregivers.

Regarding functional parameters, there is a clear overall improvement in MET/h-week compared to baseline. Adherence to recommended minimum level of LTPA nearly doubled after three months from the event, indicating considerable patient compliance and adherence to the program. These results agree with previous research, suggesting that a reduced number of supervised sessions and periodic exercise testing may significantly enhance adherence and promoting the maintenance of an active lifestyle.[203–205] Increased LTPA was associated with the significant linear improvement of walking speed. This was paralleled by an increase in the length of the standardized walking distance during the test, as patients became progressively able to walk longer and faster at a given perceived moderate intensity. These findings are consistent with self-efficacy sources that influence behavior change,[206,207] and agree with the recommendation to entail having a patient successfully achieve a goal that is reasonable and proximal, such as being able to walk a mile.[208] In addition, as previously demonstrated, this improvement is significantly and inversely associated with all-cause mortality and hospitalization.[209–211] Similarly, the increase in VO_{2peak} proved to be a relevant prognostic value for hospitalization and mortality rates in the examined population,[212,213] and was consistent with previous studies that demonstrate an average VO_{2peak} improvement of 16-29% among older patients following exercise training.[214] This is clinically relevant considering that each 1 ml/kg/min increase is associated with a 10% reduction in cardiovascular mortality.[214]

Finally, regarding the comparison between genders, the progressive increase in LTPA, and the subsequent linear increase in WS and VO_{2peak} levels in women holds significant clinical relevance. Recent evidence underscores the growing need to consider gender in clinical decision-making, given the significant differences in diagnosis, therapy, exercise testing, and prescription. Women are still labeled as a "special population" in CVD guidelines, leading to disparities in preventive and rehabilitative healthcare.[96,215–217]

This research has several limitations. First, data about adherence and functional parameters are available only in the intervention group. Second, patients with severe cognitive or physical limitations were excluded. Third, the proposed intervention was not compared with standard CR. Fourth, results about women should interpreted carefully given the limited number of females in the sample.

4.3.1 Conclusions

These results demonstrate the efficacy of an innovative supervised / home-based intervention strategy in treating older patients with AMI. During the first year of follow-up participants were able to maintain a high adherence rate increasing their self-reported PA and achieving a significant functional improvement. Therefore, this study can have significant implications for exercise testing and prescription as components of more effective CR/SP programs aimed at patients whose participation and adherence may be limited by the characteristics of traditional approaches.

Chapter 5

Patients' experience and perceptions

5.1 Methods

The description of methods in this chapter has been adapted from *"Experience and Perceptions among Older Outpatients after Myocardial Infarction following an Exercise Intervention: A Qualitative Analysis from the PIpELINe Trial" (Raisi A, et al. IJERPH 2023)*.[218]

To further support the quantitative research, the current qualitative study was designed. The purpose was to analyze feelings and experiences of the patients enrolled in the study and to identify barriers or limitations that may reduce adherence and quality of life. Indeed, a qualitative study allows to gain in-depth knowledge about the experiences, perceptions, and emotions of patients. Specifically, patients' interpretations of their illness within their recovery path, their capacity to manage daily problems, and their relationship with family members were investigated. Therefore, this study will provide a novel contribution by analyzing the psychological and emotional experiences of patients and emphasizing the importance of a person-centered approach. A semi-structured interview composed of six questions was developed. Questions aimed to address different areas of interest, such as: patients' perceptions about their condition; impressions about the intervention program and possible barriers; experiences about the relationship with caregivers. An interview guide is reported in **Table 4**. Interviews were administered after approximately six months following the event, to give patients the time for managing the new "scenery". Data were collected from 31 outpatients between September 2021 and June 2022 during a routine follow-up visit at the Center for Exercise Science and Sport. The initial purpose was to reach a sample of 25-30 patients, in line with the literature and qualitative analysis guidelines.[219,220] The interviewer (AR) was trained to conduct interviews by EPV (co-supervisor) who has expertise in psychological qualitative

research. In particular, the interviewer received training to foster open discussion, exhibit flexibility in changing the order of questions or offering cues if necessary, and to be sensitive to interviewees' requirements, emotions, and their willingness to engage in conversation. Participation in interviews was fully voluntary. The interviews were audio recorded, and patients could leave at any moment if they were uncomfortable. All recordings were transcribed verbatim. To guarantee accuracy and consistency of each interview, they were independently reviewed. Data were subsequently coded and grouped by their thematic similarity to describe the content of each interview and define, main themes and subthemes. They were subsequently revised by SM (co-supervisor) who supported data analysis. As the interviews were conducted and transcribed in Italian, all the extracts reported in the article have been converted to English by a translator, to maintain their precise meaning.

5.2 Results

5.2.1 Qualitative findings

Three themes were developed: 1) personal feelings after the event; 2) lifestyle change and perception of physical or psychological barriers; 3) relationships with persons familiar with the participant: support and overprotection. Themes are schematized in **Figure 15** and described below with representative participant quotes. Quotes have been extracted from the reference article without any change.[218]

Main theme 1: personal feelings after the event

When questioned about their emotions and feelings following the diagnosis, patients' responses underscored a shared experience in their perception of the event. Most of them (n = 19) described feelings of fear, dissatisfaction, and, in some cases, astonishment.

P3 (male, 78 years old): "The truth? A bit of a scare, so that when I still think about it, I feel like crying. This was my feeling, fear and the urge to cry."

P5 (female, 88 years old): "Bewilderment, disbelief, a bolt from the blue. But my nature is to react. I said to myself "I'll do what needs to be done" and the procedure (operation and hospitalization) began."

Some of the participants (n = 12) reported a sense of safety, especially those who were already hospitalized for AMI or underwent surgical interventions.

P23 (female, 79 years old): "Overall, I have to say that I was surprised but I kept pretty quiet...When they told me that I had to stay there they said they would have to warn my husband, but I told them to go slowly and not to aggravate the situation...the experience was quite calm, I didn't get agitated."

P10 (male, 73 years old): "No feelings, it was a normal thing to me...I felt no emotions at all after the diagnosis, because I was so used to it like the first time I was operated on, delighted with all the operators, doctors and nurses, when I had the stroke. I was there as if I were home."

Main theme 2: lifestyle change and perception of physical or psychological barriers

Almost all patients (n = 27) showed awareness of the importance of following specific indications given by cardiologists at the time of the discharge. These indications were mainly related to physical activity, eating habits, and risk factor control. Not a single participant encountered any obstacle in discuss these recommendations with family members.

P1 (male, 72 years old): "They suggested to change my diet slightly: less fat and more vegetables; to stop smoking as well, although I still smoke 4-5 a day, and to lead a dynamic life: moving around and walking without pushing myself...I then quietly talked about it with my family when they came to visit."

P7 (male, 77 years old): "I focused on nutrition. I changed it radically. Everything that was heavy like sausages or cheese, I eliminated them. I don't take them anymore, and my wife said we must continue like this. The cardiologist wrote it down for me and I'm putting it into practice. I quietly talked about it with my wife and daughter. I also noticed improvements in weight size: I can walk easier, I can do the movements, I can breathe better, all of these things here."

Participants who initially were not motivated to change their life habits (n = 16), described a modification in previous behavior, but also highlighted various obstacles. These complications were especially related to physical fatigue, sense of fear, and difficulty in carrying out daily activities.

P17 (male, 83 years old): "I would say yes, because I'm not the type to cry on, I try to move and react. I try to leave it behind and move on...I've been perceiving physical obstacles, especially in my legs during walks or when I go dancing."

P25 (female, 75 years old): "I'd rather have died, because I used to do a lot of things in the countryside, now I can't anymore, and I get nervous. Not doing the things I used to do hurts me."

Most patients (n = 23) perceived the need for periodic controls, to reduce the risk of recurrence and increase their feeling of safety. Furthermore, almost all (n = 26) highlighted the feasibility and effectiveness of the program, as well as their willingness to attend visits.

P5 (female, 88 years old): "Ah yes! It is reassuring because you never know. Luckily there are these checks and so I feel protected."

P1 (male, 72 years old): "I think that control visits are valid because they encourage the patient. […] I continue to improve slowly, and this is important. Because we know that these are things that will never go away, but if you keep improving it means that the program works."

P13 (female, 76 years old): "Initially, I didn't feel comfortable with it, so much so that the first time I failed. Then I gradually changed my mind. So, I have a positive view."

Most patients (n = 27) stated that they feel confident in carrying out daily activities, and few interviewees (n = 3) were afraid to engage in physical activity. This is relevant, considering that achieving control of own health is usually perceived as a struggle, including dealing with common obstacles such as frailty and cognitive impairment.

P6 (male, 76 years old): "I feel very confident, but I don't have the chance. My legs collapse beneath me. As for the heart I feel confident for a simple reason, the doctor who operated on me said I am lucky, that I have a strong heart. As regards to physical activity, I don't really like it, because I would rather rest, but I still do it."

P27 (male, 79 years old): "I feel absolutely confident doing everything, to see that step by step I am recovering, and I am coming back, not as much as before but I feel I can withstand greater efforts."

Main theme 3: relationship with familiars: support and overprotection

Some patients (n = 7) described a unpleasant feeling of overprotection and surveillance, especially from their partner or children.

P2 (male, 79 years old): "Obviously I feel a lot of apprehension when others (family members) tell me -Be careful doing this, be careful doing that-. These things bother you a little bit, I understand that they do it for my own good, but it also hurts me. Overall, I feel constrained by my family, sometimes I start off with enthusiasm to do something and then I am told -but be careful, don't do this, don't do that-."

However, most of them (n = 24) did not report excessive pressure, and in some cases (n = 2), they perceived higher apprehension as a positive factor.

P9 (male, 79 years old): "When I was feeling well my children never asked me how I was, now they ask me how my breathing or my heart is. I don't perceive too much protection, but on the other hand there is more apprehension on their part. For me it is a positive sign."

5.3 Discussion

The purpose of this qualitative analysis was to in-depth investigate the experiences of outpatients enrolled in the exercise-based program, by analyzing their capacity to change their lifestyle, modify their previous habits, and attempt to overcome typical barriers that affect their peers. Most of the qualitative analyses in the literature are focused on younger patients or related to traditional center-based CR/SP programs.[108,150–152,173] The present analysis aimed to extend previous research by examining the perspective of patients in the intervention groups. As stated before, these patients often have specific needs and more difficulties in participating to typical interventions.[221] In terms of feelings after the acute event, the current results are consistent with other studies.[108,150] These articles describe how the perception of an acute cardiovascular event is often interpreted as worse than it is, as several cardiac patients held a belief that a diagnosis of AMI resulted in instant death.[108] Our patients reported a homogeneous response, including a general sensation of fear and bewilderment, but also trust in the hospital staff. Regarding the

lifestyle change and the perception of barriers, responses suggest that almost all the patients were confident in terms of their prognosis and efficacy of the intervention. They were able to change their habits, especially regarding nutrition and exercise, after the advice received by cardiologists and they had no difficulties sharing thoughts and concerns with family members and friends. Concerning adherence, most of our participants were more likely to attend visits, and improvements were often a positive element in their rehabilitation path. Another fundamental point is the analysis of self-efficacy, defined as the capacity to exercise control over events that affect patients' lives.[222] Self-efficacy is a well-studied concept within CR/SP models of intervention, and evidence from several studies indicates a positive association between perceived self-efficacy and personal goals during CR programs, such as increased amount of physical activity,[223] better food choices,[224] reduced smoking habits,[225] and improved quality of life.[226] Almost all the patients felt confident in carrying out daily activities, along with maintaining their social life and improving their physical activity level. This demonstrates the efficacy of continuous motivational counselling that allowed us to reinforce the importance of continued involvement in both in physical and social activities. Finally, it is important to consider the relationship with partner and family. This is a crucial step in the recovery of the patient. Support offered by family members is often a key point for the achievement of long-term adherence and improved lifestyle.[227] Unfortunately, previous studies suggest that many patients refer feelings of frustration for being overprotected by their partners/families in the early recovery period,[108] and this is consistent with our results. Therefore, as reported in chapter 3, caregivers were encouraged to attend visits and discuss any doubt.

This analysis has some limitations. The interviews were performed considering the intervention group, without any contact with outpatients from the control arm. Moreover, as reported in the previous chapter the small proportion of women in the study is relevant, as previous studies suggest that female patients receive less care, and they are less able to maintain lasting lifestyle changes,[228,229] suggesting the need for a gender-specific analysis. Finally, social desirability may still be present despite the interviewer's encouragement for participants to communicate their thoughts and feelings as freely as possible in a non-judgmental way. This would explain replies that suggested high levels of hope, control, and self-efficacy.

5.4.1 Conclusions

Understanding patients' experiences and perceptions of their condition may be critical for improving CR-SP programs. These findings further support the efficacy of this approach and provide useful insights for developing more feasible patient-centered intervention models.

Chapter 6

Economic analysis

6.1 Methods

As stated in the first chapter, CVD generates a significant economic burden, that is set to rise in the following years.[13] Lower-cost intervention strategies could help to mitigate this trend in health care expenditures.[230] According to the literature, physical activity can be effective in reducing the negative economic impact. Expenditures can be lowered by achieving an average of 20 minutes per day of simple and inexpensive activities such as walking.[231] Therefore, the purpose of this analysis was to examine the economic impact of this innovative exercise-based intervention analyzing the association between PA and hospitalization in the first year after the index event through a cost-benefit analysis (CBA). CBA is a systematic method for evaluating and comparing costs and benefits of a project or an intervention. The process involves identifying and quantifying positive (benefits) and negative (costs) factors and subsequently determining whether a proposed action is economically favorable by subtracting the total costs from the total benefits.[232] Comparison was made considering 92 consecutive patients with MI with same characteristics of the intervention group (age ≥65 years, SPPB values between 4 and 9). These patients did not receive any form of physical or motivational intervention and were clinically treated according to the usual care. Benefits were related to hospitalization, considering type and time (in days) of the first hospitalization after the event, and the related cost. Expenditures were calculated considering the diagnoses related group (DRG) system approved by the Emilia-Romagna region in 2023.[233] DRG is a classification system used in the healthcare sector to group patients with similar medical conditions and similar resource requirements. This system was developed for estimating and managing costs in healthcare facilities.[234] Assuming that all patients received a similar type of clinical treatment after the index cardiovascular event, it was not considered in the present analysis. Normal distribution was verified through a Kolmogorov-Smirnov test.

Differences in hospitalization costs between the two groups were analyzed by computing the Mann-Whitney test for non-parametric data. Considering common cost estimation for the clinical and functional intervention program, all patients attended three cardiological visits during the first year (after one, six, and twelve months), for a total of € 92. Additionally, patients in the intervention group participated in five supervised sessions considering an overall expenditure of € 90.

6.2 Results

During the first year, a total of 14 and 20 all-cause hospitalizations occurred for an average of 9 and 6 days for the intervention group and the control group, respectively. Total hospitalization costs were € 79.255 and € 104.849, with an average cost per patient of € 862 and € 1.140 for the intervention and the control group, respectively. Therefore, the mean difference between groups was € 278 ($p<0.0001$). Further analyses were conducted extrapolating these findings to a broader context. According to national statistics, 8,876 people were diagnosed with AMI in the Emilia-Romagna region in 2022.[235] Of these, 5,977 patients were aged ≥65 years. Therefore, the estimated regional benefit of the intervention becomes noteworthy. Multiplying per-patients costs and benefits by 5,977, the benefit emerges to be € 1.661.606. Data have been schematized in **Table 9**.

6.3 Discussion

This analysis provided modest evidence on health-related outcomes and healthcare costs for the management of outpatients with AMI. Results demonstrated that patients who adhered to the intervention showed a 30% difference in hospitalization rate compared to the usual care group. These results are consistent with the literature,[236,237] and further support the inverse relationship between exercise-based intervention strategies and hospitalization. The second notable finding was the reduced overall health-related expenditure in the intervention group, with a difference of 24% in total and per patient expenditure between intervention and control group. This is relevant considering the

importance of creating more financially sustainable models of intervention. Finally, the estimation of regional projected benefits emerges as a significant outcome, suggesting the potential positive impact of the intervention model on a larger scale.

The present analysis has several limitations. First, the sample of patients involved in this investigation may not be representative of the general population with similar cardiovascular conditions. Second, analysis is based on the first year after the event, therefore it may not reflect the long-term effects and benefits of the exercise program. Third, given the complexity of assigning economic costs to health outcomes, the present research mainly depends on estimations. Therefore, a potential risk of overestimation of benefits needs to be acknowledged. Fourth, analysis only measured direct inpatient costs and rehabilitation expenditures without considering indirect costs (i.e. productivity losses, cost of personnel, intervention, and medications) or other benefits (i.e. disability adjusted life years). Considering these issues, further analyses investigating the robustness of these assumptions are recommended.

6.3.1 Conclusions

To conclude, these findings highlight the significant benefit of implementing an exercise-based intervention and contribute to growing evidence that supports the association of exercise training with lower health-care costs in CR/SP. Overall cost associated with the exercise intervention seems to be relatively smaller compared to the economic and clinical benefits. Positive outcomes are related to higher quality of life and to a reduced burden on the healthcare system. This could have substantial implications for public health suggesting potential strategies for reducing overall healthcare costs and enhancing existing hospital services. Finally, results underscore the importance of prioritizing preventive measures to foster a more sustainable healthcare system.

Chapter 7

General discussion

According to the literature, physical activity intervention has a crucial role in reducing the risk of all-cause hospitalization and mortality among patients with AMI, improving functional capacity and quality of life. Despite these benefits have been widely investigated, a notable proportion of patients, especially among older individuals, remain inactive. Therefore, more accessible, and effective approaches are advocated. In this context home-based cardiac rehabilitation emerges as a promising intervention, involving all the multidisciplinary elements of CR/SP proposed through a more feasible strategy. This model has been deeply explored in numerous studies, nonetheless the majority of them include patients of all ages, without a specific attention to older people, who have unique needs and may benefit the most from this intervention.

Hence, the main contribution of this thesis was to investigate the complex characteristics of CR/SP programs, introducing an innovative model of intervention for the management of older patients with AMI. Given the multidisciplinary purpose of this PhD course, it sought to analyze different aspects and areas of interest of this intervention strategy. The first analysis focused on adherence and functional improvement, core aspects of the program. The second part was related to understanding which barriers hinder older individuals from adopting an active lifestyle and tailoring interventions that effectively address these barriers. Finally, an economic evaluation was conducted, suggesting the efficacy of this intervention in reducing public healthcare costs.

Findings suggest that adopting a multidisciplinary motivational and educational approach within the clinical practice can be a fundamental strategy in the management of older cardiac patients, overcoming adherence limitations evidenced in traditional CR/SP programs. This intersectoral approach acknowledges the complex interplay between physical health, behavioral aspects and economic implications in the management of older cardiac patients. As described in previous chapters, the program differs from

traditional interventions providing for relatively few supervised sessions within the first year from the event. It started immediately after the acute event (after about 30 days) given that this is the period in which patients are more prone to modify their lifestyle. This enhanced the feasibility allowing patients to be relatively more able to manage their numerous scheduled visits. Moreover, the multidisciplinary framework was structured to comprehensively address clinical, psychological, and technical aspects toward a stable active lifestyle. The structure of each visit was oriented to introduce and continuously reinforce educational aspects (i.e. correct type and intensity of home-based exercise) alongside clinical and functional evaluation. During the 1km-TWT patients could experience the appropriate exercise intensity, accompanied by the continuous positive reinforcement of being physically active. They also had the possibility to discuss, together with the physician and the caregiver, any doubt about their clinical condition as well as potential issues that may occur in daily life or during exercise. Results of functional evaluations after one year of follow-up highlighted a linear improvement of physical activity levels and estimated VO_{2peak}, paralleled by an elevated adherence rate. The stable achievement of quantitative goals allowed us to assume the effectiveness of the program in promoting stable lifestyle modifications, and this was confirmed by the qualitative analysis. What emerged is that patients were confident about the program and most of them were able to change stably their habits and behavior. This underscored a positive response to the physical and motivational intervention strategy. Finally, from an economic perspective, reducing the number of supervised sessions and implementing a home-based intervention seemed to be positively associated a reduction in healthcare costs. This appeared to be confirmed by the cost-benefit projection on regional scale hypothesizing the possibility to create a more economically viable service.

There are some general limitations in this research. First, adherence during the first part of the project was affected by COVID-19 pandemic. The recruitment process was notably reduced, and patients showed increased reluctance to attend follow-up visits. Consequently, there was a decline in the adherence rate, with a trend that gradually improved with the end of the pandemic emergency. Second, the study was developed based on a “real world scenario”, in which patients were voluntarily involved considering that each of them could be characterized by different specific needs, as well as any physical or social difficulty that was not restricted by exclusion criteria. This has many

positive aspects, giving a more inclusive representation of the model, but may have affected participation in the intervention. Third, as previously specified, physical activity program was performed only by the intervention group, therefore the comparation with the usual care arm, regarding functional improvement, was not available. Finally, the motivational approach is not a standard strategy, and the efficacy of the process partly depends on the operator's experience. Overall, these considerations limit the generalizability of present findings.

7.1 Conclusion and future implications

Despite the acknowledged limitations, this interdisciplinary research program suggests that the proposed intervention is a sustainable strategy capable to improve clinical and functional aspects maintaining higher adherence rates. It allows us to hypothesize the effectiveness and the feasibility of this approach, providing valuable insights for health professionals. Further analyses will confirm its effectiveness in the stable long-term management of older cardiac patients.

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Tables and figures

Table 1: Detailed description of the search strategy, adapted for each database.

Database	String
PubMed	(myocardial infarction [MeSH Terms] OR acute coronary syndrome [MeSH Terms] OR coronary heart disease [MeSH Terms] OR coronary artery disease [MeSH Terms] OR coronary disease [MeSH Terms] OR cardiac rehabilitation [MeSH Terms] OR secondary prevention [MeSH Terms]) AND (physical activity [MeSH Terms] OR physical exercise [MeSH Terms] OR exercise [MeSH Terms])
Scopus	INDEXTERMS ("myocardial infarction" OR "acute coronary syndrome" OR "coronary heart disease" OR “coronary artery disease” OR “coronary disease” OR "cardiac rehabilitation" OR "secondary prevention") AND INDEXTERMS ("physical activity" OR "physical exercise")
Cochrane	Keyword ("myocardial infarction" OR "acute coronary syndrome " OR "coronary heart disease" OR “coronary artery disease” OR “coronary disease” OR "cardiac rehabilitation" OR "secondary prevention”) AND Keyword (“physical activity" OR "physical exercise")
Web of Science	(KP=("myocardial infarction") OR KP=("acute coronary syndrome ") OR KP=("coronary heart disease") OR KP=(“coronary artery disease”) OR KP=(“coronary disease”) OR KP=("cardiac rehabilitation") OR KP=("secondary prevention")) AND (KP=("physical activity") OR KP=("physical exercise"))

Table 2: characteristics of the studies included in the systematic review

Author, year, country	Population	Groups (*n*)	Duration	Exercise intervention	Assessment	Outcomes
Lear et al. 2003 (Canada)	302 patients Mean age: 65 ± 9.5 Sex: male (82%) female (18%)	HBCR (151) UC (151)	12 months	HBCR after 16 weeks of supervised sessions. Logbook, follow-up counseling, in addition to counseling sessions at 6 and 9 months	CPX; Minnesota LTPA questionnaire; Perceived Stress Scale – Illness Intrusive Rating	(a) Exercise capacity (b) PA levels (c) Self-efficacy (d) Quality of life
Oerkild et al. 2012 (Denmark)	40 patients Mean age: 77 ± 6.8 Sex: male (58%) female (42%)	HBCR (19) UC (21)	12 months	5-10 min of warm-up (i.e., slow walking), 30 min of exercise and 10 min of cool down, for 6 days/week	STS test; Saltin-Grimby PA Level Scale; SF-12; HADS	(a) Exercise capacity (b) PA levels (c) Anxiety and depression (d) Quality of life
Marcos-Forniol et al. 2018 (Spain)	127 patients Mean age: 76 ± 3.6 Sex: male (60%) female (40%)	HBCR (64) UC (63)	12 months	Exercise recommendation of 30 min/day, at least 3 days/week. Supervised counseling sessions every 3 months	SPPB, SF-36; OARS-IADL; Food-frequency questionnaire	(a) Physical performance (b) Dietary habits (c) Quality of life
Campo et al. 2020 (Italy)	235 patients Mean age: 76 ± 8.0 Sex: male (77%) female (23%)	HBCR (118) UC (117)	12 months	4 supervised sessions followed by prescription of aerobic PA (i.e., walking and cycling) for at least 20 min, 5 days/week, and calisthenic exercises	SPPB; EuroQol VAS, EuroQol 5D, 7-d PA recall; 1k-TWT	(d) Exercise capacity (e) Physical performance (f) PA levels (g) Anxiety and depression (h) Quality of life
Snoek et al. 2021 (Netherlands)	179 patients Mean age: 72 ± 5.4 Sex: male (81%) female (19%)	HBCR (89) UC (90)	12 months	6-month HBCR with telemonitoring and coaching. Exercise recommendation of at least 30 min/day, 5 days/week at moderate intensity	CPX; PA questionnaire; SF-36; GAD-7; PHQ-9	(a) Exercise capacity (b) PA levels (c) Anxiety and depression (d) Quality of life

CPX= cardiopulmonary exercise testing; GAD= general anxiety disorder; HADS= hospital anxiety and depression scale; HBCR= home-based cardiac rehabilitation; LTPA= leisure time physical activity; OARS-IADL= older Americans' resources and services activities of daily living; PA= physical activity; PHQ= patient health questionnaire; SPPB= short physical performance battery; SF= short form; STS= sit-to-stand; UC= usual care; VAS= visual analogue scale; 1k-TWT= 1km treadmill walking test.

Table 3: Demographic and clinical characteristics of patients

Patients, n	92
Demographics	
Age (yr)	75 (7)
Women, n (%)	20 (21.7%)
Marital status, married, n (%)	74 (80.4%)
Education (yr)	10 (4)
Current working, n (%)	6 (6.5%)
BMI (kg/m^2)	27.1 (3.7)
LVEF (%)	52 (9)
Risk factors	
Family history, n (%)	18 (19.6%)
Hypertension, n (%)	79 (85.9%)
Diabetes, n (%)	20 (21.7%)
Hyperlipidemia, n (%)	57 (62.0%)
Smoking status, n (%)	
Never	47 (51.1%)
Previous	35 (38.0%)
Current	10 (10.9%)
Weekly LTPA (MET/h-week)	6.0 [3.0-9.0]
Laboratory values	
Hemoglobin (mg/dl)	13.5 (3.6)
Total cholesterol (mg/dl)	132.7 (38.8)
HDL cholesterol (mg/dl)	42.4 (10.3)
Serum triglycerides (mg/dl)	105.9 (49.4)
Serum creatinine (mg/dl)	1.17 (0.36)
Medical history	
STEMI, n (%)	35 (38.0%)
NSTEMI, n (%)	57 (62.0%)
PCI, n (%)	87 (94.6%)
Previous MI, n (%)	20 (21.7%)
Medications	
ACE inhibitor or ARB, n (%)	77 (83.7%)
Aspirin, n (%)	72 (78.3%)
Other antiplatelet, n (%)	87 (94.6%)
β-blocker, n (%)	63 (68.5%)
Calcium antagonist, n (%)	27 (29.3%)
Statin, n (%)	91 (98.9%)
Diuretic, n (%)	34 (37.0%)

Values are presented as mean (standard deviation), median [IQR], or number (percentage).
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; HDL, high-density lipoprotein; LTPA leisure-time physical activity; LVEF, left-ventricular ejection fraction; MET, metabolic units; MI, myocardial infarction; NSTEMI non-ST-segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

Table 4: Semi-structured interview guide. Extracted from Raisi A, et al. Experience and Perceptions among Older Outpatients after Myocardial Infarction following an Exercise Intervention: A Qualitative Analysis from the PIpELINe Trial.

1. Which sensations did you feel immediately after the diagnosis of the cardiac event?
2. After the operation and the hospitalization, which health-related suggestions did you receive and from whom? Did you talk to anyone about it?
3. Did the event generate in you a motivation to lifestyle changing? After 6 months, did you perceive any obstacles? If so, which ones?
4. After the event, did you perceive the desire to be periodically checked? If so, what are your impressions about the program that you are joining?
5. After the event, how confident do you feel about carrying out your usual daily activities? And what about physical activity?
6. After the event, how do you consider your relationship and how do you feel treated by your family members and those who take care of you? Do you perceive any changes?

Table 5: Drop-out rate during the follow-up (T1-T6)

	T1	**T2**	**T3**	**T4**	**T5**	**T6**
Patients, n	134	120	113	105	94	92
Adherence (%)	100%	89.6%	84.3%	78.4%	70.1%	68.7%

Table 6: Categorization of dropouts during the exercise-based intervention subdivided into indexed factors. Inspired by the framework of Beswick et al. Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.

		Total Dropout (n = 35)	**Dropout at transition (n = 11)**	**Dropout after transition (n = 24)**
A	Not interested or lost interest	13 (37%)	6 (17%)	7 (20%)
B	Logistic difficulties (i.e., distance or transportation)	4 (11%)	1 (3%)	3 (9%)
C	Family issues (i.e., looking after a dependent relative)	6 (17%)	3 (9%)	3 (9%)
D	Worsening of cardiac disease status	3 (9%)	0 (0%)	3 (9%)
E	Other comorbidities	9 (26%)	1 (3%)	8 (23%)

Table 7: Variation of clinical and exercise parameters during the follow-up (T1-T6)

Variable	T1	T2	T3	T4	T5	T6
BMI (kg/m^2)	27.1 (3.7)	27.3 (3.7)	27.4 (4.1)	27.2 (3.8)	27.4 (3.9)	27.4 (4.1)
Systolic BP (mm/Hg)	130 [117-140]	120 [110-140]	130 [117-140]	130 [120-132	128 [120-130]	125 [115-130]
Diastolic BP (mm/Hg)	75 [75-80]	70 [62-80]	70 [65-80]	70 [60-75]	70 [60-70]	70 [60-70]
Average HR (bpm)	94.9 (14.8)	94.6 (14.1)	95.7 (14.2)	96.5 (13.3)	94.8 (14.2)	96.5 (13.5)
Higher HR (bpm)	101.9 (16.0)	103.8 (14.9)	103.5 (16.6)	105.0 (14.8)	103.7 (15.1)	105.5 (14.7)
LTPA (MET/h-sett)	6.0 [3.0-9.0]	10.8 [6.0-15.8]	12.0 [6.0-18.8]	12.0 [9.0-18.0]	12.0 [6.0-18.5]	12.0 [6.0-18.0]
Average WS (km/h)	3.1 (1.1)	3.6 (1.3)	3.9 (1.3)	4.2 (1.2)	4.4 (1.2)	4.5 (1.2)
Higher WS (km/h)	3.3 (1.1)	3.8 (1.2)	4.2 (1.2)	4.4 (1.2)	4.6 (1.2)	4.7 (1.2)
VO_{2peak} (ml/kg/min)	17.4 [13.7-20.6]	18.7 [15.3-22.8]	20.0 [16.5-23.7]	21.1 [17.1-24.3]	21.7 [17.5-24.9]	21.9 [18.2-24.8]

Values are presented as mean (standard deviation) or median [IQR].
BMI, body mass index; BP, blood pressure; HR, heart rate; LTPA, leisure time physical activity; WS, walking speed.

Table 8: Standardized walking distance at session during the follow-up (T1-T6).

	T1	T2	T3	T4	T5	T6
1000m (%)	27 (29.3%)	48 (52.2%)	55 (59.8%)	70 (76.1%)	65 (70.7%)	67 (72.8%)
500m (%)	35 (38.0%)	33 (35.9%)	30 (32.6%)	14 (15.2%)	21 (22.8%)	18 (19.6%)
200m (%)	26 (28.3%)	7 (7.6%)	6 (6.5%)	5 (5.4%)	5 (5.4%)	7 (7.6%)
<200m (%)	4 (4.3%)	4 (4.3%)	1 (1.1%)	3 (3.3%)	1 (1.1%)	0 (0.0%)

Values are presented as number (percentage).

Table 9: Details of hospitalizations and related costs

	Control group (n = 92)	**Intervention group (n = 92)**	**Δ (%)**
Hospitalizations, n	20	14	6 (30%)
Total hospitalization costs, €	104 849	79 255	25 594 (24%)
Unit hospitalization cost (per patient), €	1 140 (2 245)	862 (2 027)	278 (24%)
Regional projection of costs, €			1 661 610

Values are presented as mean (standard deviation) or number (percentage)

Figure 1: Identification and selection of studies for the review. Adapted from Moher et al. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial.

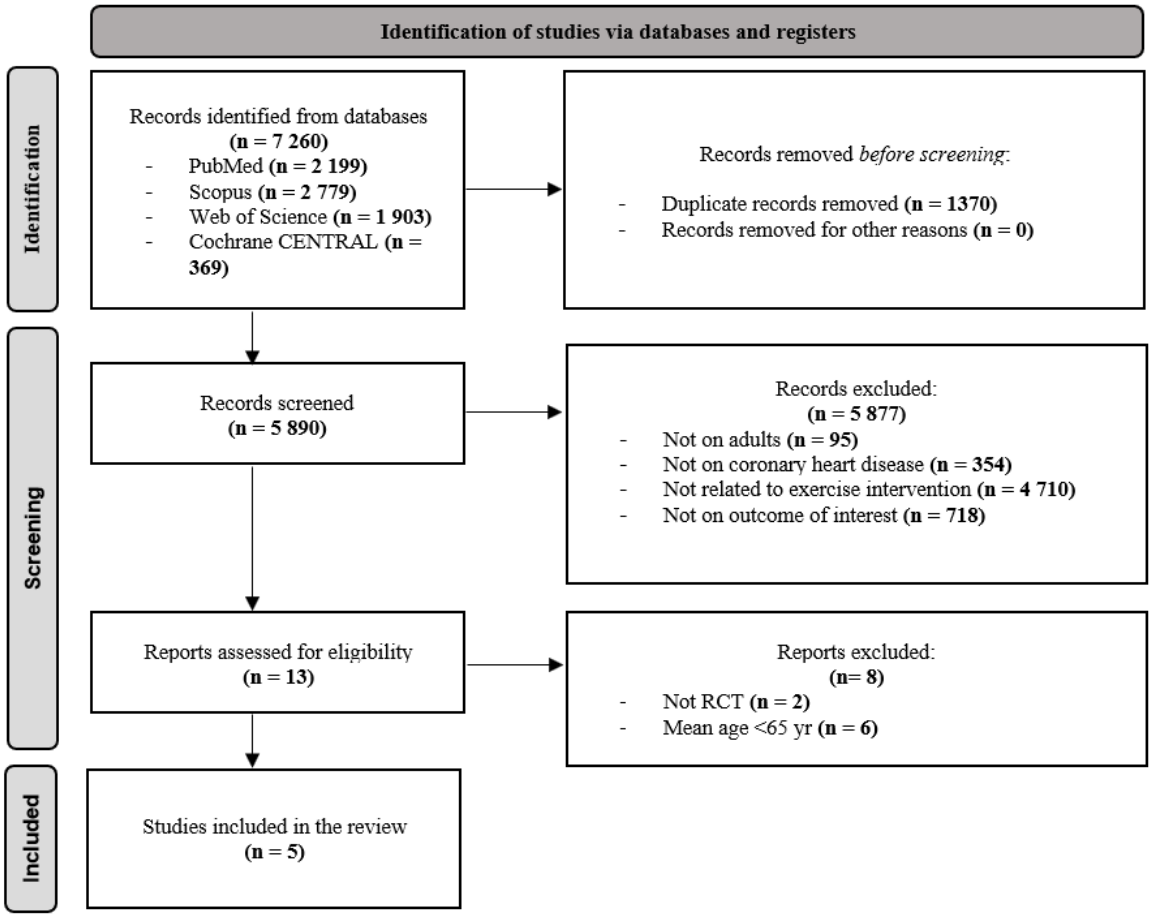


Figure 2: Assessment of risk of bias. Adapted from Sterne et al. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).

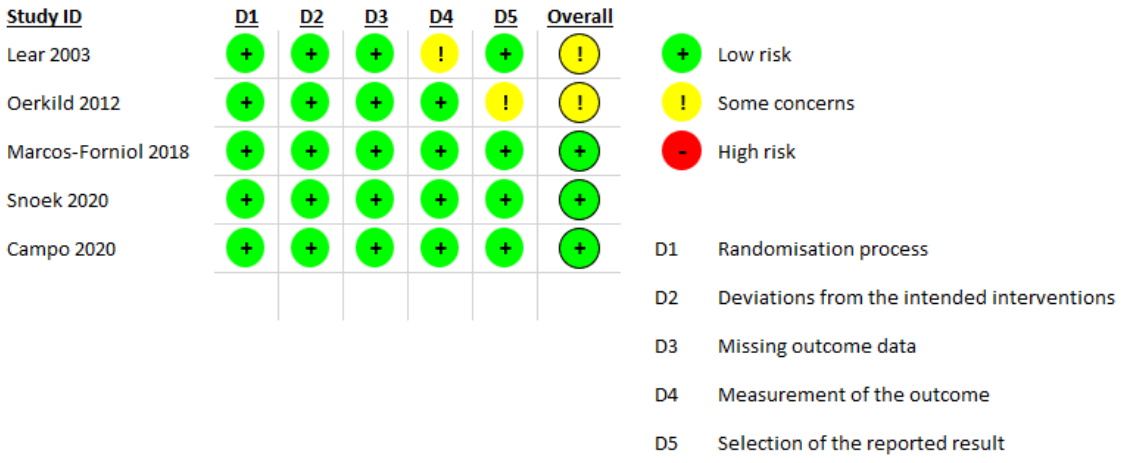


Figure 3: Study flowchart

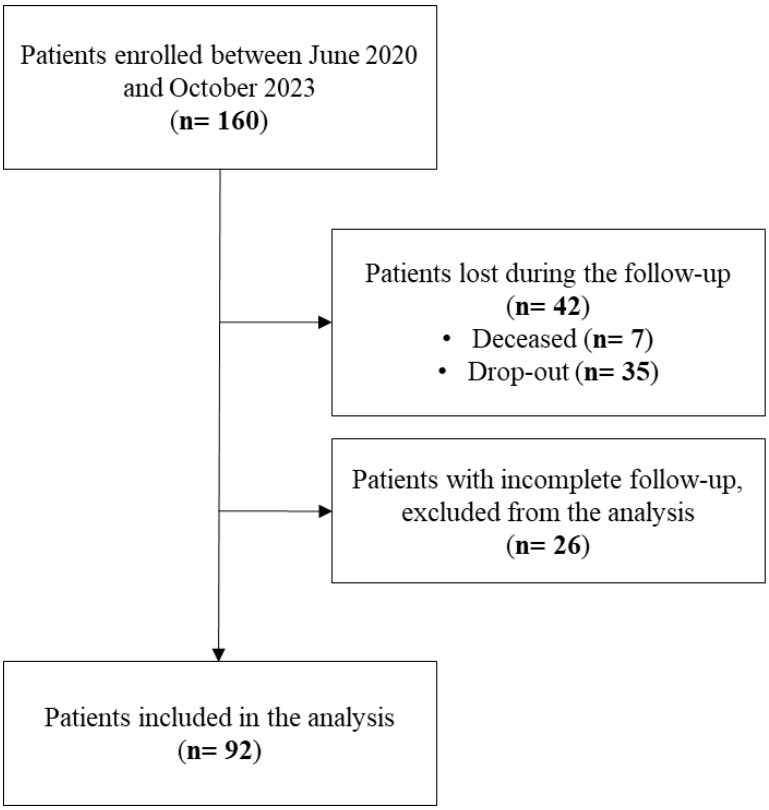


Figure 4: Study timeline

	Follow-up sessions						
	t_0	t_1	t_2	t_3	t_4	t_5	t_6
Enrollment	x						
Randomization	x						
Follow-up:							
Cardiological visit		x			x		x
Functional evaluation			o—	—	—	—	—o
Outcome measures:							
1k-TWT		o—	—	—	—	—	—o
7-day PA recall		o—	—	—	—	—	—o

Figure 5: 1-km Treadmill Walking Test protocol

Figure 6: Percentages of patients for each exercise modality, and percentage of inactive patients at baseline (T1) and after 12-months follow-up (T6).

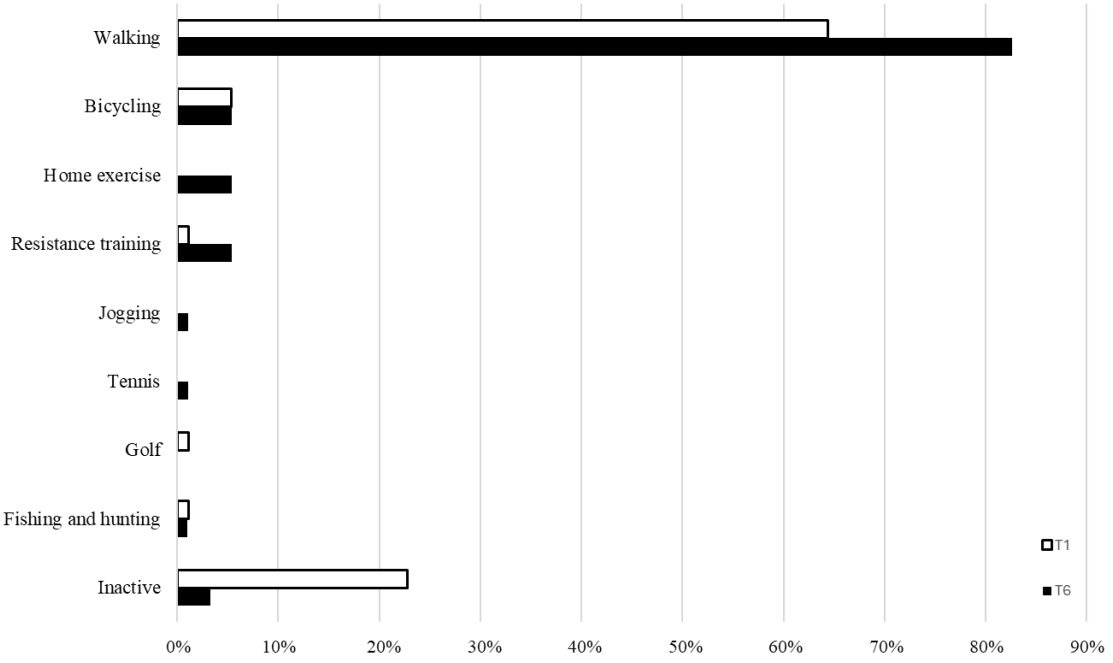
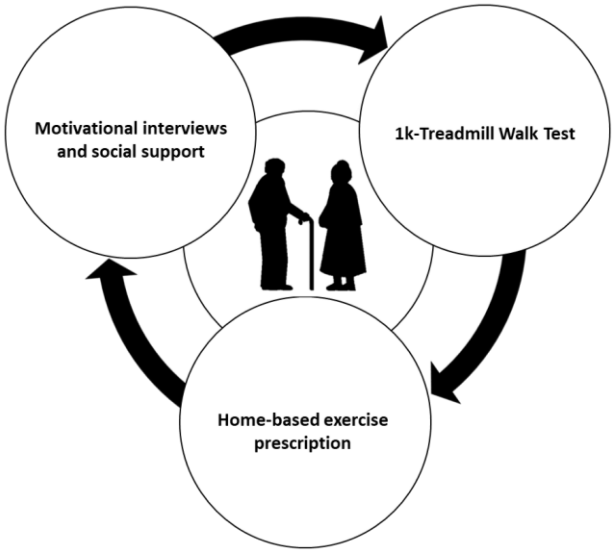


Figure 7: Detailed exercise-based and patient-centered cycle of intervention. Adapted from Raisi et al. A novel motivational approach in the management of older patients with cardiovascular disease.



Motivational interviews and social support:

- Investigation of patient's point of view about the illness, after the acute event and during the follow-up;
- Patient's impressions about the program, perceptions of physical and psychological barriers;
- Relationship with family members;
- Continuous counselling about physical activity individualized goals.

1k-Treadmill Walk Test:

- Test starts at a walking speed of 2.0 km/h, with successive increases of 0.3 km/h every 30 seconds, up to a speed corresponding to a perceived exertion of 11–13 on the 6–20 Rate of Perceived Exertion (RPE) Borg scale. Patients are encouraged to maintain such intensity for up to 1000m. RPE is assessed approximately every two minutes, adjusting speed if necessary. Heart rate is continuously monitored;
- Patients unable to complete the test at a speed ≥ 3.0 km/h can perform the test over 500m or 200m and the time to walk is multiplied for 2 or 4, respectively.

Home-based exercise prescription:

- At least 20 minutes of moderate walking, based on the intensity maintained during the test;
- Selection of calisthenics exercises based on the OTAGO Exercise Program, to improve strength and balance;
- Adjustment of the home-based program during each follow-up visit.

Figure 8: Adherence trend during the follow-up time.

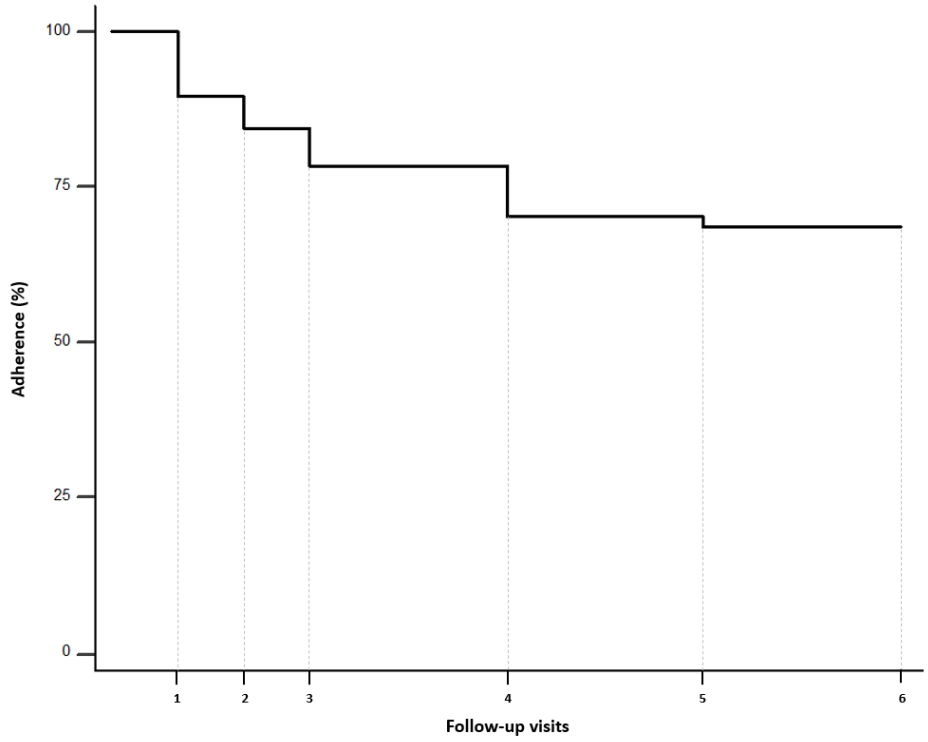


Figure 9: Changes in leisure time physical activity during the follow-up (T1-T6)

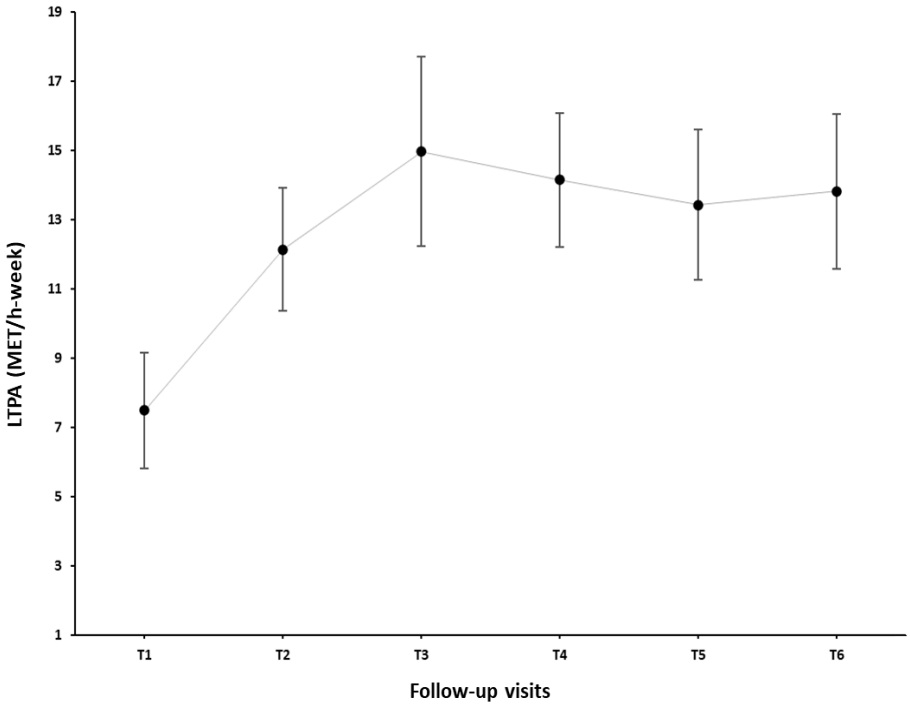


Figure 10: Changes in average walking speed during the follow-up (T1-T6)

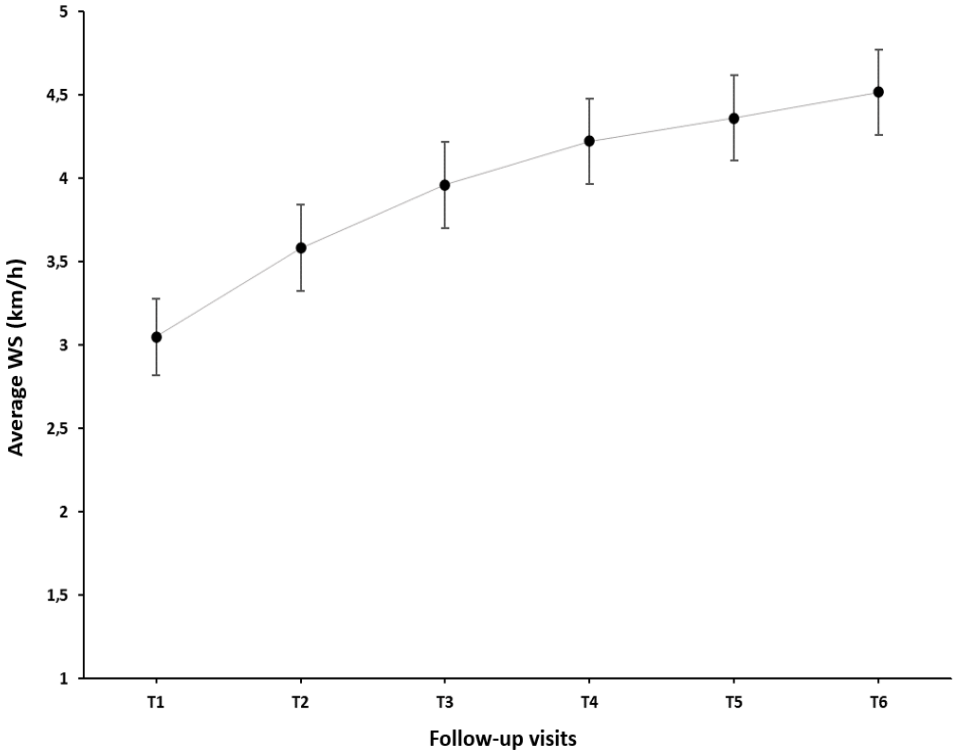


Figure 11: Changes in estimated peak oxygen consumption during the follow-up (T1-T6)

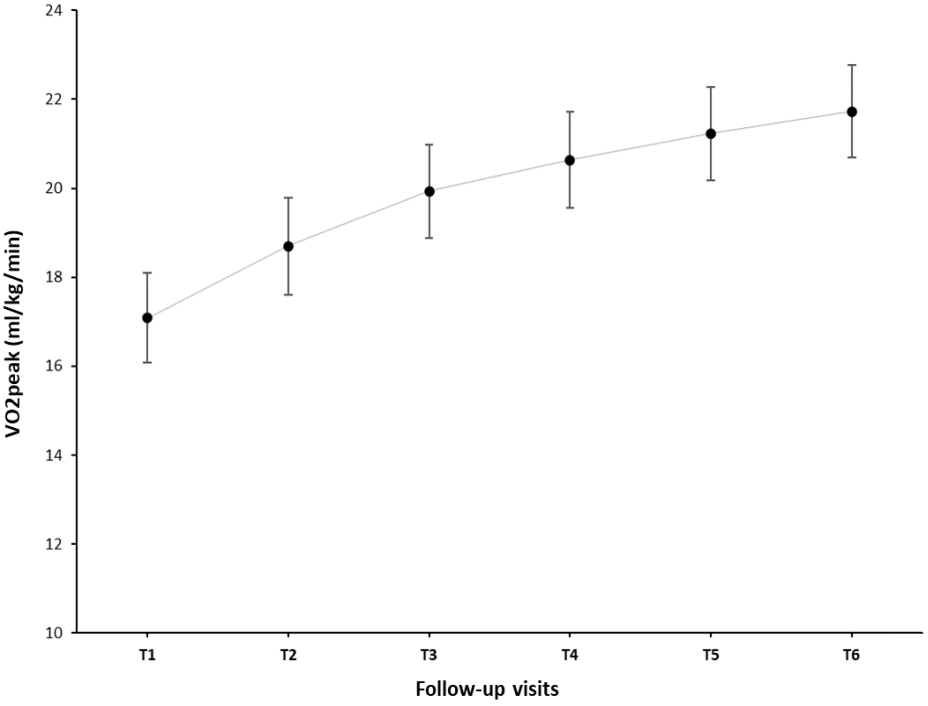


Figure 12: Changes in leisure time physical activity during the follow-up, categorized by sex

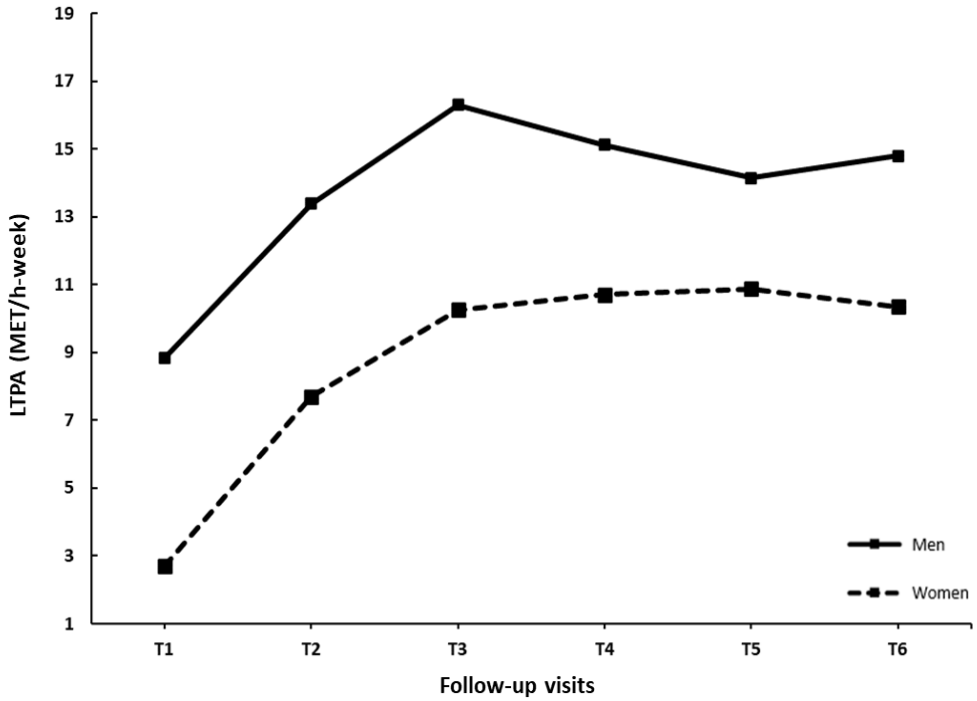


Figure 13: Changes in average walking speed during the follow-up, categorized by sex

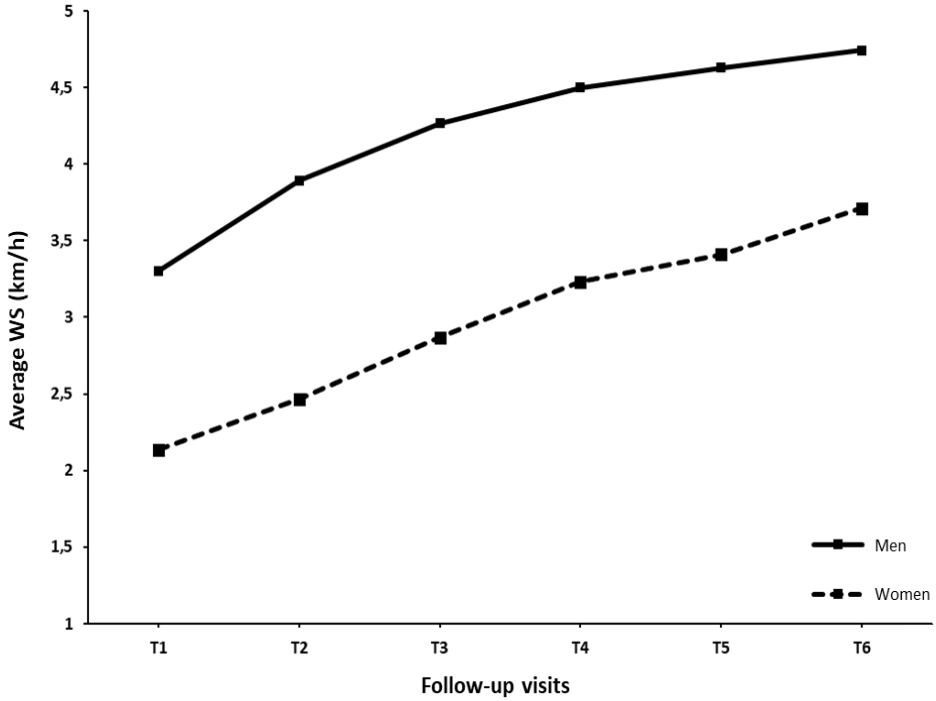


Figure 14: Changes in estimated peak oxygen consumption during the follow-up, categorized by sex

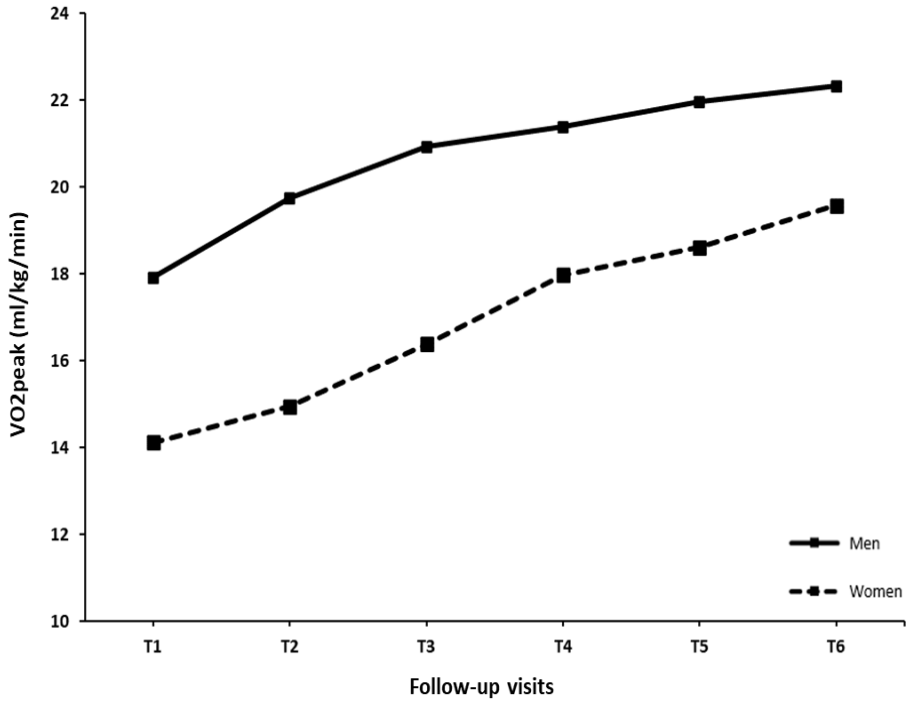
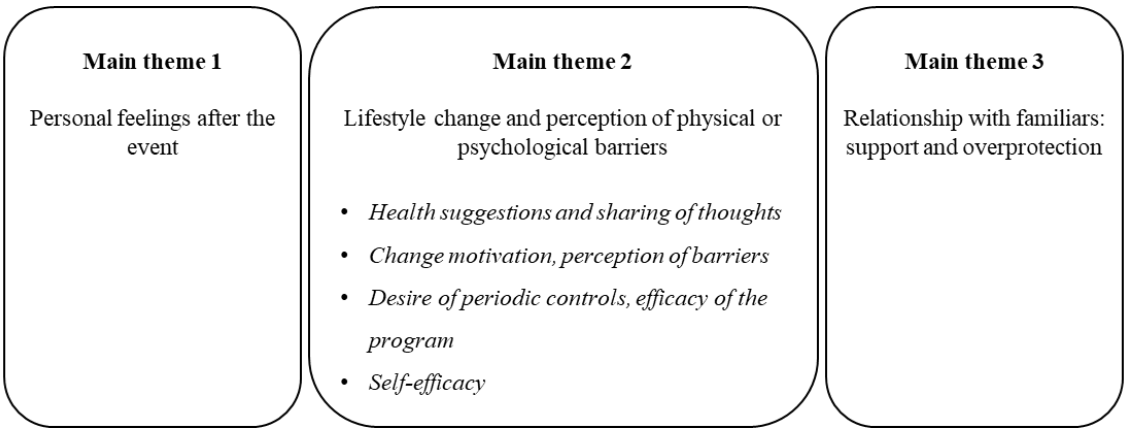


Figure 15: Main themes and sub-themes identified in qualitative interviews. Extracted from Raisi A, et al. Experience and Perceptions among Older Outpatients after Myocardial Infarction following an Exercise Intervention: A Qualitative Analysis from the PIpELINe Trial.



Appendix A: List of publications

1. Tonet E, Arzenton M, De Pietri M, Canovi L, Lapolla D, Sarti A, Amantea V, **Raisi A**, Mazzoni G, Campo G, Grazzi G. Coronary Plaque in Athletes. *J Clin Med*. 2024; 13(7):2044. https://doi.org/10.3390/jcm13072044

2. Piva T, **Raisi A**, Myers J, Zerbini V, Menegatti E, Mazzoni G, Grazzi G, Mandini S. Attenuation of the increase of heart rate and oxygen consumption during progressive exercise in professional rugby players. *J Sports Med Phys Fitness*. 2023 Nov 28. doi: 10.23736/S0022-4707.23.15151-6.

3. Tonet E, Boccadoro A, Berloni ML, Amantea V, Grazzi G, Mazzoni G, Zagnoni S, **Raisi A**, Canovi L, Vitali F, Pavasini R, Scala A, Matese C, Guidi Colombi G, DE Pietri M, Chiaranda G, Campo G. Effect of physical activity on left ventricular dimensions and function after myocardial infarction: a systematic review. *Minerva Cardiol Angiol*. 2023 Oct 23. doi: 10.23736/S2724-5683.23.06356-1.

4. Masotti S, Mandini S, Mazzoni G, Zerbini V, **Raisi A**, Piva T, Zanuso S, Grazzi G. Biocircuit®: An Innovative Adaptive Circuit Training for Outpatients with Cardiovascular Disease. Methodological Approach. *IEEE International Workshop on Sport, Technology and Research 2023.*

5. **Raisi A**, Boonpor J, Breheny M, Vasquez J, Matus C, Diaz-Martinez X, Pell JP, Ho FK, Celis-Morales C. Association of stair use with risk of major chronic diseases. *Am J Prev Med*. 2023 Oct 7:S0749-3797(23)00405-1. doi: 10.1016/j.amepre.2023.10.007.

6. **Raisi A**, Bernardi E, Myers J, Piva T, Zerbini V, Masotti S, Menegatti E, Caruso L, Mazzoni G, Grazzi G, Mandini S. Change in Peak Oxygen Uptake Predicted by the Moderate 1-km Treadmill Walking Test After Walking Training in Outpatients With

Cardiovascular Disease. *J Cardiopulm Rehabil Prev*. 2023 Aug 25. doi: 10.1097/HCR.0000000000000812.

7. **Raisi A**, Zerbini V, Myers J, Piva T, Campo G, Mazzoni G, Grazzi G, Mandini S. A Novel Motivational Approach in the Management of Older Patients With Cardiovascular Disease. *J Cardiopulm Rehabil Prev*. 2023 Jul 1;43(4):309-310. doi: 10.1097/HCR.0000000000000791.

8. **Raisi A**, Zerbini V, Piva T, Belvederi Murri M, Menegatti E, Caruso L, Masotti S, Grazzi G, Mazzoni G, Mandini S. Treating Binge Eating Disorder With Physical Exercise: A Systematic Review and Meta-analysis. *J Nutr Educ Behav*. 2023 Jul;55(7):523-530. doi: 10.1016/j.jneb.2023.03.010.

9. **Raisi A**, Piva T, Myers J, Lordi R, Zerbini V, Masotti S, Chiaranda G, Grazzi G, Mazzoni G, Mandini S. A Moderate Walking Test Predicts Survival in Women With Cardiovascular Disease. Am J Prev Med. 2023 Mar 5:S0749-3797(23)00115-0. doi: 10.1016/j.amepre.2023.02.025.

10. Tonet E, **Raisi A**, Zagnoni S, Chiaranda G, Pavasini R, Vitali F, Gibiino F, Campana R, Boccadoro A, Scala A, Canovi L, Amantea V, Matese C, Berloni ML, Piva T, Zerbini V, Cardelli LS, Pasanisi G, Mazzoni G, Casella G, Grazzi G, Campo G. Multi-domain lifestyle intervention in older adults after myocardial infarction: rationale and design of the PIpELINe randomized clinical trial. Aging Clin Exp Res. 2023 Mar 25. doi: 10.1007/s40520-023-02389-9.

11. Boonpor J, Parra-Soto S, Gore J, Talebi A, Lynskey N, **Raisi A**, Welsh P, Sattar N, Pell JP, Gill JMR, Gray SR, Ho FK, Celis-Morales CA. Association Between Walking Pace and Incident Type 2 Diabetes by Adiposity Levels - A Prospective Cohort Study from The UK Biobank. Diabetes Obes Metab. 2023 Mar 23. doi: 10.1111/dom.15053.

12. **Raisi A**, Piva T, Myers J, Zerbini V, Mandini S, Zappaterra T, Mazzoni G, Tonet E, Pavasini R, Campo G, Grazzi G, Visintin EP. Experience and Perceptions among

Older Outpatients after Myocardial Infarction following an Exercise Intervention: A Qualitative Analysis from the PIpELINe Trial. Int J Environ Res Public Health. 2023; 20(3):2196. https://doi.org/10.3390/ijerph20032196.

13. Piva T, Masotti S, **Raisi A***, Zerbini V, Grazzi G, Mazzoni G, Murri MB, Mandini S. Exercise program for the management of anxiety and depression in adults and elderly subjects: Is it applicable to patients with post-covid-19 condition? A systematic review and meta-analysis. *J Affect Disord*. 2023 Jan 9:S0165-0327(22)01515-4. doi: 10.1016/j.jad.2022.12.155.

14. Mandini S, Menegatti E, Zerbini Z, **Raisi A**, Masotti S, Mazzoni G, Zattoni L, Grazzi G, Piva T. A Guided Walking Program in Urban Environment for a Healthy, Active Community: The Experience of the University of Ferrara. *IEEE International Workshop on Sport, Technology and Research 2022*.

15. Menegatti E, Proto A, Paternò G, Gianesini S, Pagani A, Piva T, **Raisi A**, Zerbini A, Taibi A, Zamboni P, Mazzoni G, Grazzi G, Mandini S. Assessment of Jugular Venous Pulse During Walking by Wearable Strain-Gauge Plethysmograph: A Pilot Study. *IEEE International Workshop on Sport, Technology and Research 2022*.
16. Piva T, Menegatti E, Zerbini V, **Raisi A**, Lordi R, Mazzoni G, Zattoni L, Grazzi G, Mandini S. The "Urban Walking Metro" an Innovative Tool to Face Inactivity and Facilitate Urban Mobility. Study Protocol. *IEEE International Workshop on Sport, Technology and Research 2022*.

17. Zattoni L, Ercolin L, Mandini S, Piva T, Zerbini V, **Raisi A**, Zaccagni L. Video-Analysis of "High-Risk" On-Field Movements Biomechanics in Amateur Male Futsal Players: Preliminary Findings. *IEEE International Workshop on Sport, Technology and Research 2022*.

18. Menegatti E**,** Mandini S, Pagani A, Mandini B, Zerbini V, Piva T, **Raisi A**, Fabbri M, Fogli M, Mazzoni G, Zamboni P, Gianesini S. The Effect of Active Stretching

Training in Patients with Chronic Venous Insufficiency Monitored by Raster-Stereography. *Sensors (Basel)*. 2022 Nov 4;22(21):8509. doi: 10.3390/s22218509.

19. Menegatti E, Proto A, Paternò G, Gadda G, Gianesini S, **Raisi A**, Pagani A, Piva T, Zerbini V, Mazzoni G, Grazzi G, Taibi A, Zamboni P, Mandini S. The Effect of Submaximal Exercise on Jugular Venous Pulse Assessed by a Wearable Cervical Plethysmography System. *Diagnostics (Basel)*. 2022 Oct 4;12(10):2407. doi: 10.3390/diagnostics12102407.

20. **Raisi A**, Zerbini V, Myers J, Lordi R, Piva T, Mazzoni G, Grazzi G, Mandini S. Relationship between exercise capacity and grip strength in a cohort of older cardiac outpatients. *J Sports Med Phys Fitness*. 2022 Oct;62(10):1404-1409. doi: 10.23736/S0022-4707.21.13106-8.

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Appendix B: Oral presentations and posters

1. **Raisi A**, Zerbini V, Myers J, Lordi R, Piva T, Mazzoni G, Grazzi G, Mandini S. Relationship between exercise capacity and grip strength in elderly outpatients with coronary artery disease. *XII Congresso Nazionale SISMeS 2021.*

2. **Raisi A**, Zerbini V, Myers J, Piva T, Campo G, Tonet E, Pavasini R, Grazzi G, Mazzoni G, Mandini S. Exercise-based secondary prevention program impacts physical activity behavior and cardiorespiratory fitness in older outpatients after acute coronary syndrome. *IBTN Conference 2022.* ***CMDO Award of Merit for an Outstanding Poster Presentation – 2022 IBTN Conference.***

3. **Raisi A**, Piva T, Zerbini V, Lordi R, Pavasini R, Tonet E, Campo G, Grazzi G, Mazzoni G, Mandini S. Exercise-based secondary prevention program positively improves functional parameters in older outpatients after acute coronary syndrome. Findings from the PIpELINe study. *XIII Congresso Nazionale SISMeS 2022.*

4. **Raisi A**, Piva T, Zerbini V, Masotti S, Menegatti E, Mazzoni G, Grazzi G, Mandini S. Association between fitness, fatness, and all-cause mortality in outpatients with cardiovascular disease: a prospective cohort study. *XIV Congresso Nazionale SISMeS 2023.*

5. **Raisi A**, Zerbini V, Piva T, Masotti S, Lordi R, Menegatti E, Mazzoni G, Grazzi G, Mandini S. Association between walking speed and mortality in patients with cardiovascular disease: a prospective cohort study. *Exercise for Health Summit 2023.*

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