ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΤΟΜΕΑΣ ΠΑΘΟΛΟΓΙΑΣ

Α ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ

Δ/ΝΤΗΣ ΚΑΘΗΓΗΤΗΣ ΝΙΚΟΛΑΟΣ ΚΟΥΛΟΥΡΗΣ

ΠΜΣ ΚΑΡΔΙΟΠΝΕΥΜΟΝΙΚΗ ΑΠΟΚΑΤΑΣΤΑΣΗ ΚΑΙ ΑΠΟΚΑΤΑΣΤΑΣΗ ΠΑΣΧΟΝΤΩΝ ΜΕΘ

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Προγράμματα καρδιακής αποκατάστασης σε ασθενείς με στεφανιαία νόσο, αποτελέσματα μεταναλύσεων

ΤΣΟΚΑΝΗ ΑΡΙΣΤΗ

ΑΘΗΝΑ 2019

ΤΡΙΜΕΛΗΣ ΕΠΙΤΡΟΠΗ

ΔΑΒΟΣ ΚΩΝΣΤΑΝΤΙΝΟΣ ΕΡΕΥΝΗΤΗΣ Β

ΖΑΚΙΝΘΥΝΟΣ ΣΠΥΡΟΣ ΚΑΘΗΓΗΤΗΣ

ΚΟΥΛΟΥΡΗΣ ΝΙΚΟΣ ΚΑΘΗΓΗΤΗΣ

Contents

Περίληψη

Εισαγωγή: Η καρδιακή αποκατάσταση βασισμένη σε άσκηση μπορεί να έχει ευνοϊκά αποτελέσματα για τους ασθενείς με στεφανιαία νόσο. Ο σκοπός αυτής της μελέτης ήταν να ερευνήσει τα αποτελέσματα πρόσφατων μετα-αναλύσεων που αφορούν τα προγράμματα καρδιακής αποκατάστασης βασισμένα σε άσκηση.

Σκοποί: Να αξιολογηθούν τα αποτελέσματα που έχει η άσκηση στην επιβίωση, τη δευτερογενή πρόληψη και τους καρδιαγγειακούς παράγοντες κινδύνου. Επιπλέον να βρεθεί ποιο είδος άσκησης είναι πιο ωφέλιμο για τους ασθενείς με στεφανιαία νόσο.

Ερευνητικές μέθοδοι: Η βιβλιογραφική αναζήτηση πραγματοποιήθηκε στο Pubmed, την Cochrane Library και στο Scopus για μετα-αναλύσεις σχετικές με την καρδιακή αποκατάσταση βασισμένη σε άσκηση από το 2003 έως το 2018. Υπήρξαν συγκεκριμένα κριτήρια εισαγωγής και αποκλεισμού βάση των οποίων επιλέχθηκαν οι μελέτες. Σύμφωνα με τα συμπεράσματα των ερευνητών, οι μετα-αναλύσεις χωρίστηκαν σε δύο ομάδες. Η πρώτη ομάδα είχε μετα-αναλύσεις που σύγκριναν τα διαφορετικά ήδη άσκησης ενώ η δεύτερη αφορούσε την επίδραση της άσκησης στην επιβίωση, την δευτερογενή πρόληψη και τους καρδιαγγειακούς παράγοντες κινδύνου.

Αποτελέσματα: Μετά τη βιβλιογραφική αναζήτηση συμπεριλήφθηκαν 23 μετα-αναλύσεις οι οποίες ανταποκρίνονταν στα κριτήρια εισαγωγής. Δώδεκα από τις μελέτες αφορούσαν τα διαφορετικά είδη άσκησης που εφαρμόζονται στην καρδιακή αποκατάσταση. Οι υπόλοιπες 11 δημοσιεύσεις μελετούσαν την επίδραση της άσκησης στην καρδιακή αποκατάσταση

Συμπεράσματα: Η ανασκόπηση αυτή έδειξε ότι τα προγράμματα άσκησης στην αποκατάσταση ασθενών με στεφανιαία νόσο είναι ασφαλή και μπορούν να μειώσουν την καρδιοαγγειακή θνητότητα. Ακόμη φάνηκε ότι η άσκηση μπορεί να τροποποιήσει καρδιαγγειακούς

παράγοντες κινδύνου και να βελτιώσει τη σχετιζόμενη με την υγεία ποιότητα ζωής. Ο αριθμός των μετα-αναλύσεων που αφορούσαν τα διαφορετικά είδη άσκησης δεν ήταν αρκετός ώστε να αναδειχθεί ποιο είδος είναι πιο ωφέλιμο για τους ασθενείς με στεφανιαία νόσο. Παρ' όλα αυτά τα μέχρι στιγμής δεδομένα δείχνουν ότι ένας συνδυασμός διαλειμματικής άσκησης αυξημένης έντασης με άσκηση αντίστασης θα μπορούσε να είναι ιδανική για αυτούς τους ασθενείς αυτούς.

Abstract

Background: Exercise-based cardiac rehabilitation may benefit coronary heart disease patients. The aim of this study was to investigate the results of recent meta-analyses on exercise based cardiac rehabilitation programs.

Objectives: To assess the effects of exercise-based cardiac rehabilitation programs on survival, secondary prevention and cardiovascular risk factors modification. Furthermore, to investigate which type of exercise is more beneficial for coronary artery disease patients.

Search methods: Literature search was performed in Pubmed, The Cochrane Library and Scopus for meta-analyses on exercise-based cardiac rehabilitation interventions between 2003 and 2018. Articles were screened for relevance, based on pre-set inclusion and exclusion criteria. Based on the conclusions drawn by the authors of the included publications, meta-analyses were divided in two groups. The first group included meta-analyses examining the different types of exercise that were used in cardiac rehabilitation programs. The second group included meta-analyses that investigated the effect of the intervention on survival, secondary prevention and cardiovascular risk factors.

Results: After finalizing our literature searches, we included 23 meta-analyses which fulfilled our inclusion criteria. Twelve publications compared the different types of exercise training and eleven studies assessed the effect of exercise training on coronary heart disease.

Conclusions: This study showed that exercise-based cardiac rehabilitation is safe for coronary artery disease patients. Most publications report a reduction in cardiovascular mortality, a significant modification of cardiovascular risk factors and an improvement in health-related quality of life. The number of meta-analyses comparing different types of exercise is not enough to indicate which one is most beneficial for coronary heart disease patients. However, current evidence show

that a combination of high intensity interval training and resistance training could the best for this group of patients.

List of figures and tables

Abbreviations

AT	Aerobic Training
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCT	Controlled Clinical Trial
CHD	Coronary Heart Disease
CR	Cardiac Rehabilitation
CT	Combined Training
CV	Cardiovascular
CVD	Cardiovascular Disease
ET	Exercise Training
HIIT	High Intensity Interval Training
HDL	High Density Lipoproteins
HR	Heart Rate
HRQL	Health Related Quality of Life
LDL	Low Density Lipoproteins
MI	Myocardial Infarction
MCT	Moderate intensity Continuous Training
NO	Nitric Oxide
PCI	Percutaneous Coronary Intervention
QOL	Quality of Life
RCT	Randomized Control Trial
RT	Resistance Training
SBP	Systolic Blood Pressure
TG	Triglycerides
VO_2max	Maximum Oxygen Uptake
VO_2peak	Peak Oxygen Uptake

Theoretical Basis

1. Coronary heart disease

Coronary heart disease (CHD) is the most common cardiovascular disease [1]. Of the 56.9 million deaths worldwide in 2016, ischemic heart disease was the world's number one cause of death, accounting for more than 9 million deaths. Ischemic heart disease and stroke have remained the leading causes of death globally for the last 15 years [2].

Coronary artery disease (CHD) is the spectrum of symptoms and diseases due to coronary artery damages [3]. The term CHD refers to the pathologic process called atherosclerosis affecting the coronary arteries. Angina pectoris, myocardial infarction, silent myocardial ischemia are manifestations of CHD [4].

The main cause of CHD is atherosclerosis, a progressive chronic inflammatory process of arterial wall thickening. Atherosclerosis launches retention of cholesterol transported by low-density lipoproteins (LDLs) in the artery wall. The subsequent primarily oxidative modification of vascular LDL particles is believed to be the key process that promotes an inflammatory response to this endothelial injury. Recruited macrophages ingest modified LDL particles, evolve into lipid-laden foam cells, and further urge local inflammation, e.g., by secreting inflammatory mediators such as pro-inflammatory cytokines. Early atherosclerotic lesions which are called "fatty streaks" consist of sub-endothelial lipid depositions, cholesterol-loaded macrophage foam cells, and T-cells. While this situation progresses, interactions between immune and resident vessel wall cells finally end-up in the formation of an atherosclerotic plaque. Atherosclerotic plaques have a necrotic core that consists of apoptotic and necrotic cells, cell debris, and cholesterol crystals. The necrotic core is concealed by a fibrous cap, with "shoulder" regions infiltrated by activated T-cells, macrophages, and mast cells that produce pro-inflammatory mediators and enzymes. Plaque growth can constrict the lumen of an artery and in this way bring on stenosis that can contribute to ischemia in the surrounding tissue. The result of plaque rupture is the exposure of its thrombogenic content to the blood. This may trigger a thrombotic response that either eliminates the lumen immediately or detaches and becomes an embolus that may induce ischemia distal to its point of origin [5].

1.1 Atherosclerosis

Atherosclerosis is an inflammatory disease within the arterial wall that is responsible for several important adverse vascular events, including coronary artery disease. Both innate and adaptive immunity play important roles in the development of atherosclerosis. In particular, monocytes/macrophages, which are the surrogate cells of innate immunity, have important proatherogenic effects. In addition, adaptive immune responses effected by T cells play important roles in atherosclerosis [6].

Atherogenesis involves highly specific cellular and molecular responses with constant interactions between various cellular players. There is recognition of inflammatory reaction in the atherosclerotic region from beginning of the fatty streak to culmination into an acute event resulting from plaque erosion or rupture. Inflammation influences plaque progression and its vulnerability to rupture [7].

It is proven that high plasma LDL cholesterol concentrations lead to the initiation and progression of atherosclerosis. On the contrary, plasma High Density Lipoproteins (HDL) cholesterol concentrations are negatively associated with atherosclerosis. Both LDL and HDL particles are heterogenous. Firstly, small dense LDL particles have been shown in human studies to be positively associated with coronary heart disease. Endothelial dysfunction of the arterial wall is the premier step to provoke monocyte adhesion. What comes next is the macrophage intruding the sub-endothelial area to form foam cells. Hypercholesterolemia is a contributor to endothelial dysfunction of great importance [7]. In a gene expression analysis of mouse aortic endothelium in response to hypercholesterolemia, inflammation, or aging, 14 genes were significantly different between these different atherogenic stimulations and normal condition. [8,9]

2. Epidemiology and Prognosis

Coronary artery disease, is the most important precursor of myocardial infarction (MI) and is the main component of total cardiovascular mortality. In approximately 20% of infarcted patients, MI is recurrent in the first year after the event. Moreover, among cardiovascular disease, coronary artery disease accounts for the most increased index of life years lost due to morbidity and/or mortality [10].

Although the mortality rate for CHD has declined over the past four decades in western countries, this condition still remains responsible for one-third of all deaths in people older than age 35 years. Between 1999 and 2007, the level and rate of decline in CHD mortality displayed persistent disparities. Nearly one-half of all middle-aged men and one third of middle-aged women in the USA will develop some expression of CHD. A long-term decline in CHD mortality rates has continued during the first decade of the new century. However, CHD is a major cause of death and disability in developed countries. The 2016 Heart Disease and Stroke Statistics update of the American Heart Association has recently reported that 15.5 million persons ≥20 years of age in the USA have CHD. Given the progression of atherosclerosis over decades, patients are typically asymptomatic for years in spite of the evidence of CHD. Despite lack of symptoms, the presence and extent of non-obstructive CHD are associated with a worse prognosis compared with patients with no evidence of CHD [11-12].

As far as the Greek population is concerned, premature deaths from ischemic heart disease for Greek males have been in decline since 2000, although to a lesser extent than in the EU15 (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom). Greece is one of the European Union member states that top the list of total deaths due to ischemic heart disease and stroke, a fact that is mainly attributed to unfavourable changes in modifiable risk factors. By 2011, the premature mortality rate from diseases of the circulatory system in Greece had decreased to 45/100 000, more than double the EU15 rate of 22/100 000. For women, the premature mortality rate from ischemic heart disease was approximately 10/100 000 for decades with only minor annual variations. The most recent rate for women in Greece (in 2011) was double the average rate of the EU15 [13-14].

Zhu et al found a positive association between males and rural areas and developing countries and a negative association between females and developed European countries. Furthermore, the prevalence of CHD between developing and developed countries had no statistical difference. In addition, they demonstrated a growing CHD epidemic trend in developing countries and a reverse trend in developed countries over the past decades. Many studies conducted in the developed countries have found a reliable negative association between socioeconomic status and CHD prevalence, with the evidence showing that low medical facilities and limited social support may have negative effects. Their results suggest that a higher national socioeconomic status may lead to a higher CHD prevalence in developing countries but a lower prevalence in developed countries. Moreover, there was no disparity in CHD prevalence between developing and developed countries. In addition, the prevalence of CHD was observed to increase in developing countries and decrease in developed countries over the past several decades [15].

Cardiovascular diseases were the leading causes of death in the United States with 166 deaths per 100,000 in 2016. Thus, heart disease accounts for every one in four deaths in the U.S. [16]. In the next decades, the population of individuals aged 65 years and older will grow until 17% of the world's total population. It is predicted that the global burden of cardiovascular diseases (CVD) will increase proportionally in this group [16-17].

The importance of coronary heart disease as a disease of both genders tends to be underappreciated. Just below one in five male deaths and one in ten female deaths were attributed to CHD. The British Heart Foundation's report in that same year states that CHD by itself is the biggest single cause of death in the UK. In general, women with CHD have worse outcomes than their male counterparts when no adjustments are made for other characteristics and comorbidities. Women tend to present with coronary artery disease later in life, and even when they present young, they tend to receive less evidence-based treatment than their male counterparts [18].

In India the annual death rates due to cardiovascular disease are predicted to rise from 2.26 million in 1990 to 4.77 million by 2020. There were estimated 17.5 million deaths in 2005 due to CHD alone which is expected to increase by 120% in women and 137% in men by 2020 in the developing countries. The estimated prevalence of cardiovascular disease in India is about 10.5% which extrapolates to a burden of about 32 million affected individuals, and amounts to a loss of 15 million disease adjusted life years [19].

Despite large reductions in mortality from CHD, it has remained a substantial burden to the UK, with rises in treatment and hospital admissions for all CVD. Coronary heart disease prevalence has remained constant at around 3% in England and 4% in Scotland, Wales, and Northern Ireland. Hospital admissions for all CVD increased by over 46000 between 2010/2011 and 2013/2014, with more than 36500 of these increased admissions for men. Hospital admission trends vary by country and CVD condition. CVD prescriptions and operations have increased over the last decade. CVD mortality has declined notably for both men and women while hospital admissions have increased [20].

3. Pharmacological and non-pharmacological therapeutic approaches for coronary heart disease

Coronary artery disease is characterized by the formation of an atherosclerotic plaque following a long-term and complex process. Briefly, when the atherosclerotic plaque suffers a rupture, the disruption of the endothelium stimulates a coagulation process, which results in the formation of a thrombus. Myocardial infarction occurs when the thrombus occludes coronary blood flow and the surrounding myocardium area lacks oxygen supply, thus leading to the necrosis of the cardiac tissue. Depending on the level of the occlusion, the extent of the necrotic area, and the presence of collateral circulation, MI can be fatal or not. When the heart survives to the ischemia, several events occur at molecular, cellular, neurohumoral, hemodynamic, and morphological levels. Adaptive stimuli start at early and late stages, going through a pathological remodeling process. As MI occurs, inflammation takes place in the necrotic area, where matrix metalloproteinases stimulate the disintegration of intra-myocyte collagen, resulting in the loss of support tissue. The cardiac wall of the infarcted area gets thinner and the ventricular cavity dilates, a phenomenon known as infarct expansion. Functionally, because of myocyte loss, there is a decrease in ejection volume, thus increasing preload due to elevated diastolic final volume, and an increase in ventricular wall stress. The elevated cardiac wall stress is a stimulus to serial myocyte replication, resulting in ventricular hypertrophy. The survived heart can continue its pumping function facing this new pattern for a long term; nevertheless, when cardiac hypertrophy cannot compensate the increased ventricular volume, it suffers progressive ventricular enlargement and dysfunction. There are several mechanisms which are altered after MI as a cause or a consequence of the remodeling process. These altered mechanisms encompass hemodynamics, cardiac autonomic nervous system function, baroreflex sensitivity, renin-angiotensin-aldosterone system, sarcoplasmic reticulum calcium transient, beta-adrenergic pathway, and oxidative stress. Among others, these mechanisms are the main targets of pharmacological and non-pharmacological therapeutic strategies to improve prognosis after MI [10].

Several invasive and noninvasive techniques have been developed for endothelial function testing into clinical practice. Invasive assessment by catheterization is considered the reference standard for evaluating coronary endothelial function. Catheterization involves intra-arterial administration of endothelium-dependent substances such as acetylcholine that enhance release of endothelial nitric oxide and lead to measurable vasodilatation and increase in coronary blood flow in normal subjects but vasoconstriction and lack of increase in coronary blood flow in patients with endothelial dysfunction. The obvious disadvantage with such a method is that its invasive nature precludes widespread use in the population. Therefore, other non-invasive techniques have been developed based on the diffuse nature of endothelial dysfunction, most of which are based on the same principle of reactive hyperemia. The forearm flow mediated vasodilatation is a non-invasive method to evaluate peripheral endothelial function, and its measures correlate well with coronary artery endothelial function by catheterization. One method also vastly used, based on the same principle to assess peripheral endothelial function is the reactive hyperemia-peripheral arterial tonometry, whose response also correlates well with the presence of coronary artery endothelial dysfunction. Although, the majority of the non-invasive endothelial function tests use reactive hyperemia after occlusion as a trigger to detect endothelial dependent vasodilation, forearm flow mediated vasodilatation represents conduit artery vasodilation, and reactive hyperemia-peripheral arterial tonometry represents micro vessel vasodilation. Moreover, reactive hyperemia-peripheral arterial tonometry is adjusted for any changes that occur in the control arm, a distinction from the forearm flow mediated vasodilatation method. Given its repeatability, non-invasive endothelial function assessment is useful in evaluating the clinical efficacy of traditional and new approaches for cardiovascular diseases [21].

Blumenthal et al searched the literature in order to conclude which treatment should be generally chosen for patients with stable CHD. For the unstable coronary symptoms, percutaneous transluminal coronary angioplasty and medical therapy should be viewed as complementary, and not as opposing, strategies. For stable angina, while angioplasty improves coronary blood flow considerably more than lipid lowering does, its effects are restricted to the target vessel, and they may not be maintained over time without concomitant lipid lowering therapy. All CHD patients would benefit from comprehensive risk factor modification and prudent use of revascularization procedures. Before a relatively stable patient with angina is referred for percutaneous transluminal coronary angioplasty, practitioners should employ the fundamental ABC's of stable angina management: **A**spirin and **A**nti-anginals, **B**eta-blockers and **B**lood pressure control, **C**holesterol management and **C**igarette cessation, **D**ietary improvements and **D**iabetes control, **E**ducation and **E**xercise [22].

4. Description of the exercise intervention

Exercise-based cardiac rehabilitation is an intervention that is applied to patients with cardiovascular health issues. It is prescribed for patients by cardiologists that coordinate a rehabilitation team of health professionals specialized in cardiac health. The health care professionals that are members of the rehabilitation team could be exercise physiologists, physiotherapists, nurses, dieticians, psychologists and pharmacists.

Exercise-based cardiac rehabilitation for coronary heart disease patients is multipurpose. Firstly, it aims to modify the ability of the patient to exercise. Secondly, it changes the risk factors that could lead to a new heart-related episode. What is more, exercise programs strengthen the musculoskeletal system of the cardiac patient.

Exercise-based cardiac rehabilitation following a cardiac event is a Class IA recommendation from the American College of Cardiology/American Heart Association and the European Society of Cardiology. Many definitions of cardiac rehabilitation have been proposed. The following definition encompasses the key concepts of cardiac rehabilitation: “The coordinated sum of activities required to influence favourably the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behavior, slow or reverse progression of disease”. Cardiac rehabilitation is a complex intervention that may involve a variety of therapies, including exercise, risk factor education, behavior change, psychological support, and strategies that are aimed at targeting traditional risk factors for cardiovascular disease. Cardiac rehabilitation is an essential part of contemporary heart disease care and is considered a priority in countries with a high prevalence of CHD [23-24].

Patient education is defined as "the process by which health professionals and others impart information to patients that will alter their health behaviors or improve their health status". Self-management education programmes are designed to allow people with chronic conditions to take an active part in managing their own condition. They are complex behavioral interventions which target patient education and promote self-care behavior and risk-factor modification and aim to improve health outcomes and decrease the incidence of complications for patients by supporting, not replacing, medical care. This in turn may lead to reduced hospitalizations and medical appointments and an associated reduction in costs, both for the patient and the healthcare system. Educational interventions within cardiac care increase patients' knowledge and facilitate behavior change. Educational interventions in cardiac care have been shown to increase physical activity, and lead to healthier dietary habits and smoking cessation, although any related improvement in response to cardiac symptoms, medication compliance or psychosocial well-being is more equivocal [11,23].

These rehabilitation programs are usually performed in a specialized cardiac rehabilitation centre. Alternatively, health providers can use technology innovations of telehealth in order to help patients that live in distant communities complete the rehabilitation program. Common topics include nutrition, exercise, risk factor modification, psychosocial well-being, and medications. Duration, frequency and ongoing maintenance or reinforcement also varies between programmes. Some programmes are developed according to validated educational theory and by trained professionals who are part of an interdisciplinary team, whilst others are delivered by peers. Some programmes may use adjunctive written materials or videotapes that supplement clinical consultations, while internet- and mobile phone-based applications may be used to deliver educational material and messages to patients. Telephone follow-up is increasingly used by healthcare providers to reach patients more frequently and in their own environment without the burden of a clinic visit [23].

Both the American College of Cardiology/American Heart Association and the European Society of Cardiology recognize education as an important component of comprehensive cardiac rehabilitation programmes [23].

Cardiac rehabilitation (CR) programs are, in their most common form, medically supervised exercise programs that have shown to improve function, exercise capacity, quality of life (QoL), psychosocial well-being, morbidity, and mortality. In addition to providing an exercise program, these individually tailored regimens take a multidisciplinary approach to the patient's well-being by focusing on the psychological, nutritional, and risk factor status of the individual. Yet, despite the benefit of formal CR programs, referral and participation rates for eligible patients are poor especially among those individuals belonging to rural populations, lower socioeconomic status, advanced aged, and female sex [25].

CR was found to be effective by Deveza et al for reducing cardiovascular mortality when compared with usual care but not for reducing total mortality, based on moderate quality evidence. Exercise-based CR provides benefits by reducing cardiovascular mortality and hospitalization, although it does not reduce total mortality. All forms of CR appear to be equally effective [26].

Exercise based cardiac rehabilitation for coronary heart disease may include many different forms of exercise. For example, aerobic training that could be continuous or interval. Furthermore, resistance training and other forms like Tai Chi have been used in CHD rehabilitation. The different types of exercise can be used individually or combined.

High levels of physical activity and aerobic capacity are associated with low risk of cardiovascular disease and mortality. Aerobic exercise is therefore strongly recommended both for healthy individuals and for patients with cardiovascular disease to improve cardiovascular health and reduce the risk of premature mortality. If the total energy expenditure of exercise is held constant, exercise performed at higher relative intensities has been found to elicit greater increase in aerobic capacity and greater cardioprotective effects than exercise at moderate intensities. An inverse association has also been detected between the relative intensity of physical activity and the risk of developing coronary heart disease, independent of the total volume of physical activity [27]. Despite that higher levels of physical activity reduce cardiovascular events; it is advocated that vigorous activity could also acutely and transiently increase the risk of sudden cardiac death and myocardial infarction in susceptible persons. Therefore, current guidelines recommend that patients in cardiac rehabilitation or secondary prevention programs perform moderate exercise between 50-90% of peak heart rate (HRpeak). The results demonstrate that such high-intensity exercise is superior to moderate intensity for improving both peak oxygen uptake (VO_2peak) and cardiac function, as well as reducing the risk factors associated with cardiovascular disease. The safety aspect of such high intensity exercise training programs should however be evaluated before it is used in large, unselected groups of CHD patients. The aim of this study was therefore to assess if there is an increased risk of cardiovascular events or death during, or immediately after, exercising with high- compared to moderate-intensity in a large group of CHD patients undergoing cardiac rehabilitation [27-28].

In patients with coronary artery disease, combined exercise training, including both aerobic activities and strength training, is currently recommended. However, physical training in patients suffering from ischemic heart disease should be carefully prescribed, in order to maximize the positive effects and minimize the risks. It is also important that physical training programs are conducted in suitable facilities, with appropriately trained staff and with technical equipment suitable to deal with any emergency situations [28].

Sedentarism highly contributes to cardiovascular disease burden, especially for coronary artery disease, and is also one of the MI risk factors. For many years, it was recommended to avoid physical activity after a cardiovascular event; nowadays, it is a consensus that exercise training (ET) should be part of cardiac rehabilitation programs. Exercise training after MI follows international specialized guidelines; however, there are different protocols adopted by several societies worldwide in cardiac rehabilitation, and there is still lack of information on which type and regimen of exercise may be the ideal after MI, as well as how these exercises act to promote beneficial effects to cardiovascular and other organic systems. Thus, experimental studies are important contributors to elicit mechanisms behind clinical results, and to test and compare different ET protocols. Therefore, exercise prescription can be optimized, individualized, and safely practiced by patients. In this chapter, we present a brief review of MI patho-physiology followed by an updated discussion of the most relevant discoveries regarding ET and MI in basic science [10].

5. Meta-analyses

What is a meta-analysis and why this study included meta-analyses?

The purpose of this study is to provide evidence about cardiac rehabilitation for patients with coronary artery disease. The most valid and reliable resources to collect data are meta-analyses related to this subject.

Meta-analysis refers to any systematic statistical method for combining data from independent clinical studies for two basic purposes [29]. The first is to determine if similar treatment effects exist for a therapy examined in independent clinical studies and, if so, to estimate a net effect for this therapy [29]. In this way, meta-analysis overcomes the limitation of interpreting a number of small, underpowered clinical trials [29]. Alternatively, if treatment effects differ substantially for a therapy among independent clinical studies, the second purpose of a meta-analysis is to examine factors that may explain these differing effects [29]. Meta-analysis has become a popular approach for summarizing a large number of clinical trials and resolving discrepancies raised by these trials [29].

The classical meta-analysis compares two treatments while network meta-analysis (or multiple treatment meta-analysis) can provide estimates of treatment efficacy of multiple treatment regimens, even when direct comparisons are unavailable by indirect comparisons [30]. An example of a network analysis would be the following. An initial trial compares drug A to drug B. A different trial studying the same patient population compares drug B to drug C. Assume that drug A is found to be superior to drug B in the first trial. Assume drug B is found to be equivalent to drug C in a second trial. Network analysis then, allows to potentially say statistically that drug A is also superior to drug C for this particular patient population. (Since drug A is better than drug B, and drug B is equivalent to drug C, then drug A is also better to drug C even though it was not directly tested against drug C) [30].

Meta-analysis is no longer a novelty in medicine. Numerous meta-analyses have been conducted for the same medical topic by different researchers. Recently, there is a trend to combine the results of different meta-analyses, known as a meta-epidemiological study, to assess the risk of bias, Meta-analysis of randomized clinical trials is not an infallible tool, and several examples exist of meta-analyses which were later contradicted by single large randomized controlled trials, and of meta-analyses addressing the same issue which have reached at opposite conclusions. No single study, whether meta-analytic or not, will provide the definitive understanding of responses to treatment, diagnostic tests, or risk factors influencing disease. Despite this limitation, meta-analytic approaches have demonstrable benefits in addressing the limitations of study size, can include diverse populations, provide the opportunity to evaluate new hypotheses, and are more valuable than any single study contributing to the analysis. The conduct of the studies is critical to the value of a meta-analysis and the methods used need to be as rigorous as any other study conducted [30].

Decisions about the utility of an intervention cannot be based on the results of a single study, because results typically vary from one study to another. Rather, a mechanism is needed to synthesize evidence across studies. The extraction of data based on a meta-analysis can lead to right and safe conclusions as far as medical decision making is concerned.

The most important reason for practicing evidence-based medicine is to improve health care of quality through the identification and promotion of practices that work, and the elimination of those that are ineffective or harmful. Evidence-based practice promotes critical thinking. It demands that the effectiveness of clinical interventions, the accuracy and precision of diagnostic tests, and the power of prognostic markers should be scrutinized and their usefulness proven. It requires clinicians to be openminded and look for and try new methods that are scientifically proven to be effective and to discard methods shown to be ineffective or harmful. It is important that health care professionals develop key evidence-based medicine skills including the ability to find, critically appraise, and incorporate sound scientific evidence into their own practice [31].

Methods

Inclusion criteria

To conduct this review, we searched only for studies that were meta-analyses. The meta-analyses included should concern exercise-based rehabilitation programs for patients with coronary heart disease. The exercise-based rehabilitation programs should have examined either the effect of exercise on the physiological factors concerning CHD or the different types of exercise that can be used. Only open access meta-analyses could be included in this review.

Exclusion criteria

Studies that did not report outcomes about secondary prevention or cardiovascular risk factors affecting these conditions were excluded from this review.

Literature search

Literature search was performed in the Cochrane Library, Scopus and Medline through PubMed for meta-analyses on exercise-based cardiac rehabilitation interventions between 2003 and 2018. Based on conclusions drawn by the authors of the included articles, meta-analyses were divided in two groups. The first group included meta-analyses that compared the different types of exercise used in cardiac rehabilitation programs. The second group included meta-analyses that investigated the results of the intervention on survival, secondary prevention and cardiovascular risk factors.

Results

After our literature searches, we included 23 meta-analyses that fulfilled our inclusion criteria. There were 12 studies comparing different forms of exercise trying to indicate the best for coronary disease. The other 11 meta-analyses investigated the outcomes of exercise-based cardiac rehabilitation in these patients as far as mortality and risk physiological factors were considered. In table 1 we present the first group of meta-analyses and in table 2 the second group.

Table 1. Meta-analyses indicating the different forms of exercise in CHD

Study	Intervention	Total patients/ Amount of included RCTs	Outcomes
Chen et al. 2017 [32] China	Endurance and moderate-high intensity exercise	1286/ 18	Endurance exercise training has a positive effect on major modifiable cardiovascular risk factors and functional capacity.
Claes et al 2017[33] Belgium	Centre-based telehealth and home-based	1440/ 7	Increased exercise capacity for the home-based.
Huang et al 2018 [34] China		1546/ 9	More hospitalisations and better quality of life for the home-based
Liou et al 2015 [35] Australia	High intensity interval-moderate intensity	472/ 10	HIIT improves VO_2peak more than MCT, MCT was associated with numerical decline in patients' resting heart rate and body weight.
Elliott et al 2015 [36] Australia	High intensity interval-moderate intensity	229/ 6	HIIT more effective than MCT.
Gomes-Neto 2017 [37] Brazil	High intensity interval-moderate intensity	609/ 12	HIIT may improve VO_2peak more than MCT. This superiority disappears with isocaloric protocols.
Marzollini et al 2012 [38] Canada	Resistance, Aerobic and combined training	504/ 12	CT is more effective than AT in improving body composition, strength, and some indicators of

			cardio-vascular fitness.
Yamamoto et al 2016 [39] Japan		1095/ 22	Resistance training increases exercise capacity and muscle strength in middle-aged and elderly patients and mobility in elderly patients.
Xanthos et al 2016 [40] Australia	Resistance, aerobic and combined training	2410/ 23	CT is more beneficial than AT alone for improving physical function. Shorter duration interventions that include resistance training allow patients to return to their normal activities of daily living earlier.
Hollings et al 2017 [41] Australia, USA	Progressive resistance, aerobic, combined training	1940/ 34	Isolated progressive resistance training increases lower and upper body strength and aerobic fitness same as aerobic training. CT is more beneficial than AT alone.
Yang et al 2018 [42] China	Tai Chi versus other forms of exercise or non-exercise	291/ 5	Tai Chi is beneficial compared to no exercise or other types of exercise with low-to-moderate intensity.
Liu et al 2018 [43] China		972/ 13	Tai Chi improves aerobic endurance and psychosocial well-being. Tai Chi could be a cost-effective and safe exercise option in cardiac rehabilitation.

1. **Chen et al 2017** [32]

Chen et al. conducted a meta-analysis in order to detect the advantages of endurance training for patients with CHD. They included 18 RCTs with a total of 1286 patients. They searched for RCTs that investigated the effects of a dynamic endurance exercise program combined with aerobic training compared with usual care or no endurance exercise intervention. The participants should have experienced myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention or had been diagnosed with CHD through angiography. All participants were over twenty years old. The exercise intervention had to last from eight to twenty-four weeks. The sessions were over twenty minutes with a frequency from three to seven times a week. Studies that included patients with other medical conditions than CHD were excluded from this meta-analysis. Their results are summarized below:

- Primary outcomes:
    - Systolic blood pressure decrease of 3.8 mm Hg (p=0.01)
    - Diastolic blood pressure decrease of 1.4 mmHg (p=NS), LDL cholesterol decrease of 5.5 mg/dL (p=0.02)
    - HDL cholesterol increase of 3.8 mg/dL (p<0.001)
    - Triglyceride decrease of 4.8 mg/dL (p=NS)
    - Total cholesterol decrease of 13.2 mg/dL (p=NS)
- Secondary outcomes
    - Peak VO_2 increase of 3.47 mL/kg/min (p<0.001)
    - LVEF increase of 2.6% (p=0.03)

Duration of exercise intervention ≤ 12 weeks

- Systolic blood pressure decrease of 3.3 mmHg (p=0.03)
- Peak VO_2 increase 3.6 mL/Kg/min (p=0.03)

Duration of exercise intervention > 12 weeks

- LDL cholesterol decrease of 8.92 mg/dL (p=0.04)
- HDL cholesterol increase of 4.5 mg/dL (p=0.01)
- Triglyceride decrease of 29 mg/dL (p<0.001)

- Peak VO_2 increase of 3.1 mL/kg/min ($p<0.001$)
- LVEF increase of 4.2% ($p<0.001$)

Supervised exercise based cardiac rehabilitation programmes

- Systolic blood pressure decrease of 3.2 mmHg ($p=0.04$)
- HDL cholesterol increase of 2 mg/dL ($p<0.001$)
- LDL cholesterol decrease of 5.7 mg/dL ($p=0.04$)
- Peak VO_2 increase of 3.6 mL/kg/min ($p<0.001$)
- LVEF increase of 3.4% ($p=0.01$)

Home-based exercise programmes

- Systolic blood pressure decrease of 8.63 mmHg ($p=0.04$)
- Peak VO_2 increase of 2.3 mL/kg/min ($p=0.01$)

Volume of exercise training 60-90 minutes per week

- Systolic blood pressure decrease of 4.2 mmHg ($p=0.02$)
- HDL cholesterol increase of 3.5 mg/dL ($p=0.03$)
- Triglyceride decrease of 29.4 mg/dL ($p<0.001$)
- Peak VO_2 increase of 4.1 mL/kg/min ($p<0.001$)
- LVEF increase of 3.4% ($p=0.01$)

These results demonstrate that endurance exercise training has a positive effect on the primary outcomes of the modifiable cardiovascular risk factors of SBP, LDL cholesterol and HDL cholesterol . Their findings demonstrated a significant improvement in secondary outcomes (peak VO_2 and LVEF).

Notably, there were significant effects for exercise programmes with exercise durations ranging from 60 to 90 minutes weekly. A total of 20–30 minutes/day and 3–5 days/week of moderate- to vigorous-intensity exercise are recommended for most adults in order to obtain health/fitness benefits so the minimum dose selected was 60–90 minutes per week.

2. **Claes et al 2017** [33]

Claes et al also conducted a meta-analysis about telehealth interventions and especially for home-based programmes. They included 7 studies with a total of 1440 patients. The studies included had to compare home-based with centre-based interventions or with usual care with twelve months evaluation of longer-term effects. Exercise capacity and physical activity had to be reported in all analyses. Their results are presented below:

- Physical activities: No significant differences for home-based group(p=NS)
- Exercise capacity:
  - No significant differences between home-based and usual care (p=NS)
  - Small but significant difference between home-based and centre-based rehabilitation in favour of home-based (p=0.03)

The results demonstrate that a telehealth rehabilitation program could be as effective as centre-based program for patients with CHD.

3. **Huang 2015** [34]

Huang et al conducted a meta-analysis in order to compare centre-based with telehealth interventions for CHD. They included 9 RCTs with a total of 1546 patients. The participants should have experienced an MI, angina or revascularization and should have participated in a community-based, a home-based or a centre-based programme. Telehealth interventions were accomplished by telephone, computer or video conference communication. Centre-based programmes were conducted in a hospital or a rehabilitation centre. All RCTs reported mortality, adverse events, modifiable coronary risk factors, exercise capacity, health related QoL and psychological state of the patients. Analyses without a structured exercise regime for rehabilitation were excluded from this study.

The telehealth intervention included 781 patients who participated in a programme from six weeks to six months. They performed one to six sessions per week with session duration from 25-60 minutes. The centre-based programmes included 765 patients with generally the same intervention as the telehealth interventions. All studies had a short-term follow up from twelve to twenty-four weeks and a long-term follow-up from twenty-four months to six years. The results of this meta-analysis are listed below:

- No significant difference in the rate of participants with outcome was found between the telehealth intervention and centre-based groups.
- All-cause mortality: no statistically significant differences
- Cardiovascular events:
  - No statistically significant difference during short-term follow-up
  - Higher number of hospitalizations for the telehealth group during long-term six years follow-up
- Blood lipids:
  - No significant differences in total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride in the short term (12 weeks to 12 months)
  - No significant differences in total cholesterol, HDL cholesterol during long-term follow up.
- Blood pressure: No difference in systolic and diastolic blood pressure was found between the groups during the short term (12 weeks to 12 months) and the long term follow up
- Smoking prevalence: No significant difference during the short term (12 weeks to 12 months) and the long term follow up

- Weight: No difference in weight or BMI was found between the groups during the short term (Figure 6) and during the long-term follow up
- Exercise capacity and peak heart rate:
  - Using at least one kind of measurement scales, including: peak metabolic equivalent of energy (peak METs), maximal oxygen uptake (VO_2max), distance on incremental shuttle walking test or max-workload (Watts) no significant difference in exercise capacity between telehealth intervention and centre-based CR during short term follow up
  - At one-year follow up with telehealth intervention there was significant improvement in exercise capacity (peak METs)
  - no difference was found in the HRpeak between the groups either
- Health-related quality of life:
  - the short term (12 weeks to 12 months), no difference in physical score or the mental score was found between the groups.
  - At long term follow-up, (one-year follow up) reported that the telehealth intervention group demonstrated significantly higher physical HRQL
  - No difference in physical activity score at 24 months.
- Psychosocial state: no significant difference in anxiety score or depression score between the groups during short-term and long-term follow up.
- Cost: Studies show different results.

The results demonstrate that a telehealth rehabilitation program could be as effective as centre-based program for patients with CHD.

4. **Liou et al 2015** [35]

Liou et al conducted a meta-analysis in order to compare High Intensity Interval Training (HIIT) with Moderate Intensity Continuous Training (MCT). They included ten RCTs with a total of 472 patients. The duration of the programmes should be at least four weeks including CHD patients with or without left ventricular impairment. Their RCTs should compare respectively and directly the physiological and clinical outcomes for HIIT and MCT groups with 95%confidence intervals (95%CI). The exercise intervention should last from four to sixteen weeks.

The HIIT group included 218 patients with a mean age of 60.9 years. They performed from 80% to 95% of peak heart rate (HR) and sessions had a frequency of two to five per week. The MCT group included 254 patients with a mean age of 63 years old. They performed from 50% to 75% of peak HR with the same sessions' frequency. Their results are presented below:

- Improvement in mean VO_2 peak: in favour for HIIT; mean difference= 1.78 ml/kg/min (95% CI: 0.45-3.1)
- Metabolic profile: No statistically significant differences for glucose levels, triglyceride and HDL
- Weight reduction: in favour of MCT; mean difference = -0.48 kg (95% CI:0.15-0.8)
- Resting HR decline: in favour for MCT mean difference= -1.80/min (95% CI: 0.71-2.89)

These results indicate that the HIIT improves the mean VO_2peak in patients with CHD more than the MCT, although the MCT was associated with a more pronounced numerical decline in patients' resting heart rate and body weight.

5. **Elliott et al 2015** [36]

Elliot et al conducted a meta-analysis to compare interval with continuous training. They included six RCTs comparing these types of exercise in 229 patients with stable CHD in the absence of heart failure. Aerobic capacity should have been reported in the outcomes of the included studies. The sessions lasted from four to sixteen weeks. The HIIT programmes had intensity from 80% - 90% of the VO_2peak or from 85% - 95% of HR peak and frequency from two to five sessions per week. The MCT programmes had intensity from 50% to 60% of VO_2peak and frequency from two to five sessions per week. Their results are presented below.

- VO_2peak: 1.53 ml/kg/min more increased with HIIT (p=0.0001)
- Anaerobic threshold: 1.95 ml/kg/min more increased with HIIT (p=0.0001)
- Cardiovascular risk factors:
    a) Blood pressure: -3.44 mmHG (p=NS)
    b) HDL: 0.04 (p=NS)

These results indicate that in patients with CHD, HIIT appears more effective than CT for the improvement of aerobic capacity.

6. **Gomes-Neto et al 2017** [37]

Gomes-Neto et al conducted a meta-analysis in order to compare HIIT and MCT as well. They included twelve studies with a total number of 609 patients with CHD. They included RCTs with patients randomized to a group of HIIT or to MCT. Studies including patients with other cardiac diseases or with respiratory diseases were excluded from this meta-analysis.

High Intensity Interval Training regimes had an intensity of 85% - 95% of peak HR and a frequency from two to five sessions per week. The MCT programmes had an intensity of 70% - 75% peak HR and also a frequency from two to five sessions per week. They also performed a subgroup analysis considering only studies with isocaloric protocols. Isocaloric protocols aim to adjust the energy expenditure among aerobic exercise sessions performed with different intensities. This subgroup analysis included 5 studies. The results are listed below.

- VO_2peak: improvement of 1.3 ml/kg/min for HIIT ($p<0.05$)
- Quality of life: No significant difference

Non isocaloric studies

- VO_2peak: improvement of 1.9 ml/kg/min for HIIT ($p<0.05$)

Isocaloric studies

- VO_2peak: improvement of 0.7 ml/kg/min for HIIT (p=NS)

The above results indicate that HIIT may improve peak oxygen uptake and should be considered as a component of care in coronary artery disease patients. However, this superiority disappeared when isocaloric protocol is compared.

7. **Marzolini et al 2012** [38]

Marzolini et al conducted a meta-analysis to compare the effect of combined aerobic (CT) and resistance training (RT) and aerobic training (AT) alone in individuals with CHD. They included twelve RCTs with totally 504 patients from 49-71 years old with CHD (MI, CABG, PCI, or CHD defined by angiography). In these studies, at least one group received CT (defined as AT and RT) and one group received AT alone. The outcomes included at least one of the following: body composition measured by dual energy X-ray absorptiometry (DEXA), cardiovascular fitness, VAT, muscular strength, and HRQL. Studies with heart failure patients were excluded from this meta-analysis.

The interventions lasted 13.3 ±7.8 weeks (4 weeks - 29 weeks). The aerobic training had duration of each session from twenty to sixty minutes and frequency from two to six times per week. Its intensity was from 40% to 85% of peak heart rate. Combined aerobic and resistance training had a duration of each session from eight to sixty minutes of AT, and RT of two to four sets of two to ten exercises. Its frequency was from two to four times per week AT and two to three times per week RT. Its intensity was from 40% to 85% of peak HR for the AT and from 40% to 80% of the repetition lifted maximum. Their results are listed below:

- VO_2peak: 0.41 ml kg/min increase for the combined training group (p=NS)
- Ventilatory anaerobic threshold: 1.42 ml/kg/min for the combined training group (p=NS)
- Body composition: 0.88 kg reduction for the combined training group and 2.3% reduction of the body fat mass (p=0.0004)
- Muscular strength: statistically significant increase in lower and upper body mass strength for the combined training group
- Quality of life:
    - Only women study: physical and social QoL improvement for the combined training group
    - Role limitation: No significant differences
    - Emotional dimension: greater improvement for the combined training group
    - Physical component: Not statistically significant differences

These results indicate that CT is more effective than AT in improving body composition, strength, and some indicators of cardiovascular fitness, and does not compromise study completion or safety when compared to AT

8. **Yamamoto et al 2016** [39]

Yamamoto et al also conducted a meta-analysis to see the effects of resistance training on muscle strength, exercise capacity, and mobility in middle-aged and elderly patients with CHD.

They included twenty-two RCTs comparing resistance training and usual care or combined resistance training and aerobic training with aerobic training alone. The study participants should have myocardial infarction, coronary revascularization, angina pectoris or CHD and should not have heart failure or cardiac resynchronization therapy devices or implantable defibrillators.

Of the twenty-two studies included, seventeen had middle-aged participants that were trained training with a duration from one to two months in eleven studies, from three to five months in three studies, from six to seven months in two studies and over 7 months in one study. The intensity of their sessions was from 40% to 49% of one repetition maximum (RM) in six studies, from 50% to 69% in eight studies and over 80% in two studies. The other five studies had an elderly group with a training duration from one to two months in two studies and from six to seven months in three studies (60%). The intensity of their sessions was from 50% to 69% in two studies (40%) and over 80% in three studies (60%), respectively. Their results are presented below

- Lower extremity muscle strength: RT had a significantly greater favourable effect in middle-aged and elderly patients ($p<0.05$)
- Upper extremity muscle strength: RT had a significantly greater favourable effect in middle-aged and elderly patients ($p<0.05$)
-
- Exercise capacity:
    - Peak VO_2: RT had a significantly greater effect in middle-aged and elderly patients ($p<0.05$)
    - Exercise time during cardiopulmonary exercise testing: RT had a significantly greater effect in middle-aged and elderly patients ($p<0.05$)
- Mobility:
    - Household physical activity: No significant difference for the middle-aged patients and a significantly greater favourable effect for the elderly patients ($p<0.05$)

- Functional mobility scores: No significant difference r the middle-aged patients and a significantly greater favourable effect for the elderly patients ($p<0.05$)

These results indicate that RT should be a part of the rehabilitation program for both middle-aged and elderly people.

9. **Xanthos et al 2016** [40]

Xanthos et al searched also the implementation of resistance training in the rehabilitation of coronary heart disease patients. They included twenty-three studies with a total of 2410 patients. These studies should have CT or RT interventions with an AT control, investigate cardio-respiratory fitness or muscular strength and mention functional capacity. Their results are presented below.

- Peak oxygen uptake: Significant improvement for combined training over aerobic training alone ($p<0.05$)
- Peak work capacity: Significant improvement for combined training over aerobic training alone ($p=0.002$)
- Muscular strength: significant improvement for combined training over aerobic training ($p<0.00001$)
- There was no evidence of a difference when comparing resistance training and aerobic training

These results indicate that CT is more beneficial than AT alone for improving physical function.

10. **Hollings et al 2017** [41]

Hollings et al conducted a meta-analysis in order to investigate the effect of progressive resistance training on aerobic fitness and strength in adults with coronary heart disease. They included 34

RCTs with a total number of 1940 of patients with mean age 60+- 7 years (range 49-79 years) with CHD (recent myocardial infarction, coronary artery bypass grafting, angioplasty, stent implantation). The RCTs should have interventions of progressive resistance or combined training compared with control or/and aerobic training. Studies with intervention duration of less than three weeks and participants with heart transplantation or valvular surgery were excluded from this meta-analysis. Their results are presented below.

Progressive resistance training vs control:

- Cardiorespiratory fitness ($p<0.0001$)
  - 11.9% improvement for the exercise group
  - 3.1 % improvement for the control group
- Muscular strength: (p=NS)
  - 24.7% improvement of median lower body strength and 45.6% improvement of median upper body strength for the exercise group
  - 2.6% improvement of median lower body strength and 10.2% improvement of median upper body strength for the control group

Progressive resistance training vs aerobic training

- Cardiorespiratory fitness (p=NS)
  - 15.6% improvement for the progressive resistance training group
  - 20.1% improvement for the aerobic training group
- VO_2peak: no significant difference between comparison groups
- Work capacity: no significant difference: no significant difference between comparison groups
- Muscular strength: Insufficient data to report any differences

Combined training vs aerobic training

- Cardiorespiratory fitness: (p=NS)
  - 18.4% improvement for the combined training group
  - 15.4% improvement for the aerobic training group
- VO_2peak: no significant difference

- Muscular strength: ($p=0.0007$)
    - 19.9% improvement of lower body strength and 20.8% improvement of upper body strength for the combined training group
    - 6.3% improvement of lower body strength and 1.3% improvement of upper body strength for the aerobic training group

These results indicate that isolated progressive resistance training may result in an increase in lower and upper body strength, and improve aerobic fitness to a similar degree as aerobic training in coronary heart disease cohorts. Importantly, when progressive resistance training was added to aerobic training, effects on both fitness and strength were enhanced compared to aerobic training alone.

11. **Yang et al 2018** [42]

Yang et al investigated the effect of Tai Chi on cardio-respiratory fitness for coronary disease rehabilitation. In their meta-analysis they included five studies with 291 patients in total. These studies had Tai Chi as an intervention with at least three times a week frequency and thirty minutes duration. Their reports should concern cardio-respiratory fitness, vital signs and adverse events of the intervention and there should have been a control group of no exercise or any other form of exercise. The results of the meta-analysis are:

- Tai Chi vs other forms of exercise group
    - VO_2max: Tai Chi was less effective than high intensity exercise ($p<0.00001$)
    - HRmax: Tai Chi was less effective than high intensity exercise
- Tai Chi vs no other exercise intervention
    - VO_2max: not enough evidence (reports from only one study) ($p=0.0002$)
    - HRpeak: Tai Chi can significantly improve HRmax in comparison with no exercise intervention ($p<0.00001$)

These results indicate that Tai Chi is not the exercise to choose for CHD patients compared to HIIT. However, its outcomes are better than no exercise at all.

12. **Liu et al 2018** [43]

Liu et al also conducted a meta-analysis for the effects of Tai Chi-based cardiac rehabilitation on aerobic endurance, psychosocial well-being, and cardiovascular risk reduction in patients with coronary heart disease. They included thirteen RCTs or CCTs with 972 CHD patients with a mean age of 64 years, regardless of disease stage and severity. These studies should have control groups with no other form of exercise and report aerobic endurance, psychosocial well-being or CVD risk reduction (i.e. blood lipids or blood pressure). Their results are presented below.

- Aerobic endurance: Participants in the Tai Chi group had a significantly better improvement in aerobic endurance compared with the control groups ($p<0.00001$)
- Psychosocial well-being: The Tai Chi group had a significantly lower score of anxiety and lower score of depression ($p<0.05$)
- Quality of life: Tai Chi group had significantly better improvements in QOL compared with the non-active group ($p<0.0001$)
- Blood lipids:
    - No significant improvements in LDL Cholesterol, triglycerides or total cholesterol among participants in the Tai Chi group compared with the non-active control groups
    - Significantly higher level of HDL Cholesterol of 0.2 mg/dL was found in the Tai Chi group ($p<0.001$)
- Blood pressure: Non-significant effects of Tai Chi in reducing SBP compared with the non-active controls
- Physical function: Only one study examined physical function and found significant improvement for the Tai Chi group compared with those in the non-active control group
- Cardiac mortality: No significant difference in resting heart rate variability was noted between the Tai Chi and the non-active control groups

These results indicate that Tai Chi can improve aerobic endurance and psychosocial well-being among coronary heart disease patients. However, the effect of Tai Chi on cardiovascular disease risk reduction has not been proven by this study.

Table 2. Meta-analyses reporting the outcomes of exercise-based cardiac rehabilitation in CHD

Study	Total patients/ Nr of included RCTs	Outcomes
Kraal et al 2017 [44] The Netherlands	585/ 20	Total energy expenditure should be the target of exercise regimes.
Yang et al 2017 [45] China	682/ 6	Exercise improves angina, and maximum exercise tolerance.
Swardfager et al 2012 [46] Canada	1691/ 21	Exercise reduces inflammatory activity. C-reactive protein and fibrinogen have provided the strongest evidence.
Taylor et al 2004 [47] UK	8940/ 48	Exercise improves cardiac and all-cause mortality, and reduces primary risk factors.
Lawler et al 2011 [48] Canada	6111/37	Exercise reduces mortality and reinfarction.
Anderson et al 2016 [49] UK	14486/ 63	Exercise reduces the risk of cardiovascular mortality and hospitalisation, it does not affect total mortality, the risk of MI and revascularisation. It improves HRQL.
Rauch et al 2016 [50], Europe	219702/25	CR participation after acute coronary syndrome and CABG is associated with reduced mortality.
Sumner et al 2017 [51], UK	9836/8	CR was found to reduce the risk of all-cause and cardiac-related mortality and improve HRQL
Van Halewijn et al 2017 [52], UK, The Netherlands	7691/18	CV prevention and rehabilitation programmes reduce all-cause mortality, cardiovascular mortality, myocardial infarction and cerebrovascular events
Uddin et al 2016 [53] Denmark, UK	1940/34	Higher exercise intensities are associated with a greater level of post-rehabilitation exercise capacity.
Abell et al 2017 [54], Australia	13419/69	Exercise-based cardiac rehabilitation programs which focus on achieving increased adherence to the exercise intervention have improved outcomes for CHD patients

13. **Kraal et al 2017** [44]

Kraal et al conducted a meta-analysis in order to investigate the influence of training characteristics on the effect of exercise training in patients with coronary artery disease. They included twenty RCTs with 585 patients participating in continuous aerobic exercise programmes. The RCTs should have a control group of no exercise and report change in VO_2peak to evaluate training effects. The programme should have been described in detail, with at least information regarding session frequency, session duration, programme length and training intensity. All other forms of exercise were excluded from this study.

The programme duration was about 12weeks (range two to twenty-eight) and its frequency was about 3 sessions per week (range two to four), The sessions lasted from ten minutes to forty-five minutes, with a median of thirty minutes. The median training intensity was 65% of VO_2 peak (range from 45% to 79% of VO_2 peak) and the total energy expenditure from 74 to 1300 J/kg with a median of 324 J/kg. Their results are presented below:

- VO_2peak: mean difference in improvement of VO_2 peak 3.97 ml/min/kg for the training group ($p<0.01$)
- Total energy expenditure: an increase in energy expenditure of 100 J/kg was associated with a VO_2 peak improvement of 0.91ml/min/kg ($p<0.01$)
- Programme duration, intensity and length were significantly associated with the VO_2 peak improvement in the univariate analyses

The researchers concluded that the design of an exercise programme should primarily aim at optimizing total energy expenditure rather than on one specific training characteristic.

14. **Yang et al 2017** [45]

Yang et al conducted a metanalysis to assess the effects of exercise-based cardiac rehabilitation in patients after percutaneous coronary intervention (PCI). They included six RCTs and a total of 682 patients that underwent exercise and pharmacological therapy while the control group was under usual care and pharmacological therapy. The patients of the study should have had undergone PCI and been followed- up for at least two months. Studies with participants who had modifiable cardiovascular risk factors or severe complications were excluded from this meta-analysis. Their results are presented below.

- Cardiac death: exercise was not associated with significantly improved cardiac death rates
- Recurrence of myocardial infarction: exercise was not associated with a significantly improved recurrence of MI
- Repeated percutaneous coronary intervention: exercise was not associated with significantly improved repeated PCI rates
- Coronary artery bypass grafting: exercise was not associated with significantly improved CABG rates
- Restenosis: exercise was not associated with significantly improved restenosis rates
- Recurrent angina: exercise was associated with significantly improved recurrent angina rates
- Treadmill exercise stress testing:

Individuals in the exercise group were significantly more likely to recover after PCI than those in the control group.

  - Significantly improved total exercise time ($p=0.0006$)
  - Significantly improved ST-segment elevation ($p<0.00001$)
  - Significantly improved angina ($p<0.00001$)
  - Significantly improved maximum exercise tolerance ($p=0.0003$)

These results indicate that exercise can improve recurrent angina, total exercise time, ST-segment decline, angina, and maximum exercise tolerance compared with no exercise. However, cardiac death, recurrence of MI, repeated PCI, CABG, and restenosis were not affected by the exercise intervention.

15. **Swardfager et al 2012** [46]

Swardfager et al conducted a meta-analysis to examine if exercise intervention can modify inflammatory markers in coronary artery disease. They included twenty-three studies (1691 CAD patients), reporting peripheral inflammatory biomarker concentrations. The patients should have been diagnosed with myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, stable angina, or angiographic confirmation of ≥50% blockage in at least 1 major coronary artery. Inflammatory biomarkers should have been measured before and after aerobic exercise intervention. The intervention should last more than 2 weeks. Studies with patients with non-ischemic heart failure were excluded from this study.

The patients of the included studies were of mean age: 63.1 years and underwent a mean exercise duration of 41.5 ± 15.8 (20-80) minutes. The mean exercise frequency was 3.9 ± 1.7 (2-7) and the mean program duration was 11.3 ± 5.3 (2-24) weeks. Their results are presented below.

Results:

- BMI: Decreased with standard mean difference (SMD): -0.111 kg/m2 (-0.185 to – 0,037) (p=0.003)
- HDL cholesterol: Increased with SMD: 0.249 mmol/L (-0,003 to 0,503) (p=NS)
- LDL cholesterol: Decreased with SMD: -0.411 mmol/L (-0.648 to –0.175) (p=0.01)
- Total cholesterol: Decreased with SMD: -0.417 mmol/L (-0.608 to –0.226) (p<0.01)
- Total/ HDL ratio: Decreased with SMD: -0.478 (-0.695 to – 0.262) (p=0.02)
- Triglycerides: Decreased with SMD: -0.217 mmol/L (-0.357 to –0.077) (p<0.01)
- VO_2peak: Increased with SMD: 0.865 mL/kg/min (0.583 to 1.146) (p<0.01)

These results indicate that exercise training is associated with reduced inflammatory activity in patients with CAD.

16. **Taylor et al 2004** [47]

Taylor et al also evaluated Exercise-Based Rehabilitation in patients with CHD They included 48 RCTs with a total of 8940 CHD patients with a median age of 55 years. These RCTs should have a follow-up of 6 months or more with any form of supervised or unsupervised structured exercise program undertaken in an inpatient-, outpatient-, community- or home-based setting or in combination with psychosocial or educational interventions. The patients of these studies should have been diagnosed with myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, or angina pectoris or coronary heart disease defined by angiography. The control group was not receiving any form of structured exercise training or advice but that could include standard medical care such as drug therapy. Their results are presented below.

- All-cause mortality: Significant reduction for the rehabilitation group
- Cardiac mortality: Significant reduction for the rehabilitation group
- Nonfatal myocardial infarction: No statistically significant difference
- Revascularization: No statistically significant difference
- Health related quality of life: Improved for both the rehabilitation and the control group

Results with regards to modified cardiac risk factors:

- Total cholesterol: Significant reduction for the rehabilitation group
- Triglycerides: Significant reduction for the rehabilitation group
- Low density lipoprotein cholesterol: No statistically significant difference
- High density lipoprotein cholesterol: No statistically significant difference

These results indicate that exercise improves cardiac and all-cause mortality, and reduces primary risk factors of CAD.

17. **Lawler et al 2011** [48]

Lawler et al conducted a meta-analysis to determine the efficacy of exercise-based cardiac rehabilitation in post–myocardial infarction patients. They included 37 RCTs with a total number of

6111 patients who recently survived an MI. The studies had interventions that involved any form of supervised or unsupervised exercise-based CR program in an outpatient, community, or inpatient setting with a minimum intervention duration of two weeks and a minimum follow-up of twelve weeks. The control group did not receive any form of exercise. The outcomes should have reported all-cause mortality, cardiac mortality, re-infarction, revascularization or modifiable cardiovascular risk factors (weight, lipids, blood pressure, and smoking). Their results are presented below.

- Secondary prevention: Exercise-based CR significantly reduces re-infarction Cardiac mortality: Exercise-based CR significantly reduces cardiac All-cause mortality: Exercise-based CR significantly reduces all-cause mortality
- Revascularization: No significant difference between exercise and control group
- Program duration: No significant difference between <3 months and >3 months exercise groups
- Persisting benefits: the benefits of a CR program post-MI persist beyond the period of active intervention for
    - Rei-infarction
    - Cardiac mortality
    - All-cause mortality
- Systolic blood pressure: more favourable for the exercise group (p=NS)
- Diastolic blood pressure: more favourable for the exercise group (p=NS)
- Smoking: more favourable for the exercise group (p=NS)
- Body weight: Minimal changes (p=NS)

This study shows that exercise-based CR is associated with reductions in mortality and reinfarction post-MI. The secondary analyses suggest that even shorter CR programs may translate into improved long-term outcomes.

18. **Anderson et al 2016** [49]

Anderson et al conducted a meta-analysis about exercise-based cardiac rehabilitation in CHD patients. They included 63 RCTs (14486 patients, mean age 56 years), comparing exercise based cardiac rehabilitation to no-exercise controls. RCTs should have at least 6 months of follow-up and include patients with myocardial infarction, revascularization, percutaneous coronary intervention, angina pectoris or CHD defined by angiography. The reports of these studies should include total or cardiovascular (CV) mortality, fatal or nonfatal myocardial infarction, revascularizations, hospitalizations, health related QoL, cost and cost effectiveness. Their results are presented below.

- All-cause mortality: No statistically significant difference
- Cardiovascular mortality: Statistically significant difference for the exercise group
- Myocardial infarction: No significant difference
- Coronary artery bypass graft: No significant difference
- Percutaneous coronary intervention: No significant difference
- Hospital admissions: Significantly reduced with cardiac rehabilitation
- Health related quality of life: Significant improvement for the exercise group
- Cost effectiveness: Cardiac rehabilitation was proved to be significantly cost effective

These results show that exercise reduces the risk of cardiovascular mortality and hospitalisation and improves HRQL. However, it does not affect total mortality, the risk of MI and revascularisation.

19. **Rauch et al 2016** [50]

Raugh et al aimed to evaluate the effect of CR on total mortality and other clinical endpoints after an acute coronary event. They included 25 studies with totally 219,702 patients with CHD. The studies were controlled cohort studies or RCTs. The researchers assessed the actual evidence of CR’s effectiveness by focusing on CHD patients after a recent cardiac event and treated in the era of acute revascularisation and routine medication with statins. The index events should have been after 1994 with patients following in-hospital standard therapy according to current guidelines. The intervention had to be supervised, begin at least 3 months after hospital discharge with a minimum exercise training frequency of 2 times a week. Their results showed that:

- Total mortality: significantly reduced for the exercise-based CR group
- Mortality after CABG: significantly reduced for the exercise-based CR group
- Mortality after ACS: significantly reduced for the exercise-based CR group
- Hospital readmissions: no effect observed

These results indicate that CR participation after ACS and CABG is associated with reduced mortality even in the modern era of CHD treatment.

20. Sumner et al 2017 [51]

Sumner et al conducted a meta-analysis in order to test the effectiveness of modern CR. They included 8 studies with a total of 2656 patients. All cause and cardiac-related mortality had to be mentioned in the outcomes of each study. CR could be delivered as a structured, multi-component programme which included exercise and/or structured physical activity in addition to at least one of the following: information provision, education, health behaviour change, psychological support or intervention and social support. Secondary outcomes included all cause and cardiac-related hospital re-admission, re-occurrence of AMI, re-vascularisation and HRQL. Their results are listed below:

- Total mortality: Significantly reduced for the exercise-based CR
- HRQL: Significantly improved for the exercise-based CR
- Recurrent MI: No significant differences
- Re-vascularisation: No significant differences
- Re-hospitalisation: No significant differences

These results show that CR may reduce the risk of all-cause and cardiac-related mortality and improve HRQL.

21. Van Halewiin et al 2017 [52]

Van Halewiin et al tested cardiovascular prevention and rehabilitation for CHD patients. For their meta-analysis they included 18 trials with 7,691 patients in total. All studies had to be RCTs of cardiovascular prevention and rehabilitation with a follow-up period of at least six months, written in either English, Chinese, Spanish, German, French or Dutch languages. The patients included had undergone CABG or PCI, or had angina pectoris or coronary artery disease established by angiography. Their results are listed below:

- Total mortality: No difference between intervention and control groups
- Cardiovascular mortality: 58% reduction for the exercise-based CR programme
- Myocardial infarction: 30% reduction for the exercise-based CR programme
- Cerebrovascular events: 60% reduction for the exercise-based CR programme

These results indicate that exercise-based CR reduced cardiovascular mortality and myocardial infarction and cerebrovascular events in patients with CHD

22. **Uddin et al 2016** [53]

Uddin et al examined the predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure. They included 55 RCTs with 7553 patients participating in an exercise-based rehabilitation group. The RCTs should have a follow-up reporting exercise capacity. Their results are the following

- Exercise capacity:
    - 3.3 ml/kg/min in favour of exercise rehabilitation ($p<0.0001$)

    - No significant difference between exercise rehabilitation groups of CHD and heart failure
- Exercise control:
    - 1 ml/kg/min greater for each 10-percentage point increase in exercise intensity (p=0.04)
    - 1.8 ml/kg/min for each 10-year reduction in mean age (p=NS)
    - 0.5 ml/kg/min for each 10-percentage increase of males (p=NS)

These results indicate that higher exercise intensities were associated with a greater level of post-rehabilitation exercise capacity.

23. Abell et al 2017 [54]

Abell et al conducted a meta-analysis in order to examine the relationship between individual components of the exercise intervention in cardiac rehabilitation (such as intensity and frequency) and clinical outcomes for people with CHD. They examined 69 studies with a total 13419 patients comparing structured exercise intervention and usual care. All studies included reported cardiovascular mortality, total mortality, myocardial infarction or revascularisation outcomes. The 69 analyses had a total number of 72 interventions. Their results are listed below:

- Total mortality risk: 10% reduction for CR compared to usual care over a follow-up period of 10 years (p=0.03)
- Cardiovascular mortality with follow-up of 10 years: reduction for CR compared to usual (p< 0.0001)
- Cardiovascular mortality with follow-up of 19 years: reduction in risk with exercise-based cardiac rehabilitation compared to usual care (p= 0.0004)
- Myocardial infarction: 20% reduction CR compared to usual care (p=0.002)

- CABG: no demonstrable reduction (p=NS)
- PCI: no difference between CR and usual care (p=NS)
- Level of adherence to the exercise intervention and cardiovascular mortality: 28% reduction in relative risk observed for high levels of adherence to the prescribed exercise intervention compared to those reporting only moderate levels of adherence (p= 0.045)

These results indicate that adherence to the exercise intervention may be important in affecting mortality outcomes among CHD patients.

Outcomes

One of the 23 meta-analyses found out that endurance training is able to modify the functional capacity and the cardiovascular risk factors [32]. Its results demonstrate that endurance exercise training has a positive effect on the primary outcomes of the modifiable cardiovascular risk factors of SBP, HDL cholesterol and LDL cholesterol. There were significant effects for exercise programmes with exercise durations ranging from 60 to 90 minutes weekly.

Of the 23 studies included two were on home-based interventions [33,34]. The first [33] on telerehabilitation suggested that CR in distance can provide similar effects as centre-based cardiac rehabilitation to patients with CAD. So did the second that examined if home-based rehabilitation is equally effective to centre-based rehabilitation concluding that when CR is not performed in a hospital or a rehabilitation centre can be importantly effective.

Three of the studies [35-37] tried to investigate the advantages of interval training for CHD. All of them showed that interval training may significantly improve aerobic capacity. Two of these studies [35,36] indicated that interval training and especially high intensity interval training are more beneficial than continuous exercise. The other meta-analysis showed that when energy expenditure was the same in HIIT and MCT there were no statistically significant differences. This is something that we should keep in mind because the effectiveness of an intervention might be mainly associated with its caloric load [44].

We found four meta-analyses on resistance training [38-41]. Three of them [38,39,41] included RCTs and one of them [40] also included non-RCTs. They all showed that resistant training is efficient and should be preferably combined with aerobic training. RT improved skeletal muscle strength in patients with CAD. Fat-free mass, percent body fat, trunk fat, upper and lower limb strength, and peak work capacity showed a general improvement for the combined training group. There was a trend for the CT group to have a favourable effect on VO_2peak when compared to AT, even with similar total exercise volume. There were no adverse events related to AT or RT. HRQL seems to be more improved with CT than with AT alone. in summary, the results favour the addition of RT to AT as the standard exercise paradigm in CR programs.

There were two meta-analyses involving Tai Chi type of exercise [42.43]. Compared with control group with no intervention, Tai Chi proved to be safe and affected positively the CAD patients. Nevertheless, none of the meta-analyses excluded studies that were not RCTs and as a result we need more evidence for this kind of exercise. At this point it is vital to mention that in comparison with HIIT, Tai Chi was an inferior intervention as it could not modify HRmax and VO_2max at the levels that HIIT did. However, it seems more beneficial to have Tai Chi exercise than no intervention at all.

Exercise-based cardiac rehabilitation was proven to be beneficial for CAD patients [44-54] compared to no exercise interventions. It decreases inflammatory activity [46], however we are not able to yet to identify which form of exercise is more effective for this. There were two studies which showed that exercise is beneficial for the patients' quality of life [49,51]. It improves secondary prevention [47] with a decrease in mortality, re-infarctions and angina while it increases maximum exercise tolerance [45]. Exercise capacity was increased in exercise groups compared to no exercise controls, and higher intensities of exercise seem to improve more the VO_2peak. Some evidence could not confirm the effects on myocardial infarction and revascularization, and on changes in high- and low-density lipoprotein cholesterol nor on health-related quality of life [49]. However, this study associated exercise with all-cause and cardiac mortality reduction [46].

Discussion

This review of meta-analyses was designed to examine the effects of exercise-based CR on patients with coronary heart disease. It proved that this kind of intervention is safe for these patients and can reduce mortality. Furthermore, it can improve quality of life. Patients that attended programs of exercise-based CR had less hospitalizations than others. Finally, the exercise capacity was greatly improved for those who participated in an exercise rehabilitation programme.

The mechanism that leads to these results is not completely elucidated yet. It is believed that exercise modifies the factors that could lead to a re-infarction. It reduces inflammatory markers and this might be the reason for its positive effects. As far as the kind of exercise that is better for CHD patients, the reviewers' opinion varies. However, a majority of them proposes a combination of styles including high intensity interval training and resistance training. Possible mechanisms that explain these statements are analysed below.

Longitudinal training interventions have reported increases in HDL cholesterol. It is possible that the efficient metabolism of TG Rich Lipoproteins has as result elevated HDL cholesterol concentrations. It has been verified that regular aerobic exercise improves HDL level [55].

What is more, physical exercise increases coronary blood flow, resulting in increased shear stress on the surface of the endothelium. Endothelial cells respond to short-term increases in shear stress by producing vasodilator compounds such as prostacyclin and NO. Nitric Oxide (NO) is possibly a mediator of some assets derived from regular exercise. Vasodilatation in active muscle promotes a pressure gradient and thus increases blood flow which stimulates NO production from upstream arteries [55].

Physical inactivity is a major risk factor for CHD, and exercise-training programs can improve endothelium-dependent vasodilatation both in epicardial coronary vessels and in resistance vessels in patients with CHD. For many years it has been postulated that a so-called exercise factor was responsible for mediating several metabolic responses that occur during exercise [56]. Skeletal muscle-derived IL-6 has now been identified as a key metabolic intermediary and research has defined IL-6 as an energy sensor, functioning to preserve fuel availability during exertion. Specifically, during exercise IL-6 serves to augment hepatic glucose and adipose tissue fatty acid release to provide sufficient fuel to meet the extra metabolic demand. Accordingly, exercise performed with depleted muscle glycogen or with exogenous glucose ingestion has been shown to augment and suppress the exercise-induced IL-6 response, respectively [56].

Data from intervention studies suggest that accumulated physical activity training can reduce chronic low-grade inflammation. However, the type of activity undertaken has a significant bearing on the benefits achieved. Low-intensity exercise programmes, such as walking and other ‘lifestyle’ related efforts to increase physical activity, for example, household tasks, are not sufficient to favourably impact upon circulating inflammatory markers. Instead, in order to obtain such benefits, physical activity must be of a higher intensity, that is, moderate–vigorous intensity (at least 70% of maximum aerobic capacity). A combination of aerobic activities with muscle strengthening exercise, that is, resistance training, will likely yield the greatest benefit, particularly with regards to optimizing the anti-inflammatory effect of training [56].

High-intensity interval training (HIIT) is a method that emphasizes bioenergetic adaptations for more efficient energy transfer within the metabolic pathways by using predetermined intervals of exercise and relief periods [57]. The larger amount of time spent at high exercise intensities is the reason for the exceptional maximal oxygen consumption increase and anaerobic metabolism enhancement after HIIT [57].

Many people enrolled in a CR program may be unable to sustain the high volume of AT necessary for fat mass loss, not only due to the high level of motivation and time required but also due to physical limitations such as musculoskeletal comorbidities (recently reported to affect 50% of participants entering CR), peripheral vascular disease, and diabetic neuropathy. However, replacing high impact AT sessions with RT sessions may reduce joint and peripheral limb stress while being at a volume that most patients with CAD can reasonably tolerate.

The results of this study showed that the available data concerning exercise- based rehabilitation are not enough and further investigations should be performed. Future studies may concentrate on the physiological mechanisms of exercise in order to understand how the exercise affects the patients and which type of exercise is ideal for them. Nevertheless, the program of rehabilitation should be jointly designed by the patient and the health care providers.

References

1. Fondation Suisse de cardiologie <https://www.swissheart.ch/fr/maladies-cardiaques-avc/maladies/maladie-coronarienne.html>
2. World Health Organization. The top 10 causes of death. Updated May 2018. https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death
3. Manolis A, 2008 Coronary Disease: Contemporary diagnosis and treatment, Society and health, VI. 207-216
4. James de Lemos, Torbjørn Omland, 2017 Chronic Coronary Artery Disease: A Companion to Braunwald's Heart Disease, Elsevier Health Sciences, I. 1-2
5. Wirtz, P. H., & von Känel, R. (2017). Psychological Stress, Inflammation, and Coronary Heart Disease. Current Cardiology Reports, 19(11). doi:10.1007/s11886-017-0919-x
6. Taleb, S. (2016). Inflammation in atherosclerosis. Archives of Cardiovascular Diseases, 109(12), 708–715. doi:10.1016/j.acvd.2016.04.002
7. Pant, S., Deshmukh, A., GuruMurthy, G. S., Pothineni, N. V., et al. (2013). Inflammation and Atherosclerosis—Revisited. Journal of Cardiovascular Pharmacology and Therapeutics, 19(2), 170–178. doi:10.1177/1074248413504994
8. Lu H, Daugherty A. Atherosclerosis. Arterioscler Thromb Vasc Biol. 2015 Mar;35(3):485-91. doi: 10.1161/ATVBAHA.115.305380. Erratum in: Arterioscler Thromb Vasc Biol. 2016 Apr;36(4):e32. PMID: 25717174; PMCID: PMC4511379.
9. Erbilgin A, Siemers N, Kayne P, Yang WP, Berliner J, Lusis AJ. Gene expression analyses of mouse aortic endothelium in response to atherogenic stimuli. Arterioscler Thromb Vasc Biol. 2013;33:2509–2517. OK
10. Moraes-Silva, I. C., Rodrigues, B., Coelho-Junior, H. J., Feriani, D. J., & Irigoyen, M.-C. (2017). Myocardial Infarction and Exercise Training: Evidence from Basic Science.

Exercise for Cardiovascular Disease Prevention and Treatment, 139–153. doi:10.1007 /978-981-10-4307-9_9 (proin 8)

11. Sanchis-Gomar, F., Perez-Quilis, C., Leischik, R., & Lucia, A. (2016). Epidemiology of coronary heart disease and acute coronary syndrome. Annals of Translational Medicine, 4(13), 256–256. doi:10.21037/atm.2016.06.33
12. Gillum, R. F., Mehari, A., Curry, B., & Obisesan, T. O. (2012). Racial and geographic variation in coronary heart disease mortality trends. BMC Public Health, 12(1). doi:10.1186/1471-2458-12-410
13. World Health Organization Regional Office for Europe Greece profile of health and Well-being. http://www.euro.who.int/__data/assets/pdf_file/0010/308836/Profile-Health-Well-being-Greece.pdf
14. Michas G, Karvelas G, Trikas A, Cardiovascular disease in Greece; the latest evidence on risk factors, Hellenic Journal of Cardiology (2018), doi: https://doi.org/10.1016/j.hjc.2018.09.006.
15. Zhu, K.-F., Wang, Y.-M., Zhu, J.-Z., et al. (2015). National prevalence of coronary heart disease and its relationship with human development index: A systematic review. European Journal of Preventive Cardiology, 23(5), 530–543. doi:10.1177/2047487315587402 new entry
16. Ogungbe O, Akil L, Ahmad HA. Exploring Unconventional Risk-Factors for Cardiovascular Diseases: Has Opioid Therapy Been Overlooked?. Int J Environ Res Public Health. 2019;16(14):2564. Published 2019 Jul 18. doi:10.3390/ijerph16142564 new entry
17. Validation of the Systematic COronary Risk Evaluation - Older Persons(SCORE-OP) in the EPIC-Norfolk prospective population study
18. Khamis, R. Y., Ammari, T., & Mikhail, G. W. (2016). Gender differences in coronary heart disease. Heart, 102(14), 1142–1149. doi:10.1136/heartjnl-2014-306463

19. S. Jayashree, M. Arindam, K.V. Vijay Genetic epidemiology of coronary artery disease: an Asian Indian perspective J Genetics, 94 (2015), pp. 539-549

20. Bhatnagar, P., Wickramasinghe, K., Wilkins, E., & Townsend, N. (2016). Trends in the epidemiology of cardiovascular disease in the UK. Heart, 102(24), 1945–1952. doi:10.1136/heartjnl-2016-309573

21. Matsuzawa Y, Guddeti RR, Kwon TG, Lerman LO, Lerman A. Treating coronary disease and the impact of endothelial dysfunction. Prog Cardiovasc Dis. 2015;57(5):431–442. doi:10.1016/j.pcad.2014.10.004

22. Blumenthal, R. S., Cohn, G., & Schulman, S. P. (2000). Medical therapy versus coronary angioplasty in stable coronary artery disease: a critical review of the literature. Journal of the American College of Cardiology, 36(3), 668–673. doi:10.1016/s0735-1097(00)00791-9

23. Anderson L, Brown JP, Clark AM, et al. Patient education in the management of coronary heart disease. Cochrane Database Syst Rev. 2017;6(6):CD008895. Published 2017 Jun 28. doi:10.1002/14651858.CD008895.pub3

24. British Association for Cardiovascular Prevention and Rehabilitation. The BACPR standards and core components for cardiovascular disease prevention and rehabilitation, 2nd edition. www.bacpr.com/resources/46C BACPR Standards and Core Components 2012.pdf

25. Menezes, A. R., Lavie, C. J., Milani, R. V., Forman, D. E. et al. (2014). Cardiac Rehabilitation in the United States. Progress in Cardiovascular Diseases, 56(5), 522–529. doi:10.1016/j.pcad.2013.09.018

26. Deveza, R. C., Elkins, M., & Saragiotto, B. T. (2016). PEDro systematic review update: exercise for coronary heart disease. British Journal of Sports Medicine, 51(9), 755–756. doi:10.1136/bjsports-2016-096864

27. Rognmo, O., Moholdt, T., Bakken, H., et al. (2012). Cardiovascular Risk of High- Versus Moderate-Intensity Aerobic Exercise in Coronary Heart Disease Patients. Circulation, 126(12), 1436–1440. doi:10.1161/circulationaha.112.123117

28. Pizzi R., Siccardi S., Pedrinazzi C., Durin O.,Inama G., Non linear data mining methods to assess the impact of physical training on the cardiovascular system of subjects from different age groups. International J of Biology and Biomedical Engineering, 9, 2015
29. Sun, J., Freeman, B. D., & Natanson, C. (2018). Meta-analysis of Clinical Trials. Principles and Practice of Clinical Research, 317–327. doi:10.1016/b978-0-12-849905-4.00022-8
30. Haidich AB. Meta-analysis in medical research. Hippokratia. 2010;14(Suppl 1):29-37.
31. Akobeng, A. K. (2005). Understanding systematic reviews and meta-analysis. Archives of Disease in Childhood, 90(8), 845–848. doi:10.1136/adc.2004.058230)
32. Chen, Y.-C., Tsai, J.-C., Liou, Y.-M., & Chan, P. (2016). Effectiveness of endurance exercise training in patients with coronary artery disease: A meta-analysis of randomised controlled trials. European Journal of Cardiovascular Nursing, 16(5), 397–408. doi:10.1177/1474515116684407
33. Claes, J., Buys, R., Budts, W., Smart, N., & Cornelissen, V. A. (2016). Longer-term effects of home-based exercise interventions on exercise capacity and physical activity in coronary artery disease patients: A systematic review and meta-analysis. European Journal of Preventive Cardiology, 24(3), 244–256. doi:10.1177/2047487316675823
34. Huang, K., Liu, W., He, D., Huang, B. et al. (2014). Telehealth interventions versus center-based cardiac rehabilitation of coronary artery disease: A systematic review and meta-analysis. European Journal of Preventive Cardiology, 22(8), 959–971. doi:10.1177/2047487314561168
35. Liou, K., Ho, S., Fildes, J., & Ooi, S.-Y. (2016). High Intensity Interval versus Moderate Intensity Continuous Training in Patients with Coronary Artery Disease: A Meta-analysis of Physiological and Clinical Parameters. Heart, Lung and Circulation, 25(2), 166–174. doi:10.1016/j.hlc.2015.06.828

36. Elliott, A. D., Rajopadhyaya, K., Bentley, D. J., Beltrame, J. F., & Aromataris, E. C. (2015). Interval Training Versus Continuous Exercise in Patients with Coronary Artery Disease: A Meta-Analysis. Heart, Lung and Circulation, 24(2), 149–157. doi:10.1016/j.hlc.2014.09.001
37. Gomes-Neto, M., Durães, A. R., Reis, H. F. C. dos, Neves, V. R. et al. (2017). High-intensity interval training versus moderate-intensity continuous training on exercise capacity and quality of life in patients with coronary artery disease: A systematic review and meta-analysis. European Journal of Preventive Cardiology, 24(16), 1696–1707. doi:10.1177/2047487317728370
38. Marzolini, S., Oh, P. I., & Brooks, D. (2011). Effect of combined aerobic and resistance training versus aerobic training alone in individuals with coronary artery disease: a meta-analysis. European Journal of Preventive Cardiology, 19(1), 81–94. doi:10.1177/1741826710393197
39. Yamamoto, S., Hotta, K., Ota, E. et al. (2016). Effects of resistance training on muscle strength, exercise capacity, and mobility in middle-aged and elderly patients with coronary artery disease: A meta-analysis. Journal of Cardiology, 68(2), 125–134. doi: 10.1016/j.jjcc.2015.09.005
40. Xanthos, P. D., Gordon, B. A., & Kingsley, M. I. C. (2017). Implementing resistance training in the rehabilitation of coronary heart disease: A systematic review and meta-analysis. International Journal of Cardiology, 230, 493–508. doi:10.1016/j.ijcard.2016.12.076
41. Hollings, M., Mavros, Y., Freeston, J., & Fiatarone Singh, M. (2017). The effect of progressive resistance training on aerobic fitness and strength in adults with coronary heart disease: A systematic review and meta-analysis of randomised controlled trials. European Journal of Preventive Cardiology, 24(12), 1242–1259. doi:10.1177/2047487317713329
42. Yang YL, Wang YH, Wang SR, Shi PS, Wang C. The Effect of Tai Chi on Cardiorespiratory Fitness for Coronary Disease Rehabilitation: A Systematic Review and

Meta-Analysis. Front Physiol. 2018;8:1091. Published 2018 Jan 4. doi:10.3389/fphys.2017.01091

43. Liu, T., Chan, A. W., Liu, Y. H., & Taylor-Piliae, R. E. (2017). Effects of Tai Chi-based cardiac rehabilitation on aerobic endurance, psychosocial well-being, and cardiovascular risk reduction among patients with coronary heart disease: A systematic review and meta-analysis. European Journal of Cardiovascular Nursing, 17(4), 368–383. doi:10.1177/1474515117749592
44. Kraal, J. J., Vromen, T., Spee, R., Kemps, H. M. C., & Peek, N. (2017). The influence of training characteristics on the effect of exercise training in patients with coronary artery disease: Systematic review and meta-regression analysis. International Journal of Cardiology, 245, 52–58. doi:10.1016/j.ijcard.2017.07.051
45. Yang, X., Li, Y., Ren, X., Xiong, X., Wu, L., Li, J., … Xing, Y. (2017). Effects of exercise-based cardiac rehabilitation in patients after percutaneous coronary intervention: A meta-analysis of randomized controlled trials. Scientific Reports, 7(1). doi:10.1038/srep44789
46. Swardfager, W., Herrmann, N., Cornish, S., Mazereeuw, G., Marzolini, S., Sham, L., & Lanctôt, K. L. (2012). Exercise intervention and inflammatory markers in coronary artery disease: A meta-analysis. American Heart Journal, 163(4), 666–676.e3. doi:10.1016/j.ahj.2011.12.017
47. Taylor, R. S., Brown, A., Ebrahim, S., Jolliffe, J., Noorani, H., Rees, K., … Oldridge, N. (2004). Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. The American Journal of Medicine, 116(10), 682–692. doi:10.1016/j.amjmed.2004.01.009
48. Lawler, P. R., Filion, K. B., & Eisenberg, M. J. (2011). Efficacy of exercise-based cardiac rehabilitation post–myocardial infarction: A systematic review and meta-analysis of randomized controlled trials. American Heart Journal, 162(4), 571–584.e2. doi:10.1016/j.ahj.2011.07.017

49. Anderson, L., Thompson, D. R., Oldridge, N et al (2016). Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database of Systematic Reviews. doi:10.1002/14651858.cd001800.pub3
50. Rauch, B., Davos, C. H., Doherty, P. et al (2016). The prognostic effect of cardiac rehabilitation in the era of acute revascularisation and statin therapy: A systematic review and meta-analysis of randomized and non-randomized studies – The Cardiac Rehabilitation Outcome Study (CROS). European Journal of Preventive Cardiology, 23(18), 1914–1939. doi:10.1177/2047487316671181
51. Sumner, J., Harrison, A., & Doherty, P. (2017). The effectiveness of modern cardiac rehabilitation: A systematic review of recent observational studies in non-attenders versus attenders. PLOS ONE, 12(5), e0177658. doi:10.1371/journal.pone.0177658
52. Van Halewijn, G., Deckers, J. et al (2017). Lessons from contemporary trials of cardiovascular prevention and rehabilitation: A systematic review and meta-analysis. International Journal of Cardiology, 232, 294–303. doi:10.1016/j.ijcard.2016.12.125
53. Uddin, J., Zwisler, A.-D., Lewinter, C., Moniruzzaman et al (2015). Predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure: A meta-regression analysis. European Journal of Preventive Cardiology, 23(7), 683–693. doi:10.1177/2047487315604311
54. Abell, B., Glasziou, P., & Hoffmann, T. (2017). The Contribution of Individual Exercise Training Components to Clinical Outcomes in Randomised Controlled Trials of Cardiac Rehabilitation: A Systematic Review and Meta-regression. Sports Medicine - Open, 3(1). doi:10.1186/s40798-017-0086-z
55. Al-Mamari A. (2009). Atherosclerosis and physical activity. Oman medical journal, 24(3), 173–178. doi:10.5001/omj.2009.34
56. Nimmo, M. A., Leggate, M. , Viana, J. L. and King, J. A. (2013), The effect of physical activity on mediators of inflammation. Diabetes Obes Metab, 15: 51-60.

doi:10.1111/dom.12156Cipryan L. The effect of fitness level on cardiac autonomic regulation, IL-6, total antioxidant capacity, and muscle damage responses to a single bout of high-intensity interval training. J Sport Health Sci. 2018;7(3):363–371. doi:10.1016/j.jshs.2016.11.001