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DISSERTAÇÃO ESPECIALMENTE ELABORADA PARA OBTENÇÃO DO GRAU DE MESTRE EM REABILITAÇÃO CARDIOVASCULAR

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“A impressão desta dissertação foi aprovada pelo Conselho Científico da Faculdade de Medicina de Lisboa em reunião de 11 de dezembro de 2023”

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"Ninguém escapa ao sonho de voar, de ultrapassar os limites do espaço onde nasceu, de ver novos lugares e conhecer novas pessoas. Navegar é preciso, mas reconhecer o valor das coisas e das pessoas, é mais preciso ainda"

Antoine de Saint-Exupéry

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"Tudo posso, naquele que me fortalece".
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"Às vezes, a despedida é onde começa a legítima jornada e tudo passa a fazer sentido".
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RESUMO

Um dos principais fatores de risco cardiovascular para eventos de doença arterial coronária (DAC) é a inatividade física, que pode levar a uma baixa aptidão cardiorrespiratória, que é um marcador forte e independente de risco de mortalidade cardiovascular e por todas as causas. Após um evento cardiovascular agudo, deve ser dada prioridade à modificação comportamental do estilo de vida e dos fatores de risco. O treino de exercício físico é fundamental nos programas de reabilitação cardiovascular (RC). A determinação da intensidade do exercício é um componente muito importante da prescrição de exercício físico para obter os benefícios da dose-resposta associada ao exercício, mantendo a segurança das pessoas com DAC num programa de RC. Idealmente, a intensidade do exercício prescrito deve estar dentro do primeiro e segundo limiar ventilatório (LV) avaliado por uma prova de esforço cardiorrespiratória (PECR), mas infelizmente nem sempre está disponível em muitos centros de RC, sendo um teste de caminhada de 6 minutos (TC6M) significativamente menos dispendioso e mais conveniente. No entanto, os níveis de intensidade alcançados durante um TC6M em comparação com uma PECR em pessoas com DAC que iniciam um programa de RC fase III continuam a ser escassos na literatura. **Objetivo:** o objetivo deste estudo foi avaliar a frequência cardíaca (FC) pico do TC6M como método para prescrever a intensidade do exercício aeróbio em pessoas com DAC que iniciam um programa de RC de fase III e compará-lo com os limiares ventilatórios (LV) atingidos na PECR. **Métodos:** este estudo transversal incluiu pessoas com DAC a iniciar o programa RC de fase III. Todos os participantes realizaram uma PECR e o TC6M em dias não consecutivos. As principais variáveis analisadas a partir do TC6M foram: a FC pico e a distância total percorrida enquanto na PECR foram analisados a FC máxima, os LV e o pico do VO_2. As comparações entre as variáveis da PECR e do TC6M foram realizadas utilizando o teste *t* de amostra pareada e as relações foram medidas pelo coeficiente de correlação de Pearson. A concordância entre a FC pico do TC6M e os LV foram avaliados pela análise Bland-Altman. **Resultados:** um total de 105 pessoas com DAC (61 ± 9.8 anos de idade, 88% sexo masculino) que se encontravam a iniciar um programa de RC de fase III foram incluídos e analisados neste estudo. Os doentes eram em média, fisicamente ativos (352 ± 180 minutos/semana de atividade física moderada a vigorosa) e com excesso de peso (índice de massa corporal: 27.7 ± 3.5 kg/m^2). Foram encontradas diferenças significativas entre a FC pico no TC6M *vs* a FC no primeiro LV (média 15 ± 16 bpm, IC 95% [12.62,18.89], p <0.001) e a FC pico no TC6M *vs* a FC no segundo LV (média -5 ± 17 bpm, IC 95% [-9.23, -2.36], p < 0.001). No teste de correlação do coeficiente de Pearson houve uma correlação positiva moderada com o primeiro VT (r = 0.504, p < 0.001) e positiva fraca com o segundo VT (r = 0.493, p < 0.001) em pessoas com DAC fisicamente ativos iniciando um programa de RC fase III. **Conclusão:** a prescrição de exercício aeróbio de acordo com FC pico do TC6M para pessoas fisicamente ativas com DAC que iniciam a fase III do programa de RC é segura e corresponde a uma intensidade de exercício moderada. Considerando que o TC6M é de fácil execução e bem tolerado neste tipo de população, poderá vir a ser uma alternativa a utilizar na prática clínica quando não é possível realizar uma prova de esforço.

Palavras-chave: reabilitação cardiovascular, intensidade do exercício, frequência cardíaca, teste de caminhada de 6 minutos, prova de esforço cardiorrespiratória.

ABSTRACT

One of the major cardiovascular risk factors for coronary artery disease (CAD) events is physical inactivity which can lead to poor cardiorespiratory fitness, which is a strong and independent marker of risk for cardiovascular and all-cause mortality. After an acute cardiovascular event, lifestyle and risk factor management should be prioritize. Exercise training is a cornerstone in cardiovascular rehabilitation (CR) programmes. Determining the intensity of exercise is a very important component of exercise prescription to obtain the dose-response benefits associated with exercise while maintaining the safety of the CAD patients in a CR programme. Ideally, prescribe exercise intensity should be within the first and second ventilatory threshold (VT) assessed by a cardiopulmonary exercise test (CPET), but unfortunately is not always available in many CR centres, a 6-minute walk test (6MWT) is significantly less expensive and more convenient. However, the intensity levels achieved during a 6MWT compared to a CPET in CAD patients initiating a CR programme phase III remains scarce in the literature. **Objective:** The purpose of this study was to measure the heart rate (HR) peak of the 6MWT in CAD patients starting a phase III CR programme and to compare it with the VT outcomes, including the first and second VT, and HR peak of the CPET. **Methods:** This cross-sectional study enrolled CAD patients starting a phase III CR porgramme. All patients performed at the beginning of the CR phase III a CPET and the 6MWT in non-consecutive days. The main outcomes analysed from the 6MWT were: HR_{peak} and total distance covered while in the CPET it was analysed HR_{max}, the VTs and VO_{2peak}. Comparisons between CPET and 6MWT variables were performed using paired sample t-test and relationships were measured by Pearson correlation coefficient. Agreement between HR_{peak} in the 6MWT and VTs were evaluated by Bland-Altman analysis. **Results:** A total of 105 CAD patients (61 ± 9.8 years old, 88% male) who were starting a phase III CR programme were included and analyzed in this study. Patients were on average, physically active (352 ± 180 minutes/week of moderate to vigorous physical activity) and overweight (body mass index: 27.7 ± 3.5 kg/m^2). It was found asignificant difference between the HR_{peak} in the 6MWT vs HR at first VT (mean 15 ± 16 bpm, 95% CI [12.62,18.89], p <0.001) and the HR_{peak} in the 6MWT vs HR at second VT (mean -5 ± 17 bpm, 95% CI [-9,23, -2.36], p = 0.001). Pearson´s correlation coefficient showed a moderate correlation with the first VT (r = 0.504, $p < 0.001$) and positive weak with the second VT (r = 0.482, $p < 0.001$) in physically active CAD patients initiating a CR programme phase III. **Conclusion:** aerobic exercise prescription according to HR_{peak} at 6MWT, for CAD patients starting phase III of CR programme is safe and correspond to moderate exercise intensity. Considering that the 6MWT is easy to administer and well tolerated in this population, it can be an alternative to be used in clinical practice when it is not possible to perform a stress test.

Keywords: cardiovascular rehabilitation, exercise intensity, heart rate, 6-minute walk test, cardiopulmonary exercise test.

RESUMO DESENVOLVIDO EM PORTUGUÊS

As doenças cardiovasculares (DCV), incluindo a doença arterial coronária (DAC), ainda são a principal causa de morbidade e morte a nível mundial, responsável por sérias condições de saúde e custos dos cuidados médicos. A DAC é caracterizada por um processo inflamatório crónico causado pela aterosclerose, um distúrbio inflamatório, geralmente progressiva e silenciosa. Esse processo inflamatório pode ser modificado através de um melhor estilo de vida, tratamentos farmacológicos e invasivos a fim de estabilizar ou regredir a doença. A prevenção cardiológica secundária, como programas de reabilitação cardiovascular (RC), tem por objetivo otimizar o tratamento médico, controlar os fatores de risco, melhorar o estilo de vida e assim, melhorar qualidade de vida, melhorar ou manter independência física e psicossocial e reduzir a utilização de cuidados de saúde. Um programa de RC oferece componentes essenciais envolvendo estratégias multifacetadas e uma abordagem multidisciplinar para facilitar o regresso rápido ao trabalho, ajudar a desenvolver competências de auto-gestão e oferecer a oportunidade de manter os benefícios a longo prazo. Adicionalmente, dentro dos componentes essenciais do programa de RC, o exercício físico, é um componente chave para melhorar a aptidão cardiorrespiratória dos doentes coronários, sendo este um marcador forte e independente de risco de mortalidade cardiovascular. O exercício físico, quando prescrito de forma individualizada garante benefícios clínicos com segurança e eficácia, no qual, deve ser estruturado de acordo com a frequência, intensidade, tempo e tipo. No entanto, a determinação da intensidade do exercício físico aeróbio é um fator indispensável para a prescrição do exercício físico em que a intensidade moderada é principalmente recomendada pelas principais recomendações internacionais. Idealmente, a intensidade do exercício prescrito deve estar dentro do primeiro e segundo limiar ventilatório (LV) avaliado por uma prova de esforço cardiorrespiratória (PECR), mas infelizmente nem sempre está disponível em muitos centros de RC. Um teste de terreno como o teste de caminhada de 6 minutos (TC6M) é significativamente menos dispendioso e de fácil aplicação. No entanto, a evidência científica é escassa no que toca a perceber quais os níveis de intensidade alcançados durante um TC6M em comparação com uma PECR em pessoas com DAC que iniciam um programa de RC fase III. Esta informação é relevante, uma vez que, tanto quanto sabemos, nunca foi testada anteriormente. **Objetivo:** avaliar a frequência cardíaca (FC) pico alcançada no TC6M como método para prescrever a intensidade do exercício aeróbio em pessoas com DAC que iniciam um programa de RC de fase III e compará-lo com o primeiro e segundo limiares ventilatórios (LV) determinados na PECR. **Métodos:** este estudo transversal incluiu pessoas com DAC a iniciar o programa RC de fase III no Centro de Reabilitação Cardiovascular da Universidade de Lisboa (CRECUL). Todos os dados foram recolhidos na altura em que cada doente iniciava o programa de RC.

Para avaliar a capacidade funcional todos os doentes realizaram uma PECR e o TC6M em dias não consecutivos. Adicionalmente, a composição corporal foi avaliada através de densitometria de dupla energia e o nível de atividade física foi medida objetivamente utilizando acelerómetro durante 7 dias. As principais variáveis analisadas a partir do TC6M foram a FC pico e a distância total percorrida enquanto na PECR foram analisados a FC máxima, os LV e consumo de oxigénio pico (VO_2 pico). As comparações entre as variáveis da PECR e do TC6M foram realizadas utilizando o teste *t* de amostra pareada e as relações foram medidas pelo coeficiente de correlação de Pearson. A concordância entre a FC pico do TC6M e os LV foi avaliada pela análise Bland-Altman. As análises dos dados foram realizadas utilizando o software IBM SPSS Statistics 26 (SPSS Inc, Chicago, USA). **Resultados:** Foram incluídos e analisados neste estudo um total de 105 pessoas com DAC, 83 doentes foram revascularizados com intervenção percutânea coronária e 19 doentes foram revascularizados com *bypass aorto-coronário*, por enfarte agudo do miocárdio. Os doentes tinham idade média de 61 ± 9.8 anos, a maioria do sexo masculino (88%), fisicamente ativos (352 ± 180 minutos/semana de atividade física moderada a vigorosa), com excesso de peso (índice de massa corporal: 27.7 ± 3.5 kg/m^2). Os ex-fumadores foram o maior fator de risco prevalente (66%) seguido da hipertensão arterial (49%). Em relação à terapêutica beta bloqueante, 84% dos doentes estavam betabloqueados. Houve diferenças significativas entre a FC pico do TC6M *vs* primeiro LV (média 15 ± 16 bpm, 95% IC [12.62,18.89], p <0.001) *vs* o segundo LV (média -5 ± 17 bpm, 95% IC [-9,23, -2.36], p = 0.001). Contudo, foi observado que a FC pico do TC6M (110 ± 17 bpm) encontrava-se dentro do primeiro e do segundo LV (95 ± 14 bpm e 116 ± 17 bpm, respectivamente) da PECR. No entanto, a FC pico do TC6M (110±17 bpm) estava entre os valores dos LV (95 ± 14 bpm, 116 ± 17 bpm, p < 0.001). Houve uma correlação moderada entre a FC do primeiro VT e a FC do TC6M (r = 0.504, p < 0.001), e fraca entre FC do segundo VT e a FC do TC6M (r = 0.482, p < 0.001). De acordo com a análise de Bland-Altman, foi encontrado uma fraca concordância entre a FC pico do TC6M e o primeiro e segundo LV (p <0.001 e p = 0.001, respectivamente). **Conclusão:** na ausência de uma prova de esforço, o TC6M pode ser uma alternativa para utilizar na prática clínica para prescrever exercício físico a uma intensidade aeróbia moderada em pessoas fisicamente ativas com DAC que se encontrem a iniciar um programa de RC fase III. O TC6M é seguro, simples e bem tolerado e apresenta boa reprodutibilidade em pessoas com DAC. A prescrição de exercício aeróbio de acordo com FC pico do TC6M para pessoas com DAC que iniciam a fase III do programa RC mostrou-se segura e corresponde a uma intensidade de exercício moderada. Recomenda-se utilizar outros parâmetros complementares para controlo da intensidade de exercício como a escala de Percepção de Esforço de Borg.

Palavras-chave: reabilitação cardiovascular, intensidade do exercício, frequência cardíaca, teste de caminhada de 6 minutos, prova de esforço cardiorrespiratória.

SUMMARY

TABLES

FIGURES

ABBREVIATIONS

6MWT – 6-minute walk test

AACVPR - American Association of Cardiovascular and Pulmonary Rehabilitation

ACC – American College of Cardiology

ACE - angiotensin-converting enzyme

ACSM´s – American College of Sports Medicine

AHA – American Heart Association

AMI – acute myocardial infarction

ARB - angiotensin receptor blocker

ASCVD – atherosclerotic cardiovascular disease

BL – blood lactate

BMI – body mass index

BP - blood Pressure

CAD – coronary artery disease

CABG – coronary artery bypass graft

CACs - cultured/circulating angiogenic cells

CHF - congestive heart failure

CHD – coronary heart disease

CPET – cardiopulmonary exercise test

CPM – counts per minute

CR – cardiovascular rehabilitation

CRF – cardiorespiratory fitness

CR - cardiovascular rehabilitation

CV - cardiovascular

CVD – cardiovascular disease

DXA - dual-energy radiographic absorptiometry

ECG – electrocardiogram

EPCs - endothelial progenitor cells

ESC – European Society of Cardiology

FITT – frequency, intensity

HbA1C – glycated haemohemoglobin

HDL-C: high-density lipoprotein cholesterol

HR – heart rate

HRR – heart rate reserve

IHD – ischemic heart disease

KCAL – kilocalories

LDL-C - low-density lipoprotein cholesterol

LVEF – left ventricular ejection function

MET - metabolic equivalent

MI – myocardial infarction

mmHg - millimetre of mercury

MVPA – moderate-to-vigorous physical activity

NSTEMI - non-ST–elevation myocardial infarction

PA – physical activity

PCI – percutaneous coronary intervention

PCSK9 - proprotein convertase subtilisin/kexin type 9

$P_{ET}CO2$, $P_{ET}O2$ - end-tidal pressure of carbon dioxide or oxygen

PF – physical fitness

RER - respiratory exchange ratio

RM – repetition maximum

RPE - rating of perceived exertion

SCORE - Systematic Coronary Risk Evaluation

SCORE-OP - Systematic Coronary Risk Evaluation Older Persons

SMART - Secondary Manifestations of ARTerial disease

STEMI - ST-elevation myocardial infarction

SV- stroke value

VE – ventilation

VCO2/VO2 - ventilatory equivalent for oxygen

VE/VCO_2 - ventilatory equivalent for carbon dioxide

VO_2 – oxygen consumption

VO_{2R} – oxygen uptake reserve

VCO_2 - carbon dioxide

VT – ventilatory threshold

W – workload

WR – work rate

I. INTRODUCTION

Cardiovascular diseases are still the leading cause of death worldwide. Low birth rates in high-income countries and increasing life expectancy in middle-income countries have contributed to this growth (Timmis et al., 2022). Each year more than 7 million people experience acute myocardial infarction (AMI) due to ischemic heart disease (IHD), worldwide (Piepoli et al., 2016).

Coronary artery disease (CAD) is an inflammatory disease characterized by atherosclerotic plaque accumulation causing a flow-limiting obstruction in coronary arteries. The disease is chronic, often progressive and, clinically silent and the process can be modified by lifestyle behaviours, pharmacological and invasive treatments to achieve disease stabilization or regression (Knuuti et al., 2020).

Advances in interventional and secondary prevention cardiology have dramatically improved survival for people with CAD. Cardiovascular rehabilitation (CR) is an intervention and process based on appropriate lifestyle changes, optimal medical treatment and, cardiovascular risk control aiming to improve quality of life, optimize or maintain physical and psychosocial independence, and reduce long-term health and social care utilization (Piepoli et al., 2016). Many cardiac rehabilitation studies are mainly conducted on a short-term period (up to 12 weeks), which have been widely proven their positive effects (Dibben et al., 2021). However, more studies are needed to better understand long-term CR interventions effects.

Since knowledge of the core components is an integral part of the CR programme, providing multifaceted strategies and multidisciplinary approach, exercise training is an essential component of improving cardiorespiratory fitness (CRF) when prescribed accurately. Structured exercise training should clearly specify the frequency, intensity, time, and type (FITT) of exercise (Ascenzi et al., 2022). Moreover, determining exercise intensity by using predicted heart rate equations when the patient is under the use of drug therapy, such as beta-blocker, may modify the heart rate response during exercise training. Thus, assessing functional capacity in this type of population is very important to make sure that exercise prescription is being individualized. Moderate- to vigorous-intensity exercise is strongly associated with a reduced incidence of adverse outcomes in CAD patients (Pelliccia et al., 2021).

Therefore, the 6-minute walk test (6MWT) and cardiopulmonary exercise test (CPET) are the two most used tests for assessing functional capacity in patients with cardiovascular disease (R. Ross et al., 2016), (Guazzi et al., 2009).

In one hand, the CPET is the gold standard to assess cardiorespiratory fitness and to determine the aerobic exercise intensity to individualize exercise training prescription. However, its availability and associated costs are not a reality in many CR centres (Mezzani et al., 2013). On the other hand, the 6MWT is a submaximal valid and widely used test to assess cardiorespiratory fitness in CR programmes. It is a low-cost assessment, simple and their reference values has been used to evaluate the effect of exercise-based CR programmes (Dolecinska et al., 2021).

Some studies on CAD patients before attending a phase II CR programmes have demonstrated a correlation between cardiorespiratory values from the 6MWT and from the CPET at ventilatory threshold (Gayda et al., 2004), (Calegari et al., 2021). In other words, it means that, according to the previous studies, a patient who are going to attend a phase II CR programme if a 6MWT is performed, the maximum HR attended on the 6MWT correspond to the first VT, which is the intensity that is usually prescribed when CR is starting (Ambrosetti et al., 2021). Nevertheless, it is still unknown the corresponding intensity reached on a 6MWT compared to the one reached on a CPET in already physically active patients with CAD starting a CR phase III programme. This information is important since, as far as we concern, it has never been tested before.

The primary aim of this study was to measure the heart rate (HR) peak of the six-minute walk test (6MWT) in CAD patients starting a phase III CR programme and to compare it to the HR of the first and second ventilatory thresholds (VT) at CPET. The secondary aim was to determine in which VT correspond the exercise intensity of aerobic exercise using the HR_{peak} in the 6MWT.

This dissertation is organized in the following way: chapter I, includes a full literature review with the definition of cardiovascular diseases and their aetiology, an insight into of the process of atherosclerotic plaque and, how it manifests itself until its major consequence, an acute myocardial infarction. Afterwards, it will be described the modifiable and non-modifiable risk factors for coronary artery disease, and how to diagnose and conduct treatment either by invasive and/or pharmacological intervention.

Subsequently, it will be detailed the definition of the cardiovascular rehabilitation programme and its CORE components, focusing on the exercise-based and cardiorespiratory fitness assessments through direct and indirect methods.

A detailed description of the methodology used in the present dissertation is found in Chapter III. Finally, on chapter IV the results section will be presented and discussed the main findings from this dissertation, their implication, and future directions.

In addition, two abstracts derived from this dissertation were presented at the European Association of Preventive Cardiology (EAPC) Congress 2022 (virtual mode) and at *“Reunião Conjunta Grupo de Estudo de Fisiopatologia do Esforço e Reabilitação Cardíaca (GEFERC) e Grupo de Estudo de Risco Cardiovascular (GERC)* meeting 2022 in Cascais which are attached in Chapter VI, appendices C.

II. LITERATURE REVIEW

1. Cardiovascular disease

1.1 Definition and Epidemiology of Cardiovascular Disease

Cardiovascular disease (CVD) are the major cause of global death and morbidity, responsible for serious health conditions and medical care costs (Amini et al., 2021). CVD are a group of blood vessel supply disorders involving the heart and brain (World Health Organization, 2012), namely, stroke, heart failure, hypertensive heart disease, rheumatic heart disease, peripheral arterial disease, and other vascular and cardiac problems. CVD burden may be attributed to lifestyle behaviours, dietary habits, inappropriate health care, lack of physical activity and other factors (Amini et al., 2021). Coronary heart disease (CHD) and stroke are the main form of CVD (Roth et al., 2020), responsible for over 3.9 million deaths a year, representing 45% of all deaths (Wilkins et al., 2017).

Additionally, CVD is also the most common cause of premature (age <70 years) death in males and is more common in middle-income countries in both sexes (Timmis et al., 2020). In 2019, total CVD disability-adjusted life years were higher in men than women before age 80 to 84 years, however, the reverse occurs when women are over 80 years old (Roth et al., 2020).

Several risk factors like lifestyle, dietary habits, appropriate health care accessibility, and so forth, is responsible for the increase of incidence and mortality rates of CVD and vary from region to region. While in low and middle-income countries has slightly decline or even increased in mortality rates, in high-income countries, such as the United States and England have shown a decrease in age standardized mortality which might be attributed to a remarkable improvement in population-level CVD prevention (Amini et al., 2021).

The patients who survive an acute myocardial infarction (AMI) live with chronic disabilities and impaired quality of life (Khan et al., 2020) and this number has doubled from 17.7 million (95% UI: 12.9 to 22.5 million) to 34.4 million (95% UI: 24.9 to 43.6 million) in 1990 to 2019 (Roth et al., 2020).

Coronary artery disease (CAD) is a chronic process characterized by an atherosclerotic plaque which causes a blood flow reduction to the myocardium (Severino et al., 2020) and may lead to myocardial infarction. This process usually is asymptomatic for a long period, beginning early in life, and progresses gradually through adolescence and early adulthood. The progress of the plaque may be influenced by modifiable and non-modifiable cardiovascular risk factors (Kesteloot, 1978), which will be discuss further.

1.2. Pathophysiology of coronary artery disease

Atherosclerosis is the main cause of CAD and it is characterized as an inflammatory disorder which immunological mechanisms interact with metabolic risk factors to initiate, proliferate and activate lesions in the arterial wall (Hansson, 2005). The process starts with an endothelium dysfunction driven by products or traditional risk factors, non-traditional and unknown mechanisms. The most mechanism influencing in this process are dyslipidaemia, vasoconstrictor hormones in hypertensive patients, also the products of glycoxidation related to hyperglycaemia and proinflammatory cytokines due to excess adipose tissue, where these cells provide a physiological vascular changes in the arteries, such as vasomotor tone alterations, thrombotic dysfunctions, smooth muscle cell proliferation and migration (Libby & Theroux, 2005), (Matsuzawa & Lerman, 2014). Therefore, endothelial dysfunction occupies an important place in both initiation and progression of atherosclerotic plaque. The atherosclerotic plaque consists of cells, connective tissue elements, lipids and, debris where a major part of an atheroma is constituted by blood-borne inflammatory and immune cells. The atherosclerotic lesion is characterized according to histological stages and associated with clinical manifestations (Stary et al, 1995). It starts with a fatty streak visible lesion characterized by layers of macrophage foam cells and lipid droplets within intimal smooth muscle cells (Stary et al., 1994) and the plaque process may begin in the early stages of childhood, with a thin deposit of fat in the intima layer. Steadily, the extensive accumulation of extracellular lipids in the deep intima (lipid core) tends to increase, and there may also be thickening of the intima by fibrous tissue and calcifications resulting in the growth of necrotic core (Stary et al., 1995), (Matsuzawa & Lerman, 2014).

The plaque can be presented in a stable or unstable form, where an unstable plaque is prone to rupture, occurring thrombus formation, occlusion of the artery resulting in ischemia and myocardial infarction (Boudoulas et al., 2016). The development and progression of the coronary atherosclerosis are shown in figure 1.

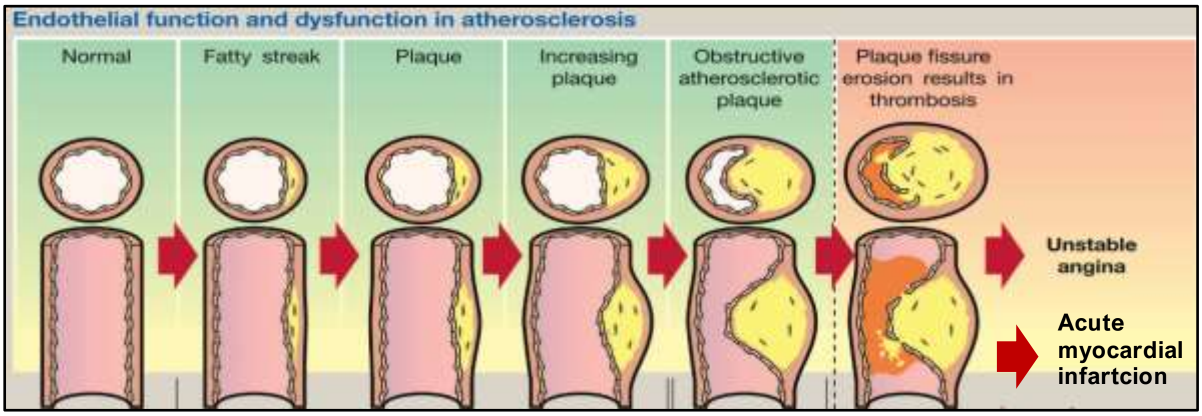

Figure 1. Coronary Atherosclerosis progression.
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1.3. Myocardial Infarction

Coronary heart disease remains a major cause of mortality and morbidity. Despite a marked reduction in cardiovascular (CV) mortality over the past 40 years, the rates of myocardial infarction (MI) are high. More than half of 30-day MI mortality occurs prior to hospital arrival, mostly within 1 hour of symptom onset (Fitchett et al., 2011). A MI may be the first manifestation of CAD, or it may occur, repeatedly, in patients with established disease (Thygesen et al., 2007).

Acute myocardial infarction (AMI) produces a significant local inflammatory response which starts in the myocardium and propagates systemically through the blood stream (Severino et al., 2020). The main mechanism of AMI is due the rupture of cholesterol-laden plaque triggered by inflammation and followed by a platelet-rich thrombus formation, although others mechanism as plaque erosion, calcific nodules, coronary spasms, spontaneous coronary dissection and coronary embolism are also responsible for the AMI (Bhatt et al., 2022). The AMI include patients with ST-elevation myocardial infarction (STEMI) and non-ST–elevation (NSTEMI), and the therapeutic strategies is prompt re-opening of the occluded artery and to prevent progression of the thrombus to total occlusion, plaque thromboembolisation, and recurrent infarction, respectively (Fitchett et al., 2011). STEMI and NSTEMI accounts approximately 30% and 70%, respectively, of AMI. When thrombosis completely occludes the vessel, STEMI occurs and when the thrombus is nonocclusive, NSTEMI occurs (Bhatt et al., 2022).

Universally, AMI is considered when it occurs a clinical evidence of acute myocardial ischemia and with detection of an increase and/or decrease of cardiac troponin values with at least 1 value above the 99^{th} percentile upper reference limit and at least 1 of the following: (1) Symptoms of myocardial ischemia; (2) New ischemic electrocardiogram changes; (3)

Development of pathological electrocardiographic (ECG) Q waves; (4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic aetiology; or (5) Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs) detect myocardial injury by abnormal biomarkers e clinical approach in the setting of evidence of acute myocardial ischemia (Thygesen et al., 2018) (Reddy et al., 2015). Patients presenting AMI, levels of cardiac troponin rise rapidly after symptom onset and may remain elevated for a long time (Collet et al., 2021).

The universal classification of myocardial infarction is characterized in five types, based on pathological, clinical and prognostic differences procedure (Reddy et al., 2015) (Thygesen et al., 2012):

TYPE 1 - Spontaneous MI mainly due to atherosclerotic plaque rupture which lead a decrease in myocardial blood flow or distal platelet emboli following myocyte necrosis.

TYPE 2 - MI secondary to an ischemic imbalance either increased oxygen demand or decreased supply, such as coronary endothelial dysfunction or vasospasms.

TYPE 3 - MI resulting in death when biomarker values are unavailable, which means, these individuals may die before blood samples for biomarkers.

TYPE 4 AND 5 - MI associated with revascularization procedures. During mechanical revascularization procedures, either percutaneous coronary intervention or coronary artery bypass graft, may occur myocardial injury or infarction, further after these procedures elevated cardiac troponins (cTn) values can lead to myocardial Injury with necrosis. Additionally, MI related to PCI is related to stent thrombosis and restenosis that may happen after the primary procedure.

Cardiac troponin can also be elevated in a myocardial injury. Myocardial injury may occur as a consequence of myocardial oxygen supply-demand mismatch as MI type 2 or may occur after small amounts of myocardial necrosis from inflammatory state (Thygesen et al., 2012), (Chapman et al., 2017). Nevertheless, an additional evaluation in patients presenting elevated cardiac troponin is necessary due to the importance of prognostic implications and the high cardiac troponin T level is associated with cardiovascular mortality (Reddy et al., 2015).

1.4 Signs and Symptoms

The blood flow obstruction, caused by a mismatch between myocardial oxygen demand and supply manifests the symptoms of CAD. The main symptom related to myocardial ischemia is angina pectoris and may accompany by shortness of breath. The angina is a discomfort usually located in the chest, near the sternum, but may be felt anywhere from the epigastrium to the lower jaw or teeth, between the shoulder blades, or in either arm to the wrist and fingers. Angina may be classified in to stable and unstable. Stable angina is characterized when the discomfort is relief at rest or nitroglycerin. Unstable angina happens at rest and for a long period (>20 min), new-onset of moderate-to-severe angina (Canadian Cardiovascular Society) or crescendo angina which the discomfort progressively increases in severity and intensity. Unstable angina usually is related to acute myocardial syndrome where there is myocardial ischemia without myocardial necrosis (Knuuti et al., 2020).

Additionally, angina is categorized according to location, duration and relationship to exertion and is classified subjectively by typical, atypical and non-cardiac chest pain. Typical angina is defined when these three criteria are meet: (I) substernal chest pain, (II) provoked by physical or psychological stress, and (III) relieved after rest or nitroglycerine (or both) (Reeh et al., 2019). The majority of patients with suspicion of CAD present with atypical or non-anginal chest pain, with only 10-15% presenting typical angina (Knuuti et al., 2020).

The discomfort duration is brief, no more than 10 min in the majority of cases, and more commonly just a few minutes or less. Another important characteristic is the relationship to exercise (Knuuti et al., 2020). The Canadian Cardiovascular Society quantifies when the symptoms of the angina threshold occur in correlation with physical activities, as shown in table 1.

Table 1. Modified Canadian Cardiovascular Society Grading for Angina Severity.

Class I	Angina occurs with strenuous or rapid or prolonged exertion
Class II	Angina occurs with moderate exertion (eg, walking >2 blocks on level ground and climbing >1flight of ordinary stairs at a normal pace and in normal conditions; walking uphill; or walking or climbing stairs rapidly, in the cold in wind, under emotional stress, or during the first few hours after awakening)
Class III	Angina occurs with mild exertion (walking 1 or 2 blocks on level ground and climbing 1 flight of stairs in normal conditions and at a normal pace)
Class IV	Angina occurs with any level of exertion and may be present at rest

Adapted from Circulation, Campeau, (1976). Grading of angina pectoris. Circulation, 54(3), 522-523.

It is also important, to assess the presence of anaemia, hypertension, valvular heart disease, arrhythmias or hypertrophic cardiomyopathy by physical examination and furthermore, to search for other signs of comorbid conditions and non-coronary vascular disease to obtain a better distinction between symptoms (Knuuti et al., 2020).

An electrocardiogram (ECG) 12-lead must be obtained to identify the presence of ST-T deviation and interpreted as soon as possible to facilitate early diagnosis and triage (Fitchett et al., 2011) (Ibanez et al., 2018). Diagnostic of Myocardial infarction will be detailed at 1.7 topic.

1.5 Risk Factors and Risk Stratification for cardiovascular disease

Multiple risk factors are attributed to cause CVD. They fall into two categories of either non-modifiable or modifiable risk factors. Non-modifiable risk factors include advancing age, sex and gender, family history of heart disease and coagulopathies, type 1 diabetes due to compromised body functions, mainly fat metabolism and glucose tolerance, childhood obesity (Buttar et al., 2005).

Modifiable risk factors are potentially related to lifestyles and dietary behaviours. According to the European Society of Cardiology (ESC) guidelines (Visseren et al., 2021) the main modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD) are blood apolipoprotein-B-containing lipoproteins [of which low-density lipoprotein (LDL) is most abundant], high blood pressure, cigarette smoking, diabetes mellitus and adiposity. Addition to these, the American College of Cardiology and American Heart Association (ACC/AHA) (Arnett et al., 2019) include socioeconomic and educational status, cultural, work, and home environments since the ASCVD begins early in life and may affect treatment adherence and ASCVD health outcomes. Table 2, shows the American College of Sports Medicine (ACSM) cardiovascular disease risk factors assessment and defining criteria (ACSM, 2017)

Table 2. Cardiovascular disease risk factors and Defining Criteria

Risk Factors	Defining Criteria
Age	Men ≥45 years; Women ≥ 55 years
Family History	Myocardial infarction, coronary revascularization or sudden death before 55 years in father or other male first-degree relative or before 65 years in mother or other female first-degree relative
Cigarette smoking	Current cigarette smoker or those who quit within the previous 6 month or exposure to environmental tobacco smoke
Physical inactivity	Not participating in at least 30 minutes of moderate intensity physical activity (40-59% VO_2R) on at least 3 days of the week for at least 3 months

Obesity	Body mass index ≥ 30 kg/m^2 or waist girth >102 cm for men and > 88 cm for women
Hypertension	Systolic blood pressure ≥ 140mmHg and/or diastolic ≥ 90mmHg, confirmed by measurements on at least two separate occasions, or on antihypertensive medication
Dyslipidaemia	Low-density lipoprotein cholesterol ≥ 130 mg/dL or high-density lipoprotein cholesterol (HDL-C) <40 mg/dL or on lipid-lowering medication. If total serum cholesterol is available, use ≥ 200 mg/dL
Diabetes	Fasting plasma glucose ≥ 126 mg/dL or 2-hour plasma glucose values in oral glucose tolerance test (OGTT) ≥ 200 mg/dL or HbA1C ≥ 6.5%
Negative Risk Factors	**Defining Criteria**
HDL-C	≥ 60 mg/dL

Abbreviations: VO_2R – oxygen uptake reserve, HbA1C – glycated haemoglobin

Adapted from ACSM. (2017). ACSM's guidelines for exercise testing and prescription. Lippincott Williams & Wilkins.

Other clinical conditions are recommended to assess which can influence cardiovascular risk include, chronic kidney disease, atrial fibrillation, heart failure, cancer, chronic obstructive pulmonary disease, inflammatory conditions, infections, sleep disorders and obstructive sleep apnoea, migraine, mental disorders, non-alcoholic fatty liver disease and sex-specific conditions (Visseren et al., 2021).

The risk stratification is needed for CVD prevention by enhancing a healthier lifestyle at long-term, optimize pharmacological treatment, individualized treatment goals, to assist healthcare professionals in their clinical process and outcomes, reduce overtreatment and costs (Rossello et al., 2019). Furthermore, risk stratification is important for people who do not yet have atherosclerotic disease but are likely to develop CVD (Francula-Zaninovic & Nola, 2018). The risk algorithms are useful to identify patients who will benefit with central treatment and prevention efforts. The SCORE 2, is an algorithm easy to measure, low cost and widely available and easy to understand. They are based on different cardiovascular risk factors values according to age and patients sex (Rossello et al., 2019).

For European population, the SCORE 2 risk charts - Systematic Coronary Risk Evaluation – is assessed by calculating the ten-year risk of fatal and non-fatal CVD risk, according European risk regions, without previous CVD or diabetes aged 40-69 years. The SCORE 2 reinforce the identification of patients at higher risk of developing CVD across Europe. European countries are grouped into four risk regions: low risk, moderate risk, high risk and very high risk (Figure 2) (SCORE2 Collaboration & Group, 2021). Portugal is considered as moderate risk. The SCORE2 charts for CVD risk estimation in four European risk regions are shown in the Appendix A.

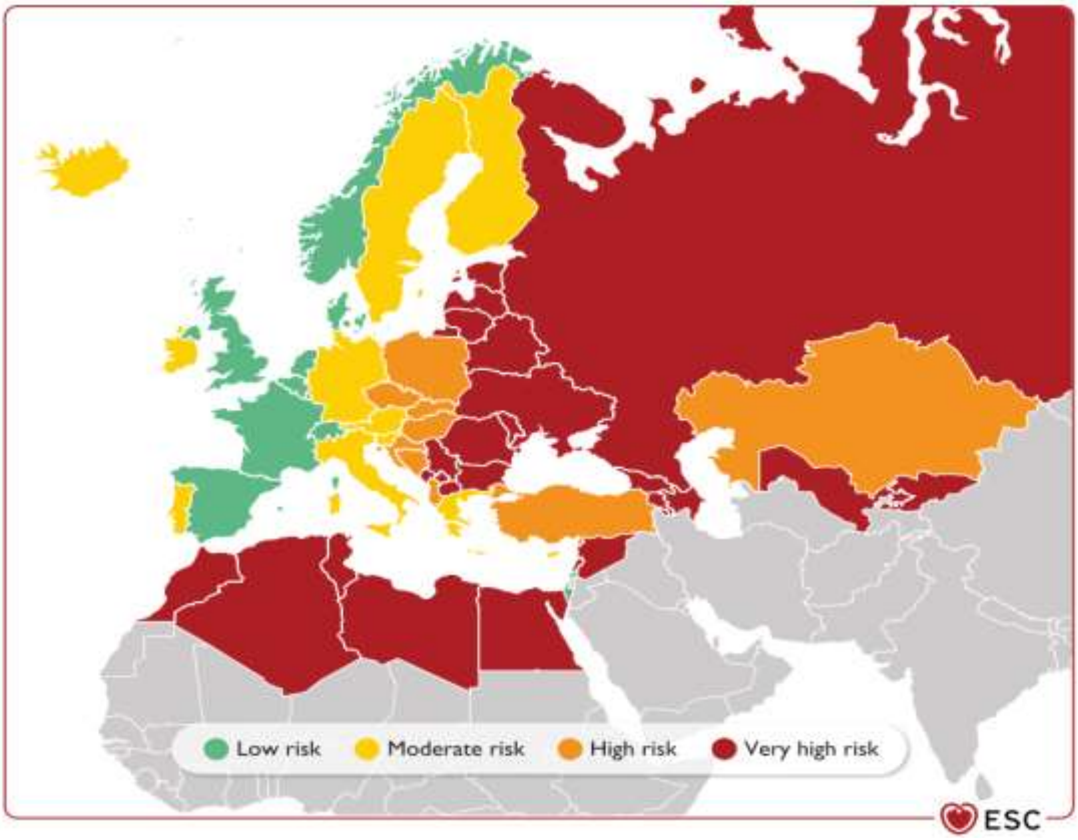

Figure 2. Risk regions based on World Health Organization cardiovascular mortality rates.
Reprinted from European Journal of Preventive Cardiology, 42(34), 3227–3337, 2021; Visseren, F. L. J., et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies; with permission from Oxford University Press and Copyright Clearance Center.

The individual risk estimate is based on population baseline risk (region risk) and individual risk factors values, among them sex, age, total- and HDL-cholesterol, smoking status and systolic blood pressure.

To avoid the overestimation of CVD risk and unnecessary treatment in older persons, an older person-specific risk score. SCORE-OP is a risk adjusted model for individuals aged over 70 years without pre-existing CVD to estimate 5- and 10-year risk of incident CVD. Furthermore, SCORE-OP can estimate blood pressure lowering or lipid lowering treatment, supporting decision-making in clinical practice (collaboration et al., 2021). Figure 3 shows both, the 10-year risk estimation for CVD and risk factor treatment recommendations according to very high, high, low-to-moderate risk. Two-dimensional risk charts of SCORE2-OP for all four risk regions are shown in the Appendix B.

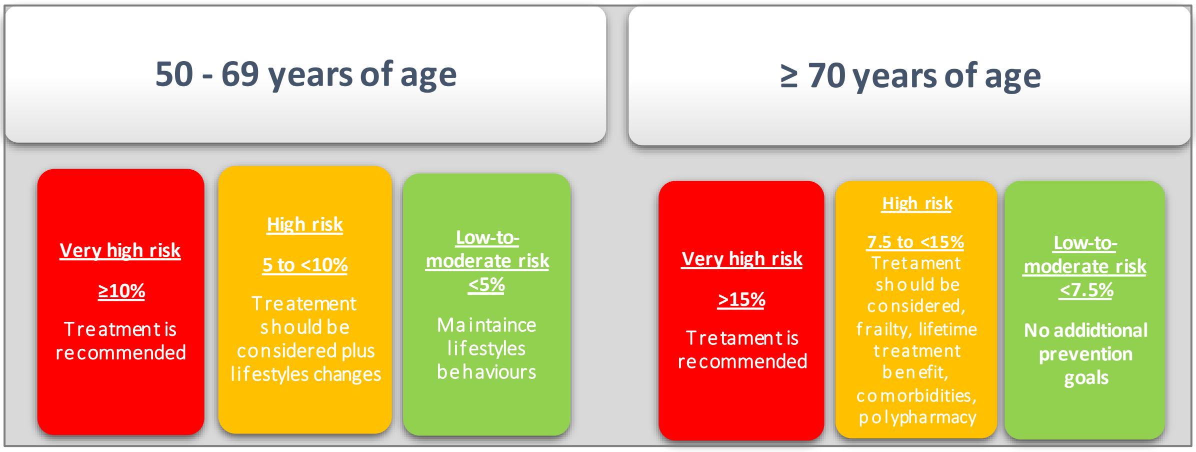

Figure 3. 10-year cardiovascular risk estimation and risk factor treatment estimation for apparently healthy people.

Furthermore, it is possible estimate the average lifetime benefit from risk factor management (smoking cessation, lipid and blood pressure lowering) (Visseren, 2022).

For those with established CVD, diabetes mellitus or chronic kidney disease are automatically categorized as very high risk. Treatment strategies will differ according to the risk level, with low risk patients being advised about lifestyle and to maintain their status, while the patients at higher risk should intensify lifestyle behaviours and they are favourable for drug therapy (Francula-Zaninovic & Nola, 2018), (Piepoli et al., 2016), (Pelliccia et al., 2021).

In patients with any clinical manifestation of arterial atherosclerosis, such as cerebrovascular disease, CAD, peripheral artery disease or abdominal aortic aneurysm, a risk estimation of 10-year has been developed. The SMART (Secondary Manifestations of ARTerial disease) risk score is used in patients in the stable phase of symptomatic vascular disease and estimate the absolute risk for recurrent major vascular events. The score is based on clinical parameters (medical history, smoking status, systolic blood pressure and laboratory biomarkers) plus age and sex, carotid ultrasound findings or both (Dorresteijn et al., 2013).

To assess SCORE2, SCORE-OP and SMART risk score tools, the calculator is available online on U-Prevent.com.

1.6 Diagnoses and treatments of myocardial infarction

Initial diagnosis consists in clinical history including any manifestation of CVD and risk factors (i.e. family history of CVD, dyslipidaemia, diabetes, hypertension, smoking, and other lifestyle factors) (Knuuti et al., 2020), symptoms, vital signs, cardiac troponins measurement with high-sensitivity assays (hs-cTn) and other physical findAnings. Detection of changes in troponins is essential to the diagnosis of acute myocardial infarction (MI) and its management (Reddy et al., 2015).

A resting 12-lead ECG is the first-line tool and it is recommended to perform as soon as possible to distinguish between ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) (Ibanez et al., 2018), (Collet et al., 2021). If STEMI is present, an emergent invasive coronary angiography should be perform to confirm the diagnosis of myocardial infarction and reperfusion therapy needs to be initiated immediate (Bhatt et al., 2022). In case the patient presents symptoms but does not have STEMI, a cardiac troponin rapid test should be performed and if necessary an echocardiography bedside may identify wall motion abnormality (Bhatt et al., 2022). Despite troponin being highly specific and sensitive marker of myocardial cell injury, its circulation can be also increase in other non-cardiac conditions (Fitchett et al., 2011).

A differential diagnosis for patients presenting acute chest pain should be considered. Several cardiac and non-cardiac conditions may confuse to NSTEMI, among them cardiomyopathies, aortic valve stenosis, coronary spasms, takotsubo syndrome, pulmonary embolism, and tension pneumothorax. A cardiac magnetic resonance may be helpful to differential diagnosis with unclear NSTEMI (Collet et al., 2021). In haemodynamically unstable patients with suspicion of cardiovascular origin, an echocardiogram should be performed urgently. Chest X-ray is recommended to detect pulmonary disorders. Additionally, others tests may be useful to identify symptoms of CAD, such as exercise stress testing with or without myocardial imaging, or non-invasive computed tomographic (CT). Patients with a normal CT angiogram do not require additional diagnostic testing (Bhatt et al., 2022).

An early diagnosis of MI must be made to provide optimal treatment while minimizing intervention's delays, thereby improving clinical outcomes and reduce mortality.

1.6.1 Invasive treatment/Reperfusion treatment

Myocardial revascularization either percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) aimed to minimize residual ischemia, reliving angina symptoms, reducing the use of anti-anginal drugs, improves exercise capacity and quality of life (Neumann et al., 2019).

The primary PCI is defined as both a therapeutic intervention and a diagnostic coronary angiography procedure (Neumann et al., 2019). PCI is considered safe and convenient, often cost-effective, and is associate with less complications and lower radiation (Neumann et al., 2019). The PCI is performed preferably via radial access to reduce site bleeding, vascular complication, and need for transfusion. The technique of choice is coronary stenting with new-generation drug-eluting stents (DES), which is associated with lower rates of definitive stent thrombosis and of target lesion and any repeat revascularization (Ibanez et al., 2018).

Reperfusion therapy should be initiated as soon as the patient has a suspicion of STEMI. PCI is the preferred reperfusion strategy in patients with STEMI within 12 hours of symptoms onset. The infarct-related artery (IRA) should be the initial intervention treated (Neumann et al., 2019). However, whether PCI is not possible fibrinolysis could be initiated injecting bolus of fibrinolytics within 10 minutes from STEMI diagnosis (Bhatt et al., 2022), (Ibanez et al., 2018). Further, primary PCI should be performed to the patients presenting clinical symptoms of acute myocardial infarction and a non-interpretable ST-segment on the ECG, such as those with bundle branch block or ventricular pacing.

The CABG was first introduced in the 1960s and became one of the most commonly performed major surgical procedure which it has improved over time. Despite the advances in PCI, CABG is recommended for patients with multivessel coronary diseases, particularly when the proximal left anterior descending coronary artery is involved, patients presenting cardiogenic shock and complex disease, as well as in diabetic patients in patients unsuitable for PCI (Head et al., 2017), (Ibanez et al., 2018), (Neumann et al., 2019). CABG is considered as completed vascularization, where the procedure is performed through a median sternotomy, the heart is arrested with cardioplegia and left internal mammary artery is the conduit of choice for CABG (Head et al., 2017), (Neumann et al., 2019).

The choice for the type of revascularization should be considered the individual cardiac and extracardiac characteristics, such as, anatomical complexity of coronary artery disease, patient preference, risk-benefit ratios, health-related quality of life, as well as long-term freedom from death, MI, or repeat revascularization (Neumann et al., 2019), (Ibanez et al., 2018).

1.6.2 Pharmacological Treatment

Pharmacological treatment aims to reduce angina symptoms and exercise-induced ischaemia, preventing cardiovascular events (Knuuti et al., 2020).

ANTITHROMBOTIC DRUGS

Antiplatelet drugs reduce the platelet aggregation and activation, thus preventing ischemic events and increased risk of bleeding. Dual antiplatelet therapy, aspirin plus $P2Y_{12}$inhibitor (prasugrel, ticagrelor, clopidogrel), is recommended for up 12 months after PCI, in addition, a proton pump inhibitor (gastric protection) in patients at high risk of gastrointestinal bleeding (Ibanez et al., 2018).

ANTICOAGULANT DRUGS

Anticoagulant drugs inhibit thrombin generation and thrombin activity (Knuuti et al., 2020). Anticoagulant drugs are recommended in addition to antiplatelet drugs (triple therapy), however, oral anticoagulant therapy duration should be short due to an increased risk of bleeding (Neumann et al., 2019), (Ibanez et al., 2018).

Patients under dual antiplatelet therapy and oral anticoagulants should avoid exercise with bodily collision, due to the risk of haemorrhage (Pelliccia et al., 2021).

ANTIANGINAL DRUGS

Oral beta-blocker treatment is well stablished mid- and long-term to reduce mortality, also is indicated in patients with reduced systolic left ventricular function (LVEF ≤40%) (Ibanez et al., 2018). Beta-blocker and/or calcium channel blocker are indicated to control heart rate and angina symptoms. For immediate angina relief, short-acting nitrates are recommended. The most used beta-blockers in Europe are those with predominant beta1 blockade (e.g., metoprolol, bisoprolol, atenolol, and nebivolol). Carvedilol, a non-beta1-selective beta-blocker, is also used. During exercise, beta-blockers reduce heart rate, contractility, and atrioventricular conduction, reducing time-to-angina onset (Knuuti et al., 2020).

LIPID-LOWERING DRUGS

Lipid-lowering treatment with statins, should be started as early as possible, in all patients with acute myocardial infarction, irrespective of cholesterol level. The treatment goal is an LDL-C concentration of<1.8mmol/L (<70mg/dL) or at least 50% reduction in LDL-C if the baseline LDL-C level is 1.8–3.5 mmol/L. In addition to statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are very effective at decreasing LDL- C. Furthermore, is recommended to combine with exercise, diet, and weight control (Ibanez et al., 2018), (Knuuti et al., 2020).

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITOR OR ANGIOTENSIN RECEPTOR BLOCKER (ARB) DRUGS

Indicated in early STEMI within the first 24 hours, in patients with systolic left ventricular dysfunction or heart failure, hypertension, or diabetes. In patients who are intolerant of ACE inhibitor an angiotensin II receptor blockers is an alternative, preferably valsartan (Ibanez et al., 2018), (Knuuti et al., 2020).

GLUCOSE-LOWERING DRUGS

The agents glucagon-like peptide-1-receptor antagonists and sodium-glucose cotransporter-2 inhibitors, is recommended in patients with type 2 diabetes mellitus with prevalent atherosclerotic cardiovascular disease (Collet et al., 2021).

The adherence to medical therapy is crucial for achieving patient's outcomes. Optimization of medical therapy and education is an important goal in a cardiac rehabilitation programme (Pavy et al., 2021). A good adherence is associates with a risk reduction of 44%, 34%, and 39% for all-cause mortality, cardiovascular mortality, and cardiovascular hospitalization/myocardial infarction, respectively (Du et al., 2017).

2. Cardiac Rehabilitation/Secondary Prevention

Secondary prevention aims to reduce or control modifiable risk factors in patients with diagnosed CVD, referral to specialised services and initiation of specific treatment in order to stop or decrease the progression of the disease and to restore quality of life, maintain or improve functional capacity and prevent recurrence (Piepoli al., 2016), (Leon et al., 2005).

Among secondary prevention programmes, the cardiovascular rehabilitation is a therapeutic intervention with the highest level of scientific evidence-class I by the European Society of Cardiology, the American Heart Association and the American College of Cardiology in the treatment of patients with coronary artery disease and heart failure (Ambrosetti et al., 2021), (Piepoli et al., 2010), (Thomas et al., 2007). It consists in a coordinated, multidisciplinary approach designed to optimize cardiovascular health, including multifaceted strategies to manage and control modifiable risk factors, advice on physical activity and nutritional habits, psychosocial and vocational counselling and to optimize the use of cardioprotective drugs (Leon et al., 2005), (Piepoli et al., 2014). Furthermore, the cardiovascular rehabilitation (CR) programmes facilitate early return to work, aid development of self-management skills and offer the opportunity to maintain the benefits in the long term (Cowie et al., 2019).

To ensure the effectiveness of the programme and achieve sustainable health outcomes, each programme should deliver the core components (figure 4). Furthermore, an optimal standard CR programmes provide a qualified and competent multidisciplinary team, although may differ, according to regions, availability and phase of the programme (phase I, II and III). Multidisciplinary team in a CR programme required, a cardiologist, an exercise specialist (physiotherapist or exercise physiologist), a nutritionist, a nurse, further psychologists, social workers, administrative personnel and other specialists for specific consultation and advise. In addition, a dedicated facilities for medical assessments, exercise training and functional evaluations in a safe, functional and effective environment is desirable, and regular team meetings (Abreu et al., 2021), (Abreu et al., 2018).

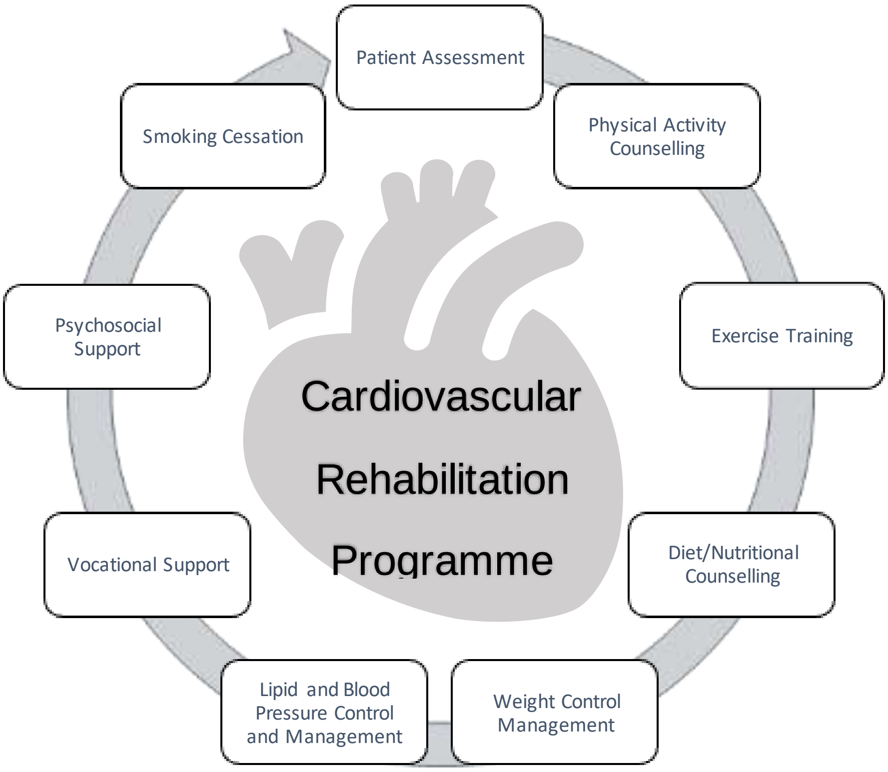

Figure 4. CORE components of cardiovascular rehabilitation programme.

PATIENT ASSESSMENT WITH MEDICAL CONTROL

The patient should be assessed for their individual needs and risks with an individual plan for CR. The evaluation consists in medical history screening for cardiovascular risk factors, co-morbidities and disabilities, medications, psychological stress, vocational situation; symptoms of angina; physical examination to assess general health status. Complementary exams required including resting 12-lead ECG, echocardiogram, 24-hour Holter monitoring (Abreu et al., 2018), blood test; physical activity level by history; symptom-limited exercise test. Whether the patients are incapable to perform the cardiopulmonary exercise test, the six-minute walk test as an alternative. Furthermore, the patients should be provided with comprehensive information about the programme and the role of each component, education about self-monitoring and self-management (Piepoli et al., 2014), (Balady et al., 2007).

PHYSICAL ACTIVITY COUNSELLING

Advice, support and counselling about daily activities over time and how to incorporate it into usual routine, increasing gradually the physical activity until the proposed exercise target is met. Encouraging to accumulate a minimum of 2.5 hours/week of moderate aerobic activity, which can be multiple bouts each lasting ≥10 minutes spready over the week, preferably most days of the week (Piepoli et al., 2014), (Balady et al., 2007). Educate about the benefits of physical activity on physical, social and psychological health, as well as, sedentary lifestyle as risk factor. Advice how to cope with adverse effects such as shortness of breath (Ambrosetti et al., 2021).

EXERCISE TRAINING

Should be prescribed by the cardiologist after careful clinical evaluation, including risk stratification, behaviour characteristics, personal goals and exercise preferences; the exercise prescription should be individualized, following the FITT principles (detailed in topic 1.9.1) and supervised by an exercise specialist (physiotherapist, exercise physiologist). (Piepoli et al., 2014), (Balady et al., 2007). Guidelines and best practice standards for physical activity and exercise prescription shall be used (Kitowski, 1978).

DIET/NUTRITIONAL COUNSELLING

Assess the nutritional status and habits, maintaining a balance between intake and expenditure calories, advice about healthy food choices focusing on the reduction of sodium-containing, trans unsaturated fatty acids fat. Sugar-sweetened soft drinks and alcoholic beverages should be discouraged (Piepoli et al., 2014), (Balady et al., 2007). Educating about adhering to dietary behavioural changes is essential to reduce cardiovascular risk (Cowie et al., 2019), (Kitowski, 1978).

WEIGHT CONTROL MANAGEMENT

Measure weight, height, waist circumference and body mass index. Weight control is very important in those who are already diabetic or have other major risk factors. Outcomes should be adjusted according to weight goals (Piepoli et al., 2014), (Balady et al., 2007). In obese (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 25 kg/m^2) patients, is recommended to reduce 5-10% of body weight (Ambrosetti et al., 2021) in 6 months and abdominal circumference <80 cm in women and <94 cm in men (Piepoli et al., 2014).

LIPID AND BLOOD PRESSURE CONTROL AND MANAGEMENT

For those with abnormal levels, have a comprehensive history to determine what is affecting the lipid levels, whether diet, drug, and/or other conditions. Elaborate an individualized strategy to achieve the therapeutic goals on LDL cholesterol (<55 mg/dL) and systolic blood pressure; expected an LDL cholesterol reduction of ≥ 50% from baseline in very high-risk patients. Blood pressure should be measured frequently at rest. When hypertension on effort is suspect, the blood pressure should be monitored during exercise. The blood pressure goals is to lower to <140/90 mmHg (Piepoli et al., 2014), (Ambrosetti et al., 2021).

VOCATIONAL SUPPORT

Discuss with the patient and their partners and return to prior activities must be promoted. Identify and overcome barriers when returning to work (Piepoli et al., 2014).

PSYCHOSOCIAL MANAGEMENT

Every patient should be assessed for psychological, psychosocial, sexual health and wellbeing (Kitowski, 1978). Interview and/or other standardised measurement tools to assess mental health is recommended. Provide and support self-help strategies and ways of obtaining effective social support. Include family members and partners during the sessions (Piepoli et al., 2014), (Ambrosetti et al., 2021), (Balady et al., 2007). Furthermore, patients with mental disorders need attention to adherence a drug treatment and lifestyle changes (Visseren et al., 2021).

SMOKING CESSATION

History of tobacco use, frequency and quantity should be assessed (Kitowski, 1978). Current smokers should be encouraged professionally to stop smoking all forms of tobacco permanently. A structured approach should be used, for example the 5As: Ask, Advise, Assess, Assist, Arrange. Also, motivational messages containing the “5 Rs”: Relevance, Risks, Rewards, Roadblocks, and Repetition to reinforce the importance of smoking cessation (Piepoli et al., 2014), (Ambrosetti et al., 2021), (Balady et al., 2007).

The benefits of CR in people with CAD are well known, including achievement of blood pressure and lipid goals, improvement in cardiorespiratory fitness and quality of life, moreover a reduction on cardiovascular mortality and hospitalisation (Fletcher et al., 2018), (Cowie et al., 2019). Despite the known benefits of CR, it is vastly underutilized with an estimated rate of participation of only 20-30%, varying according to country (Bruning & Sturek, 2016), (Thomas et al., 2007). In Portugal, only 8% of patients after acute myocardial infarction start a CR programme phase II, according to Direção Geral da Saúde (Silveira & Abreu, 2016). Such underutilization may be attributed to low referral rates by health care providers, centre distance, financial resources and delivery format. In addition, there is a large discrepancy in the utilization for woman and older patients (de Araújo Pio et al., 2019), (Lolley & Forman, 2021), supporting the study’s findings that women are significantly less likely to be referred than men (Colella et al., 2015).

Acknowledging the importance of early intervention, patients eligible to start the CR programme should be screened and referred either during the hospital stay and after hospital discharge within one to three weeks (Piepoli et al., 2014). Priority patients to attend CR programmes are acute coronary syndrome, chronic coronary syndromes, after coronary revascularization (CABG, PCI), and chronic heart failure (HF). Other groups known to benefit are stable angina, peripheral arterial disease, post-cerebrovascular event, post-implantation of cardiac defibrillators and resynchronisation devices, post-heart valve repair/replacement, post-heart transplantation and ventricular assist devices, congenital heart disease, diabetes mellitus and metabolic syndrome (Cowie et al., 2019), (Piepoli et al., 2016), (Wilhelm et al., 2022), (Piepoli et al., 2014).

2.1 Screening of patients / Eligible criteria

The cardiac risk stratification, assessed by the cardiologist, evaluates clinical and functional status of the patient before starting a CR programme. It is an indispensable tool to ensure safety during physical exercise and guide through the process of the exercise according to risk levels (da Silva et al., 2014). Furthermore, the stratification risk supports the rehabilitations providers to anticipate the occurrence of major complications and level of monitoring needed during the exercise session (Ribeiro et al., 2021).

To address this, the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) recommends that all patients undergo risk-stratification at the begging of the CR programme (Bhat et al., 2021). This tool classifies individuals in to low, moderate and high-risk for participating in exercises after a myocardial infarction. It is considered as high risk those individuals with functional capacity <5 METs and Ejection Fraction <40%. Table 4, describes the definitions of each class. Nevertheless, this guidance is based primarily on the findings of a maximal exercise test, in its absence the classification may be inappropriate for the patient (da Silva et al., 2014).

Table 3. AACVPR criteria for risk stratification in patients with low, moderate and high risk of events during the year.

LOW RISK
Absence of complex ventricular dysrhythmia during exercise testing and recovery
Absence of angina or other significant symptoms (e.g., unusual shortness of breath, light-headedness, or dizziness heart rate and systolic blood pressure with increasing workloads and recovery)
Presence of normal hemodynamic during exercise testing and recovery (i.e., appropriate increases and decreases in heart rate and systolic blood pressure with increasing workloads and recovery)
Functional capacity ≥ 7 METs
<u>Nonexercise testing findings</u>
EF ≥ 50% at rest
Uncomplicated MI or revascularization procedure
Absence of complicated ventricular arrhythmias at rest
Absence of CHF
Absence of signs or symptoms of post-event or post-procedure ischemia
Absence of clinical depression
MODERATE RISK
Presence of angina or other significant symptoms (e.g., unusual shortness of breath, light headedness, or dizziness occurring only at high levels of exertion [< 2 mm from baseline)
Function capacity < 5 METs
<u>Nonexercise testing findings</u>
EF = 40% to 49% at rest
HIGH RISK
Presence of complex ventricular arrhythmias during exercise testing or recovery
Presence of angina or other significant symptoms (e.g., unusual shortness of breath, light-headedness, or dizziness at low levels of exertion [≥ 5 METs] or during recovery)
High level of silent ischemia (ST-segment depression ≥ 2 mm from baseline) during exercise testing or recovery
Presence of abnormal hemodynamic with exercise testing (i.e., chronotropic incompetence or flat or decreasing systolic BP with increasing workloads) or recovery (i.e., severe post exercise hypotension)
<u>Nonexercise testing findings</u>
EF < 40% at rest
History of cardiac arrest or sudden death

Complex dysrhythmias at rest
Complicated MI or revascularization procedure
Presence of CHF
Presence of signs or symptoms of post event or post procedure ischemia
Presence of clinical depression

Abbreviations: BP: Blood Pressure; CHF: Congestive Heart Failure; EF: Ejection Fraction; METs: Metabolic Equivalent; MI: Myocardial Infarction
Adapted from: Da Silva et al., (2014). Cardiac risk stratification in cardiac rehabilitation programs: a review of protocols. Rev Bras Cir Cardiovasc;29(2):255-65.

The weber classification, is another grading system, based on measurement of peak VO_2 and anaerobic threshold from cardiopulmonary exercise test. This classification is used to classify functional capacity of patients with cardiac conditions, including candidates for cardiac rehabilitation. Also, the weber classification may be useful in monitoring the progress of CR (Soumagne, 2012).

Table 4. Weber classification for grading cardiac function.

Weber class	Peak oxygen uptake	Anaerobic threshold
	(Peak VO_2) (ml/kg/min)	(ml/kg/min)
A	> 20	> 14
B	16 to 20	11 to 14
C	10 to 15	8 to 11
D	< 10	< 8

Adapted from Soumagne, 2012. Soumagne, D. (2012). Weber classification in cardiac rehabilitation. Acta Cardiologica, 67(3), 285-290.

All coronary risk factors must be identified and individually targeted for the properly pharmacological and non-pharmacological interventions.

During the exercise training, low-risk patients can be monitored only with heart rate monitor, while moderate – and high risk patients need telemetry or continuous monitoring, at least during the first eight weeks of CR programmes (Abreu et al., 2018).

Although, the benefits of structured CR programme clearly outweigh the risks, a careful risk stratification and prophylactic strategies, such as, value of warm-up and cool down, educations of warnings signs and symptoms, may help reduce uncommon exercise training-related cardiovascular disease events (Kachur et al., 2017).

2.2 Phases and delivery-mode of the Cardiovascular Rehabilitation Programmes

Cardiovascular rehabilitation (CR) programmes are based on long-established models, according to local and patients' preferences, which may be ambulatory/centre-based (outpatient), residential (in-patient) or home-based settings (Piepoli et al., 2010), (Abreu et al., 2021), (Wilhelm et al., 2022).

Centre-based are the model most provided, the safety and effectiveness are well established in reducing hospital readmissions, secondary events and mortality (Thomas et al., 2019). The in-patients settings are particularly suitable for high-risk patients to promote stable clinical conditions and a rapid functional recovery (Piepoli et al., 2010b), (Ambrosetti et al., 2021).

Home-based programmes can be equally effective as centre based and tele-interventions can be efficacious in both the medium and long term, encouraging large scale deployment of innovative models of care delivery (Piepoli et al., 2016). Despite to a flexible method, many patients and providers are less comfortable with remote-based options, especially due to concerns about safety, lack of provider contact, and lack of social interaction with other patients (Lolley & Forman, 2021). A reasonable alternative to deliver the CR is a hybrid model, where combine centre-based and home-based and it has shown to beneficial improving functional capacity (Heindl et al., 2022), (Thomas et al., 2019).

The CR may be differentiated in three phases (Abreu et al., 2018), (Abreu et al., 2021), (Piepoli et al., 2014), (Thomas et al., 2007):

PHASE I

Provided during the hospital stay, beginning 24-48 hours after acute cardiovascular event be stabilized. It includes early mobilization, prevention of complications secondary to immobilization, advise on health behaviour change and lifestyle risk factor management, especially encouraging to participate in the following CR phases. Exercise testing is not indicated in this phase.

PHASE II

Supervised ambulatory outpatient programme, should be started as soon as possible after an acute event, preferably within two weeks of discharge to six months after the event and for at least 12 weeks or 24 sessions. It can be performed in the hospital facilities, in a specialized CR centre or home-based. Exercise testing is essential for stratifying cardiovascular risk and prescription of the intensity of aerobic exercise. Formal programmes highlighting adoption of healthy behaviours and development of self-management skills are considered fundamental on this phase. Phase II CR training should offer different activities, adapted to the population needs and preferences.

PHASE III

Considered long-term out-patient CR which seeks to provide sustained delivery of preventive and rehabilitative services in the out-patient setting and/or in the community and should last for the rest of patient`s life. To maintain patient`s awareness of the behaviour aspects, control of cardiovascular disease factors and adherence to pharmacological therapy is crucial on this phase. Also, to ensure annual clinical and functional assessments, laboratory tests and echocardiogram when necessary.

In some cases, when the patient is not hospitalized but is considered high risk for cardiovascular event, it is possible to enter directly to phase II, which may be out-patient, in-patient or home-based, according to the health system (Abreu et al., 2021).

It is recommended to start the CR as earlier as possible, up to 6 weeks after discharge from hospital since a delay in starting may prolong recovery, increase dependence on family/carers, and cause frustration, furthermore, contribute to poor health, especially in the older adult population where after a sedentary period they show a rapidly lose muscle and bone mass, increasing the risk of falls (Ennis et al., 2022).

To guarantee minimal and optimal CR standards, structure- and process-based measures provide quality of care to patients with CVD in the respective centres (Thomas et al., 2007), (Abreu et al., 2021).

Structure-based measures quantify both infrastructural and human resources that are needed to satisfy high-quality standards of care for CR services. A specific space and equipment for functional capacity assessments and medical evaluation and prescription are necessary, moreover, facilities for exercise training, well ventilated, good temperature and humidity conditions. The multidisciplinary team may have professional certification and specific competence on CR (Thomas et al., 2007), (Abreu et al., 2021).

Process-based measures certify whether all the patients in CR programme undergo to standardized assessment of their cardiovascular risk factors before entry to the CR programme and whether core components cover all relevant dimensions of CR care (Thomas et al., 2007), (Abreu et al., 2021).

3. Exercise-based cardiovascular rehabilitation

In a cardiac rehabilitation programme, a structured exercise training is a cornerstone to improve exercise capacity and prognosis in cardiovascular disease. Exercise-based cardiac rehabilitation programmes are typically delivered in a supervised hospital/centre-based setting and some cases in home-based setting (Anderson et al., 2016). Combined training including aerobic and resistance training are considered as the core elements to prescribe exercise in cardiac rehabilitation programmes (Yamamoto et al., 2016).

Exercise and physical activity have different concepts and characteristics. Physical activity (PA) is defined as any bodily movement produced by the skeletal muscle that results in energy expenditure, whereas, exercise is a subcategory of PA, structured, planned, repetitive, in order to improve or maintaining one or more components of physical fitness (Pelliccia et al., 2021), (Vanhees et al., 2012).

Physical fitness (PF) is a set of attributes that people have or achieve. The components of PF are expressed in five components related to health status: (1) cardiorespiratory endurance, (2) muscular endurance and strength, (3) body composition, (4) agility, balance, coordination, speed of movement, (5) substrate oxidation characteristics (Pelliccia et al., 2021), (Caspersen et al., 1985)

The benefits of regular exercise are well established, including blood pressure control, improvements of the blood lipid profile and insulin sensitivity. Exercise also improves cardiorespiratory fitness (CRF), promotes self-confidence, and may be considered as anti-depressant (Sharma et al., 2015). To obtain the exercise benefits the main guidelines recommend that adults and older adults with chronic conditions (aged 18 years and older) should engage in regular physical activity of at least 150 to 300 minutes of moderate-intensity aerobic PA or at least 75 to150 minutes of vigorous-intensity aerobic PA throughout the week. For additional health benefits perform muscle-strengthening on at least twice a week (WHO, 2020). Furthermore, achieve an energy expenditure of ≥ 500 to 1.000 MET per minute a week equal to 1000-2000 kcal per week is considered a target volume for exercise for most adults (ACSM, 2017).

Fundamentally, the exercise prescription should be based on cardiovascular risk profile, medication intake and observations during exercise testing to guaranty individualization, greater clinical benefits with optimal medical safety and adherence to exercise (Hansen et al., 2018).

Studies have shown that physical inactivity is an independent risk factor for cardiovascular disease (Kamiya et al., 2015), demonstrating the cardioprotective mechanism of regular PA at moderate intensity to reduce the risk of coronary events (Leon et al., 2005). This protective effect may be attributed to improvements in BP, plasma lipoprotein profile, insulin sensitivity, and mood (Chen et al., 2022), (Bruning & Sturek, 2016). Additionally, decrease blood coagulation, improve fibrinolytic capacity and help in vascular remodelling which may reduce the risk of ischemic cardiac events (Buttar et al., 2005). In figure 5, is summarized the cardioprotective benefits of PA in CAD patients.

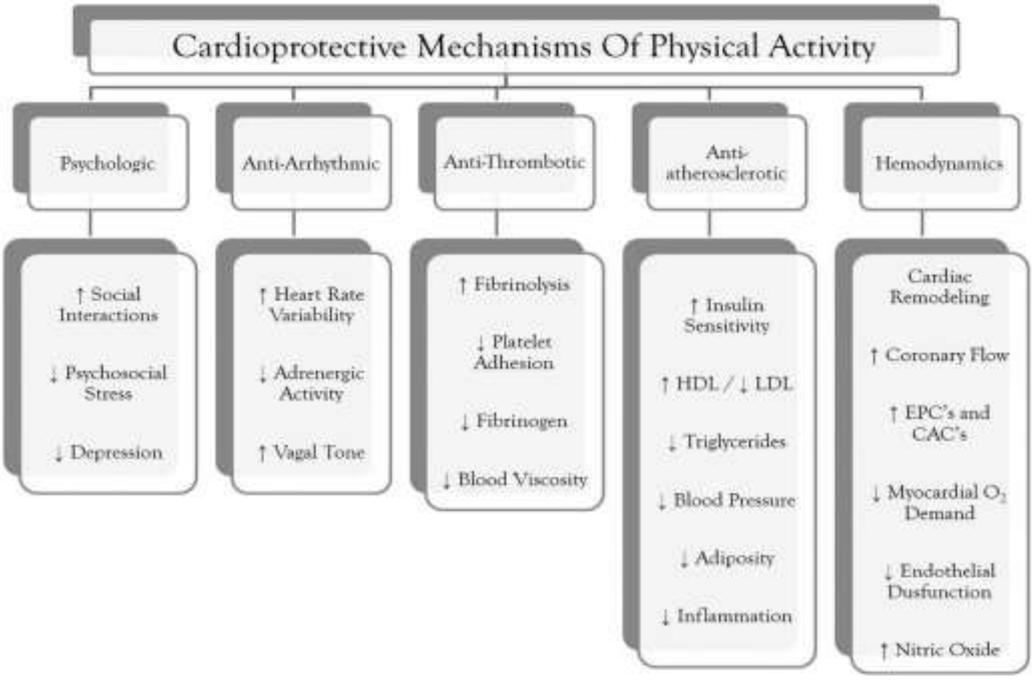

Figure 5. Mechanisms of moderate-to-vigorous exercise training on the CVD risk profile.
Abbreviations: BP: blood pressure; CVD: cardiovascular disease; CACs: cultured/circulating angiogenic cells; EPCs: endothelial progenitor cells; ↑: increased; ↓: decreased; O2: oxygen. *Nitric oxide also has antithrombotic effects.
Reprinted from Kachur et al (2017). Impact of cardiac rehabilitation and exercise training programs in coronary heart disease. Progress in cardiovascular diseases, 60(1), 103-114; with permission from Elsevier.

A study led by Chen et al., showed a direct association between physical activity and the carotid artery health, endorsing that higher level of PA is important in the prevention of vascular aging, even in population with high risk of cardiovascular disease. Additionally, increases in physical activity levels over time have been associated with reduced CAD and cardiovascular mortality risk (Lavie et al., 2015).

Cardiovascular adaptations occur during exercise, which improve cardiac output (heart rate x stroke volume) to the working muscles. The more muscle mass used during exercise, the greater the benefits for CAD patients. As exercise intensity increases, more the sympathetic nervous system will be activated, resulting in higher heart rate, greater contractility, and reducing the diastolic filling time, which increases myocardial demand while balancing with myocardial oxygen supply (figure 6). However, this response can be influenced by age and age-related neural factors, and in some cases, like in CAD patients, it can be influenced by drugs such as beta-blockers (Fletcher et al., 2013a), (Bruning & Sturek, 2016). Hence, the effect of exercise training decrease myocardial oxygen demands during moderate-to-vigorous PA, moreover, increase parasympathetic (vagal) tone, where it raises ischemic threshold, resulting in a reduction in angina symptoms and decreasing risk of sudden cardiac death (Leon et al., 2005).

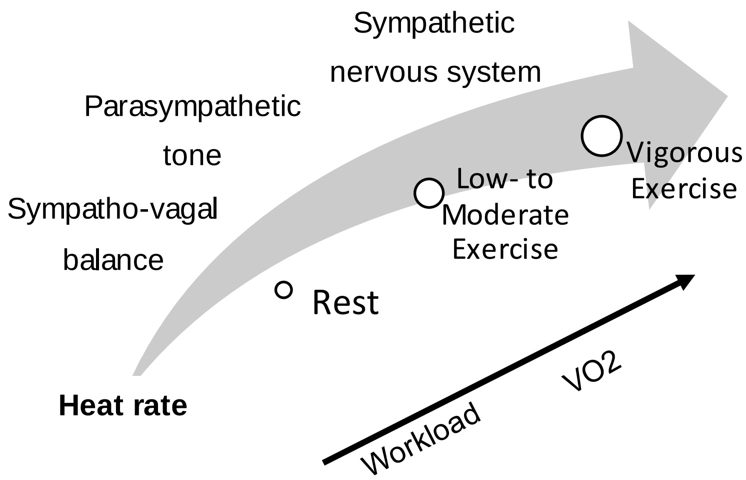

Figure 6. Heart rate response according to exercise intensity.
An increase in heart rate is attributed to a decrease in vagal tone, followed by an increase in sympathetic outflow. As exercise intensity increases, the heart rate increases linearly with workload and VO_2.
Abbreviation: VO_2: oxygen consumption.

Additionally, repetitive bouts of exercise reduce arterial stiffness due to the protection against systemic oxidative stress and inflammation induced by chronic aerobic exercise training, also increase nitric oxide production and its bioavailability enhancing endothelium-dependent vasodilation (Lavie et al., 2015). Nitric oxide it is an important vasodilator and vasoprotector capable to protect the vessel from injury and fatty lesion formation (Bruning & Sturek, 2016).

Therefore, systolic BP rises according to aerobic exercise increases, as a result of increasing cardiac output and following exercise systolic blood pressure usually declines. Diastolic BP remains the same or moderately drop due of vasodilatation of the muscle vasculature (Fletcher et al., 2013a), (Liu et al., 2012). In pre-hypertensive people, resting systolic and diastolic BP are likely to decrease after acute and chronic exercise (Liu et al., 2012) independent of exercise intensity (MacDonald, 2002).

Exercise training, as part of CR programme, improves significantly CRF (VO_{2peak}) by 5-10% according to guidelines in patients enrolled in a CR programme (Abreu et al., 2021). In fact, improvements in VO_{2peak} is associated to a decrease in mortality and morbidity and increase patient's quality of life, therefore is an endpoint for success in CR programme (Mikkelsen et al., 2020). Furthermore, the higher the level of CRF, the less an individual is likely to suffer premature cardiovascular death (Vanhees et al., 2012).

3.1 Exercise Prescription - FITT Principles

The principle of exercise prescription is designed to meet individual health and physical fitness goals within the context of individual health status, function and social environment. The optimal dose to prescribe exercise address CRF, muscular strength and endurance, flexibility, coordination, speed of movement, body composition and neuromotor fitness (American College of Sports Medicine, 2017), (Pelliccia et al., 2021). In CAD patients, the design of the exercise programme includes specification of the Frequency (F), Intensity (I), Time or duration (T), Type or mode (T), Volume (V), and Progression (P) of exercise to be performed (Table 5) (Pelliccia et al., 2021), (Ascenzi et al., 2022), (American College of Sports Medicine, 2017).

During the exercise training, measures of heart rate, blood pressure, and perceived exertion are commonly recommended (Williams et al., 2007).

Table 5. FITT-VP principle components.

Frequency	expressed as the number of times an individual engages in exercise per week
Intensity	the amount of energy expenditure/time unit during training sessions and is usually expressed in kcal/min or metabolic equivalents (METs)
Time	the duration of training sessions and the entire programme
Type of Exercise	aerobic exercise, strength or resistance training, coordination and balance, flexibility
Volume of Exercise	is the product of frequency, intensity and time of exercise
Progression	may consist of increasing any of the components of the FITT principle as tolerated by the patient

Exercise training sessions should include (Franklin et al., 2022), (American College of Sports Medicine, 2017).

- Warm-up phase (5-10 min) – is a transitional phase from rest to endurance training, where the purpose is to increase blood flow to the skeletal muscles, adjusting the body to demand of the training. This preliminary phase improves range of motion and may reduce the risk of injury and cardiovascular complications in order to facilitate coronary vasodilatation. Calisthenic exercise followed by activities that increase the heart rate, namely moderate to high intensity should be performed.
- Conditioning or exercise training (30-60 min) – should follow the warm-up phase and includes aerobic, resistance, flexibility, and neuromotor exercise.
- Cool-down phase (5-10 min) – this phase allows the gradual recovery of heart rate and blood pressure and removal of metabolic end products from the muscles, also reduce the possible post exercise hypotension. Slow walking or low-intensity exercise should include in this phase.

3.1.2 Aerobic exercise training

Aerobic exercise is the most studied and recommended modality for CAD patients, with a beneficial dose-response effect on prognosis (Piepoli et al., 2016). Aerobic exercise consists of movements of large muscle mass in a rhythmic manner which can be sustained for a period (Piepoli et al., 2016), resulting in substantial increases in heart rate and energy expenditure.

The aerobic exercise training should be prescribed according to the principle of specificity, which means that physiological adaptations to exercise are specific to the type of exercise performed (ACSM, 2017). Examples of aerobic exercise includes running, cycling, cross-country skiing, rowing or swimming (Pelliccia et al., 2021).

EXERCISE FREQUENCY

Aerobic exercise is recommended at least 5 days a week on moderate intensity, or at least 3 days a week on vigorous intensity, or a weekly combination of 3-5 days a week on moderate and vigorous exercise intensity to achieve and maintain health benefits (American College of Sports Medicine, 2017)

EXERCISE INTENSITY

The exercise intensity is the key in aerobic exercise training. The intensity of exercise may be prescribed using direct methods, first and second ventilatory threshold (VT), or indirect methods, such as, indices of peak effort, namely percentages (%) of VO_{2peak}, % of peak workload (W_{peak}), % of peak HR (HR_{peak}), and % of HR reserve (HRR), also describe as relative methods (Mezzani et al., 2013).

Direct methods are preferably used, since is based on physiological principles (first and second VT) assessed by cardiorespiratory exercise test (CPET). Where, first VT demarcates the upper limit of intensity that can be sustained aerobically, while the second VT needs to be supplemented by anaerobic energy production resulting in an increase lactate production. In the absence of VTs determination, the exercise intensity based on indirect methods could be used (Ascenzi et al., 2022), (Mezzani et al., 2013).

Peak values are also obtained by a cardiorespiratory exercise test (CPET) where is defined as the highest average value reached of the last 20-30 seconds of the test. However, not all CVD patients achieve a (near-) maximal effort during CPET, which makes the prescription inaccurate. In contrast to the indices of peak exercise capacity, first and second ventilatory threshold are effort-independent and can be achieved by the majority of CVD patients. When those methods are not possible to determine, rating of perceived exertion (RPE) as ‘Borg scale’ and ‘Talk test’, are used to assess the intensity of exercise (Ascenzi et al., 2022). The

RPE is a subjective scale based on physical sensations a person experience during the physical activity. The RPE is commonly evaluate using Borg scale and Talk test. The Borg scale is a quantifiable exercise intensity from 6 to 20, that corresponds to levels of physical exertion while 'Talk test' is based on difficulty in speak quite easily during the exercise despite increased ventilation. Moreover, the Borg scale can also be termed to as category-ratio scale (CR10 Borg scale) which utilizes a numerical range from 0 to 10 and it shows to be more intuitive for comprehension by the patient than the 6–20 scale (Mezzani et al., 2013).

Table 6 and table 7, shows exercise intensity prescription according to ACSM and ESC guidelines, respectively.

Table 6. Exercise intensity prescription according to ACSM classification.

Intensity	%HRR or VO_2R	$\%VO_2$ peak	%HR peak	RPE Borg Scale
Very light	< 20	< 20	< 35	< 10
Light	20 – 30	25 – 44	35 – 54	10 – 11
Moderate	40 – 59	45 – 59	55 – 69	12 – 13
Heavy	60 – 84	50 – 84	70 – 89	14 – 16
Very heavy	≥ 85	≥ 85	≥ 90	17 – 19
Maximal	100	100	100	20

Abbreviations: ACSM: American College of Sports Medicine; HR: heart rate; HRR: heart rate reserve; VO_2R: VO_2 reserve; RPE: rating of perceived exertion.
Adapted from Mezzani et al. (2013). Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. European journal of preventive cardiology, 20(3), 442-467.

Table 7. Exercise intensity prescription according to ESC guidelines.

Intensity	%HRR	$\%VO_2max$	%HR max	RPE Borg Scale
Low to Light	< 40	< 40	< 55	10 – 11
Moderate	40 – 69	40 – 69	55 – 74	12 – 13
High	70 – 85	70 – 85	75 – 90	14 – 16
Very High	> 85	> 85	> 90	17 – 19

Abbreviations: ESC: European Society of Cardiology; HR_{max}: maximum heart rate; HRR: heart rate reserve; RPE: rate of perceived exertion; VO_{2max}: maximum oxygen consumption.
Adapted from Pelliccia et al, (2021). 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease: The Task Force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC). European heart journal, 42(1), 17-96.

Additionally, very light exercise intensity is below the first ventilatory threshold, light and moderate exercise intensity is above the first ventilatory threshold but not reaching the second threshold zone, high exercise intensity is close to the second ventilatory threshold zone, and very intense exercise intensity is above the second ventilatory threshold (Figure 7) (Pelliccia et al., 2021), (Binder et al., 2008).

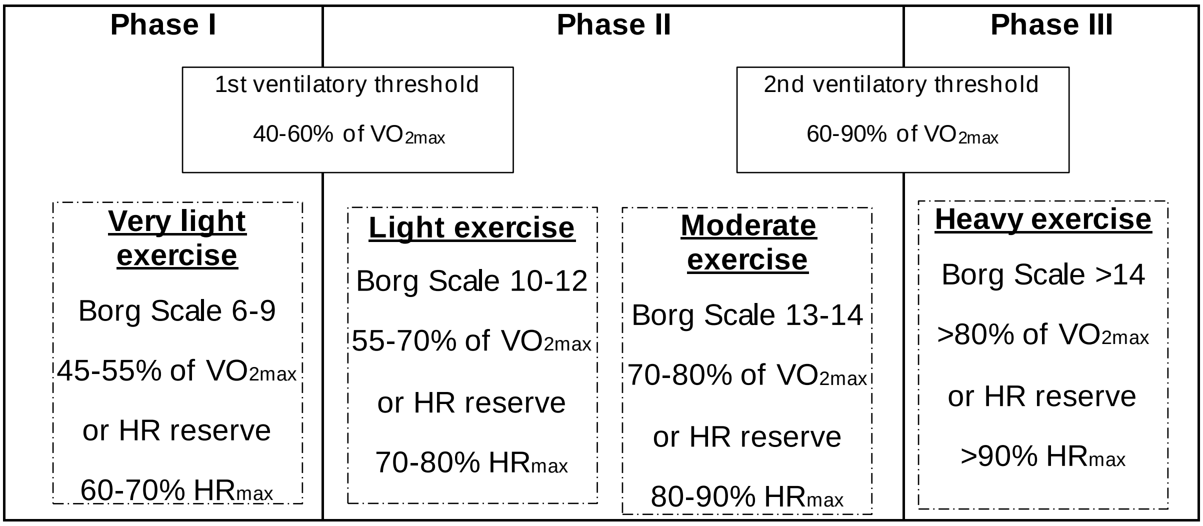

Figure 7. Relationship between ventilatory threshold and indirect exercise intensity methods.
Abbreviations: BL: blood lactate; HR: heart rate; VO_2: oxygen consumption; VO_2R: VO_2R reserve.
Adapted from: Binder, R. K., Wonisch, M., Corra, U., Cohen-Solal, A., Vanhees, L., Saner, H., & Schmid, J. P. (2008). Methodological approach to the first and second lactate threshold in incremental cardiopulmonary exercise testing. European Journal of Preventive Cardiology, 15(6), 726-734.

The intensity of exercise is prescribed according to the goals of the patient and health status. Although, to enhance cardiorespiratory fitness, is recommended to exercise in an intensity above the first ventilatory threshold, likewise the target intensity for both primary and secondary CVD prevention is usually close to the second threshold (Vanhees et al., 2012)

TIME OF EXERCISE (DURATION)

The duration of exercise is dependent on the chosen exercise intensity, that is, the higher the exercise intensity, the shorter the exercise duration. It is recommended to accumulate 30-60 minutes a day (≥150 min a week) or bouts of 10 minutes of moderate exercise intensity to achieve 30 minutes daily, 20-60 minutes a day (≥75 min a week) of vigorous exercise intensity. For weight management, longer duration of aerobic exercise (≥60-90 min a day) may be needed (American College of Sports Medicine, 2017), (Franklin et al., 2022).

EXERCISE TYPE

Aerobic exercise can either be continuous or interval based. Continuous training is performed continually for a period of time without stopping. Interval training involves short bouts of exercise in high to severe- or severe to extreme-intensity, interspersed by brief periods of active (lower-intensity intervals) or passive recovery during a single session, Figure 6, namely

High-intensity interval training (HIIT). The aerobic interval training can be used both in healthy individuals and cardiac patients (Mezzani et al., 2013). However, interval training, can be increased in total volume and/or intensity depending on goals and physical fitness levels (Pelliccia, et al., 2021), (American College of Sports Medicine, 2017).

EXERCISE PROGRESSION

Approach to progression of exercise should be gradual, adjusting duration, frequency and/or intensity until the desired goal (Hansen et al., 2022), that is, only one component of FITT-P principle at a time (American College of Sports Medicine, 2017). ACSM guidelines suggests increase the duration of aerobic exercise by 1-5 min per session until the achievement of the goal and the intensity about 5%-10% per week are generally well tolerated (American College of Sports Medicine, 2017). Moreover, the progression should respect biological adaptation of the individual which may be influenced by age, genetics, physical fitness and, environmental factors (Pelliccia et al., 2021).

EXERCISE VOLUME

Defined commonly as the total amount of energy expended during exercise training over per week. Metabolic equivalents (METs) per minute and Kilocalories (kcal) are methods to quantify the volume of the exercise. According to ACSM guidelines (American College of Sports Medicine, 2017) a total energy expenditure of ≥ 500 to 1.000 MET per minute per week is associated with lower rates of CVD and premature mortality, likewise is a volume target for an exercise training programme (Squires et al., 2018). Furthermore, a higher total exercise volume provides beneficial changes in adipose tissue mass, blood HDL cholesterol levels, and indicators for glycaemic control (Hansen et al., 2022). One MET is equivalent to an oxygen uptake (VO_2) of 3.5ml/kg at rest (Vanhees et al., 2012). To meet the kcal necessary to provide an energy expenditure in aerobic exercises is need a volume arranged in 1000 to 1500 kcal per week of moderate intensity exercise (Squires et al., 2018), (Hansen et al., 2022).

Additionally, kcal and METs are used to classify physical activity as inactive < 200 kcal/week (or < 1 MET), lightly active as 200–599 kcal/ week (or 1–3 METs), moderate activity as 600–1499 kcal/week (or 3–6 METs), and vigorous activities as > 1500 kcal/week (or >6 METs) (Vanhees et al., 2012).

3.1.2 Resistance training

Resistance training provides an effective method to increase muscle strength and endurance (Franklin et al., 2022) given that muscles weakness is a strong predictor of premature death in CVD patients (Hansen et al., 2022). Higher levels of muscular strength results in a better performance for the activities of daily life, improves physical functioning and quality of life and reduce risk of falls mainly in older adults (Grgic et al., 2020). Specifically, resistance training is any exercise that provoke muscle contraction against an external resistance, aiming to increase skeletal muscle strength, tone, mass or endurance (Hansen et al., 2019). Additionally, resistance training favourably affects bone health, glycaemic control, blood pressure, and lipid profile, at least in the elderly and patients with elevated CVD risk (Hansen et al., 2022). A systematic review with patients with heart failure with preserve ejection fraction (HFpEF), shows great effects adding resistance exercise on VO_{2peak} due to its effect on type I muscle fibres and conclude if the training goals is to improve peak VO_2 and workload (Cavero-Redondo et al., 2023).

EXERCISE INTENSITY

Commonly expressed as a percentage of one repetition maximum (%1 RM), that is, the maximal amount of weight a person can lift in one repetition. The 1RM should be performed for each target muscle group. For those patients in which a 1RM test is not suitable, a 10RM may be used to assessed muscular strength (Hansen et al., 2022). Initial trainings should be performed at 30% to 40% of 1RM for the upper body and 50% to 60% of 1RM for lower body (Williams et al., 2007). Additionally, OMNI-RES is a scale that can also be used to track the perceived intensity during the resistance training (Hansen et al., 2022). Current literature has shown that dynamic strength training at higher intensities is more effective than lower training intensity to increase muscle strength and mass in CVD patients. It is explained because the time duration of high training intensity is shorter, thus, less cardiovascular demand is needed (Table 10) (Hansen, 2019).

Table 8. Resistance training zones.

1RM	Exercise training zones
< 20%	Aerobic endurance training
> 20%	Training effects regarding muscular capillaries compression during muscle contraction
30 – 50%	Muscular endurance training - **Moderate training intensity** with 15 – 30 repetitions
50 – 70%	Strengths gains – **Higher training intensity** with 8-15 repetitions

Abbreviation: 1RM – one repetition maximum.
Adapted from: Pelliccia, A., Sharma, S., Gati, S., Bäck, M., Börjesson, M., Caselli, S., ... & Wilhelm, M. (2021). 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease: the Task Force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC). European heart journal, 42(1), 17-96.

EXERCISE PROGRESSION

As the individual progress, the exercise training increase, including increases on weight and repetitions per set or number of sets per exercise. In CR programme, first, it is recommended start increasing the number of repetitions or sets, then intensity can be gradually increased, and at last adaptations in rest period (i.e. alter rest periods, keeping volume and intensity unchanged) (Hansen et al., 2022), (Squires et al., 2018). In order to reduce the relative effort and breath holding during resistance training, the level of weight should be reduced and the number of repetitions increased (Williams et al., 2007), (Pelliccia et al., 2021).

Nevertheless, the increase in intensity is possible when the patient is medically safe (no orthopaedic symptoms, cardiac arrhythmias, or episodes of syncope or dizziness) and the patient is able to perform the exercise with the correct technique (Hansen et al., 2022).

EXERCISE VOLUME AND FREQUENCY

Resistance training, is recommended to perform 2-3 times per week, on non-consecutive days, one to three sets of 8-15 repetitions of each muscle group and a variety of 8-10 resistance exercises should be prescribed. Longer rest intervals, in patients with CVD, might be necessary to restore energy sources and recover from fatigue (Fidalgo et al., 2019). Guidelines recommend 3-5 minutes rest intervals (Pelliccia et al., 2021). Resistance training volume can be increased in 2%-10% when the patients is comfortably to complete one to two repetitions over the target repetitions on two successive days and be maintained each muscle group as little as 1 day a week as long as the training intensity is held constantly (American College of Sports Medicine, 2017).

EXERCISE TYPE (MODE)

Resistance training can either be isometric or dynamic. Isometric (static) exercise results in no movement of the limb, although at moderate to high loads, induce Valsalva manoeuvre, and may lead to an unnecessary fluctuation of blood pressure. Dynamic exercise includes a constant or variable resistance through the range of motion and is classified as concentric (shortening of the muscle fiber) or eccentric (lengthening of the muscle fibers). Dynamic exercise may be performed using free weights or weight machine (Pelliccia et al., 2021), (Vanhees et al., 2012).

Recommendations for the initial prescription of resistance training according to AHA Scientific Statements (Williams et al., 2007) and ACSM (American College of Sports Medicine, 2017).

- All individual should perform resistance training using correct technique.

- Rhythmical manner at a moderate to slow controlled speed through the full range of motion.
- Avoid breathholding and straining (Valsalva maneuver) by exhaling during the contraction or exertion phase of the lift and inhaling during the relaxation phase.
- Alternating between upper- and lower-body work to allow for adequate rest between exercises.
- Patients with recent coronary artery bypass surgery should avoid traditional upper-body resistance training exercises, that is, lifting weights 50% of maximum voluntary contraction, for up to 8 to 12 weeks to allow for proper healing of the sternum.

Exercise prescription should be adjusted for patients treated with cardioprotective medications. Patients under beta-blocker drug, may have an attenuated HR response to exercise and an increased or decreased maximal exercise capacity. Diuretic drugs, may elevate the risk for volume depletion, hypokalaemia, or orthostatic hypotension after exercise and for these patients, the blood pressure response to exercise should be monitored. Lower-lipid drugs, especially statins, may lead to myopathy which is characterized by muscle cramps and lowered tolerance to exercise training. Antidiabetic drugs, such as sulfonylurea, meglitinide and exogenous insulin administration may increase the for hypoglycaemia requiring an adjustment in exogenous insulin dose and carbohydrate intake during exercise training (American College of Sports Medicine, 2017), (Hansen et al., 2018).

Overall, it is well established that combined aerobic and dynamic strength training in CAD patients is significantly effective to improve the cardiorespiratory and functional capacity (Hansen, 2019).

4. Cardiorespiratory fitness assessment

Cardiorespiratory fitness (CRF) is directly related to the integrated function of respiratory, cardiovascular, and musculoskeletal systems, and it is thus considered a reflection of total body health (R. Ross et al., 2016). As such, the assessment of CRF is an important part of CR programmes, in order to individualized exercise training prescription, understanding the ability of an individual to perform activities of daily living for prolonged periods of time (American College of Sports Medicine, 2017), (Arena et al., 2007). CRF can be either measured directly or estimated.

Measurement of CRF in clinical settings is performed by maximal and submaximal exercise test. The choice of which test to perform depends on the patient`s ability and willingness to provide a maximal exertion, the purpose of the exercise test and, trained of personnel (American College of Sports Medicine, 2017).

Maximal exercise tests are preferred measures to assess functional capacity, where a progressive increasing workload is required up to limiting fatigue and/or exhaustion. Conventional maximal exercise testing estimated CRF and is typically obtained from achieved treadmill speed, grade and duration or the cycle ergometer workload (watts). Estimated CRF can be obtained by prediction equations converted by the highest workload attained to exercise time. For additional data, or to assess directly CRF, a ventilatory expired gas analysis combined to conventional exercise testing procedures is required. Direct measures are expressed as maximal oxygen consumption (VO_2max) and implies an individual's true physiologic limit reached such a plateau, while estimated implies the peak work achieved during a progressive exercise test, in which a plateau is not frequently observed. Peak VO_2 is more commonly reached in CVD patients (R. Ross et al., 2016), (American College of Sports Medicine, 2017). However, both direct measured and estimates CRF strongly predict health outcomes (R. Ross et al., 2016).

Submaximal test is simple, safe and closely approximates the capacity to perform activities of daily living and thus can be repeated regularly. Submaximal exercise tests can be performed on cycle ergometer, treadmills, steps, and field tests. Basically, equation to estimate CRF can be determined by the HR response to one or more submaximal work rates (R. Ross et al., 2016), (American College of Sports Medicine, 2017).

Both maximal and submaximal tests are commonly used to prescribed exercise intensity training, stratify morbidity and mortality risk in CVD patients (Guazzi et al., 2009).

5. Maximal exercise test

Exercise testing has been widely used in clinical settings in order to identify exercise impairment and/or limitation, to stratify risk for an adverse event, moreover is the standard tool to assess patients at high risk for myocardial ischemia (Guazzi et al., 2012). During the exercise test, the patient is continuously monitored while performing incremental or constant work rate exercise using standardized exercise protocol on a treadmill or cycle ergometer. It is important to guarantee the safety, considering contraindications (Table 9), endpoint indicators (Table 10), while medications, staff and facility emergency are prepared (American College of Sports Medicine, 2017).

The main categories for exercise testing indications involve diagnosis, prognosis and evaluation of the physiologic response to exercise. The diagnosis indication and contraindication are listed in Table 9. Additional indication for exercise testing, include assessment of pulmonary disease, exercise intolerance and unexplained dyspnea and preoperative risk evaluation. The utility to predict prognosis involve the inverse relationship between CRF and the risk of mortality, as discussed in chapter 4, also, the chronotropic response during and after an exercise test. In patients with known CVD, is an effective guide for returning to work after cardiac event and to exercise prescription (American College of Sports Medicine, 2017).

The purpose of the test is to assess physiological responses to increasing or sustained metabolic demand until the patient reaches a sign or symptom-limited in a maximal level of exertion (American College of Sports Medicine, 2017). This provoke response elicit cardiovascular or pulmonary abnormalities not present at rest (Fletcher et al., 2013).

Table 9. Indication and Contraindication to Exercise Training.

Indication	Contraindication
• Acute coronary syndrome • Chronic coronary syndromes, after coronary revascularization (CABG, PCI) • Chronic heart failure • Stable angina • Peripheral arterial disease • Post-cerebrovascular event • Post-implantation of cardiac defibrillators and resynchronisation devices • Post-heart valve repair/replacement • Post-heart transplantation and ventricular assist devices, • Congenital heart disease • Diabetes mellitus and metabolic syndrome	• Unstable angina • Severe or symptomatic aortic stenosis • Decompensated heart failure • Acute cardiac mural thrombus • Acute deep venous thrombus • Pulmonary embolism

Abbreviations: CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention.

The test consists of the continuous monitoring of an ECG with frequent recording 12-lead tracing, assessing heart rate and ECG changes, blood pressure and perceived exertion; clinical signs and symptoms are also assessed. Nevertheless, to a precise measurement of CRF, expired gas analysis through open circuit spirometry, namely cardiopulmonary exercise test (CPET), is a gold standard test (American College of Sports Medicine, 2017), (Fletcher et al., 2013).

Prior to each exercise test, all systems should be calibrated, including airflow, volumes and both the O_2 and CO_2 analysers, additionally temperature, barometric pressure, and humidity should be taken into account as ambient conditions may affect the concentration of O_2 in the inspired air (Balady et al., 2010).

Maximal exercise test typically is performed on a motorized treadmill or stationary cycle ergometer. In Europe, cycle ergometer is more commonly used, while in the USA treadmill is preferred used mode. Advantages about cycle ergometer mode include imbalance and orthopaedic limitations of patients, and an easier measure of blood pressure and recorded ECG, whereas treadmill has a greater familiarity with upright locomotion. The most disadvantages regarding cycle ergometer are because requires patient´s cooperation to maintain pedal speed at the desired level and could lead early test termination due of quadriceps muscles fatigue, on the other hand exercise capacity may be overestimated on a treadmill when the patient use the handrail. Nevertheless, it is noted difference of VO_{2max} ranging of 5% to 20% lower on cycle ergometer than on the treadmill (Balady et al., 2010), (Fletcher et al., 2013), (American College of Sports Medicine, 2017).

Exercise testing protocols include an initial warm-up, followed by the selected protocol and a recovery period. When performed on treadmill and cycle ergomter the workload is calibrated in percent grade (%GR) and watts (W), respectively. Exercise stage-to-stage test protocols commonly used are Bruce and Modified Bruce, Naughton and Balke protocols. These protocols provide workload increase between stages, which may not be well tolerate in some cardiovascular patients. Ramp protocols are preferred since they increase progressively at fixed intervals. Regardless the protocol chosen, the duration of the test should be tailored to the patient to yield a fatigue-limited exercise ranging between 8 and 12 minutes (Balady et al., 2010), (Fletcher et al., 2013), (American College of Sports Medicine, 2017).

Determining whether the test is maximal or near-maximal effort, the parameter achievements are often attributes to (Mezzani et al., 2013):

- Failure of VO_2 and/or HR to increase with further increases in WR;
- Peak respiratory exchange ratio (VCO_2/VO_2) ≥1.10;
- Post-exercise blood lactate concentration ≥ 8 mmol/L;
- RPE ≥ 18 in the Borg scale;
- Patient appearing exhausted.

Additionally, decision to terminate exercise testing and attention to recognise signs and symptoms are a crucial factor, as patients are verbally encouraged before and during the test to give a maximal effort (Fletcher et al., 2013).

Table 10. Absolute indications for terminating an exercise test (AHA/ACC/ACSM).

▪ ST elevation (>1.0 mm) in leads without pre-existing Q waves because of prior MI (other than aVR, Avl, or V_1)
▪ Drop in systolic BP of >10 mmHg, despite an increase in work load, when accompanied by other evidence of ischemia
▪ Onset of angina or angina-like symptoms
▪ Shortness of breath, wheezing, leg cramps, or claudication
▪ Signs of poor perfusion: cyanosis or pallor
▪ Failure of HR increase with increased exercise intensity
▪ Sustained ventricular tachycardia or other arrhythmia
▪ Technical difficulties monitoring the ECG or systolic BP
▪ The patient´s request to stop
Adapted from: American College of Sports Medicine, 2017 Abbreviations: AHA: American Heart Association; ACC: American College of Cardiology; ACSM: American College of Sports Medicine; ECG: electrocardiogram; HR: heart rate; MI: myocardial infarction.

Despite requiring a maximal patient's effort, the test is generally safe when performed by an appropriately trained clinicians (American College of Sports Medicine, 2017).

5.1 Cardiopulmonary exercise test (CPET)

The CPET involves the analysis of gas exchange at rest, during exercise, and during recovery and yield breath-by-breath measures of oxygen uptake (VO_2), carbon dioxide output (VCO_2), and ventilation (VE) which provides a comprehensive understanding about transport and use of O_2 during physical exercise (Ascenzi et al., 2022), (Balady et al., 2010).

Standards measures are obtained from CPET, including VO_{2max} or VO_{2peak}, ventilatory threshold, peak respiratory exchange ratio (RER), ventilatory efficiency (VE), ventilatory equivalents for oxygen (VE/VO_2) and for carbon dioxide (VE/VCO_2), end-tidal CO_2 partial pressure ($P_{ET}CO_2$), oxygen pulse (O_2 pulse) (Fletcher et al., 2013). The most used analysis scheme to interpret CPET, features nine different graphs to improve the efficacy and reliability of the interpretation process. A three-by-three set of specifically arranged graphical panels known as a "nine-panel plot", is a major method of representing metabolic changes at rest and during exercise (Dumitrescu & Rosenkranz, 2017).

Oxygen consumption (VO_2) is the amount of volume of O_2 extracted from the air inhaled during a pulmonary ventilation in a period of time and is defined by Fick principle: VO_2 is the product of the cardiac output (HR x SV) and arterial-venous oxygen difference ($C(a–v)O_2$), where HR is heart rate and SV is stroke value (Balady et al., 2010). VO_{2peak} is a variable describing the highest value achieved at presumed maximal effort during an incremental CPET (Mezzani, 2017). VO_{2peak} is considered abnormal when below 85% of the predict value (Herdy et al., 2016).

Ventilatory thresholds (VT) are related to alterations in energy metabolism during exercise and from a physiological perspective is differentiated in three phases:

Phase I, is observed a linear increase in VO_2, VCO_2, and VE where energy production is almost exclusively by aerobic metabolism, defined as first VT (Ascenzi et al., 2022). The first VT can be identified by (1) analysing the slope of VCO_2/VO_2 (V-slope method), where the first VT is the point of transition of the slope from < 1 to > 1 and occurs at approximately 40-60% of $VO2_{max}$ (Mezzani et al., 2009), (2) the nadir of the first increase in VE/VO_2, without a simultaneous increase in VE/VCO_2 and, (3) the nadir of $PETO_2$, while $PETCO_2$ remains constant or is increasing (Ascenzi et al., 2022);

Phase II, as exercise intensity increase above the first VT, an excess of CO_2 is produced by anaerobic metabolism, which makes the CO_2 production (VCO_2) versus VO_2 relationship become steeper. An increase in VE occurs to eliminate the excess of CO_2 and the second VT is attained (Ascenzi et al., 2022), (Mezzani, 2017); The second VT can be identified by (1) the inflexion of VE vs WR, (2) The nadir of VE/VCO_2 increase, (3) The inflexion of VE over VCO_2 and, (4) The Zenit and deflection point of $P_{ET}CO_2$ (Ascenzi et al., 2022).

Phase III, there is an increase in the production of lactate which can no longer be broken down, this point is reached in high-intensity exercise (>2VT) (Ascenzi et al., 2022).

Respiratory exchange ratio (RER) corresponds to the ratio between VCO_2 and VO_2, where a RER ≥ 1.10 is generally considered an excellent patient effort, and is exclusively obtained from ventilatory expired gas analysis (Balady et al., 2010).

Slope of the VE/VCO_2 describes the patient's ventilatory efficiency, where VE is modulated by the metabolic production and VCO_2 by anaerobic production and during exercise the relationship between these variables are strongly linked. A VE/VCO_2 relationship <30 is considered normal without modification for age and sex (Balady et al., 2010).

End-tidal CO_2 partial pressure ($P_{ET}CO_2$) reflects ventilation-perfusion within pulmonary system. Oxygen pulse (O_2 pulse) reflects the amount of oxygen consumed per heartbeat. Cardiac output is a powerful index of cardiac systolic function and it is represented by the triple product of CO x $C(a–v)O_2$ x systolic blood pressure, where CO is cardiac output and $C(A\text{-}V)O_2$ is the arteriovenous O_2 content difference (Mezzani, 2017).

The percentage of HR_{peak} is indirectly determined through regression equations or tables of its range and also, correspond indirectly to the $\%VO_{2peak}$. Additionally, the percentage of HR reserve (%HRR), defined as the difference between the HR at peak and HR at rest, is also recommended to prescribe exercise intensity (Ascenzi et al., 2022).

To determine exercise intensity from CPET, guidelines have been proposed the use of percentages of VO_{2peak}, HR_{peak}, and VTs, which, more precisely correspond to levels of intensity allowing an individual exercise prescription (Table 6 and 7) (Ascenzi et al., 2022), (Pelliccia et al., 2021).

6. Submaximal tests / Functional assessments Field Tests

Submaximal exercise tests can be applied in either clinical or fitness settings. It consists of walking or running in a predetermined distance or time. The advantages of field tests are that they easy to administer, require minimal equipment and can be self-administered. CRF can be estimated by HR measurements, obtained preferably by telemetry HR monitors with chest electrodes to be more accurate and reliable and, by the Borg Rating of Perceived Exertion Scale (R. Ross et al., 2016), (American College of Sports Medicine, 2017). The most field test performed are:

- 200 m fast walk test - is a fixed-distance walking test where the patient must to cover a distance of 200 m as quickly as possible, without running on a flat 50 m indoor walking track, encouragement being given at mid-distance (Casillas et al., 2017).
- The shuttle-walking test - is an incremental exercise test where the patient walks between 2 ground markers set 9 m apart and has to pass each marker in time with a sound pulse from an audiotape. The speed increases every minute until exhaustion (Casillas et al., 2017). This teste, is frequently used in United Kingdom (Enright, 2003).
- Two-minute step test – is determine by the number of steps performed, at own pace, in place within two minutes (Wegrzynowska-Teodorczyk et al., 2016).

In clinical settings, the 6-minute walk test is commonly test used to estimate CRF from the total distance covered, in deconditioned patients, as well as, in CR programmes (R. Ross et al., 2016) .

6.1 The 6-minute walk test

The 6-minute walk test (6MWT) is a simple, practical and well-tolerated test to perform since the walking pattern is a natural daily activity (American Thoracic Society [ATS], 2002). The 6MWT is the shorter version of 12-minute walk test that was first described by Mcgavin et al., 1976. The use of the 6MWT introduced by Butland et al., 1982 has advatages of being less stressuful and suitable for severly limited patients and it was the first walking test validated to assess functional status in cardiac patients (Guyatt et al., 1985).

The 6MWT has been widely used to evaluate functional status mainly in patients with reduced CRF levels and some clinical conditions including, advanced heart failure, left ventricular systolic dysfunction, coronary artery disease, and pulmonary disease, such as end-stage lung disease, cystic fibrosis and primary pulmonary hypertension (American College of Sports Medicine, 2017), (Mandic et al., 2013). In addition, the test is a useful predictor of morbidity and mortality in HF population where a totally distance covered <300 meters is considered a poor prognosis endpoint (Forman et al., 2012). Furthermore, the test provides information regarding the response to medical intervention before and after treatment and also guide CR (Giannitsi et al., 2019).

The 6MWT is performed in a long, flat, straight corridor during 6 minutes. The preferred walking course is 30 meters in length. During the test, standardized phrases for encouragement is used according to the American Thoracic Society Guidelines for the 6MWT (American Thoracic Society [ATS], 2002). The test aims to evaluate the global and integrated responses to a submaximal exercise on the cardiovascular, pulmonary and muscular systems (American Thoracic Society [ATS], 2002). Despite to be considered a safe test, unstable angina is an absolute contraindication. Resting HR > 120, systolic BP > 180 mmHg and diastolic BP > 100 mmHg are relative contraindications. Whether, during the test the patient presents any of these symptoms, chest pain, intolerable dyspnoea, leg cramps, staggering, diaphoresis, and pale or ashen appearance, the test should be stopped immediately (American Thoracic Society [ATS], 2002).

There has been growing attention to an effective and low-cost test for prescribing exercise intensity in CAD patients (Saba et al., 2021). Variables from the 6MWT provide both objective and subjective measurements. Objective data, including heart rate, blood pressure, speed and distance and, subjective data as rating of perceived exertion (Gremeaux et al., 2011). Given the submaximal effort achieved during the test, cardiorespiratory requirements correspond to the first ventilatory threshold in CAD patients (Gayda et al., 2004).

The HR obtained during the 6MWT is may be used to target exercise training, such as, the cover distance measured during the test can be used to estimate VO_{2max} through equations (American College of Sports Medicine, 2017). These equations have demonstrated a good correlation with anthropometric characteristics, cardiac and lung variables, especially in patients with lower maximal functional capacity (Ribeiro-Samora et al., 2017).

Gayda et al., 2004, showed a good reproducibility in the 6MWT for VO_{2peak}, VE_{peak}, and HR during exercise in elderly CAD patients with LVEF <35% using a portable gas analyser. Moreover, the walking speed determined from the 6MWT distance and may be used for exercise prescription. A walking speed at 80% of average speed reached during the 6MWT correspond to a moderate to vigorous exercise intensity in moderate chronic obstructive pulmonary disease (COPD) patients (Zainuldin et al., 2015). In patients with pulmonary disease, the distance covered is highly reproducible (r = 0.86 to 0.95) and correlates moderately well with peak VO_2 (r = 0.52 to 0.71), (Arena et al., 2007).

Furthermore, the use of 6MWT to determine patient's initial training load in walking training and its increases, is appropriate since many patients do not undergo baseline CPET to set exercise intensity (Dolecinska et al., 2021).

The guidelines (R. Ross et al., 2016) have emphasized the accuracy for exercise intensity prescription and individualization, likewise, exercise individualization and tailoring of training intensity. Most of studies are conducted in very early stages of CR programme, namely phase II and is well recognized the health benefits for those patients. However, these benefits may be extended to prolonged CR programmes, namely phase III. Where it remains highlighted the importance of developing suitable tools to assess and re-assess exercise intensity (Hansen et al., 2022)

III. METHODS

Study Design

This was a cross-sectional study included CAD patients who entered in a phase III CR programme at the Cardiovascular Rehabilitation Centre of the University of Lisbon (CRECUL) between March 2017 and July 2022. All data was collected at baseline, which was the time point that each patient started the phase III CR programme.

Ethical and Legal Issues

The study was carried out in accordance with the recommendations of the Declaration of Helsinki for Human Studies (World Medical Association, 2013) and was approved by the Faculty of Human Kinetics, University of Lisbon Ethics Council (approval number: 30/2017).

Participants

From March 2017 to July 2022, a total of 178 participants were screened for participation of the study through CRECUL database (Figure 8), where, according to our purpose, 105 participants were eligible to the study as they fitted in our inclusion criteria: diagnose of CAD with an established history of myocardial infarction, coronary revascularization (CABG or PCI) or angina pectoris, aged over 18 years old, male or female, recruited to start a phase III CR programme at CRECUL; clinically stable, performed a CPET with a RER $\geq$ 1.1 and the 6MWT before entering the programme.

Participants were excluded from the study if they had: acute and chronic pulmonary disease, unstable angina, cardiac arrhythmias, chronic heart failure; patients with other exercise limitations such as physical, arteriopathy, neurologic or orthopaedic impairments.

A power analysis for a correlation test between two variables (Pearson correlation coefficient), using a statistical software G*Power 3.1, indicated that the minimum sample size to yield a statistical power of at least 0.8 with an alpha of 0.5 and a minimum size ($r = 0.452$) was 26 patients.

The study was conducted at CRECUL, located in the University Stadium of Lisbon, clinically supervised by the Faculty of Medicine from the University of Lisbon.

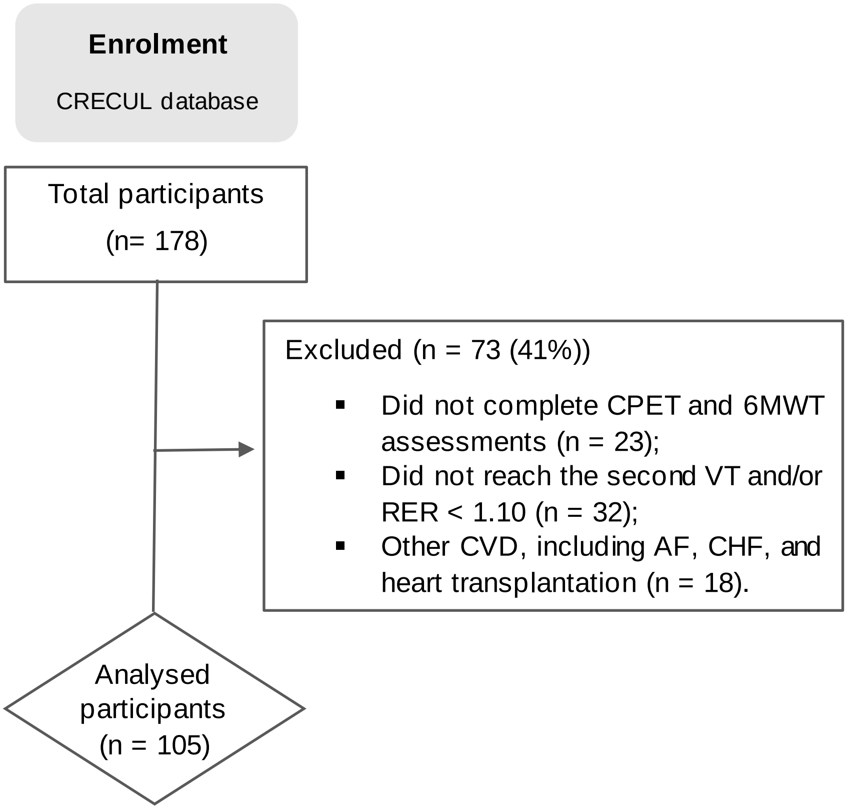

Figure 8. Study Flowchart.
Abbreviations: 6MWT: six-minute walk test; AF: atrial fibrillation; CPET: cardiopulmonary exercise test;CHF: chronic heart failure; CVD: cardiovascular disease; RER: respiratory exchange ratio; VT: ventilatory threshold.

Measurements

Before starting a phase III CR programme, all patients were assessed at baseline. To assess maximal and submaximal functional capacity the patients performed a CPET and the 6MWT, respectively in non-consecutive days at the Faculty of Medicine - University of Lisbon. Body mass index (BMI) was measured (kg/m^2) based on height and weight and physical activity was assessed by an objective measure (accelerometer).

CARDIOPULMONARY EXERCISE TEST (CPET)

A CPET was performed in a cycle ergometer (CardioWise Ergo Fit, Pirmasens, Germany) and a breath-by-breath gas analyser was used (Ergostik, Geratherm Respiratory GmbH, Bad Kissingen, Germany), following the Clinician's Guide to CPET in Adults (Balady et al., 2010). The protocol that was used was a ramp protocol with a work rate resistance of 10 to 25 W/minute on a constant pedal frequency (60 rpm) to reach approximately 8 to 12 minutes effort. Each patient was encouraged to exercise until exhaustion, as defined by intolerance, leg fatigue or dyspnoea unless clinical criteria for test termination occurred (Fletcher et al., 2013). Twelve-lead ECG was continuously monitored (Mortara X-Scribe ECG instrument Inc., Milwaukee, WI, USA) and BP measurements was recorded at baseline, every two minutes, at peak exercise and during recovery.

Determination of VO_{2peak} was considered the highest attained $\dot{V}O_2$ during the final 20-30 seconds of exercise; the first VT was estimated using the following three most common methods: (1) by the V-slope method, (2) increase in VE/VO_2 and, (3) rise in end-tidal oxygen pressure ($P_{ET}O_2$) (Balady et al., 2010); and the second VT was defined as the point at VE increase in excess of VCO_2 (VE/VCO_2) versus WR relationship (Mezzani et al., 2013). All patients achieved a respiratory exchange ratio of >1.1, an indicator of maximal effort in the CPET. All CPET were performed by the same technician and cardiologist.

The prediction equation for VO_{2peak} was according to Hansen et al., 1984, based on age and measured weight. The age-predicted maximal HR was derived from the Fox equation HR_{max} = 220-age (Fox et al., 1971). HRR was calculated by the difference between HR_{peak} and resting HR, and were expressed to a percentage of the first and second VT.

THE 6-MINUTE WALK TEST (6MWT)

The 6MWT was performed indoor, along a flat, straight, enclosed 15-m corridor with a hard surface. Patients were instructed to walk as far as possible for 6 minutes with rest stops if needed. Patients were verbally encouraged and were advised of time remaining every minute during the test according to the Guidelines for the 6MWT of the American Thoracic Society (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002).

Before the test, the patient's resting HR and BP were assessed by using an automatic sphygmomanometer (OMRON HBP-1300, Tokyo, Japan). During the test, the patients were continuously monitored with a chest strap HR band (Polar H10, Electro, Kempele, Finland), the distance walked was recorded and the rate of perceived exertion (RPE) was asked in every minute using the modified Borg scale (from 0-10) according to the participants' own perceived effort. After completion the 6MWT, HR, BP and RPE were measured at the first and third minutes of the recovery period.

The HR_{peak} of the 6MWT was defined as the maximum HR reached during the test. It was also determined the average of the 3rd, 4th, 5th and 6th minute to obtain the $HR_{peakaverage}$. The predicted equation used to estimate VO_{2peak} at the 6MWT was VO_{2peak} = 0.03 x distance (in meters) + 3.98 (Ross et al., 2010).

BODY MASS INDEX

Body mass index (BMI) was calculated (kg/m2), based on height, measured to the nearest 0.5 cm with a stadiometer (SECA, Hamburg, Germany) and body weight, measured on a weight scale (SECA, Hamburg, Germany). The BMI was assessed at the same as the CPET.

OBJECTIVE MEASURED PHYSICAL ACTIVITY

All patients wore an accelerometer ActiGraph GT3X+ (AG; ActiGraph, Pensacola, FL, USA) during seven days. The ActiGraph GT3X+ was attached to an elastic waist belt and placed in line with the axillary line of the right iliac crest. Participants were instructed to wear the accelerometer continuously from waking up until bedtime, with exceptions for water-based activities (e.g., showering, swimming) and sleep. A valid day was defined as having at least 600 minutes (10 hours) of usage time and all participants with at least 3 valid days (including a weekend day). The devices were activated in raw mode with a sampling frequency of 100 Hz and subsequently analyzed in epochs of 10 seconds (Actilife v.6.9.1). Cut-off values and time-use validation criteria were defined according to a previous publication (Troiano et al., 2008). The cut-off values were as follows: sedentary: <100 counts.min-1; light PA: 100-2019 counts·min-1; moderate PA: 2020-5998 counts·min-1 (corresponding to 3-5.9 METs); Vigorous PA ≥ 5999 counts·min-1 (corresponding to ≥ 6 METs). All physical activity variables were converted to time (in minutes) per valid day.

Data Analysis

Data analysis was obtained from the original raw data of the Cardiovascular Rehabilitation centre of the University of Lisbon – CRECUL, and the data was organized and transformed in a dataset according to our goals and inclusion criteria.

Primary and secondary outcome variables were presented as means ± standard deviation, whereas categorical variables were reported as percentages and absolute frequencies. Normality distribution was tested graphically by histogram and confirmed by Shapiro-Wilk´s test.

Parametric test using paired-sample t test was perform to compare whether the mean values of variables differ significantly from each other to compare the means of two samples when each observation in one sample can be paired with an observation in the other sample. A paired-sample t-test assumes that the differences between the pairs should be approximately normally distributed. When this assumption is violated, the Wilcoxon signed-rank test is a viable nonparametric alternative.

Pearson´s correlation coefficient was used to evaluate the association between normal variables from HR at first and second VT at CPET and HR_{peak} in the 6MWT, where, the value of *r* near the upper limit, +1, indicates a substantial positive relationship, whereas an *r* close to the lower limit, -1, suggests a substantial negative relationship. The *r* value between 0 to 0.5 was considered weak, 0.5 to 0.8 was considered moderate and 0.8 to +1 was considered a strong correlation (Peck, Olsen, & Devore, 2008).

Bland-Altman analysis was used to evaluate the association between HR_{peak} in the 6MWT vs HR at first and second VT at CPET. Limits of agreement were calculated (mean ± SDx1.96) for each Bland-Altman assessment. We also used the plot to identify any outliers in the data and identify systematic bias. The scatterplot was drawn to show dispersion of variables using X-axis (average) and Y-axis (difference).

Statistics analysis was performed by IBM SPSS Statistics 26 (SPSS Inc, Chicago, USA). A p-value less than 0.05 was considered statistically significant.

IV. RESULTS

The demographic and clinical characteristics of the study sample are presented in table 11. A total of one hundred and five CAD patients were included and analyzed in this study with a mean age of 61 ± 9.8 years old and 88% were male. Regarding BMI classification, 58% of the patients had overweight and 23% had obesity (BMI ≥30kg/m^2). One hundred and one (96%) patients had MI and seven patients had an implantable device. 91% of patients attended a phase II outpatient CR programme before entering in the phase III CR programme. Nighty-three percent of the patients met the WHO recommendations for PA (>150min/week of MVPA), among them, 53% reached more than 300 minutes per week of MVPA. Ex-smokers were the most prevalent risk factor (66%), followed by hypertension (49%), family history (48%) and hyperlipidemia (45%). In addition, most patients were on beta-blocker (84% of total group), antiplatelet (81% of total group) and statin (93% of total group) therapy.

Table 11. CAD patients' clinical characteristics.

Characteristics	Value n=105
Sex, Male/Female	92/13
Age (yr)	61.2 ± 9.7
CABG (n, %)	19 (18)
PCI (n, %)	83 (79)
Body mass index (kg/m^2)	27.7 ± 3.5
MVPA (min/week)	352 ± 180
Cardiovascular Risk Factors	
Family history (n, %)	51 (48)
Hypertension (n, %)	52 (49)
Hyperlipidaemia (n, %)	47 (45)
Ex-smoker (n, %)	70 (66)
Diabetes mellitus (n, %)	15 (14)
Medications	
Beta-blocker (n, %)	88 (84)
ACE inhibitors (n, %)	75 (71)
Diuretic (n, %)	24 (24)
Antiplatelet (n, %)	86 (81)
Statins (n, %)	98 (93)

Values are presented as mean ± standard deviation or Absolute frequency (%) for quantitative or qualitative variables, respectively.
Abbreviations: ACE: angiotensin converting enzyme; CABG: coronary artery bypass graft; MVPA: moderate-to-vigorous physical activity; PCI: percutaneous coronary intervention; yr: year.

HR measures on the 6MWT and CPET are presented in table 12, along with other variables.

It was found differences between the HR_{peak} in the 6MWT vs HR at first VT (mean 15 ± 16 bpm, 95% CI [12.62,18.89], p <0.001) and the HR_{peak} in the 6MWT vs HR at second VT (mean -5 ± 17 bpm, 95% CI [-9.23, -2.36], p < 0.001).

The HR_{peak} in the 6MWT was lower compared to the HR_{peak} at CPET (110 ± 17 vs 128 ± 19 bpm, p < 0.001) and HR at second VT (110 ± 18 vs 116 ± 17 bpm, p = 0.001). On the other hand, the HR_{peak} in the 6MWT was higher than the HR at first VT (95 ± 14 bpm, p < 0.001), figure 9. The HR_{peak} reached on the 6MWT and the average of the 3^{rd} to 6^{th} minute of the 6MWT HR were different (mean 4.0 ± 3.6 bpm, 95% CI [3.32,4.73], p < 0.001), but with a strong correlation (r = 0.978, p < 0.001).

Table 12. Variable measured on the CPET and 6MWT.

Variables	Value
Cardiopulmonary exercise test	
VO_{2peak} (mL/kg/min)	21.5 ± 6.2
HR_{peak} (bpm)	128 ± 19
HRR (bpm)	64 ± 16
$Load_{max}$	149.7 ± 47.6
RER_{peak}	1.16 ± 0.09
VO_2 at first VT (mL/kg/min)	13.9 ± 4.0
HR at first VT (bpm)	95 ± 14
VO_2 at second VT (mL/kg/min)	19.1 ± 5.4
HR at second VT (bpm)	116 ± 17
6-minute walk test	
HR_{peak} (bpm)	110 ± 17
$HRaverage_{3-4-5-6mins}$ (bpm)	106 ± 16
HR_{rest} (bpm)	65 ± 11
Total distance (m)	562 ± 81
VO_{2max}estimated (mL/kg/min)	20.9 ± 2.4

Values are presented as mean± standard deviation.
Abbreviations: 6MWT: the 6-minute walk test; bpm: beats per minute; CPET: cardiopulmonary exercise test; HR: heart rate; HR_{peak}: maximum; HRR: heart rate reserve; HR_{rest}: HR at rest; RER: respiratory exchange ratio; VT: ventilatory threshold; VO_2: oxygen uptake.

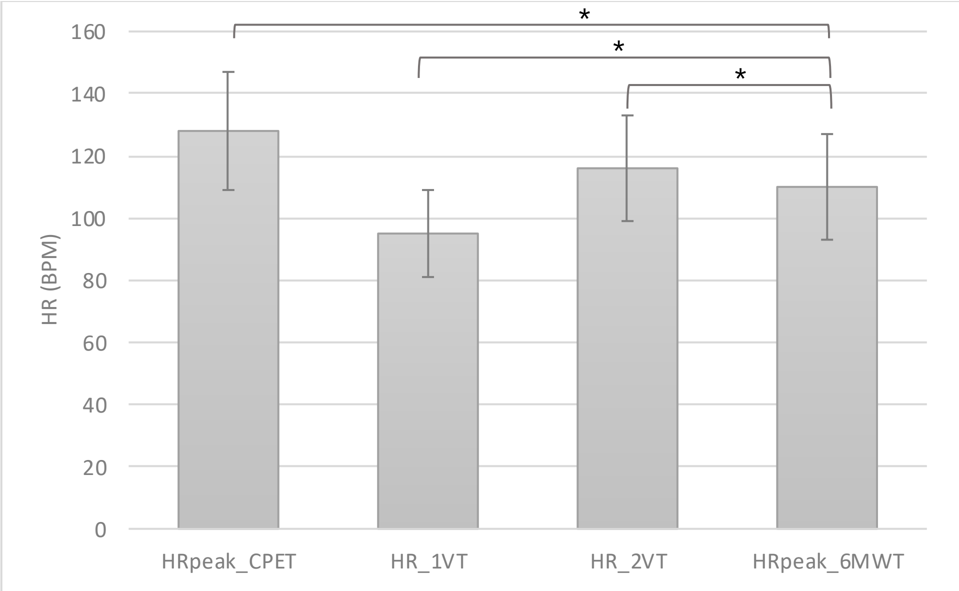

Figure 9. Heart rate measures at CPET and 6MWT.
Abbreviations: 6MWT: six-minute walk test; CPET: cardiopulmonary exercise test; HR: heart rate; VT: ventilatory threshold. **Significant at p < 0.05*

In terms of percentages, the HR_{peak} in the 6MWT corresponded to 86% of the HR_{peak} at CPET. The first VT was observed at 74.0 ± 7.0% of the HR_{peak} at CPET and the second VT was detected at 90.6 ± 4.3% HR_{peak} at CPET. Both HR_{peak} and $HRaverage_{3-4-5-6mins}$ on the 6MWT assessment were different ($p < 0.001$). Measured HRR (64 ± 16 bpm) determined from CPET, was reached at 48% of the first VT and 81% of the second VT.

As it is possible to observe in Figure 9, HR_{peak} in the 6MWT was statistically significant different in all CPET HR measurements (peak, first and second VT).

Regarding VO_2 values, the patients reached 79% of the VO_2 predicted according to age and weight (Hansen et al., 1984). The lower value was 29% and the upper value was 143%. Peak VO_2 measured at CPET was reached at 65% on the first VT and 84% on the second VT. The VO_2 estimated from the 6MWT corresponded to 97% of VO_{2peak} at CPET. It was not found differences among VO_{2peak} at CPET vs VO_2 estimated in the 6MWT (0.65 ± 5.46, $p = 0.225$). When performing Pearson´s r correlation, it was found a positive and weak correlation among VO_{2peak} at CPET vs VO_2 estimated in the 6MWT ($r = 0.488$, $p < 0.001$). Moreover, no differences were found among VO_{2peak} and VO_2 predicted at CPET (-5.77 ± 6.2, $p < 0.001$). Additionally, a weak correlation among VO_{2peak} and VO_2 predicted at CPET ($r = 0.407$, $p < 0.001$) was found.

The CPET was considered a maximal effort test due the respiratory exchange ratio was higher than 1.10 (1.15 ± 0.09).

When performing the Pearson´s *r* correlation, it was found a positive, weak and significative correlation between HR_{peak} at CPET and HR_{peak} in the 6MWT (r = 0.452, p <0.001). Equally to the VTs, where a positive, moderate and significative correlation between HR_{peak} in the 6MWT and HR at first VT (r = 0.504, p < 0.001) and a positive, weak and significative correlation between HR_{peak} in the 6MWT and HR at second VT (r = 0.482, p < 0.001) were found.

A simple linear regression was calculated, and the result was displayed using a scatterplot where, visually, the relationship between the first (figure 10) and second VT (figure 11) at CPET vs HR_{peak} show some linear pattern.

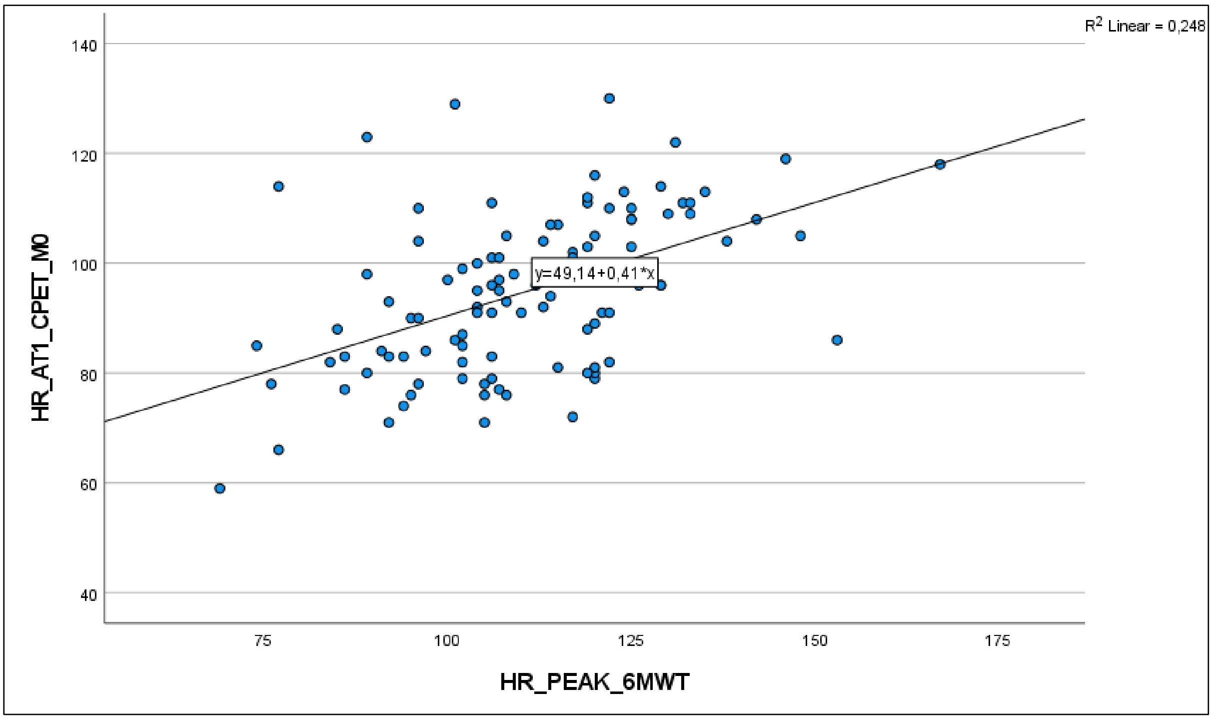

Figure 10. Scatterplot illustrating the relationship between HR at first VT (y axis) and HR_{peak} at 6MWT (x axis).
Abbreviations: 6MWT: the 6-minute walk test; HR: heart rate; VT: ventilatory threshold.

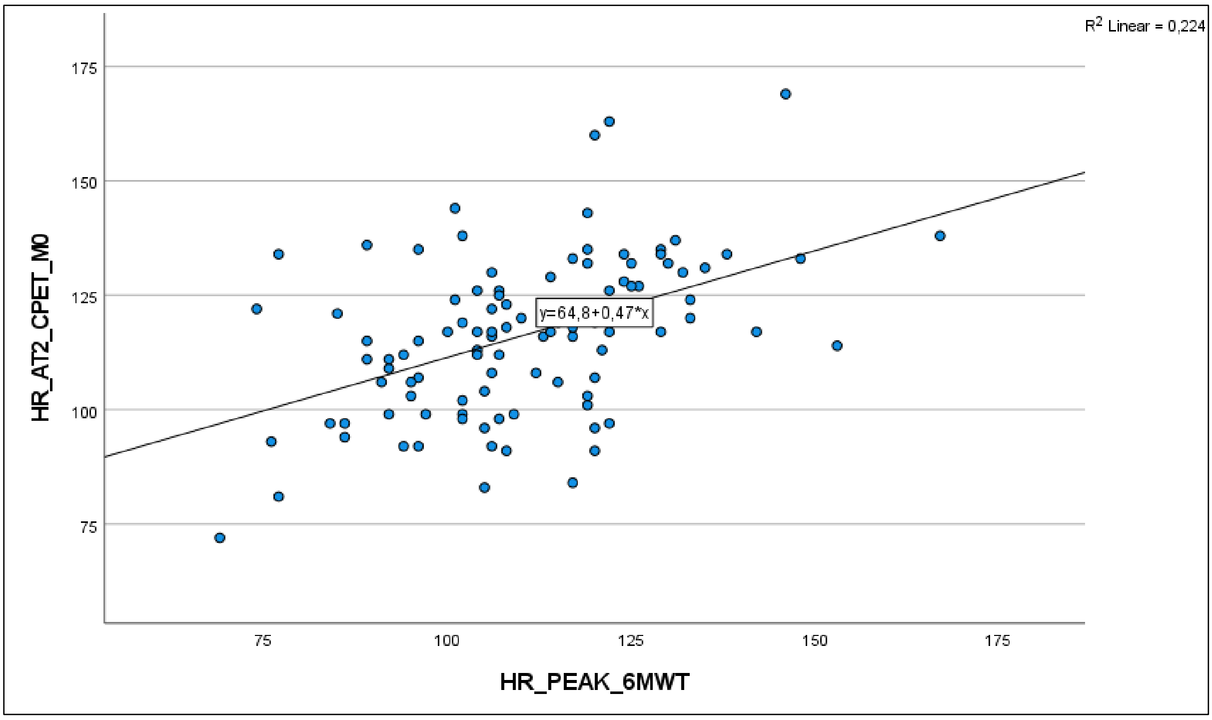

Figure 11. Scatterplot illustrating the relationship between HR at second VT (y axis) and HR_{peak} at 6MWT (x axis).
Abbreviations: 6MWT: the 6-minute walk test; HR: heart rate; VT: ventilatory threshold.

Additionally, when performing the correlation test of $HRaverege_{3\text{-}4\text{-}5\text{-}6}$ 6MWT vs HR at first and second VT, a moderate and significant correlation were found (r = 0.526 and r = 0.516, respectively and the same $p < 0.001$).

To understand if there was an agreement between HR_{peak} in the 6MWT vs HR at VTs, we performed Bland-Altman analysis. According to Bland-Altman analysis, a lack of agreement between the HR_{peak} in the 6MWT vs HR at first and second VT (p <0.001 and p = 0.001, respectively) was found. The mean differences (bias) between HR_{peak} in the 6MWT vs HR at first and second VT were -15.7 ± 16.1 bpm and 5.8 ± 17.7 bpm, respectively. However, the HR at second VT was closer to zero; but both measurements presented very large limits of agreement as shown in Figures 12 and 13.

Bland-Altman showed that the average of the differences between HR_{peak} in the 6MWT vs HR at first and second VT was -15.7 ± 16.1 bpm and 5.8 ± 17.7 bpm, respectively. There was a low and significative agreement between HR_{peak} in the 6MWT vs HR at first VT ($r^2 = 0.182$, p <0.001) (figure 10) and between HR_{peak} in the 6MWT vs HR at second VT ($r^2 = 0.029$, p = 0.001) (figure 11). Moreover, no proportion bias was found for HR_{peak} in the 6MWT vs HR at second VT (p = 0.77) whereas, a proportion bias was found between HR_{peak} in the 6MWT vs HR at first VT (p = 0.006).

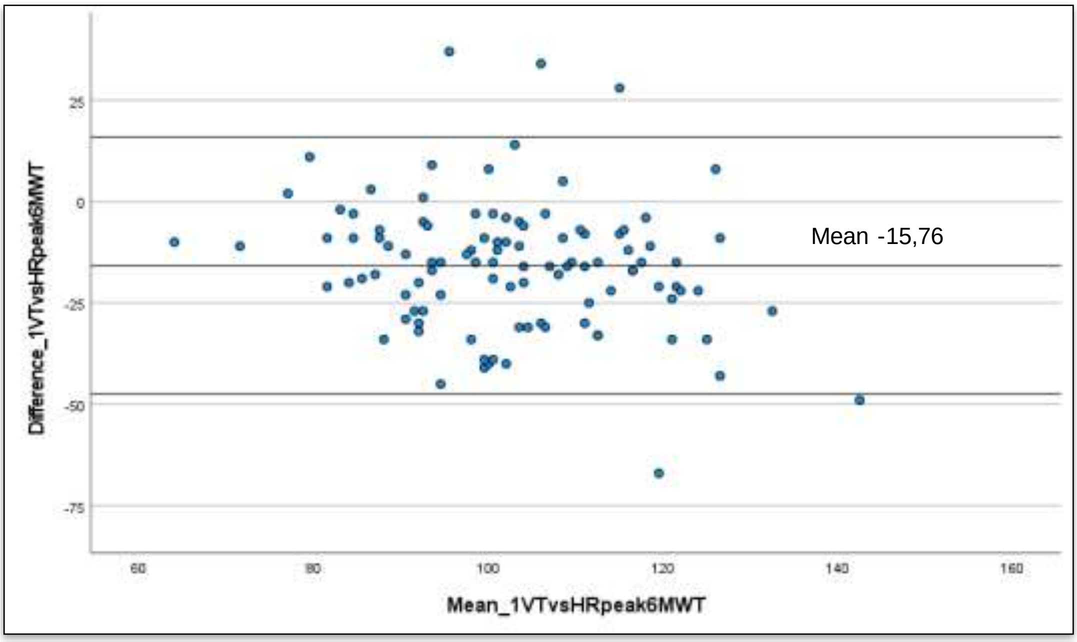

Figure 12.Bland-Altman agreement between HR peak in the 6MWT vs HR at first VT.

The Bland-Altman plot showed the mean difference ± standard deviation between HR_{peak} in the 6MWT and HR at first VT at CPET. The middle line represents the mean difference between variables. Confidence interval limits for the mean (95% confidence interval [CI], -18.79 to -12.46). The upper limit of agreement was 15.94 and lower limit was -47.47. In a good agreement, the scattering points is diminished, and the points lie relatively close to the line representing mean difference.

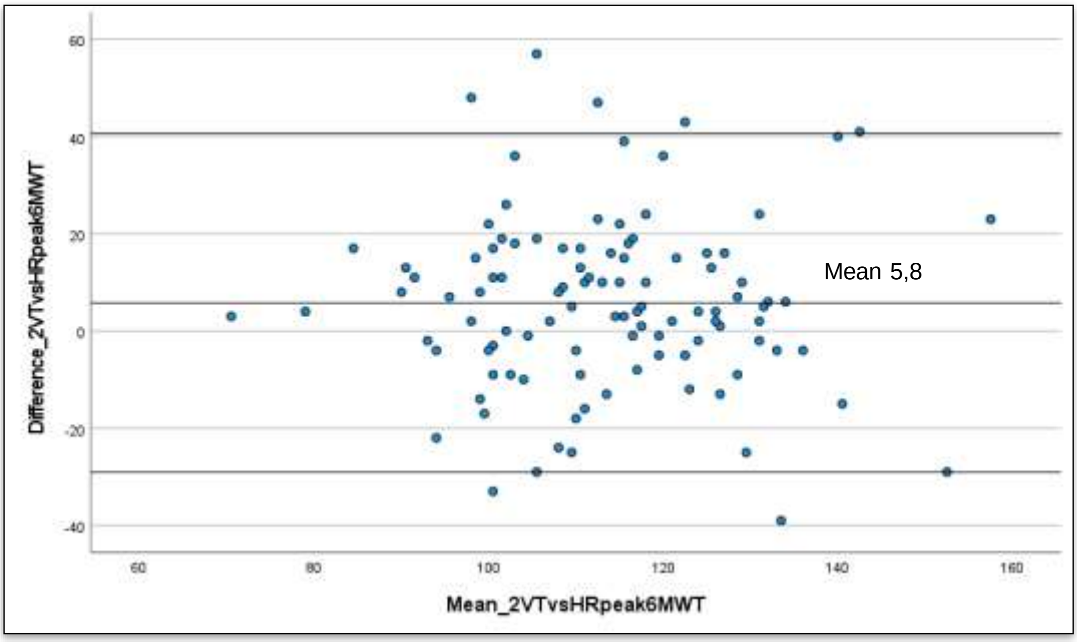

Figure 13. Bland-Altman agreement between HRpeak in the 6MWT vs HR at second VT.

The Bland-Altman plot showed the mean difference ± standard deviation between HR_{peak} in the 6MWT and HR at second VT at CPET. The middle line represents the mean difference between variables. Confidence interval limits for the mean (95% confidence interval [CI], 2.36 to 9.24). The upper limit of agreement was 40.60 and lower limit was -29.00. In a good agreement, the scattering points is diminished, and the points lie relatively close to the line representing mean difference.

V. DISCUSSION

According to our results, the HR_{peak} at 6MWT was equivalent to the intensity reached between the first and second VT at the CPET in CAD patients starting a phase III CR programme. This knowledge is of interest for the exercise training prescription in phase III CR programmes, as intensity is an important component of the FITT principle (frequency, intensity, type, and time) according to the European guidelines (Ambrosetti et al., 2021). Using this information enables accurate determination of the exercise intensity level for optimal outcomes in phase III CR programmes. Contrary to what we found, the study by Gayda et al, showed that HR peak reached at the 6MWT did not differ from the first VT in the CPET. However, it should be taken into account that the participants in our study were in a different phase of CR programme, as well as, different characteristics were presented such as aerobic capacity (higher in our study), and the timing of the cardiac event.

HR measurement during exercise has been widely used for quantifying and monitoring the intensity of exercise training prescription in CR programmes. Based on our findings, the HR_{peak} at 6MWT may be considered as moderate exercise intensity in CAD patients starting a phase III CR programme, since the mean value reached on the 6MWT HR_{peak} (110 ± 17 bpm) was in between the first (95 ± 14 bpm) and second (116 ± 17 bpm) VT.

In CR programmes, the percentage of maximal HR is commonly used to prescribe exercise intensity. The current recommendations in CVD patients for exercise intensity training using $\%HR_{peak}$ is between 55-90% (ACSM, 2017), (Pelliccia et al., 2021). In our study it was reached in the 6 MWT a HR_{peak} predicted of 86%, which goes in line with the current recommendations.

Target HR can also be calculated using the Karvonen formula where, 40–69% of HRR is recommended according to the European guidelines (Pelliccia et al., 2021). In our study the first VT occurred on the mean of 48% of HRR, where is between the range of the 40-70% exercise training zones and it corresponds to moderate intensity, while, the second VT occurred on the mean of 81% of HRR, corresponding to high intensity (Pelliccia et al., 2021). However, inaccuracy in achieve individual values using percentages methods might have some limitations as suggested by Pymer et al., 2020. Pymer et al. found that less than half of the participants who did a CPET (44.6%) reached their first VT between 40-70% of the HRR, 45.4% of the participants achieved the first VT at <40% HRR, and 9.8% at >70% HRR, suggesting that determining LV are more individualized for exercise prescription than using equations.

VO_{peak} is another parameter used to determine exercise intensity and is a good indicator for measuring cardiorespiratory fitness and mortality (Mikkelsen et al., 2020). The 6MWT distance has been proven to adequately predict the VO_2 obtained by CPET (Dourado et al., 2021) which is in agreement with our results. The total distance performed by our participants was 562 ± 81 meters and when estimated VO_{2peak} using the formula, our results showed positive and strong correlation between VO_{2peak} from CPET vs VO_2 estimated from 6MWT ($r = 0,516$, $p < 0.001$). Additionally, according to Dourado's study, our participants are classified according to their cardiorespiratory fitness as regular based on the 6MWT distance. Similar to, Uszko-Lencer et al., where they retrospectively investigated determinants of the distance covered in the 6MWT in 337 chronic heart failure patients (median age 65 years, 70% male, ejection fraction 35%) and they found a moderate correlation ($r_s = 0.58$ (95% CI 0.50, 0.65 mL/min/kg) between the 6MWT distance to VO_{2peak}, where the mean distance walked was 488 meters.

The VO_{2peak} derived from CPET was reached at 78 ± 20.6% of VO_2 predicted to age and sex. Additionally, our participants attained approximately 65% at first VT and 84% at second VT of measured peak VO_2, suggesting a moderate-to-high intensity exercise training zone (Pelliccia et al., 2021).

When performing Bland-Altman analysis, we analysed how much the HR_{peak} in the 6MWT is likely to differ from the VTs. Our results suggest low and significative agreement between HR_{peak} in the 6MWT vs HR at first and second VT at CPET. In contrast to what was found by Calegari et al., an agreement between HR_{peak} in the 6MWT vs HR at first VT CPET values in 17 CAD patients on beta-blocker treatment undergoing phase II CR programme, with a negative bias of -0.41±6.4 bpm and 95% limits of agreements (-13 to 12.2 bpm). Furthermore, this study showed a strong and positive relationship between HR_{peak} in the 6MWT vs HR at first VT CPET values from Pearson´s correlation ($r = 0.85$, $p < 0.0001$). However, it should be taken into account that the Bland-Altman plot does not say whether the agreement is sufficient or suitable to use a method or the other independently (Giavarina, 2015).

Regarding maximal effort attainment on the CPET, the mean HR_{peak} reached at CPET was 81% of age-predicted maximal HR, despite the peak respiratory exchange ratio (RER) was 1.16 indicating a maximal effort during a CPET. One of the parameters to consider a maximal exercise test, besides the RER being above 1.1, is to reach 85% of the predicted maximal HR (Balady et al., 2010). In our study, the % of aged predicted maximal HR did not reach 85%, this may be attributed to a chronotropic incompetence in cardiac patients, as beta-blocker therapy can modify HR responses during exercise. In our study, 84% of the patients were taking beta-blockers. Likewise, Díaz-Buschmann et al., showed when exercise intensity is based on percentages of HR peak (%HR), training effectiveness is greater with higher HR, however the safety decreases and patients using beta-blocker drug and the HR target exercise should be lower, as assumed by Wonisch et al., 2003 that the upper limit for %HRR and %HR should be lower in patients under beta-blocker.

CPET duration was according to what is recommended in the literature when a ramp protocol is used (Fletcher et al., 2013), between 8 to 12 minutes and in our study, it was on average 9 minutes and 38 seconds.

Clearly, decisions about which is the best method to determine exercise intensity in CVD patients is still a challenge. CVD patients seems to present different transition speeds from aerobic to anaerobic metabolism which is expected a metabolic uniformity and highly variable physiological responses recommending the exercise prescription according to VTs (Hansen et al., 2019). Indeed, exercise intensity prescription according to VTs is the most reliable method, but unfortunately it is not always available in many CR centres (Ascenzi et al., 2022). Also, data indicates that when the physical fitness of the patient changes during CR, the exercise training intensity should be carefully re-assed, which makes the CPET not so feasible (Hansen et al., 2022). Furthermore, our results suggest that HR_{peak} obtained from the 6MWT can also be used safely in physically active CAD patients starting a CR phase III since we do not register any major adverse event. Hence, the 6MWT is a useful tool for assessing physical performance and effectiveness of the CR programme, and predictor of morbidity and mortality (Arena et al., 2007).

Moreover, the majority of the patients in our study were male, with a mean age of sixty-one years old, revascularized either after CABG surgery or PCI, most of them have no signs or symptoms of clinically important ischemia or heart failure, were physically active and so, most of them are stratified as low-risk according to AACVPR criteria risk stratification (da Silva et al., 2014).

VI. LIMITATIONS

Potential limitations of the present study include its retrospective nature and was conducted at a single centre. Also, the ergometer used in the CPET would have been more relevant whether used a treadmill instead of a cycle ergometer since walking is a more familiar pattern and larger muscle mass are required during the test, which more work against gravity is done (Gibbons et al., 1997). The use of peak indices to define the exercise intensity may be a concern due to the fact that not all patients achieve maximal effort during CPET (Mezzani et al., 2009). Thus, these results cannot be extrapolated to those patients since we excluded patients who did not reach the second ventilatory threshold. Considering that most participants were predominantly male, physically active and had previous history of myocardial infarction, our results cannot be directly extrapolated to female, physically inactive or other patients with CAD, respectively. We did not measure gas analysis in the 6MWT, it would have been more relevant to measure it to compare the VT between both tests as it happens previously in other studies (Kervio et al., 2004, Gayda et al., 2004, Faggiano et al., 1997).

VII. CONCLUSION

This present study showed that HR_{peak} from the 6MWT can be used as an alternative strategy to prescribe moderate exercise intensity in CAD patients starting a phase III CR programme. Setting the proper exercise intensity in CAD patients is a cornerstone in exercise-based CR. Assessing and monitor the HR is widely used to assess and prescribe exercise intensity, since HR, in clinical routine, is easy to measure and there are several devices who can measure it. However, HR_{peak} determined by CPET or stress test, is limited to infrastructures and requires expensive resources. Contrarily, field tests, as the 6MWT, is simple, low cost and well tolerated.

VIII. FUTURE DIRECTIONS

Future research is warranted to explore the use of the 6MWT throughout all the phases in CR programmes in all types of patients or, perhaps, to identify the patients who better tolerate this test. Especially, regarding the use of HR_{peak} for prescribing exercise intensity, since the majority of studies are based on the 6MWT distance and speed and in phase II CR programme.

It would be interesting to include ECG assessment during the 6MWT to identify potential silent ischemic or CPET replacement in case of low to moderate risk stratification patients.

Additionally, it would be intriguing to follow up patients attending a long-term basis CR programme to identify how useful the 6MWT could be on prescribing exercise, since prolonged CR programmes may benefit CAD patients through observed clinical improvements in CV risk and physical fitness.

The use of digital health tools supporting cardiac telemedicine has been increased widely and may help to individualize exercise prescription in CR programmes. A self-administered smartphone-based 6MWTcould be a useful tool to assess functional capacity in the patient's outside of the hospital environment and without healthcare professional supervision, (Scherrenberg et al., 2022). Brooks et al., 2015, found that mobile self-administered 6MWT application accurately estimates 6MWT distance in the clinic and at patients with chronic heart failure and pulmonary hypertension home, moreover, it was demonstrated as feasible to remotely monitor functional capacity in those patients.

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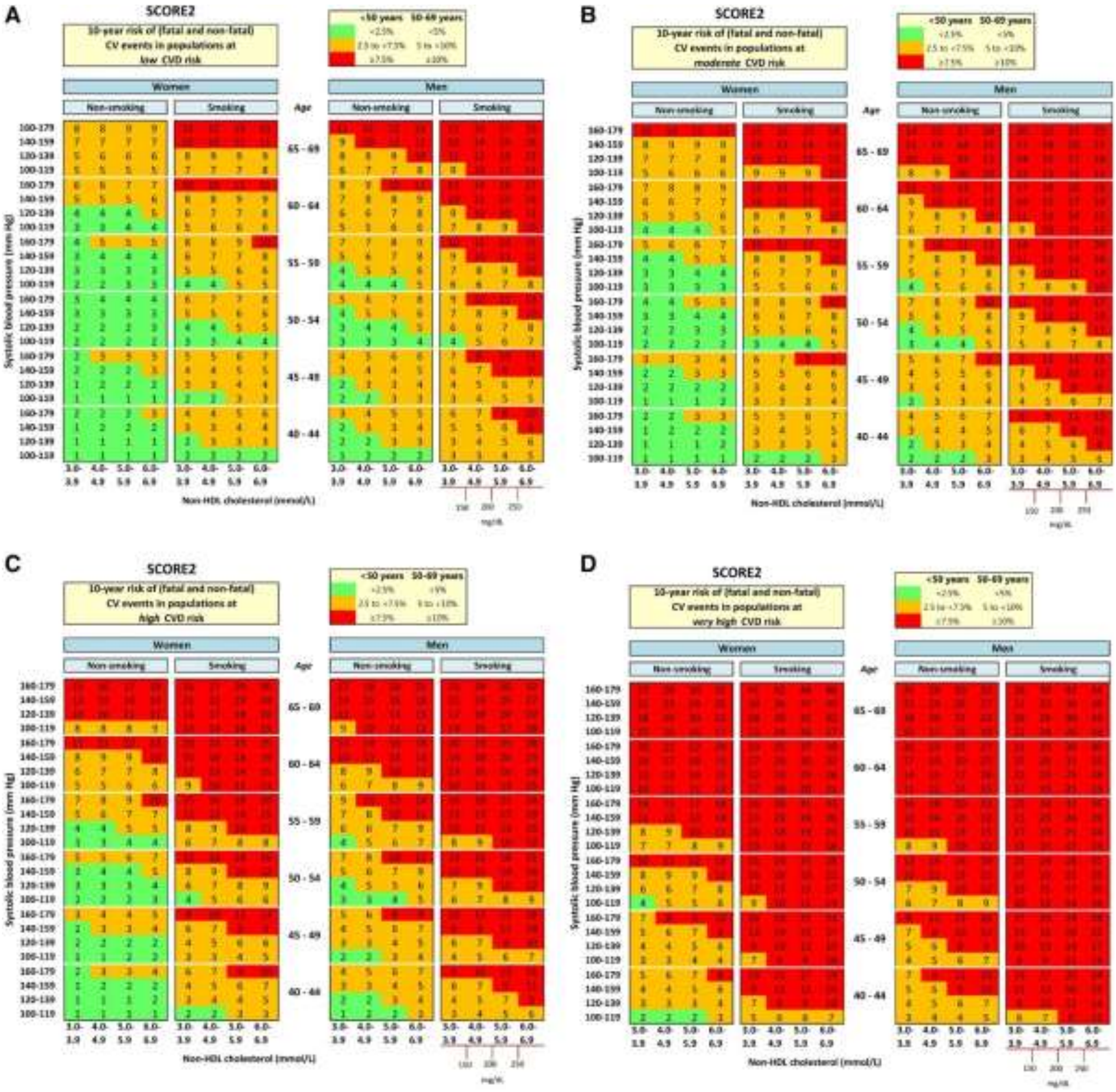
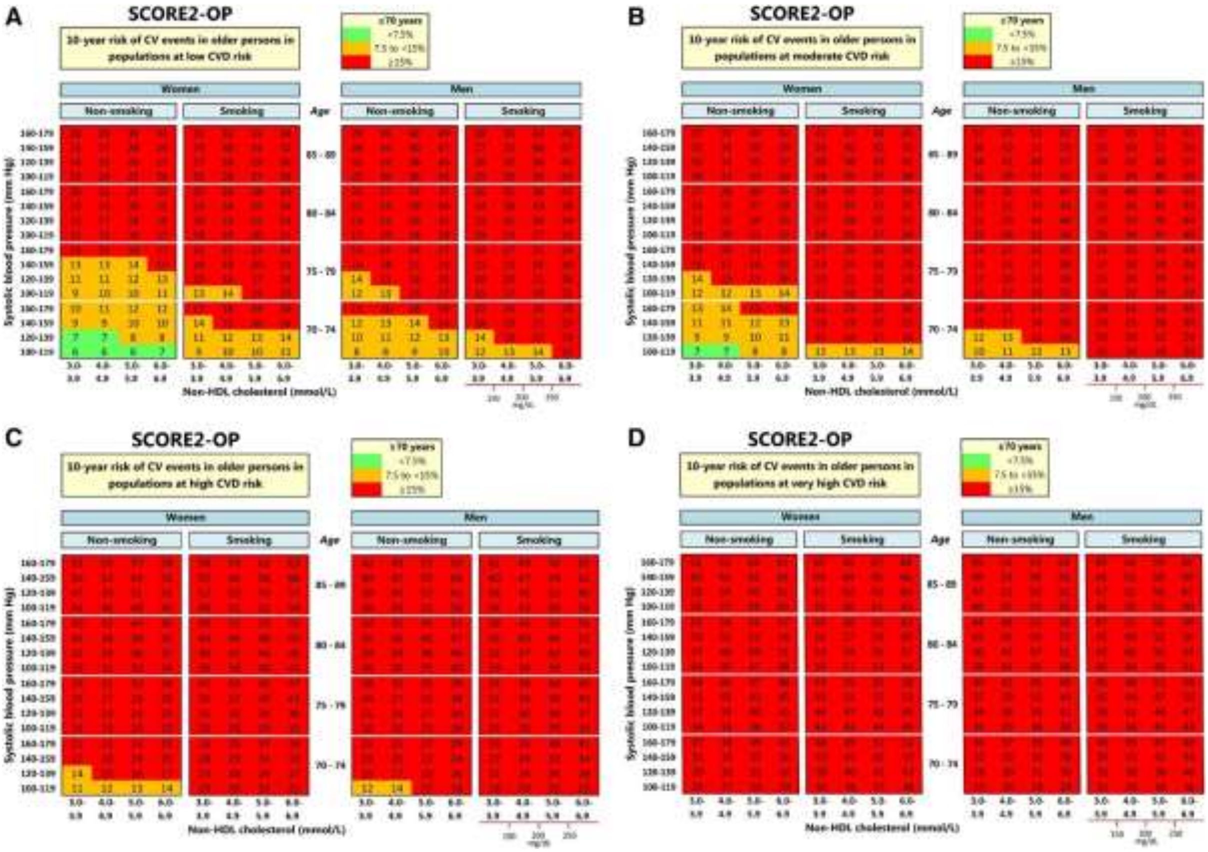
X. APPENDICES

A. SCORE2 charts for estimation of CVD risk in four European risk regions.
B. SCORE2-OP Regional risk charts of predicted 10-year cardiovascular disease risks.
C. List of publications and conference abstracts associated with this dissertation

APPENDIX A: SCORE2 charts for estimation of CVD risk in four European risk regions.



APPENDIX B: SCORE2-OP Regional risk charts of predicted 10-year Cardiovascular Disease Risks.



APPENDIX C. List of publications and conference abstracts associated with this dissertation

Sociedade Portuguesa de CARDIOLOGIA

GEFERC Grupo de Estudo de Fisiopatologia do Esforço e Reabilitação Cardíaca — Sociedade Portuguesa de CARDIOLOGIA

GERC Grupo de Estudo de Risco Cardiovascular — Sociedade Portuguesa de CARDIOLOGIA

CERTIFICADO DE PRESENÇA

Certifica-se para os devidos efeitos que

Camila Sevegnani

Esteve presente na Reunião conjunta Grupo de Estudo de Fisiopatologia do Esforço e Reabilitação Cardíaca e Grupo de Estudo de Risco Cardiovascular, que teve lugar nos dias 6 e 7 de Maio de 2022, na Casa das Histórias, Auditório Maria de Jesus Barroso, Cascais.

Cascais, 7 de Maio de 2022

Ana Abreu
Coordenadora GERCV

Maria Luísa Bento
Coordenadora GEFERC

Title: **The 6-minute walk test as an alternative to prescribe exercise intensity in coronary artery disease patients starting a phase III cardiac rehabilitation programme**

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Background: Exercise training intensity in cardiovascular rehabilitation (CR) programmes is mainly prescribed on a specific target heart rate (HR), usually corresponding to the ventilatory thresholds (VT) when a cardiopulmonary exercise testing (CPET) is performed. However, CPET availability is not a reality in many CR centres. An alternative method to prescribe exercise intensity has been proposed using the 6-minute walk test (6MWT). Nevertheless, it is unclear whether it is possible to determine the training intensity considering the 6MWT in physically active patients with coronary artery disease (CAD) starting a CR phase III programme.

Purpose: to determine the exercise target HR using the peak HR of the 6MWT as a method to prescribe the intensity of aerobic exercise in CAD patients starting a phase III CR programme and to compare it with the VT of the CPET.

Methods: In this retrospective study, a cohort of CAD patients enrolled in a phase III CR programme were included. All patients performed a 6MWT and a CPET on a cycle ergometer in the same week with at least 48-hour difference. The HR on the 6MWT was recorded continuously using a HR polar band (H10 Polar) and on CPET using a twelve-lead ECG. Other parameters were assessed including objectively measured physical activity (accelerometer) and body composition. Comparisons between CPET and 6MWT variables were performed by paired sample t-test. Relationships between variables were measured by the Pearson correlation coefficient.

Results: Ninety-five CAD patients (male, 87.4%; age, 60.7 ± 10.0 years) were included. Patients were, on average, physically active (348 ± 188 minutes/week of moderate to vigorous physical activity) and overweight (body mass index: 27.8 ± 3.5 kg/m^2). The VO_2 peak reached on the CPET was 21.1 ± 6.2 ml/kg/min and the percentage of predicted maximum HR was 80.3 ± 11.2%. The first and second VT corresponded to 74.8 ± 8.3% and 90.1 ± 4.9% of the peak HR obtained with CPET, respectively.

There were no differences between the % of the peak HR reached on the 2nd VT and the 6MWT HR peak (90.1 ± 4.9% vs 88.4 ± 14.9%, $p>0.05$). However, the 6MWT HR peak was significantly higher than the HR of the 1st VT (88.4 ± 14.9% vs 74.8 ± 8.3%, $p<0.001$).

There was a positive correlation between the HR of the 2nd VT and the HR of the 6MWT ($r= 0.53$, $P< 0.001$), and a positive correlation between the 6MWT distance and VO2 peak ($r = 0.60$, $p < 0.01$), independently of age.

Conclusion: This study showed that 6MWT HR peak can be used as an alternative strategy to prescribe aerobic exercise intensity, close to the second VT in physically active patients with CAD starting a phase III CR programme. Considering that the 6MWT is easily performed, widely available and well tolerated, it can be an alternative to use in clinical practice when CPET is not possible to be performed.

JOURNAL ARTICLE

Usefulness of the 6-minute walk test vs cardiopulmonary exercise test for exercise prescription in coronary artery disease patients going into a phase III cardiac rehabilitation program

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Background/Introduction: Determining the intensity of exercise is a very important component to obtain the dose-benefits associated with exercise, while maitaining the safaty of the patient with coronary artery disease (CAD) in a cardiovascular rehabilitation (CR) programme. The cardiopulmonary exercise test (CPET) is the gols standard for exercise prescription according to the intend intensisty of aerobic workout. However, its availability is not a reality in many CR centres. The 6-minute walk test (6MWT) is a valid and widely used method because it is low-cost and simple to apply. Nevertheless, it is still unknown the corresponding intensity reached on a 6MWT compared to the one reached on a CPET in already physically active patients with CAD starting a CR phase III programme.

Purpose: To use the peak heart rate (HR) of the 6MWT as a method to prescribe the intensity of aerobic exercise in CAD patients starting a phase III CR programme and to compare it with the ventilatory threshold (VT) of the CPET.

Methods: In this retrospective study, a cohort of patients with CAD enrolled in a phase III CR programme. At the beginning of the programme, all patients performed a 6MWT and a CPET in the same week with at least 48-hour difference. The HR on the 6MWT was recorded continuously using a HR polar (H10 Polar) and on CPET using a twelve-lead ECG. Other parameters were assessed such as objective physical activity (accelerometer) and body composition.

Results: Eighty patients (87.5% males, 60.8 ± 9.4 years old) with CAD were included in this study. Patients were, on average, physically active (361 ± 182 minutes/week of moderate to vigorous physical activity) and overweight (body mass index: 27.7 ± 3.5 kg/m2). The VO2 peak reached on the CPET was 20.3 ± 5.4 ml/kg/min and the percentage of predicted maximum HR was 78.3 ± 11.4 %. The first and second VT corresponded to 75.6 ± 7.8% and 91.2 ± 4.5% of the peak HR obtained with CPET, respectively. The 6MWT HR peak was 113 ± 16 bpm (90.0 ± 13.0 HR peak CPET) and did not differ from the HR of the second VT with a mean value of 115 ± 16 bpm (91.2 ± 4.5% HR peak CPET), p>0.05. Although, the 6MWT HR peak was significantly higher than the HR oh the first VT (95 ± 14 bpm, p<0.001). In a subgroup analysis, the patients who, during the 6MWT, reached more the 90% of the HR peak CPET (n=35, 44% oof the sample) were the ones with lower functional capacity (VO2 peak: 18.4 ± 5.4 ml/kg/min vs 21.7 ± 5.0 ml/kg/min, p=0.006) and higher age (64.4 ± 8.7 years old vs 60.8 ± 9.4 years old, p=0.002).

Conclusion(s): In the absence of a CPET, the use of a 6MWT HR peak in physically active patients with CAD starting a phase III CR programme has shown to be an efficient method to prescribe moderate to vigorous exercise intensity, corresponding to the second VT. Higher intensities on the 6MWT might be reached in active elderly patients with reduced functional capacity.