UNIVERSIDADE DE LISBOA

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Risk factor management in a community-based cardiac rehabilitation program. What still needs to be done?

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Orientadores: Prof. Doutora Maria Rita da Silva Alexandre Pinto
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Dissertação especialmente elaborada para obtenção do grau de mestre em Reabilitação Cardiovascular

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Abbreviations

AAD - Antiarrhythmics

ACE - Angiotensin Converting Enzyme

ACS - Acute Coronary Syndrome

AMI - Acute Myocardial Infarction

ARBs - Angiotensin II receptor blockers

ARNIs - Angiotensin Receptor-Neprilysin Inhibitors

BMI - Body Mass Index

CABG - Coronary Artery Bypass Graft

CAD - Coronary Artery Disease

CCBs - Calcium Channel Blockers

CHD - Coronary Heart Disease

CHULN - Centro Hospitalar Universitário Lisboa Norte

CPET - Cardiopulmonary Exercise Testing

CR - Cardiac Rehabilitation

CRECUL - Centro de Reabilitação Cardiovascular da Universidade de Lisboa

CV - Cardiovascular

CVD - Cardiovascular Disease

DAPT - Dual Antiplatelet Therapy

DBP - Diastolic Blood Pressure

DM - Diabetes Mellitus

DXA - Dual Energy X-ray Absorptiometry

ECG - Electrocardiogram

FMUL - Faculdade de Medicina da Universidade de Lisboa

FPG - Fasting Plasma Glucose

HbA1C - Haemoglobin A1c

HDL - High-Density Lipoprotein

HF - Heart Failure

HMG-CoA - 3-Hydroxy-3-Methyl–Glutaryl-Coenzyme A

HR - Heart Rate

hs-ctn - High Sensitivity Cardiac Troponin

LDL - Low-Density Lipoprotein

LPA - Light-Intensity Physical Activity

LV – Left Ventricular

MPA - Moderate-Intensity Physical Activity

MVPA - Moderate-to-Vigorous Intensity Physical Activity

NSTEMI - Non-ST-segment Elevation Myocardial Infarction

PCI - Percutaneous Coronary Intervention

PCSK-9 - Proprotein Convertase Subtilisin/Kexin Type-9

RAAS - Renin-Angiotensin-Aldosterone System

SB - Sedentary Behavior

SBP - Systolic Blood Pressure

SD - Standard Deviation

ST - Sedentary Time

STEMI - ST-segment Elevation Myocardial Infarction

TG – Triglycerides

total-c - Total Cholesterol

VPA - Vigorous-Intensity Physical Activity

WHO - World Health Organization

β-blockers - Beta-Adrenergic Antagonists

Abstract

Cardiac rehabilitation (CR) is a multidisciplinary intervention designed to reduce cardiovascular (CV) risk through an active lifestyle promotion and risk factor management. After completing a phase II CR program, it is important to maintain long-term CV risk factor control. However, many patients do not achieve the guidelines targets on a long-term basis. Therefore, it is of interest to understand which risk factors are not being well controlled to personalize and improve the efficacy of long-term community-based CR programs.

This observational study was designed to characterize the modifiable CV risk factors, including lipid profile, body composition, physical activity, and sedentary behavior (SB) of coronary artery disease (CAD) patients admitted in the CR program at Centro de Reabilitação Cardiovascular da Universidade de Lisboa (CRECUL). A cross-sectional analysis was performed upon entry into the CR program and a longitudinal analysis was performed after 1-year entry into the CR program.

Patients were evaluated at baseline, and annually thereafter, performing assessments to define CV risk factor prevalence and evaluate body composition (weight and body mass index (BMI), physical activity (moderate-to-vigorous intensity physical activity (MVPA), average MVPA and sedentary time (ST)) and lipid profile (total cholesterol (total-c), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, non-high-density lipoprotein (non-HDL) cholesterol and triglycerides (TG)).

Body composition was evaluated using dual energy X-ray absorptiometry (DXA), with the aim of assessing body weight and fat mass. Regarding BMI, it was classified as follows: BMI ≥ 30.0 kg/m^2 for obesity and BMI between 25.0 and 30.0 kg/m^2 for overweight. Physical activity pattern and SB were objectively assessed using an accelerometer. The classification of physically inactive person was considered whenever less than 150 min/week of moderate-intensity physical activity (MPA) or 75 min/week of aerobic vigorous-intensity physical activity (VPA) or an equivalent combination of both intensities were practiced, and a sedentary person was considered to have a TS > 7.5 hours/day. The lipid profile was obtained from blood tests, considering uncontrolled LDL cholesterol levels for an LDL cholesterol value > 55 mg/dL.

The sample was composed by 96 CAD patients before entering a phase III community-based CR program (61.8 ± 9.7 years old, 12.5% female), in which 89.6% attended in a previous phase II CR program. Statistical differences were observed in dyslipidaemia prevalence being higher in patients that did not performed a phase II CR program ($p < 0.050$).

At the beginning of the phase III CR program, 53.1% of the patients were hypertensive, 20.8% had diabetes mellitus (DM) and 55.2% were dyslipidaemic patients. The most prevalent risk factor was SB (100.0%), followed by high values of LDL cholesterol (72.9%). Mean BMI was 27.4 ± 4.3 kg/m^2, with most patients classified as overweight (40.6%) or obese (20.8%). Mean MVPA was 334.5 ± 177.2 min/week. Only 11.5% was considered physically inactive, however, all patients were considered sedentary.

After a 12-month intervention (n = 31, 9.7% female, mean age 63.8 ± 8.1 years old), LDL cholesterol levels were kept above the targets (Baseline: 69.5 ± 23.8 mg/dL and follow-up: 64.8 ± 14.8 mg/dL, $p = 0.230$), BMI did not change (Baseline: 27.0 ± 3.1 kg/m^2 and follow-up: 27.3 ± 3.2 kg/m^2, $p = 0.132$) and SB remained high (Baseline: 11.5 ± 2.6 hours/day and follow-up: 11.9 ± 2.9 hours/day, $p = 0.845$). Although, MVPA decreased (Baseline: 309.4 ± 157.8 mins/week and

follow-up: 274.8 ± 165.6 mins/week, p = 0.224), participants were still on target, between 150 to 300 mins MVPA week.

In conclusion, the results of this research revealed that most people with CAD who entered and participated for 1 year in a phase III CR program did not have an ideal body composition, LDL cholesterol, and SB levels. Physical activity was the best controlled CV risk factor.

To complete, this study highlights the importance of optimizing strategies to improve CV risk factors management. Future strategies should be implemented to better control LDL cholesterol, body composition and SB.

Key words: Coronary Artery Disease, Cardiac Rehabilitation, Risk Factor Management, Body Composition, Sedentary Behavior, Cholesterol

Resumo

A reabilitação cardíaca (RC) é uma intervenção multidisciplinar concebida para reduzir o risco cardiovascular (CV) através da promoção de um estilo de vida ativo e da gestão dos fatores de risco. Depois de completar um programa de RC de fase II, é importante manter o controlo dos fatores de risco CV a longo prazo. No entanto, muitos doentes CV não atingem, a longo prazo, as metas propostas pelas recomendações europeias. Portanto, é relevante entender quais os fatores de risco que não estão a ser devidamente controlados de modo a que seja possível personalizar e melhorar a eficácia de programas comunitários de RC de longo prazo.

Este estudo observacional foi desenhado para caracterizar os fatores de risco CV modificáveis, incluindo o perfil lipídico, a composição corporal, a atividade física e o CS de pessoas com doença arterial coronária (DAC) admitidos no programa RC realizado no Centro de Reabilitação Cardiovascular da Universidade de Lisboa (CRECUL). Foram realizadas uma análise transversal no momento de entrada no programa de RC e uma análise longitudinal passados 12 meses após a entrada no programa de RC.

Os doentes foram avaliados no início do estudo e, posteriormente, anualmente, realizando avaliações com o objetivo de definir a prevalência de fatores de risco CV e avaliar a composição corporal (peso e índice de massa corporal (IMC), atividade física (atividade física de intensidade moderada a vigorosa (AFMV), média da AFMV e tempo sedentário (TS)) e perfil lipídico (colesterol total, colesterol de lipoproteína de alta densidade (LDL), colesterol de lipoproteína de baixa densidade (HDL), colesterol de lipoproteína de não alta (não-HDL) densidade e triglicéridos (TG)).

A composição corporal foi avaliada através de uma densitometria raio-x de dupla energia, com o objetivo de avaliar o peso corporal e massa gorda. Em relação ao IMC, este foi classificado da seguinte forma: IMC ≥ 30.0 kg/m^2 para obesidade e IMC entre 25.0 e 30.0 kg/m^2 para excesso de peso. O padrão de atividade física e o CS foram avaliados objetivamente através do uso de um acelerómetro. A classificação de pessoa fisicamente inativa foi considerada sempre que fossem praticados menos de 150 minutos de atividade física de intensidade moderada por semana ou 75 minutos de atividade física aeróbica de intensidade vigorosa por semana ou uma combinação equivalente de ambas as intensidades e foi considerada uma pessoa sedentária quem tivesse um TS > 7,5 horas/dia. O perfil lipídico foi obtido a partir de análises ao sangue, sendo considerados níveis de colesterol LDL não controlados para um valor de colesterol LDL > 55 mg/dL.

A amostra foi composta por 96 pessoas com DAC antes de entrar num programa comunitário de RC de fase III (61.8 ± 9.7 anos, 12.5% do sexo feminino), em que 89.6% participaram num programa anterior de RC de fase II. Diferenças estatísticas foram observadas na prevalência de dislipidemia sendo maior em doentes que não realizaram um programa de RC de fase II ($p < 0.050$).

No início do programa de RC fase III, 53.1% dos doentes estavam diagnosticados com hipertensão, 20.8% com diabetes mellitus e 55.2% com dislipidemia. O fator de risco mais prevalente foi o CS (100.0%), seguido dos valores altos apresentados do colesterol LDL (72.9%). O valor médio do IMC foi de 27.4 ± 4.3 kg/m^2, sendo a maioria dos doentes classificados com excesso de peso (40.6%) ou obesidade (20.8%). A média da AFMV foi de 334.5 ± 177.2 min/semana. Apenas 11.5% foram considerados fisicamente inativos, contudo todos os pacientes foram considerados sedentários.

Após uma intervenção de 12 meses (n = 31, 9.7% do sexo feminino, idade média de 63.8 ± 8.1 anos), os níveis de colesterol LDL foram mantidos acima das metas (linha de base: 69.5 ± 23.8 mg/dL e acompanhamento: 64.8 ± 14.8 mg /dL, p = 0.230), o IMC não se alterou (linha de base: 27.0 ± 3.1 kg/m^2 e acompanhamento: 27.3 ± 3.2 kg/m^2, p = 0.132) e o CS permaneceu alto (linha de base: 11.5 ± 2.6 horas/dia e acompanhamento: 11.9 ± 2.9 horas/dia, p = 0.845). Embora a AFMV tenha diminuído (linha de base: 309.4 ± 157.8 min/semana e acompanhamento: 274.8 ± 165.6 min/semana, p = 0.224), os participantes ainda estavam no alvo, entre 150 e 300 min de AFMV por semana.

Em conclusão, os resultados desta pesquisa revelaram que a grande maioria das pessoas com DAC que entraram e participaram durante 12 meses num programa de RC de fase III não apresentavam uma composição corporal, níveis de colesterol LDL ou CS ideais. A atividade física foi o fator de risco CV mais bem controlado.

Para concluir, este estudo destaca a importância da otimização de estratégias para melhorar o controlo dos fatores de risco CV. Futuras estratégias devem ser implementadas para melhor controlo do colesterol LDL, da composição corporal e do CS.

Palavras-chave: Doença Arterial Coronária, Reabilitação Cardíaca, Gestão de Fatores de Risco, Composição Corporal, Comportamento Sedentário, Colesterol

Resumo alargado

As doenças cardiovasculares (DCV) continuam a ser a causa mais comum de morte em todo o mundo e tornaram-se um grave problema de saúde pública, estando relacionadas com o aumento da mortalidade, morbilidade e incapacidade física. A DAC é a forma mais prevalente de DCV.

A progressão da doença está diretamente relacionada com fatores como a idade, o sexo da pessoa, entre outros, bem como com o estilo de vida e hábitos diários do paciente sendo considerados fatores de risco CV, podendo ter um carácter modificável ou não-modificável. A hipertensão é um fator de risco modificável e considerada o principal fator de risco para o desenvolvimento da DAC.

Atualmente já estão disponíveis muitos recursos para o tratamento da DAC, seja por meio de terapia farmacológica (terapia de modificação de lipoproteínas, terapia anti isquémica, entre outras) ou por estratégias de revascularização (intervenção coronária percutânea, cirurgia de revascularização do miocárdio). Contudo, é recomendado que estes sejam acompanhados por uma intervenção adicional para prevenção secundária como a RC.

A RC é uma intervenção multidisciplinar concebida para reduzir o risco CV através da promoção de um estilo de vida ativo e da gestão dos fatores de risco cujos principais componentes incluem avaliação médica, sessões de exercício físico e aconselhamento de atividade física, identificação e controlo de fatores de risco, avaliação e aconselhamento nutricional, avaliação e intervenção psicológica, entre outros.

A RC é constituída por 3 fases em que as primeiras duas são consideradas de curta duração e realizadas a nível hospitalar. Contudo, depois de completar um programa de RC de fase II, é importante manter o controlo dos fatores de risco CV a longo prazo, o que é possível através da adesão a um programa de RC de fase III, que deve durar o resto da vida do doente ou, até que o doente esteja clinicamente estável.

No entanto, muitos doentes CV não atingem, a longo prazo, as metas propostas pelas recomendações europeias, principalmente ao nível do perfil lipídico, e torna-se necessário entender quais os fatores de risco que não estão a ser devidamente controlados de modo a que seja possível personalizar e melhorar a eficácia de programas comunitários de RC de longo prazo, sendo este o principal objetivo desta dissertação.

O programa de RC que foi analisado para a realização da presente dissertação foi o programa CRECUL que é um programa comunitário de RC de fase III. Este programa disponibiliza às pessoas com DCV a oportunidade de frequentar 2 a 3 vezes por semana, durante 11 meses por ano sessões de exercício físico em grupo e personalizadas bem como a participação em 2 a 3 sessões educativas anuais. As sessões de exercício físico têm a duração de 60 minutos e são agendadas de acordo com a disponibilidade dos doentes.

Este estudo observacional foi desenhado para caracterizar os fatores de risco CV modificáveis, incluindo o perfil lipídico, a composição corporal, a atividade física e o CS de pessoas com doença arterial coronária (DAC) admitidos no programa RC no CRECUL. Foram realizadas uma análise transversal no momento de entrada no programa de RC e uma análise longitudinal passados 12 meses após a entrada no programa de RC.

Os doentes foram avaliados no início do estudo e, posteriormente, anualmente, realizando avaliações com o objetivo de definir a prevalência de fatores de risco CV e avaliar a

composição corporal (peso e IMC), atividade física (AFMV, média da AFMV e TS) e perfil lipídico (colesterol total, colesterol HDL colesterol LDL, colesterol não-HDL e TG).

A composição corporal foi avaliada através de uma densitometria raio-x de dupla energia, com o objetivo de avaliar o peso corporal e massa gorda. Em relação ao IMC, este foi classificado da seguinte forma: IMC ≥ 30.0 kg/m^2 para obesidade e IMC entre 25.0 e 30.0 kg/m^2 para excesso de peso. O padrão de atividade física e o CS foram avaliados objetivamente através do uso de um acelerómetro. A classificação de pessoa fisicamente inativa foi considerada sempre que fossem praticados menos de 150 minutos de atividade física de intensidade moderada por semana ou 75 minutos de atividade física aeróbica de intensidade vigorosa por semana ou uma combinação equivalente de ambas as intensidades e foi considerada uma pessoa sedentária quem tivesse um TS > 7,5 horas/dia. O perfil lipídico foi obtido a partir de análises ao sangue, sendo considerados níveis de colesterol LDL não controlados para um valor de colesterol LDL > 55 mg/dL.

Outros fatores de risco como a hipertensão, a dislipidemia, a diabetes, o tabagismo e o consumo de álcool foram avaliados através de um questionário de avaliação inicial e dos registos clínicos de cada doente. Na avaliação do controlo de cada fator de risco foram utilizados os valores de corte para classificação e metas definidas pelas recomendações europeias de cardiologia mais recentes. Para além disso foi definida e calculada a frequência de cada doente nos primeiros 12 meses do programa, denominada como adesão ao programa de RC.

A amostra foi composta por 96 pessoas com DAC antes de entrar num programa comunitário de RC de fase III (61.8 ± 9.7 anos, 12.5% do sexo feminino), em que 89.6% participaram num programa anterior de RC de fase II. Diferenças estatísticas foram observadas na prevalência de dislipidemia sendo maior em doentes que não realizaram um programa de RC de fase II ($p < 0.050$).

No início do programa de RC fase III, 53.1% dos doentes estavam diagnosticados com hipertensão, 20.8% com diabetes mellitus e 55.2% com dislipidemia. O fator de risco mais prevalente foi o CS (100.0%), seguido dos valores altos apresentados do colesterol LDL (72.9%). O valor médio do IMC foi de 27.4 ± 4.3 kg/m^2, sendo a maioria dos doentes classificados com excesso de peso (40.6%) ou obesidade (20.8%). A média da AFMV foi de 334.5 ± 177.2 min/semana. Apenas 11.5% foram considerados fisicamente inativos, contudo todos os pacientes foram considerados sedentários.

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Não houve diferenças significativas nem no IMC, nem nos níveis de AFMV nem nos níveis de TS. Apesar disso, foram observadas diferenças na prevalência de excesso de peso e obesidade (aumento da prevalência de excesso de peso (de 38.7% para 54.8%) e redução da prevalência de obesidade (de 28.6% para 12.9%)) e um aumento estatisticamente significativo ($p < 0.050$) na prevalência de incumprimento das metas do colesterol LDL (de 71.0% para 74.2%).

De maneira geral, a composição corporal, os níveis de atividade física e os níveis de perfil lipídico não mudaram, não sendo observadas diferenças estatísticas significativas entre os grupos de acordo com a assiduidade às sessões de exercício do programa de RC.

Em conclusão, os resultados desta pesquisa revelaram que a grande maioria das pessoas com DAC que entraram e participaram durante 12 meses num programa de RC de fase III não apresentavam uma composição corporal, níveis de colesterol LDL ou CS ideais. A atividade física foi o fator de risco CV mais bem controlado.

Para concluir, este estudo destaca a importância da otimização de estratégias para melhorar o controlo dos fatores de risco CV. Por exemplo, adicionar uma intervenção nutricional mais específica e personalizada como parte integrante do programa de RC pode ajudar a controlar os resultados da composição corporal. Outra sugestão com potencial é a adição de uma estratégia que vise a redução e interrupção do TS, por exemplo através de intervenções apoiadas em programas baseados em tecnologia e complementados com aconselhamento digital. No geral, futuras estratégias devem ser implementadas para melhor controlo do colesterol LDL, da composição corporal e do CS.

Introduction

Coronary artery disease is the most prevalent form of cardiovascular disease (CVD) and is increasing in the middle-aged and elderly populations, being responsible, in 2019, for the death of more than 18.0 million people worldwide, of which 37.0 thousand occurred in Portugal. (Timmis et al., 2022) Over the years it remains one of the leading causes of mortality and disability worldwide and its prevalence is expected to increase even more in the coming years. (Chen et al., 2017; Sayols-Baixeras et al., 2014; Timmis et al., 2022)

Statistical data on CVD worldwide highlight the need to develop strategies to fight this disease and one of the most widely used strategies with demonstrated benefits is cardiac rehabilitation (CR), offered through structured programs. (Abreu et al., 2018; Ambrosetti et al., 2021; Anderson et al., 2021; Javaherian et al., 2020)

CR program is a multidisciplinary intervention that includes several components designed to reduce cardiovascular (CV) risk, encourage healthy behaviors, reduce physical impairment, and promote an active lifestyle. It is an essential part of contemporary heart disease care and a priority in countries with high prevalence of coronary artery disease (CAD). (Abreu et al., 2018; Ambrosetti et al., 2021; Anderson et al., 2021; Ibanez et al., 2018; Noites et al., 2015; Visseren et al., 2021) A CR program generally consists of three phases and, in this thesis phase III CR is the one that is going to be the focus. The CR programs act at the level of CV risk factors control, particularly in those who are modifiable.

CV risk factors can be divided into non-modifiable and modifiable, more risk factors increase the probability of developing CVD or worsen the previous CVD of the individual. (Papageorgiou et al., 2017; Visseren et al., 2021)

Despite all the efforts across the years, in general, the prevalence of most modifiable CV risk factors is still very high worldwide. (Cosentino et al., 2020; Timmis et al., 2022) In Portugal, data from the last decade estimate that 24.4% of the Portuguese population was hypertensive, 6.6% was diabetic, 14.2% was regular smoker, 20.8% was obese, 43.0% was physically inactive and 9.0% had high levels of ST. Besides, there were also identified high levels of alcohol consumption and abnormalities in lipid profile. (Cosentino et al., 2020; Timmis et al., 2022)

CR programs have been shown to be effective in secondary prevention decreasing CV risk events and CV mortality through the implementation of healthy lifestyle behaviors and risk factors control. (Javaherian et al., 2020; Knuuti et al., 2020; Visseren et al., 2021; WHO, 2021) However, the implementation of those measures is far from optimal and it is necessary to improve them. (Kotseva et al., 2016, 2019; Timmis et al., 2022)

Although CR has proven to have short- and mid-term benefits, its long-term benefit is less certain. More long-term studies are needed to understand the impact of risk factor management and evaluate the effectiveness of phase III CR programs. Besides, it is more and more necessary to take an individual and specific approach for each patient and so it is important to carry out studies that integrate the under-represented groups, for example, the elderly.

The purpose of this thesis was to characterize the modifiable CV risk factors profile in CAD patients admitted to a community-based phase III CR program, including lipid profile, overweight/obesity, physical activity and sedentary behavior (SB) at the beginning and after completing the first year of the CR program.

To reach this purpose, this thesis is organized into 7 chapters. Chapter 1 includes a review of the literature on CVD, particularly on CAD, its epidemiology, pathophysiology, and treatment, and a review on CR, the structure of a CR program, its purpose and importance in controlling risk factors. The methods used in the study design, the approach taken to each risk factor that will be analyzed and the description of the statistical analysis will be presented in chapter 2. Then, in chapter 3, the results are presented, and the most relevant ones will be discussed in chapter 4 according to the objectives of the study.

Some of the preliminary results presented in this thesis were presented in national and international meetings and congresses (Attachment 1):

- Ribeiro, M; Salgueiro, D; Borges, M; Lemos Pires, M; Ricardo, I; Cunha, N; Pinto, FJ; Abreu, A; Pinto, R. "Cardiovascular risk factors in patients admitted in a community-based phase III cardiac rehabilitation program". Presented in Reunião conjunta Grupo de Estudo de Fisiopatologia do Esforço e Reabilitação Cardíaca e Grupo de Estudo de Risco Cardiovascular, Cascais, 2022.
- Salgueiro, D; Borges, M; Pires, ML; Guerreiro, CS; Pinto, FJ; Abreu, A; Pinto, R. “Which cardiovascular risk factors are not being controlled in patients attending a community-based cardiac rehabilitation program after one year?”. Presented in ESC Preventive Cardiology 2023, Málaga, Spain, 2023.

1. Literature Review

1.1. Cardiovascular disease epidemiology

CVD remain the most common cause of death worldwide and have become a serious public health issue, being related to increases in mortality, morbidity, and physical disability. Death is one of the most accurately ascertained CVD outcomes providing a useful measure of disease burden. (Javaherian et al., 2020; Timmis et al., 2022; Zhuang et al., 2020)

The most recent data refer to the year of 2019 and at that time, 18.5 million people with > 20 years died from CVD, and the number of deaths was slightly higher in men (9.6 million deaths) than women (8.9 million deaths), representing 37.0% of all global deaths. The number of deaths has increased since 1990, when 11.9 million people died from CVD, however a downward trend was observed in annual median deaths estimate from CVD, from 354.4, in 1990, to 239.9 deaths per 100 000 inhabitants, in 2019. (Timmis et al., 2022)

A relatively similar pattern was observed in Europe with 4.2 million deaths from CVD (2.3 million in women and 1.9 million in men), representing 45.0% of all deaths in the region, and although the number of deaths from CVD remained constant over the years, the annual median deaths estimate decreased from 393.2 to 241.8 deaths per 100 000 inhabitants, between 1990 and 2019. (Timmis et al., 2022)

Regarding Portugal, in 2019, 37.3 thousand people died from CVD (21.1 thousand in women and 16.2 thousand in men), representing 32.0% of all deaths. This indicator decreased between 1990 to 2015, from 45.8 thousand to 33.1 thousand deaths from CVD, however in the recent years it has increased. In terms of percentage, the number of deaths from CVD decreased from 48% in 1990 to 32% in 2019, however this decrease was slightly greater in women (from 54.0% to 36.0%) than in men (from 42.0% to 28.0%). (Timmis et al., 2022) The annual median deaths estimate also decreased between 1990 and 2015, from 365.6 to 127.7 deaths per 100 000 inhabitants of the country and remained relatively constant in the last years. (Timmis et al., 2022)

Furthermore, in 2019, 9.1 million people with > 20 years died from CAD (4.9 million men and 4.2 million women), representing almost 50.0% of CVD deaths worldwide and having been on the rise since 1990, when there were 5.7 million deaths from CAD (3.0 million in men and 2.7 million in women). (Timmis et al., 2022) On the opposite, the annual median deaths estimate for CAD decreased from 170.5 to 117.9 (144.6 in men and 95.1 in women) deaths per 100 000 inhabitants between 1990 and 2019. (Timmis et al., 2022)

In Europe, in 2019, 2.3 million people died from CAD (1.1 million men and 1.2 million women), representing a little more than 50.0% of CVD deaths and it was very similar to what happened in the region in 1990, however the annual median deaths estimate for CAD decreased from 222.8 to 132.0 (163.9 in men and 105.5 in women) deaths per 100 000 inhabitants of the region. (Timmis et al., 2022)

Regarding Portugal, in 2019, 13.0 thousand people (6.2 thousand men and 6.8 thousand women) died from CAD, representing around 33.0% of CVD deaths, decreasing from 15.9 to 11.7 thousand deaths from CAD, however it has increased a little in the last years, similarly to the pattern described by the number of deaths from CVD in the country. (Timmis et al., 2022) The annual median deaths estimate for CAD also decreased between 1990 and 2015, from 127.1 to

46.1 (59.0 in men and 35.0 in women) deaths per 100 000 inhabitants of the country and remained constant in the last few years. (Timmis et al., 2022)

In 2019, 53.1 million new cases of CVD were registered worldwide (26.7 million in men and 26.4 million in women), of which 21.2 million were newly diagnosed with CAD (12.5 million in men and 8.7 million in women). (Timmis et al., 2022) Of these numbers, 10.9 million (5.2 million in men and 5.7 million in women) new cases of CVD and 4.8 million (2.6 million in men and 2.2 million in women) new CAD diagnosis were registered in Europe and, more particularly, 95.7 thousand (46.0 thousand in men and 49.7 thousand in women) new cases of CVD and 19.2 thousand (12.3 thousand in men and 7.0 thousand in women) new CAD diagnosis in Portugal. (Timmis et al., 2022)

These differences observed between men and women were also verified in the annual median incidence estimates corresponding to each situation described immediately above being always higher in men. (Timmis et al., 2022)

At that time there were 506.3 million people living with CVD worldwide (239.6 million in men and 266.7 million in women), of which 197.1 million with CAD (113.6 million in men and 83.5 million in women). Of these numbers, 98.1 million (45.3 million in men and 53.5 million in women) CVD patients and 40.0 million (21.8 million in men and 18.2 million in women) CAD were living in Europe. In Portugal, there were 1.1 million people living with CVD (501.5 thousand in men and 583.0 thousand in women) of which 303.9 thousand people with CAD (186.5 thousand in men and 117.4 thousand in women). (Timmis et al., 2022)

In the same way as the annual median incidence estimates, the annual median prevalence estimates for the situations described immediately above was always higher in men. (Timmis et al., 2022)

1.2. Cardiovascular disease and coronary artery disease

CVDs are a group of disorders of the heart and blood vessels that include coronary heart disease (CHD) (disease of the blood vessels supplying the heart muscle), cerebrovascular disease (disease of the blood vessels supplying the brain), peripheral arterial disease (disease of blood vessels supplying the upper and lower limbs), rheumatic heart disease (damage to the heart muscle and heart valves from rheumatic fever), congenital heart disease (birth defects that affect the normal development and functioning of the heart caused by malformations); and deep vein thrombosis and pulmonary embolism (blood clots in the leg veins, which can dislodge and move to the heart and lungs). (WHO, 2021) In this project we are going to focus on CHD and its clinical presentation.

CHD is commonly used to describe CAD however they do not have the same meaning. CHD can be caused by CAD that affects the larger coronary arteries of the heart or coronary microvascular disease that affects the small arteries. Coronary microvascular disease happens when the heart's small blood vessels do not work normally. (American Heart Association, 2015; National Heart, Lung & Truth, 2018)

In most of the times, CHD is the result of CAD. CAD is a pathological process that can start in childhood and is characterized by atherosclerotic plaque accumulation in the coronary arteries. (Chen et al., 2017; Knuuti et al., 2020; Zhuang et al., 2020) CAD is a complex chronic inflammatory disease, characterized by remodeling and narrowing of the coronary arteries

supplying oxygen to the heart. (Sayols-Baixeras et al., 2014) It is a significant health concern, with a complex etiopathogenesis, including genetics and environmental factors such as diet and lifestyle and its prevalence is increasing. However, is preventable and can be reversed. This process can be modified by lifestyle adjustments, pharmacological therapies, and invasive interventions that will delay disease progression, promoting disease stabilization or regression. It is possible to prevent and regress the progression of CAD even before it causes CHD. (Chen et al., 2017; Knuuti et al., 2020; Sayols-Baixeras et al., 2014; Zhuang et al., 2020)

1.2.1. Pathophysiology

Atherosclerosis is the main process that causes CAD, with an important role of inflammation. It is a silent progressive chronic process characterized by accumulation of lipids, fibrous elements, and inflammatory molecules, primarily in the intima of the large- and medium-sized arteries. (Hansoon, 2005; Sayols-Baixeras et al., 2014)

This process is influenced by several CV risk factors and progresses throughout a person's life before finally manifesting itself. (Hansoon, 2005; Kumar & Cannon, 2009a; Sayols-Baixeras et al., 2014)

Atherosclerosis begins with the efflux of low-density lipoprotein (LDL) cholesterol to the subendothelial space. (Sayols-Baixeras et al., 2014) CV risk factors damage the endothelium resulting in endothelial dysfunction, for example, due to vasoconstrictor hormones inculpated in hypertension, the products of glycoxidation associated with hyperglycaemia or proinflammatory cytokines derived from excess adipose tissue, which impairs vascular hemostasis and increase thrombogenicity of blood. (Kumar & Cannon, 2009a; Libby & Theroux, 2005)

Furthermore, the increase in plasma cholesterol levels, associated to dyslipidaemia, results in changes of the arterial endothelial permeability allowing the infiltration and retention of lipids, especially LDL particles, in the arterial intima, where they can be modified and oxidized by various agents. (Bergheanu et al., 2017; Hansoon, 2005; Sayols-Baixeras et al., 2014; Visseren et al., 2021)

Oxidized LDL particles are potent chemotactic molecules that induce an increased expression of adhesion molecules, like the vascular-cell adhesion molecule 1 at the endothelial surface and inflammatory genes by endothelial cells, promoting monocyte adhesion and migration to the subendothelial space. (Bergheanu et al., 2017; Hansoon, 2005; Kumar & Cannon, 2009a; Sayols-Baixeras et al., 2014)

Once in the intima media, monocytes are induced to differentiate into macrophages by the macrophage colony-stimulating factor, produced in the inflamed intima. (Bergheanu et al., 2017; Hansoon, 2005; Kumar & Cannon, 2009a; Sayols-Baixeras et al., 2014)

Macrophages binds to oxidized LDL particles via scavenger receptors and if the cholesterol derived from the uptake of those LDL particles cannot be mobilized from the cell to a sufficient extent, this process enhances the accumulation of massive intracellular cholesterol, transforming the cell into a foam cell, the prototypical cell in atherosclerosis. (Bergheanu et al., 2017; Hansoon, 2005; Kumar & Cannon, 2009a; Sayols-Baixeras et al., 2014)

The result of this process is the formation of a fatty plaque, ich is considered the first typical atherosclerotic lesion. (Sayols-Baixeras et al., 2014)

Besides macrophages, other types of leukocytes, such as lymphocytes and mast cells, also accumulate in the subendothelial space and the cross-talk between them all results in a chronic inflammatory state with the production of several proinflammatory molecules, such as interleukins and tumor necrosis factor, that contribute to the process by recruiting additional macrophages and vascular smooth muscle cells into the plaque site. (Bergheanu et al., 2017; Hansoon, 2005; Sayols-Baixeras et al., 2014)

Once in the intima media, smooth muscle cells proliferate and produce extracellular matrix molecules, creating a fibrous cap that covers the original fatty streak. (Kumar & Cannon, 2009a; Libby & Theroux, 2005; Sayols-Baixeras et al., 2014)

Therefore, foam cells inside the fibrous cap die and release lipids that accumulate in the extracellular space. The result of this process is the formation of a fibrous plaque, which is considered the second atherosclerotic lesion. (Sayols-Baixeras et al., 2014)

The rate of progression of atherosclerotic lesions and the stability of atherosclerotic plaques are variable and unpredictable, however the thickness of the fibrous cap is the key for maintaining its integrity. (Bergheanu et al., 2017; Hansoon, 2005; Kumar & Cannon, 2009a; Sayols-Baixeras et al., 2014)

Taking this into account, atherosclerotic plaques can be divided into stable and unstable or vulnerable. (Bergheanu et al., 2017; Hansoon, 2005; Kumar & Cannon, 2009a; Sayols-Baixeras et al., 2014)

Stable plaques have an intact, thick fibrous cap composed of smooth muscle cells in a matrix rich in type I and III collagen, and displacement of this type of plaque in the lumen of the artery produces stenosis that limits blood flow, leading to tissue ischaemia and usually to stable angina. (Sayols-Baixeras et al., 2014)

Vulnerable plaques have a thin fibrous cap made mostly of type I collagen and few or none smooth muscle cells, but abundant macrophages and proinflammatory and prothrombotic molecules, capable of destabilize lesions. (Bergheanu et al., 2017; Hansoon, 2005; Kumar & Cannon, 2009a; Sayols-Baixeras et al., 2014)

These plaques are prone to erosion or rupture, exposing the core of the plaque to circulating coagulation proteins, leading to platelet adhesion, activation and aggregation and the subsequent formation of a thrombus, causing thrombosis, ischaemia, and usually result in an acute coronary syndrome (ACS). (Bergheanu et al., 2017; Hansoon, 2005; Kumar & Cannon, 2009a; Libby & Theroux, 2005; Sayols-Baixeras et al., 2014)

1.2.2. Signs and symptoms

Clinical sequelae of atherosclerosis are vessel narrowing with symptoms and ACS due to plaque instability. (Bergheanu et al., 2017) CAD can have long and stable periods but can also become unstable at any time. (Knuuti et al., 2020) Even in clinically apparently silent periods the disease is most often progressive and noncritical coronary lesions may be associated with abrupt progression to severe or total occlusion, underlining the importance of being aware to any sign or symptom. (Knuuti et al., 2020; Kumar & Cannon, 2009a) Furthermore, around 80% of patients with ACS exhibit multiple plaque ruptures distinct from the culprit lesion. (Kumar & Cannon, 2009a)

The results of CAD process can be categorized as either ACS or chronic coronary syndrome.

Chronic coronary syndromes are defined by the different evolutionary phases of CAD, excluding situations in which an ACS dominates the clinical presentation. Thus, patients with suspected or established chronic coronary syndromes can be presented according to the following clinical scenarios (Knuuti et al., 2020):

- Patients with suspected CAD and stable anginal symptoms, and/or dyspnea.
- Patients with new onset of heart failure (HF) or left ventricular (LV) dysfunction and suspected CAD.
- Asymptomatic and symptomatic patients with stabilized symptoms < 1 year after an ACS, or patients with recent revascularization, or > 1 year after initial diagnosis or revascularization.
- Patients with angina and suspected vasospastic or microvascular disease.
- Asymptomatic subjects in whom CAD is detected at screening.

However, all these scenarios involve different risks for future CV events and can be destabilized by the development of an ACS. This risk may be decreased in result of an appropriate secondary prevention and successful treatment. (Knuuti et al., 2020)

ACS, the ones being on focus on this research, refer to any group of symptoms compatible with acute myocardial infarction (AMI) and his clinical presentation ranges from patients with cardiac arrest, electrical or hemodynamic instability, in the presence of ongoing ischaemia or mechanical complications, to patients who are already pain free again at the time of the presentation. (Collet et al., 2021; Kumar & Cannon, 2009a)

Women, older patients, patients with diabetes mellitus (DM) type I or II, chronic renal disease, or dementia tend to present more often atypical symptoms. (Collet et al., 2021; Ibanez et al., 2018)

The leading symptom initiating the diagnostic and therapeutic cascade in patients with suspected ACS is chest discomfort described by a retrosternal sensation of pain, pressure, tightness, and burning. (Collet et al., 2021) This typical chest discomfort is called angina pectoris, commonly just angina, and is characterized into four categories: location, character, duration, and relationship to exertion, and other exacerbating or relieving factors. (Collet et al., 2021; Knuuti et al., 2020)

It is usually located in the chest, near the sternum but may radiate to the left arm, both arms, the right arm, the neck, or the jaw. Some additional less-specific symptoms such as sweating, nausea epigastric pain, dyspnea, syncope, and fatigue may be observed. Sometimes dyspnea is the only symptom of CAD and makes it challenging to diagnosis. (Collet et al., 2021; Knuuti et al., 2020)

Angina can be intermittent or persistent and in most of the cases the duration is brief (≤ 10 min), and more commonly just a few minutes or less. Chest pain lasting for seconds is unlikely to be due to CAD. (Collet et al., 2021; Knuuti et al., 2020)

The relationship to exercise is another parameter that helps characterize angina. Symptoms of angina classically appear or become more severe with increased levels of exertion and rapidly disappear within a few minutes when exercise is interrupted. Exacerbation of symptoms is also very common after a heavy meal (postprandial angina) or after waking up in the morning, although the mechanism is not still fully known. Findings suggest in those two moments there's a decrease in blood pressure lowering even more the already reduced blood

flow to the heart in CVD patients and a compensatory increase in cardiac output and heart rate (HR) that can lead to an earlier onset of angina. (Chung et al., 2002; Kearney et al., 1997; Knuuti et al., 2020) Angina may be reduced with further exercise (walk-through angina), on second exertion (warm-up angina), or through sublingual nitrates, that rapidly relieve the symptoms. (Knuuti et al., 2020)

According to all this, chest discomfort can be classified into typical or atypical angina or non-anginal chest-pain (Knuuti et al., 2020):

- Typical angina - meets the following three conditions:
  (i) Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm.
  (ii) Precipitated by physical exertion.
  (iii) Relieved by rest or nitrates within 5 min.
- Atypical angina - meets two of these conditions.
- Non-anginal chest pain - meets only one or none of these conditions.

This classification is practical and of proven value in determining the likelihood of obstructive CAD. Most patients suspected of having CAD present atypical or non-anginal chest pain, and just 10.0 – 15.0% present typical angina. (Knuuti et al., 2020)

Some of the characteristics of typical angina are its predictability, with a specific pattern, severity, and relief with rest; and its reproducibility, appearing in similar efforts. (Knuuti et al., 2020)

Other useful tool to characterize and classify angina is the Canadian Cardiovascular Society classification. It consists in a grading system, divided into 4 classes, used to quantify the threshold on which symptoms occur in relation to physical activities (Knuuti et al., 2020):

- Grade I - Angina only with strenuous exertion: Presence of angina during strenuous, rapid, or prolonged ordinary activity, such as brisk walking or climbing stairs.
- Grade II - Angina with moderate exertion: Slight limitation on ordinary activities when they are performed rapidly, after meals, in cold, in wind, under emotional stress, or during the first few hours after waking up, but also walking uphill, climbing more than one flight of stairs at a normal pace, and in normal conditions.
- Grade III - Angina with mild exertion: Having difficulties to walk one or two blocks, or climbing one flight of stairs, at normal pace and conditions.
- Grade IV - Angina at rest: No exertion needed to trigger angina.

Physical examination is important to assess the presence of other clinical conditions such as anemia, hypertension, arrhythmias, among others, and therefore it is recommended to try to reproduce the symptoms through palpation and to test the reaction to the administration of sublingual nitroglycerin. In addition, it is recommended that professionals obtain body mass index (BMI) and look for evidence of non-coronary vascular disease, which may be asymptomatic, and other signs of comorbidities, such as thyroid disease, kidney disease or DM. (Knuuti et al., 2020)

Angina can also be characterized into stable or unstable. Unstable angina is defined as myocardial ischaemia at rest or on minimal exertion in the absence of acute cardiomyocyte

injury/necrosis and may present in one of three ways (Collet et al., 2021; Knuuti et al., 2020; Kumar & Cannon, 2009a):

- As rest angina, i.e. pain of characteristic nature and location occurring at rest and for prolonged periods, usually lasting > 20 min.
- New-onset angina, i.e. recent (2 months) onset of moderate-to-severe angina (Canadian Cardiovascular Society grade II or III).
- Crescendo angina, i.e. previous angina, which progressively increases in severity and intensity, and at a lower threshold, over a short period of time.

Some of the characteristics of unstable angina are its variable pattern, its occurrence at rest or in minimal physical efforts, occurring more frequently and with a greater degree of severity than stable angina. (Collet et al., 2021; Knuuti et al., 2020; Kumar & Cannon, 2009a)

ACS covers the spectrum of clinical conditions ranging from unstable angina to ST-segment elevation myocardial infarction (STEMI) to non-ST-segment elevation myocardial infarction (NSTEMI). (Kumar & Cannon, 2009a) Patients with ST-segment elevation acute coronary syndrome and patients with no persistent ST-segment elevation, which can develop STEMI and NSTEMI, respectively, can be differentiated based on the electrocardiogram (ECG) (Collet et al., 2021; Kumar & Cannon, 2009b):

- ST-segment elevation ACS patients: Patients with acute chest pain and persistent (> 20 min) ST-segment elevation that generally reflects an acute total or subtotal coronary occlusion.
- No persistent ST-segment elevation ACS patients: Patients with acute chest discomfort but no persistent ST-segment elevation. These patients exhibit ECG changes like transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, among others, however, in some cases, the ECG may be normal.

There are several clinical conditions that can mimic the effects of ACS. Thus, among patients presenting with acute chest pain in the emergency department, the estimated prevalence of disease is 5.0 – 10.0% for STEMI, 15.0 – 20.0% for NSTEMI, 10.0% for UA, 15.0% for other cardiac conditions, and 50.0% for non-cardiac diseases. (Collet et al., 2021)

Unstable angina and NSTEMI are closely related conditions, with similar pathophysiology and clinical presentations, but differ in severity. A diagnosis of NSTEMI may be made when the ischaemia is severe enough to cause myocardial damage that results in the release of biomarkers of myocardial necrosis into the bloodstream, such as cardiac specific troponins T or I. If hours after onset of pain, no biomarker is detected in blood circulation, the diagnosis will be UA. (Kumar & Cannon, 2009a) Compared with NSTEMI, unstable angina patients have a lower risk of death. The use of measurements such as high sensitivity cardiac troponin (hs-cTn) T or I allows to improve and specify the diagnosis between these two clinical conditions, resulting in an increase in the detection of AMI and a decrease in the diagnosis of unstable angina. (Collet et al., 2021)

The term AMI defines cardiomyocyte necrosis in a clinical picture compatible with acute myocardial ischaemia and should be used when there is evidence of myocardial injury, defined as an increase in cardiac troponin values. (Collet et al., 2021; Ibanez et al., 2018)

AMI's usually are the first manifestations of CAD and its diagnosis requires a combination of criteria, namely the detection of an increase and/or decrease in a cardiac biomarker, preferably hs-cTn T or I, and at least one of the following (Collet et al., 2021):

- Symptoms of myocardial ischaemia.
- New ischemic ECG changes.
- Development of pathological Q waves on ECG.
- Imaging evidence of loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.
- Intracoronary thrombus detected on angiography or autopsy.

There are several types of AMI's which are described below (Collet et al., 2021):

- Type 1 AMI: Type 1 AMI is characterized by atherosclerotic plaque rupture, ulceration, fissure, or erosion with resulting intraluminal thrombus in one or more coronary arteries leading to decreased myocardial blood flow and/or distal embolization and subsequent myocardial necrosis. The patient may have underlying CAD or, in some cases, non-obstructive coronary atherosclerosis or no angiographic evidence of CAD, particularly in women.
- Type 2 AMI: Type 2 AMI is defined when myocardial necrosis occurs due to a condition other than coronary plaque instability that leads to an imbalance between myocardial oxygen supply and demand. Blood pressure alterations, arrhythmias, anemia, and hypoxemia are some of the mechanisms but also coronary artery spasm, spontaneous coronary artery dissection, coronary embolism, and coronary microvascular dysfunction can lead to type 2 AMI.
- Types 3, 4 and 5 AMI: Besides the previous types, type 3 AMI is described when death occurs as a result of AMI and biomarkers are not available, and types 4 and 5 AMI are related to percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), respectively.

1.2.3. Diagnosis

The diagnosis has an impact on the prognosis of CVD and is essential for choosing therapeutic options. Thus, a quick and accurate diagnosis has long-term benefits for the patient. In suspected CAD patients, several diagnostic tests should be performed in order to assess cardiac anatomy and function as standard laboratory biochemical testing, a resting ECG, a possible ambulatory ECG monitoring, an echocardiographic study, a possible ultrasound of the carotid arteries, a cardiac magnetic resonance, in some cases, a chest X-ray, and a coronary angiography. (Collet et al., 2021; Knuuti et al., 2020; Montalescot et al., 2013)

Laboratory tests are useful in identifying causes of ischaemia, for example through haemoglobin or thyroid hormone levels, and help to detect CV risk factors. (Knuuti et al., 2020; Montalescot et al., 2013)

Fasting plasma glucose (FPG) and glycated haemoglobin should be measured in every CAD patient, and if both tests are inconclusive, an additional oral glucose tolerance test is recommended. (Knuuti et al., 2020; Montalescot et al., 2013)

A lipid profile analysis, including total cholesterol (total-c), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (TG), should also be evaluated to ascertain establish the risk profile of the patient and, consequently, determine the need for treatment. (Knuuti et al., 2020; Montalescot et al., 2013)

Renal dysfunction is often associated with other CV risk factors and has a negative impact on prognosis, so baseline renal function should also be evaluated, with estimation of the glomerular filtration rate using a creatinine-based method. (Montalescot et al., 2013)

If there is clinical suspicion of CAD instability, biochemical markers of myocardial injury should be measured, preferably using high sensitivity assays such as hs-cTn T or I. Elevated troponin levels indicate possible incremental value in diagnosing CAD and in addition to this diagnostic utility, baseline cardiac troponin levels add prognostic information in short- and long-term mortality. Serial measurements of troponin will also allow identifying peaks of cardiac troponin and stratifying risk in patients with previous AMI. Although hs-cTn T and I have comparable diagnostic accuracy, hs-cTn T has greater prognostic accuracy. (Collet et al., 2021; Knuuti et al., 2020; Montalescot et al., 2013)

The resting 12-lead ECG is the first-line diagnostic tool in the assessment of patients with suspected ACS and allows identifying signs of CAD, including previous AMI's or abnormal repolarization pattern. It also provides information about dynamic changes in the ST segment in the presence of ischaemia, LV hypertrophy, left or right bundle branch block, arrhythmias, or conduction defects electric and may be helpful in defining the mechanisms responsible for chest pain. (Collet et al., 2021; Knuuti et al., 2020; Montalescot et al., 2013)

It is also possible to perform an ambulatory ECG monitoring (Holter). Holter is a non-invasive test useful in detecting signs of myocardial ischaemia during normal daily activities, and in detecting and characterizing cardiac arrhythmias, although in CAD patients, it rarely adds important diagnostic information. (Montalescot et al., 2013)

An echocardiographic study, through resting two-dimensional and Doppler transthoracic echocardiography, is useful to identify abnormalities suggestive of myocardial ischaemia or necrosis and will provide important information about cardiac function, for example about LV function, and cardiac anatomy. (Collet et al., 2021; Knuuti et al., 2020; Montalescot et al., 2013)

Although LV function is often normal in CAD patients, regional wall motion abnormalities may be detected. A decreased LV function and/or regional wall motion abnormalities may increase the suspicion of ischemic myocardial damage and the probability of CAD. Thus, assessment of LV function should be performed in all symptomatic patients with suspected CAD. (Collet et al., 2021; Knuuti et al., 2020; Montalescot et al., 2013)

It is also possible to observe patterns of LV dysfunction making echocardiography particularly useful in patients with murmurs, previous AMI, or symptoms/signs of HF. (Collet et al., 2021; Knuuti et al., 2020; Montalescot et al., 2013)

Moreover, echocardiography can help in detecting alternative pathologies associated with chest pain, such as acute aortic dissection, pericardial effusion, aortic valve stenosis, hypertrophic cardiomyopathy, among others, and is the diagnostic tool of choice for patients with hemodynamic instability of suspected cardiac origin. (Collet et al., 2021; Knuuti et al., 2020; Montalescot et al., 2013)

After the echocardiogram, ultrasound of the carotid arteries can be added to the examination to detect possible increases in intima-media thickness and/or plaques and thus

establish the presence of atherosclerotic disease increasing the probability of CAD. (Montalescot et al., 2013)

Cardiac magnetic resonance may also be used to define structural cardiac abnormalities and evaluate LV function and should be considered in patients with suspected CAD when the echocardiogram is inconclusive. (Collet et al., 2021; Knuuti et al., 2020; Montalescot et al., 2013) This exam can assess both perfusion and wall motion abnormalities, detect of scar tissue from a previous AMI and facilitate the diagnosis between AMI or other CVDs. Patients with a normal cardiac magnetic resonance have an excellent short- and mid-term prognosis. (Collet et al., 2021) Myocardial perfusion imaging is also widely used to diagnose regional ischaemia caused by obstructive coronary plaque. (Timmis et al., 2022)

Chest X-ray is frequently used in the assessment of patients with chest pain, however, in CAD patients, it does not provide specific information for diagnosis. It might be useful in CAD patients with pulmonary problems or to rule out another cause of chest pain in atypical situations. (Knuuti et al., 2020; Montalescot et al., 2013)

Coronary angiography is a procedure that aims to identity the stenosis in coronary arteries and can clarify the origin of supposed anginal chest pain and whether it is effectively the result of myocardial ischaemia. It carries a certain risk for procedure related complications. Coronary angiography can be done in both invasive and non-invasive methods, but the European guidelines recommend the use of non-invasive diagnostic tests and they have been shown to establish the probability of CAD with an acceptable degree of certainty. (Collet et al., 2021; Montalescot et al., 2013; Timmis et al., 2022)

Computed tomography coronary angiography provides a non-invasive diagnostic method that allows visualization of the coronary arteries, and a normal scan can be used to exclude obstructive CAD. (Collet et al., 2021; Timmis et al., 2022)

However, invasive coronary angiography, as the cardiac catheterization with coronary angiography, is still one of the most frequently performed diagnostic tests in patients with suspected CAD and the gold-standard exam in the diagnosis of anatomical evaluation. (Timmis et al., 2022) Invasive coronary angiography will only be performed after recurrent symptoms, objective evidence of inducible ischaemia on non-invasive testing, or detection of obstructive CAD by computed tomography coronary angiography and never in patients with angina who refuse invasive procedures, who are not eligible for PCI or CABG, or in whom revascularization is not expected to improve functional status or quality of life. (Collet et al., 2021; Montalescot et al., 2013)

Invasive coronary angiography has some limitations in the identification of vulnerable plaques, however, the extent, severity of luminal obstruction and location of CAD observed in the exam have been demonstrated to be important prognostic indicators, for example used to relate severity of disease and the risk of subsequent CV events. One of the most widely used indicators is the classification of disease into one-vessel, two vessel, three-vessel, or left main stem CAD. (Montalescot et al., 2013)

1.2.4. Treatment of Coronary Artery Disease

Currently, there are many resources that can be used in the treatment of CAD, particularly through pharmacological therapy or revascularization strategies. The two are not mutually exclusive, on the contrary, CAD can be treated only by pharmacological therapy or combined with one of the existing revascularization techniques.

After the angiographic diagnosis, some important factors, such as coronary anatomy, ventricular function, functional capacity, severity of symptoms and the amount of viable myocardium at risk, must be taken into account in order to understand the need for a strategy of revascularization and help in the decision to revascularize a patient. (Ibanez et al., 2018; Kumar & Cannon, 2009b)

1.2.4.1. Pharmacological therapy

The two aims of the pharmacological management of CAD patients are to obtain relief of symptoms and to prevent CV events. (Montalescot et al., 2013) In secondary prevention, medical therapy is almost invariably needed in addition to lifestyle optimization. (Bergheanu et al., 2017) Within pharmacological therapy it is important to talk about lipoprotein modification, anti-ischemic, antithrombotic, glucose-lowering, diuretics and antiarrhythmics (AAD) therapies.

Lipoprotein modification therapy: Medication to adequately control lipoprotein levels, according to the 2018 ESC/EACTS Guidelines on myocardial revascularization, needs to be initiated when risk reduction through lifestyle modifications is not sufficient and after a CV event, it should be started as early as possible and administered as high-intensity treatment as it increases patient compliance after discharge and is associated with clinical benefits. (Bergheanu et al., 2017; Ibanez et al., 2018) This therapy includes 3-hydroxy-3-methyl–glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, cholesterol absorption inhibitors, bempedoic acid, cholesteryl ester transfer protein inhibitors, proprotein convertase subtilisin/kexin type-9 (PCSK-9) inhibitors and fibrates.

- **HMG-CoA reductase inhibitors:** HMG-CoA reductase inhibitors**,** also known as statins, for example, atorvastatin, pitavastatin, rosuvastatin or simvastatin, induce an increased expression of LDL receptors on the surface of the hepatocytes leading to an increase in the uptake of LDL from the blood. (American Heart Association, 2020b; Bergheanu et al., 2017) The benefits of statins in secondary prevention have been unequivocally demonstrated, leading to a decrease in plasma concentration of LDL cholesterol and TG, and HDL cholesterol elevations between 5.0 – 10.0%. Statins effectively prevent CV events and reduce CVD mortality. Thus, they are the first-choice therapy approach in patients with high TG. Besides they are also recommended in all AMI patients, independently of cholesterol concentration at presentation. (Bergheanu et al., 2017; Cosentino et al., 2020; Ibanez et al., 2018; Visseren et al., 2021) Drugs other than statins are generally used only for patients in whom statins are not effective or who experience serious side effects from statin therapy. (American Heart Association, 2020b)

- **Cholesterol absorption inhibitors:** Cholesterol absorption inhibitors like ezetimibe inhibits intestinal cholesterol uptake and thereby reduces cholesterol transport to the liver, which can lead to reductions in plasma concentration of LDL cholesterol up to 15.0 – 22.0%. (Krychtiuk & Speidl, 2021) Sometimes it is used in combination with statins leading to a further reduction in LDL cholesterol levels of 15.0 – 20.0%. (Bergheanu et al., 2017; Cosentino et al., 2020; Visseren et al., 2021)

- **Bempedoic acid:** Bempedoic acid is an oral small molecule inhibiting cholesterol synthesis within the liver by blocking adenosine triphosphate citrate lyase, an enzyme upstream of HMG-CoA reductase, and it has less side effects compared with statins. It can be used in combined therapies with statins, decreasing LDL cholesterol levels by 17.0%, or with ezetimibe, decreasing LDL cholesterol levels by 36.0%. (Krychtiuk & Speidl, 2021)

- **Cholesteryl ester transfer protein inhibitors:** Cholesteryl ester transfer protein inhibitors are the most efficient drugs to increase HDL cholesterol and frequently lead to a reduction in LDL cholesterol levels as well. (Bergheanu et al., 2017)

- **PCSK-9 inhibitors:** PCSK-9 binds to LDL receptors and stimulates their absorption and degradation. Thus, the PCSK-9 inhibition prevents LDL receptors degradation thereby improving LDL cholesterol absorption and consequently a decrease in LDL cholesterol plasma levels, that can reach up to 60.0%, and also have beneficial effects on TG and HDL cholesterol. (Bergheanu et al., 2017; Ibanez et al., 2018; Timmis et al., 2022) This therapy can achieve even lower levels than the statin and ezetimibe combination and is recommended for secondary prevention patients that cannot achieve targets on a maximum tolerated dose of the statin and ezetimibe combination. (Bergheanu et al., 2017; Timmis et al., 2022; Visseren et al., 2021)

- **Fibrates:** Fibrates are agonists of peroxisome proliferator-activated receptor-α and have important functions in lipid and lipoprotein metabolism steps. They are used primarily for TG lowering, decreasing TG levels up to more than 50.0%, and occasionally, for increasing HDL cholesterol values, reaching increases between 5.0 – 15.0%. (Bergheanu et al., 2017; Visseren et al., 2021)

Anti-ischemic therapy: Anti-ischemic therapy is important in the relieve of ischemic pain and for secondary prevention, decreasing the rates of CV events and improving CV prognosis. (Kumar & Cannon, 2009b) It includes beta-adrenergic antagonists (β-blockers), calcium channel blockers, nitrates, and blockers of renin-angiotensin-aldosterone system (RAAS).

- **β-Blockers:** β-blockers, like atenolol, bisoprolol, carvedilol, metoprolol, nebivolol and propranolol, among others, act directly on the heart reducing myocardial oxygen consumption by lowering HR, blood pressure and myocardial contractility. (American Heart Association, 2020b; Collet et al., 2021; Montalescot et al., 2013; Rosendorff et al., 2015) Additionally, they may increase perfusion of ischemic areas and vascular resistance in non-ischemic areas. (Montalescot et al., 2013) They are indicated to post-

AMI patients, patients with stable angina or LV dysfunction and their benefits are well established, decreasing the rates of recurrent ischaemia and reinfarction, CVD mortality and all-cause mortality. (Cosentino et al., 2020; Dan et al., 2018; Ibanez et al., 2018; Kumar & Cannon, 2009b; Montalescot et al., 2013; Rosendorff et al., 2015) In addition, they are effective at reducing both exercise induced angina and asymptomatic ischemic episodes, while improving exercise capacity. Carvedilol and nebivolol may be preferred because of their ability to improve insulin sensitivity. (Cosentino et al., 2020)

- **Calcium Channel Blockers:** Calcium channel blockers, like verapamil, diltiazem, felodipine and nifedipine, among others, interrupt the movement of calcium into the cells of the heart and blood vessels leading to vasodilation and reduction of the peripheral vascular resistance, and are associated with a reduction of CV events and mortality in post-AMI patients. (American Heart Association, 2020b; Kumar & Cannon, 2009b; Montalescot et al., 2013; Rosendorff et al., 2015) This drugs are indicated for the relief of angina symptoms and are reasonable options when β-blockers are contraindicated or not tolerated. (Cosentino et al., 2020; Ibanez et al., 2018; Rosendorff et al., 2015)

- **Nitrates:** Nitrates offer coronary arteriolar and venous vasodilatation, which are the basis of symptomatic relief of angina symptoms, acting by their active component nitric oxide and by the reduction of preload. (Montalescot et al., 2013) There are short-acting, like nitroglycerin, and long-acting nitrates. Short-acting nitrates are useful during the acute phase of angina and are frequently used when β-blockers are contraindicated or not tolerated. (Cosentino et al., 2020; Ibanez et al., 2018; Montalescot et al., 2013) Within these, sublingual nitroglycerin is the standard initial therapy for effort angina and can be used when angina can be expected, however intravenous nitrates are more effective for symptom relief and resolution of ST depressions in the ECG. (Collet et al., 2021; Montalescot et al., 2013) On the other hand, long-acting nitrates are used for angina prophylaxis. (Montalescot et al., 2013) In addition, following the acute phase, nitrates remain important to control residual angina symptoms however must be taken with nitrate-free or nitrate-low intervals to be continuously effective. (Ibanez et al., 2018)

- **RAAS blockers:** The activation of the RAAS plays a key role in the development and progression of CVD, especially in arterial hypertension, HF and CAD. (Asenjo et al., 2017) Thus, blockers of this system, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), are useful tools and have beneficial effects in CAD treatment. Angiotensin Receptor-Neprilysin Inhibitors (ARNIs) may also be considered for therapy by combination.

    - **ACE inhibitors:** ACE inhibitors, like benazepril, enalapril, lisinopril or ramipril, are the most used and studied RAAS blockers and act by lowering levels of angiotensin II promoting neurohormonal modulatory effects, which have vasodilatory, anti-inflammatory, plaque-stabilizing, antithrombotic and anti-proliferative effects. (American Heart Association, 2020b; Asenjo et al., 2017) Treatment with ACE inhibitors is recommended in CAD patients, especially in those who experienced a STEMI, or in those with co-existing hypertension, systolic LV dysfunction, DM or chronic kidney disease. (Cosentino et al., 2020;

Ibanez et al., 2018; Kumar & Cannon, 2009b; Montalescot et al., 2013; Rosendorff et al., 2015) They are associated with a decrease in total mortality, AMI, stroke, and HF. (Kumar & Cannon, 2009b; Montalescot et al., 2013) It has been demonstrated that the greatest reduction in mortality occurs in the first 5 days after AMI, reinforcing the benefits and the need for early treatment with ACE inhibitors. (Kumar & Cannon, 2009b)

- **ARBs:** ARBs, like candesartan, losartan, olmesartan or valsartan, have similar pharmacological properties to ACE inhibitors although rather than lowering levels of angiotensin II, they also prevent this chemical from having any effect on the heart and blood vessels, preventing increases in blood pressure. (American Heart Association, 2020b; Asenjo et al., 2017) As ARBs are more expensive and have not shown any additional clinical benefits over ACE inhibitors, they are usually considered as an alternative therapy and so ARBs, preferably valsartan, should be given when ACE inhibitors are indicated but not tolerated. (Asenjo et al., 2017; Cosentino et al., 2020; Ibanez et al., 2018; Montalescot et al., 2013; Rosendorff et al., 2015) Combining ACE inhibitors and ARBs has been shown not to be beneficial for secondary prevention of CV events, so they are not usually used in combination. (Rosendorff et al., 2015)

- **ARNIs:** ARNIs are a drug combination of a neprilysin inhibitor, like sacubitril, and ARBs in a single pill and the first-in-class ARNIs is the combination sacubitril/valsartan. Neprilysin is an endogenous enzyme that degrades natural vasoactive peptides in the body, blocking its effects in the vessels. Thus, pharmacological inhibition of neprilysin will lead to increase in the levels of those peptides, enhancing natriuresis, myocardial relaxation and a decrease in renin and aldosterone secretion. (American Heart Association, 2020b; Collet et al., 2021)

Antithrombotic therapy: Antithrombotic therapy includes both antiplatelet and/or anticoagulation therapy and it is used to limit the consequences of myocardial ischaemia, enhance myocardial healing, and reduce the likelihood of recurrent events. Moreover, in STEMI patients the therapy goal is to establish and maintain patency of the infarct-related artery. (Kumar & Cannon, 2009b) Regarding NSTEMI patients, activation of blood platelets and the coagulation cascade play a key role in the initial phase and evolution, so it is a mandatory treatment. (Collet et al., 2021) All these targets are reached through a combination of platelet inhibition and temporary anticoagulation, particularly in NSTEMI patients undergoing PCI. (Collet et al., 2021; Kumar & Cannon, 2009b)

- **Antiplatelets:** Antiplatelets, like aspirin, P2Y12 receptor inhibitors and glycoprotein IIb/IIIa inhibitors prevent the formation of blood clots by inhibiting blood platelet adhesion. (American Heart Association, 2020b)

    - **Aspirin:** Aspirin acts via irreversible inhibition of platelet cyclooxygenase and thromboxane A2-dependent platelet aggregation. (Collet et al., 2021; Cosentino et al., 2020; Montalescot et al., 2013) It is recommended for secondary prevention in low doses (75.0 – 100.0 mg), due to those anti-ischemic

effects and is associated to a decrease in mortality rates among patients with evolving AMI. (Collet et al., 2021; Cosentino et al., 2020; Ibanez et al., 2018; Kumar & Cannon, 2009b; Visseren et al., 2021)

- **P2Y12 receptor inhibitors:** P2Y12 receptor inhibitors, like clopidogrel, ticagrelor and prasugrel, act as antagonists of the platelet adenosine diphosphate receptor P2Y12, thereby inhibiting platelet aggregation. (Collet et al., 2021; Montalescot et al., 2013) Clopidogrel is characterized by a less potent and variable platelet inhibition and should only be used when prasugrel or ticagrelor are contraindicated, not available, or cannot be tolerated; Ticagrelor led to more patients stopping medication because of side effects; Prasugrel is associated with an improved endothelial function, that lead to a decrease in CV events incidence and should be considered the preferred P2Y12 receptor inhibitor. (Collet et al., 2021; Cosentino et al., 2020)

- **Dual antiplatelet therapy (DAPT):** DAPT consists in combining aspirin and a P2Y12 receptor inhibitor and is the standard antithrombotic treatment for patients with ACS, including after the acute phase, for secondary prevention. (Collet et al., 2021; Cosentino et al., 2020; Ibanez et al., 2018; Montalescot et al., 2013) It is recommended for up to 12 months unless there are contraindications such as excessive risk of bleeding. (Ibanez et al., 2018; Visseren et al., 2021) In patients with ACS, DAPT with prasugrel or ticagrelor on a background of low-dose aspirin was superior to DAPT with clopidogrel, leading to a decrease in CV events incidence, without an increase in major bleeding. (Cosentino et al., 2020)

- **Anticoagulants:** Anticoagulants like apixaban, dabigatran, edoxaban, heparin, rivaroxaban and warfarin are used to decrease the clotting ability of the blood, although they do not dissolve existing blood clots. (American Heart Association, 2020b) Anticoagulation therapy is recommended for all NSTEMI patients, in addition to antiplatelet treatment, at the time of diagnosis and, especially, during revascularization procedures. (Collet et al., 2021) For example, unfractionated heparin has been the mainstay of STEMI treatment for many years and the standard of care for NSTEMI patients due to its favorable risk benefit profile. (Collet et al., 2021; Kumar & Cannon, 2009b)

Glucose-lowering therapy: Several drugs, such as metformin, sulfonylureas, insulin, glucagon-like peptide-1 receptor agonists, sodium-glucose co-transporter 2 inhibitors, among others, can be used to lower blood glucose levels contributing to the improvement of CVD prognosis by reducing CV risk. (Cosentino et al., 2020)

- **Insulin:** Insulin is the hormone produced and secreted in the ideal amount by the pancreas in normal conditions, but not in DM patients. Various different types may be prescribed according to their time of action but all of them are injected into the fat under the skin to reach the bloodstream. (American Heart Association, 2021)

- **Metformin:** Metformin is an oral antidiabetic drug of the biguanide class that decreases the amount of glucose produced in the liver and is the first-line therapy in type 2 DM patients. (American Heart Association, 2021)

- **Sulfonylureas:** Sulfonylureas, such as glimepiride and glipizide, helps the pancreatic cells release more insulin however, is less effective than the therapy with metformin. (American Heart Association, 2021; Cosentino et al., 2020)

- **Thiazolidinediones:** Thiazolidinediones, such as pioglitazone, helps insulin work better and lowers the glucose produced in the liver. (American Heart Association, 2021)

- **Dipeptidyl peptidase-4 inhibitors:** Dipeptidyl peptidase-4 inhibitors, such as linagliptin and sitagliptin, prevents the breakdown of the hormone incretin that is involved in the control of insulin production and therefore can help in blood glucose decrease. (American Heart Association, 2021)

- **Glucagon-like peptide-1 receptor agonists:** Glucagon-like peptide-1 receptor agonists, such as exenatide, liraglutide, lixisenatide and semaglutide, are indicated in primary and secondary prevention of CV events in DM patients. (American Heart Association, 2021; Cosentino et al., 2020; Visseren et al., 2021) It helps release insulin when nedeed and lowers the glucose produce by the liver. (American Heart Association, 2021) They improve CV parameters, including a reduction in SBP and weight loss, and have direct vascular and cardiac effects that lead to CV benefits like a decrease in the rates of major adverse CV events, CV death, and all-cause mortality by around 12.0% and and also a 9.0% reduction in the occurrence of AMI and 16.0% in the case of stroke. (Cosentino et al., 2020; Visseren et al., 2021)

- **Sodium-glucose co-transporter 2 inhibitors:** Sodium-glucose co-transporter 2 inhibitors, such as empagliflozin, canagliflozin and dapagliflozin, prevent glucose from being reabsorbed in the kidneys and are associated to a reduction in the rate of major adverse CV events by 14.0% and in CV death by 24.0%. (American Heart Association, 2021; Cosentino et al., 2020; Timmis et al., 2022; Visseren et al., 2021) Reductions in renal endpoints were also seen suggesting these benefits are more related to cardiorenal hemodynamic effects than to atherosclerosis. (Visseren et al., 2021)

Diuretics therapy: Diuretics, in which thiazide/thiazide-like diuretics and mineralocorticoid receptor antagonists are included, have an important role in hypertension treatment and are effective in primary and secondary prevention of CV events, being associated to the prevention of CVD morbidities and a decrease in mortality. (Rosendorff et al., 2015; Williams et al., 2018) Besides they appear to be the most effective drug in HF prevention. (Williams et al., 2018) Diuretics increase the excretion of sodium and water by the kidneys, leading to a decrease in blood volume and blood pressure, helping to reduce the heart's workload. (American Heart Association, 2020b; Mullens et al., 2019)

- **Thiazide/thiazide-like diuretics:** Classical thiazide diuretics, such as hydrochlorothiazide and bendrofluazide, and thiazide-like diuretics, such as chlorthalidone and indapamide, are highly effective in the long-term control of blood pressure and preventing

cerebrovascular events. (Rosendorff et al., 2015) Although chlorthalidone and indapamide are more potent than hydrochlorothiazide in lowering blood pressure and have a longer duration of action, it has not been given any preference between classical thiazide or thiazide-like diuretics. (Williams et al., 2018) Combining RAAS with thiazide diuretics has shown important clinical benefits in secondary prevention. (Rosendorff et al., 2015)

- **Mineralocorticoid receptor antagonists:** Mineralocorticoid receptor antagonists, such as eplerenone or spironolactone, are recommended in post-AMI patients with LV dysfunction and have either DM or HF and some studies indicate benefits for early treatment. (Cosentino et al., 2020; Ibanez et al., 2018; Montalescot et al., 2013) Eplerenone and spironolactone are aldosterone receptor antagonists that can decrease blood pressure and have been shown to reduce morbidity and mortality. (Cosentino et al., 2020; Ibanez et al., 2018; Rosendorff et al., 2015)

AAD therapy: AADs have an important role as symptomatic therapy, to prevent the deterioration of cardiac function by tachycardia, irregular rhythm, or dyssynchrony and the transformation of well-tolerated arrhythmias into malignant arrhythmias. Most of them act on the cardiac ion channels and can lead to the alteration of excitability, effective refractory period, conduction, or abnormal automaticity. AADs include other some of other drugs already mentioned and are divided in four classes: Class I - Na+ channel blockers; Class II - β-blockers; Class III - K+ channel blockers and Class IV - Non-dihydropyridine L-type Ca2þ channel blockers. (Dan et al., 2018)

Regarding ACS, it is recommended the early use of β-blockers, particularly in cases of recurrent of polymorphic ventricular tachycardia because it reduces the incidence ventricular arrhythmias. Amiodarone, a class III AAD, may be considered for relief of symptoms from ventricular arrhythmias, particularly in cases of frequent ventricular tachycardia or ventricular fiblrillation episodes no longer controlled by electrical cardioversion or defibrillation, and represent an alternative in patients who are not eligible for, or who do not have access to the therapy with implantable devices. Lidocaine, a class I AAD, can also be used and reduce the incidence of ventricular arrhythmias related to myocardial ischaemia. Compared with amiodarone it seems to have a more favorable safety profile. (Dan et al., 2018)

Despite all this, there is no evidence that AADs decrease total mortality in patients with ventricular arrhythmias post-AMI and neither as prophylactic treatment in ACS patients without ventricular arrhythmias. (Dan et al., 2018)

1.2.4.2. Revascularization strategies

Currently, the three available revascularization strategies are PCI, fibrinolysis, and CABG, with PCI and CABG being the most widely used. Regardless of the reperfusion mode, the concept aims to minimize the total ischaemia time and prevent associated complications, relieve symptoms, and improve prognosis and functional capacity. (Kumar & Cannon, 2009b) Studies have shown that revascularization by PCI or CABG are more effective on relieving angina, reducing the use of anti-anginal drugs, and to improve exercise capacity and quality of life compared with a strategy of medical therapy alone. (Neumann et al., 2019)

PCI: PCI refers to a family of percutaneous techniques, considered less invasive, that utilizes cardiac catheters for revascularization of obstructed coronary arteries which includes percutaneous transluminal coronary angioplasty, intracoronary stenting, among others and can be described as a therapeutic intervention performed within the same procedure as the diagnostic coronary angiography.(American Heart Association, 2020a; Kumar & Cannon, 2009a; Neumann et al., 2019; Timmis et al., 2022)

The majority of performed PCIs involve balloon dilatation and coronary stenting. (Kumar & Cannon, 2009b) An attached deflated balloon is threaded up to the coronary arteries and inflated to widen blocked areas where blood flow to the heart muscle has been reduced or cutoff. A stent is then implanted to help in the artery dilatation and thus reduce the risk of future obstructions. (American Heart Association, 2020a)

A median of 1879.0 PCI procedures per million inhabitants of European countries were reported in 2020. (Timmis et al., 2022)

Besides the increase in blood flow, PCI decreases chest pain and increases ability for physical activity that has been limited by angina or ischaemia. (American Heart Association, 2020a) In stable CAD patients, it does not necessarily protect against AMI, however, in patients with AMI, primary PCI reduces eventual infarct size and mortality. (Neumann et al., 2019; Timmis et al., 2022)

Primary PCI is the preferred reperfusion strategy in patients with STEMI within 12 h of symptom onset and the main challenge lies in the ability to implement it promptly. (Ibanez et al., 2018; Kumar & Cannon, 2009b; Neumann et al., 2019)

A median of 523.0 primary PCI procedures per million inhabitants of European countries were reported in 2020. (Timmis et al., 2022)

Fibrinolysis: Fibrinolysis is an important pharmacological reperfusion strategy indicated for STEMI patients and consists in the injection of fibrinolytics bolus preferably within 10 min from STEMI diagnosis. It is recommended within 12 hours of symptom onset if primary PCI cannot be performed within 120 min from STEMI diagnosis. (Ibanez et al., 2018; Kumar & Cannon, 2009b)

This therapy is demonstrated to reduce mortality preventing 30 early deaths per 1000 patients treated within 6 hours after symptom onset. (Ibanez et al., 2018; Kumar & Cannon, 2009b) This benefit was observed among CAD patients irrespective of age, sex, blood pressure, HR, or a history of AMI or DM. (Ibanez et al., 2018)

Primary PCI vs Fibrinolysis: Primary PCI is generally preferable if it is rapidly available, although in the circumstances it is not an immediate option the benefit of fibrinolysis should be balanced against the risk of bleeding so that the therapy can be initiated. (Collet et al., 2021; Ibanez et al., 2018; Kumar & Cannon, 2009b) The effectiveness of fibrinolysis and primary PCI decreases with time. (Kumar & Cannon, 2009b) However, PCI has been shown to be superior to fibrinolysis in reducing mortality and the incidence of short- and long-term adverse outcomes, like reinfarction or stroke. (Ibanez et al., 2018; Kumar & Cannon, 2009b) Furthermore, the ability of PCI to produce a patent infarct-related artery is much less time-dependent. (Kumar & Cannon, 2009b)

CABG: CABG surgery consists in an open-chest surgery that aims to treat blocked heart arteries by taking arteries or veins from other parts of your body - called grafts - and using them to reroute the blood around the obstructed artery to supply blood flow to heart muscle. (American Heart Association, 2020a; Timmis et al., 2022) The most common are the saphenous vein and the mammary artery. The patient can undergo to one, two, three or more bypass grafts, depending on how many coronary arteries are narrowed. (American Heart Association, 2020a)

It occupies a central role in the treatment of obstructive CAD increasing the supply of blood and oxygen to the heart therefore relieving angina symptoms and improving ability for physical activity that might be limited by angina or ischaemia. CABG procedures have also been shown to reduce the risk of AMI and in left main and multivessel CAD can prolong life compared with medical therapy, particularly when LV function is impaired. (American Heart Association, 2020a; Timmis et al., 2022) Approximately 5.0 – 10.0% of NSTEMI patients require CABG. (Neumann et al., 2019)

A median of 272.0 CABG procedures per million inhabitants of European countries were reported in 2020, with Portugal below the median (241.0 CABG procedures per million inhabitants). (Timmis et al., 2022)

CABG vs PCI: Revascularization by PCI is often preferred, and in most patients, the outcomes of PCI and CABG are similar, however there are some clinical characteristics that may favors one or another strategy. (Neumann et al., 2019; Timmis et al., 2022) PCI is the procedure of choice in patients with the presence of severe co-morbidities, advanced age, frailty or reduced life expectancy, or with restricted mobility and conditions that affect the rehabilitation process, while CABG is the procedure of choice in patients with DM, reduced LV function or contraindication to DAPT therapy. (Neumann et al., 2019)

Among NSTEMI patients, the risk of death, AMI, or stroke was significantly reduced with CABG compared to PCI. (Collet et al., 2021) Regarding STEMI patients, the usual choice is PCI, however, an emergency CABG may be indicated in selected patients unsuitable for PCI. (Neumann et al., 2019)

1.2.5. Risk factors

Cardiovascular risk factors are the situations or behaviors that tend to increase the probability of developing CVD or worsen the previous CVD of the individual. The relationship between CVDs and risk factors is well documented. (Papageorgiou et al., 2017; Visseren et al., 2021) They can be divided into non-modifiable and modifiable. Non-modifiable risk factors are those dependent on genotypic or phenotypic characteristics, such as age, sex, ethnicity, family history of premature CVD, genetic markers and epigenetics and the CV risk of the country. Modifiable risk factors are those related to habits and lifestyle such as hypertension, DM, dyslipidaemia, tobacco use, alcohol consumption, obesity, physical inactivity, SB, nutritional status and psychological factors. (WHO, 2021)

Thus it is recommended a systematic global CV risk assessment with or without any of this major CV risk factors to control them before the disease develops so that the onset of the CVD can be prevented and also in patients with established CVD to control the disease progression and improve the prognosis. (Papageorgiou et al., 2017; Visseren et al., 2021)

There are some tools of risk prediction to be used in populations without established CVD, such as SCORE2 and SCORE2-OP (older persons) algorithms, used to estimate 10-year risk of CV events (fatal or non-fatal) in Europe, according to four geographical risk regions, in which specific cut-off values of some risk factors are used to stratify the CV risk. (SCORE2-OP working group and ESC Cardiovascular risk collaboration, 2021; SCORE2 working group and ESC Cardiovascular risk collaboration, 2021)

For people with established CVD, is possible to predict the 10-year risk of CV events through the SMART Risk Score or to predict the 1- or 2-year risk of CV events through the EUROASPIRE Risk Calculator. (De Bacquer, Ueda, et al., 2022; Dorresteijn et al., 2013; McKay et al., 2022)

The SMART Risk Score can be used for all individual patients with clinical manifest atherosclerotic vascular disease and is based in easy-to-measure clinical patient characteristics and it will be assessed. It estimates individual residual risk for recurrent CV events or vascular death in the next 10 years if standard care is provided. (Dorresteijn et al., 2013; McKay et al., 2022)

1.2.5.1. Non-modifiable

Age: Age is the major driver of CV risk. CVD becomes progressively more common as age increases in both men and women, but CAD typically affects men at an earlier age than women. (Papageorgiou et al., 2017) Thus, CV risk is considered higher in men with more than 45 years old and in women with more than 55 years old. (Riebe et al., 2018) Women below 50 years and men below 40 years are mostly at low long-term CV risk but can quickly increase that risk because of the modifiable risk factors they may already have. (Visseren et al., 2021)

In Portugal it was estimated that in 2021 the total population was about 10.3 million people with 8.6 million (83.6%) considered adult population (age ≥ 18 years). The median age has raised from 25 years old in 1950 to 45 years old in 2021 showing that the Portuguese population is getting older and that age will be an increasingly important factor in CV risk. Among adult population there were around 2.4 million men (27.6% of adult population) with more than 45 years and around 2.2 million women (24.6% million of adult population) with more than 55 years. (Timmis et al., 2022)

Sex: In many studies, some differences in CV risk according to gender have been observed, like the onset of CVD earlier in men than in women. In a genetic study, men with the most common haplogroup of the Y chromosome were shown to have a 50.0% higher risk of CAD, independently of traditional and socioeconomic risk factors. (Papageorgiou et al., 2017) On the other hand, women with type 2 DM appear to have a particularly higher risk for stroke and an increased CV risk at lower blood pressure thresholds. (Visseren et al., 2021)

In Portugal it was estimated that in 2021, among the total population there were 5.5 million women (52.8% of total population) and 4.9 million men (47.2% of total population) and the same pattern was observed among adult population with 4.6 million women (53.6% of adult population) and 4.0 million men (46.4% of adult population). (Timmis et al., 2022)

Ethnicity: Europe includes many citizens with different ethnic background that bring considerable variability in CV risk factors so ethnicity should be considered independently of other risk factors. For example, immigrants from South Asia present higher CVD rates, whereas adjusted CV risks appear lower in most other ethnic groups. (Timmis et al., 2022; Visseren et al., 2021)

This inequalities between ethnic groups have been attributed to the interplay of multiple factors like diminished access to healthy lifestyle choices, exaggerated exposure to CV risk factors, among others. (Timmis et al., 2022) So, correction factors must be used to assess risk score adequately: Southern Asian - multiply the risk by 1.3 for Indians and Bangladeshis, and 1.7 for Pakistanis; Other Asian - multiply the risk by 1.1; Black Caribbean - multiply the risk by 0.85; Black African and Chinese - multiply the risk by 0.7). (Visseren et al., 2021)

In Portugal it is estimated that 95.0% of the population are Caucasian and the remaining 5.0% refer to citizens from Portugal's former colonies in Africa, Asia (Han Chinese), and South America (Brazilian) and other foreign. (Timmis et al., 2022)

Family history of premature cardiovascular disease: Family history of premature CVD is a simple indicator that reflects both the genetic trait and the environment shared among household members. It's positively associated with CVD, independently of other risk factors, and improves the prediction of CV risk. (Visseren et al., 2021; Wahrenberg et al., 2021) This risk factor must be considered when at least one of the following conditions is met: Myocardial infarction, coronary revascularization, or sudden death before 55 years old in father or other first-degree relative or before 65 years old in mother or in other first-degree relative. (Riebe et al., 2018; Wahrenberg et al., 2021)

Genetic markers and epigenetics: Some genes have been identified as candidates' genes associated with CVD from which it is possible to define a CAD specific genetic score. Genetic screening and counselling can be effective in preventing a new or an additional CV event by measuring CAD score in addition to other risk factors. Besides, a different genetic score enabled the identification of subjects at increased risk of CAD, who would benefit the most from statin therapy. Regarding epigenetics, lower DNA methylation levels have been associated with an increased risk of CAD or stroke. (Piepoli et al., 2016)

Cardiovascular risk of the country: Based on national CVD mortality rates, countries are grouped in four clusters of CV risk (low, moderate, high, and very high CV risk), according to their most recently reported WHO age- and sex-standardized overall CVD mortality rates per 100,000 population. Portugal was classified as a moderate (100.0 to < 150.0 CVD deaths per 100,000 population) CV risk country. This information must be considered in any patients' evaluation, in order to avoid and over-estimation of risk in low-risk countries and under-estimation of risk in very high-risk countries so that high-risk individuals with higher observed lifetime CVD risk, who are priorities in all stages of CVD prevention, can be more properly classified. (SCORE2 working group and ESC Cardiovascular risk collaboration, 2021; Timmis et al., 2022; Visseren et al., 2021)

1.2.5.2. Modifiable

Hypertension: Hypertension consists in the elevation of blood pressure values and is the leading risk factor for the development of CAD. In 2015, the median prevalence of hypertension among adults ≥ 18 years of age in Europe was 25.0%, with Portugal below but near that value (24.4%) and in 2019, 45.41% of total CVD deaths in Portugal were caused by high SBP values. (Institute for Health Metrics and Evaluation, 2019; Timmis et al., 2022)

In Europe, hypertension is defined and confirmed by the measurements of systolic blood pressure (SBP) ≥ 140.0 mmHg or diastolic blood pressure (DBP) ≥ 90.0 mmHg on at least two separate occasions, or on antihypertensive medication. Besides, hypertension can be classified in a grading system according to the following criteria (Riebe et al., 2018; Visseren et al., 2021):

- Grade 1: 140.0 ≥ SBP > 160.0 mmHg and/or 90.0 mmHg ≥ DBP > 100.0 mmHg
- Grade 2: 160.0 ≥ SBP > 180.0 mmHg and/or 100.0 mmHg ≥ DBP > 110.0 mmHg
- Grade 3: SBP ≥ 180.0 mmHg and/or DBP ≥ 110.0 mmHg

It is recommended to lower SBP to < 140.0 mmHg and DBP < 90.0 mmHg as first target in all patients, with some considerations for CVD patients according to their ages. For patients aged 18 - 69 years, it is recommended an SBP < 120.0 – 130.0 mmHg and DBP < 80.0 mmHg, and for patients aged > 70 years, for safety reasons, SBP should be targeted to < 140.0 mmHg and down to 130.0 mmHg, only if tolerated, and DBP < 80.0 mmHg. This further intensification of SBP treatment by aiming at lower treatment goals is beneficial in most patients and must be considered, taking in account comorbidities, lifetime risk and treatment benefit, frailty. (Ambrosetti et al., 2021; Ibanez et al., 2018; Riebe et al., 2018; Timmis et al., 2022; Visseren et al., 2021)

There is a linear relationship between hypertension and risk of stroke, myocardial infarction, and risk of death from SBP levels of 90.0 mmHg and DBP levels of 75.0 mmHg, and thus, treatments to lower blood pressure provide protection against CV events, with incremental benefits especially in higher-risk patients. (Riebe et al., 2018; Visseren et al., 2021)

Diabetes Mellitus: DM is defined as a chronic hyperglycaemia resulting from the defect, action and/or secretion of insulin and can be divided in 3 categories: Type 1 DM, type 2 DM and pre-DM.

Type 1 DM is a genetic disease, type 2 DM is a result of modifiable and non-modifiable risk factors than lead to defect in β cells. Type 2 DM is much more common than type 1 DM and most of the cases can be prevented. Pre-DM (impaired fasting glycaemia and impaired glucose tolerance) is considered the progression from normoglycaemia to type 2 DM. (Cosentino et al., 2020)

The prevalence of DM is increasing among all ages in the European Region. In 2017, about 60 million Europeans adult (aged 20 - 79 years) were thought to have type 2 DM, of which 50% are undiagnosed, and in 2021 the median prevalence in Europe was 6.6%, with Portugal above the median (9.1%). (Cosentino et al., 2020; Timmis et al., 2022) In 2019, 25.86% of total CVD deaths in Portugal were caused by high FPG values. (Institute for Health Metrics and Evaluation, 2019)

DM should be investigated using FPG or haemoglobin A1c (HbA1c). To diagnose pre-DM the methods aresimilar: FPG and HBA1c and if inconclusive, an oral glucose tolerance test. (Cosentino et al., 2020)

The criteria for diagnosing DM are FPG values ≥ 126.0 mg/dL or 2h plasma glucose values ≥ 200.0 mg/dL or HbA1c > 6.5%. Regarding pre-DM the criteria for impaired fasting glycaemia are FPG values < 126.0 mg/dL and 2h plasma glucose values between 140.0 – 199.0 mg/dL; and for impaired glucose tolerance are FPG values between 100.0 – 125.0 mg/dL and 2h plasma glucose values < 140.0 mg/dL. (Cosentino et al., 2020; Riebe et al., 2018)

An early glucose control demonstrated benefecial effects on macrovascular complications and is associated with long-term CV benefits. An HbA1c target of < 7.0% reduces microvascular complications but these targets shoul be individualized. In younger patients, targets between 6.0 - 6.5% are recommended if tolerable. Regarding elderly patients, HbA1c goals are < 8.0% or < 9.0% may be adequate. (Cosentino et al., 2020) (Ambrosetti et al., 2021; Cosentino et al., 2020)

DM is considered an independent CV risk factor and increase CV risk and the risk of death in about two times. Furthermore, this excess relative risk was shown to be greater in young women. Type 2 DM patients are also more susceptible to other risk factors and so they might have an even higher CV risk and risk of death. The elevated CAD risk starts at glucose levels below the cut-off point for DM and increases as the glucose levels raise. Thus, DM is very common in CAD patients and is associated with a poor prognosis, emphasizing the need for intensive secondary prevention in these patients. (Cosentino et al., 2020; Timmis et al., 2022; Visseren et al., 2021)

Dyslipidaemia: Dyslipidaemia refer to alterations in lipoproteins metabolism. Lipoproteins are responsible for lipids transportation to the tissues and lipid deposition, among others, and alterations in their metabolism cause an abnormal amount of lipids in the blood and affect CV risk. (Mach et al., 2020; Riebe et al., 2018)

LDL and high-density lipoprotein (HDL) are two of the major lipoproteins and can be used as biomarkers in mortality risk estimation in general population and CVD population. (Ou et al., 2017; Visseren et al., 2021) LDL are molecules directly involved in the atherosclerotic process, being retained in atheromatous plaques. HDL are involved in the efflux of cholesterol and TG.

Regarding TG they are not directly atherogenic but can be used as biomarkers of the presence of atherogenic particles. Other useful biomarkers that can be used are total-c and non-high-density lipoprotein cholesterol (non-HDL) cholesterol that encompasses all atherogenic lipoproteins and is calculated as: total-c – HDL cholesterol = non-HDL cholesterol. Non-HDL cholesterol increases with cumulative exposure to LDL during young adulthood and middle age. (Ou et al., 2017; Timmis et al., 2022; Visseren et al., 2021)

Thus, dyslipidaemia it is further defined by the presence of elevated levels of total-c or LDL cholesterol, elevated levels of TG, or low levels of HDL cholesterol. (Riebe et al., 2018)

In 2018, the median total-c concentrations in Portugal was 191.0 mg/dL, very close to the European value (190.0 mg/dL), and higher in women (196.0 mg/dL) than in men (186 mg/dL). Regarding non-HDL cholesterol the same trend was observed with a median value of 138.5 mg/dL, a little beat above the European value (133.5 mg/dL), and higher in women (140.0 mg/dL) than in men (137 mg/dL). A different pattern was observed in HDL cholesterol

concentrations with a median value of 53.5 mg/dL, also very close to the European value (54.0 mg/dL), higher in women (60.0 mg/dL) than in men (47.0 mg/dL). (Timmis et al., 2022) It is also important to notice that, in 2019, 23.1% of total CVD deaths in Portugal were caused by high levels of LDL cholesterol. (Institute for Health Metrics and Evaluation, 2019)

The criteria for diagnosing dyslipidaemia are total-c serum ≥ 200.0 mg/dL, LDL cholesterol ≥ 130.0 mg/dL, TG ≥ 200.0 mg/dL or HDL cholesterol ≤ 40.0 mg/dL. (Riebe et al., 2018; U.S. Department of Health and Human Services (HHS) & National Heart, 2013)

The elevation serum cholesterol concentrations is a major target of risk reduction programs. (Timmis et al., 2022) For secondary prevention there are some recommendations especially regarding LDL cholesterol, individualized according patient's CV risk. CAD patients are considered very high-risk patients and so an LDL cholesterol reduction of ≥ 50.0% from baseline and an LDL cholesterol goal of < 55.0 mg/dL is recommended. For patients with CAD who experience a second CV event within 2 years an LDL cholesterol goal of < 40.0 mg/dL may be considered. (Ambrosetti et al., 2021; Visseren et al., 2021) It is not considered a mandatory goal for TG, but < 150.0 mg/dL is associated to lower risk. (Ambrosetti et al., 2021)

High LDL cholesterol levels are directly associated with an increased CV risk. (Mach et al., 2020) Low HDL cholesterol has been shown to be a strong independent predictor of premature atherosclerosis and inversely associated with CV risk. However, it is not reflected in any protective effect because raising HDL cholesterol to very high levels does not necessarily lead to CV risk reduction. (Bergheanu et al., 2017; Visseren et al., 2021) Regarding TG, high levels are often associated with low HDL cholesterol and high LDL cholesterol levels, being associated with an increased CV risk. (Bergheanu et al., 2017) Within the causes of dyslipidaemia, the most commons are poor dietary and lifestyle choices, although genetics play a very important role, for example in hypercholesterolaemia - increase in serum cholesterol concentrations -, often related to familial history. Some diseases, like hypothyroidism or the nephrotic syndrome, can also affect blood lipids concentrations, particularly LDL cholesterol levels, leading to an increase. Besides, patients with obesity, insulin resistance, or DM are often associated with high levels of TG. (Riebe et al., 2018)

Tobacco use: Tobacco use has been described as the single largest avoidable health risk in the Europe. (Timmis et al., 2022)

Recent data from 2019 in Europe, showed that a median of 21.6% of the population with age ≥ 15 years were regular daily smokers, with Portugal below that value (14.2%). (Timmis et al., 2022) Besides, 7.24% and 1.5% of total CVD deaths in Portugal were caused by active smoking and passive smoking, respectively. (Institute for Health Metrics and Evaluation, 2019)

Any current cigarette smoker, those who quit within the previous 6 months and those who have been exposed to environmental tobacco smoke – passive smokers – are considered at higher CV risk. (Riebe et al., 2018; Verrill et al., 2009) There is no minimum level of smoking recommended and so patients should stop smoking and avoid passive smoking. (Ambrosetti et al., 2021; Ibanez et al., 2018; Knuuti et al., 2020; Timmis et al., 2022; Visseren et al., 2021)

Cigarette smoking has a strong pro-thrombotic effect and is responsible for 50.0% of all avoidable deaths in smokers, with half of these due to CVD. (Timmis et al., 2022) It has a more dangerous impact in men that in women in cases of many years of smoking. Comparing a smoker with < 50 years with a non-smoker with the same age, smoking increases up to five times the CV risk. Regarding passive smokers, their CV risk has been associated with a similar relative risk as

light active exposure. (Ibanez et al., 2018; Knuuti et al., 2020; Timmis et al., 2022; Visseren et al., 2021)

Alcohol consumption: Europe has been considered the heaviest-drinking region in the world and has the highest proportion of total ill health and premature death due to alcohol. (Timmis et al., 2022)

Latest data from 2018 showed that the median pure alcohol consumption in Europe was 184.6 g/week in people aged ≥ 15 years, with Portugal much above the median (230.8 g/week). Overall, in Europe alcohol consumption in women (86 g/week) was lower than in men (288.5 g/week) and this was a consistent finding across nearly all countries in Europe. In Portugal either in women (107.7 g/week) and men (373.1 g/week) the median consumption values were above the one found in Europe. (Timmis et al., 2022) In 2019, 4.27% of total CVD deaths in Portugal were caused by alcohol consumption. (Institute for Health Metrics and Evaluation, 2019)

It is recommended to restrict alcohol consumption to a daily maximum of 2 glasses for men and 1 for women, although it is difficult to translate it for grams of alcohol, because of its dependency on portion size (1 glass should considered more or less 10.0 g of alcohol). (Ambrosetti et al., 2021; Ibanez et al., 2018) Some more recent data begin to point out that there should be no difference in the upper safe limit of alcohol consumption between men and women, placing the bar on the alcohol consumption of 100.0 g/week, being a little more conservative with alcohol consumption in men. (Visseren et al., 2021) Recommended upper limits for alcohol consumption vary substantially by country, reflecting a lack of consensus about precise risk thresholds.

There is also some uncertainty about the associations between alcohol consumption and CVD. For example, regarding all-cause mortality and CAD, a positive linear association was demonstrated, with the threshold for lower risk at 100.0 g/week but for AMI increased alcohol consumption above this threshold was associated with a lower risk. (Timmis et al., 2022; Visseren et al., 2021)

Obesity: Obesity is defined as the abnormal or excessive fat accumulation that presents a risk to health, which is characterized by a body weight greater than what would be healthy for a given individual, according to their morphological characteristics, being one of the main risk factors for CVD. (WHO, 2021) It occurs when energy intake exceeds energy expenditure leading to an overweight state. (De Bacquer, Jennings, et al., 2022; Ibanez et al., 2018) It is important to say that all obese patients are overweight but not all overweight patients are considered obese. Overweight can be stratified according BMI, splitting obesity from overweight, and is commonly defined as an intermediate state before obesity, sometimes called pre-obesity. In this study that intermediate state will be treated as overweight. However, the absolute quantity of body fat is less important than its anatomical distribution and so it is also important to talk about abdominal overweight and central obesity which can be measured using waist circumference.

The prevalence of overweight and obesity is increasing globally, and it is now higher than that of underweight. (De Bacquer et al., 2022) In 2016, 22.5% of adults > 18 years old in Europe were obese and In Portugal it was a little beat lower (20.8%), a little beat higher in women (21.2%) that in men (20.3%). (Timmis et al., 2022)

Recent estimates suggest that overweight and obesity cause more than 1.2 million deaths across Europe every year, being responsible for 13.03% of total CVD deaths in Portugal,

in 2019. (Institute for Health Metrics and Evaluation, 2019; WHO. Regional Office for Europe, 2022)

BMI is one of the most used tools that allows the stratification of body composition and it uses body weight and height. According to the Quetelet's index (De Bacquer, Jennings, et al., 2022; Ibanez et al., 2018):

- Patients with BMI < 18.5 kg/m^2 are considered underweight.
- Patients with 18.5 ≥ BMI > 25.0 $kg/m^2$are considered at normal weight.
- Patients with 25.0 ≥ BMI > 30.0 kg/m^2 are considered overweight.
- Patients with 30.0 ≥ BMI > 35.0 kg/m^2 are considered grade I obese.
- Patients with 35.0 ≥ BMI > 40.0 kg/m^2 are considered grade II obese.
- Patients with BMI ≥ 40.0 kg/m^2 are considered grade III obese or morbidly obese.

However, BMI classification for older adults (age ≥ 65 years) is not very consensual and it has been suggested higher values for the cut-offs to define obesity and overweight. (Chang et al., 2013; Heiat et al., 2001; Kıskaç et al., 2022) The following classification might be adequate for older adults (Heiat et al., 2001; Kıskaç et al., 2022):

- Patients with BMI < 22.0 kg/m^2 are considered underweight.
- Patients with 22.0 ≥ BMI > 24.0 kg/m^2 are considered at risk of undernutrition.
- Patients with 24.0 ≥ BMI > 27.0 kg/m^2 are considered at normal weight.
- Male patients with 27.0 ≥ BMI > 30.0 kg/m^2 are considered overweight.
- Female patients with 27.0 ≥ BMI > 32.0 kg/m^2 are considered overweight.
- Male patients with BMI ≥ 30.0 kg/m^2 are considered obese.
- Female patients with BMI ≥ 32.0 kg/m^2 are considered obese.

Another measure that aids in the interpretation of body composition and is useful in evaluating health-risks is the fat mass index (FMI). FMI is a dual energy X-ray absorptiometry (DXA) derived measure obtained by dividing total fat mass by height squared. FMI classification can be done according the following criteria (Imboden et al., 2017):

- In men: FMI > 6.0 kg/m^2 indicates overweight and FMI > 9.0 kg/m^2 indicates obesity.
- In women: FMI > 9.0 kg/m^2 indicates overweight and FMI > 13.0 kg/m^2 indicates obesity.

Waist circumference complements the classification made through BMI, providing a more accurate CV risk estimate. The thresholds defined by the World Health Organization (WHO) are different for men and women (Ambrosetti et al., 2021; De Bacquer, Jennings, et al., 2022; Ross et al., 2020; Stepaniak et al., 2016; Visseren et al., 2021):

- In men: Waist circumference ≥ 94.0 cm indicates abdominal overweight and waist circumference ≥ 102.0 cm indicates central obesity.
- In women: Waist circumference ≥ 80.0 cm indicates abdominal overweight and waist circumference ≥ 88.0 cm indicates central obesity.

In general, weight loss is recommended for both overweight and obese CAD patients, in order to obtain and maintain a healthy weight, according to the age of the patient, and some guidelines talk in an initial 10% body weight loss. (De Bacquer, Jennings, et al., 2022; Knuuti et al., 2020) (Ambrosetti et al., 2021; De Bacquer, Jennings, et al., 2022; Ibanez et al., 2018; Kıskaç et al., 2022) The WHO defined two actions levels regarding abdominal fat recommending no further weight gain in abdominal overweight patients and weight reduction advice in central obese patients. (Visseren et al., 2021)

The safest and most effective method is to adopt a healthy eating pattern (reducing fat and sugar intake, consuming more fruit, vegetables, and fish) and to increase physical activity levels. (De Bacquer, Jennings, et al., 2022) The amount of weight loss following an exercise training is variable and is not reached through exercise alone, so it is important to establish this combination with diet. (Castro et al., 2017; De Bacquer, Jennings, et al., 2022) Significant weight loss has been associated with the adherence to a CR program and by professional advice to follow dietary recommendations, showing the effectiveness of comprehensive, multidisciplinary secondary prevention programs that incorporate both aspects of lifestyle modification in achieving lifestyle goals in overweight and obese CAD patients. (De Bacquer, Jennings, et al., 2022)

Weight loss is similarly strongly associated with CV risk in the elderly and the young, in both sexes. However, among those with established CVD, there are some inconsistencies in the literature described as an obesity paradox. In CAD patients, obesity appears to be protective, although this evidence should be interpreted with great caution. (Visseren et al., 2021)

Overweight and obesity are considered independent risk factors for CAD and are associated with lower HDL cholesterol levels and higher LDL cholesterol and TG levels, all contributing to an increase in all-cause mortality. (Ibanez et al., 2018; Jahangir et al., 2014) Body fat stored in visceral and other ectopic depots, like the accumulation of adipose tissue in the abdominal region, carries a higher risk than subcutaneous fat, being associated with metabolic complications. (Ibanez et al., 2018; Noites et al., 2015; Visseren et al., 2021) Also, obese patients have significantly higher rates of DM, hypertension, dyslipidaemia, and HF prior to hospital admission. (De Bacquer, Jennings, et al., 2022)

Physical inactivity: Physical inactivity can be also known as insufficient physical activity, which means not reaching, at least, 150 min of aerobic moderate-intensity physical activity (MPA) per week or 75 min of aerobic vigorous-intensity physical activity (VPA) per week or an equivalent combination of both intensities. (Bull et al., 2020)

Data from 2016 showed that the median prevalence of insufficient physical activity in Europe was 30.8% with Portugal above the median (43.0%), either in men (37.5%) as in women (48.5%). (Timmis et al., 2022) More recent data show that in Europe 45.0% of the population aged ≥ 15 years does not exercise or practice any sport and 31.0% does not practice any type of light-intensity physical activity (LPA). In Portugal the numbers are much higher with 73.0% not practicing any exercise or sport and 72.0% not practicing any type of LPA. (European Union, 2022) In 2019, 5.9% of total CVD deaths in Portugal were caused by physical inactivity. (Institute for Health Metrics and Evaluation, 2019)

According to the time of physical activity performed per week, individuals can be classified into inactive, active, or even very active (Bull et al., 2020):

- Inactive: Performing less than 150 min a week of MPA per week or 75 min of aerobic VPA per week or an equivalent combination of both intensities.
- Active: Performing 150 - 300 min a week of MPA per week or 75 – 150 min of aerobic VPA per week or an equivalent combination of both intensities.
- Very active: Performing more than 300 min a week of MPA per week or 150 min of aerobic VPA per week or an equivalent combination of both intensities.

It is recommended for adults of all ages to perform at least the minimum to be considered an active individual. The recommendations for patients with CAD are 30 - 60 min of aerobic MPA > 5 days per week and in sedentary individuals and it is recommended a gradual increase in physical activity intensity. Examples of aerobic physical activity include walking, jogging, cycling, etc. (Ambrosetti et al., 2021; Bull et al., 2020; Visseren et al., 2021)

In addition, it is also recommended to perform resistance exercise 2 or more days per week. The suggested prescription is one to three sets of 8 - 12 repetitions at the intensity of 60.0 – 80.0% of 1 repetition maximum in a variety of 8 - 10 different exercises involving each major muscle group. (Ambrosetti et al., 2021; Visseren et al., 2021)

For older adults or deconditioned individuals, it is suggested to start with one set of 10 - 15 repetitions at 40.0 – 50.0% of 1 repetition maximum. These last should also perform varied multicomponent physical activity that emphasizes functional balance and strength training at MPA or greater intensity, on 3 or more days a week, to enhance functional capacity and to prevent falls. (Ambrosetti et al., 2021; Bull et al., 2020; Visseren et al., 2021)

Furthermore, adults may increase their physical activity to very active levels to reach additional health benefits. (Bull et al., 2020)

Physical activity counselling should be individual and tailored according to patients' preferences and limitations. For example, for those who cannot perform the targets, the recommendations are to stay as active as possible, according to their health condition. (Bull et al., 2020; Visseren et al., 2021)

Physical inactivity is associated with an increased risk for AMI, ischemic HF, DM and breast and colon cancer. (Timmis et al., 2022)

Sedentary Behavior: SB is defined as the class of behaviors characterized by reduced body movement and low caloric expenditure. However, this concept is different from the concept of physical inactivity. (Bull et al., 2020; Castro et al., 2017; Ploeg & Hillsdon, 2017; Visseren et al., 2021)

SB is the most prevalent behavior in daily routine and the time occupied on this pattern is called ST. (Bull et al., 2020; Ploeg & Hillsdon, 2017)

SB is being considered a public health issue, responsible for 3.8% of all-cause mortality in adults, and the results showed that in Europe, on a normal day, 11.0% spent more than 8.5 hours min sitting, with Portugal very close to that value (9.0%). (Bull et al., 2020; Castro et al., 2017; European Union, 2022; Visseren et al., 2021)

There isn't a consensus cut-off for daily ST in literature with some authors defending 7.5 hours, others 7.0 hours, others 9.0 hours and even some 9.5 hours. (Bakel et al., 2023; Chau et al., 2013; Ku et al., 2018) Although, it is recommended to limit ST and replace it for physical activity, even if it is just LPA. (Bull et al., 2020)

SB is becoming an important risk factor because of his negative impact on adiposity and CV risk. (Bull et al., 2020; Castro et al., 2017; Visseren et al., 2021) Strong associations have been observed between SB and elevated blood pressure and also between increased ST and increased mortality risk, elevated BMI, and waist circumference. (Castro et al., 2017; Ku et al., 2018)

Psychological factors: Psychological factors, like mental disorders, psychosocial stress (stress symptoms and stressors such as loneliness and critical life events), depression and anxiety are considered independent risk factors. (Knuuti et al., 2020; Visseren et al., 2021)

In these cases, it is recommended to refer the patients to psychiatrist so that psychotherapy, medication, or collaborative care can be provided, and to encourage them to attend multimodal behavioral interventions. (Ambrosetti et al., 2021) This are associated with the development and progression of CVD, due to problems in adherence to positive lifestyle changes and to a therapeutic regimen. (Knuuti et al., 2020; Visseren et al., 2021)

Psychological factors and CVD are often connected in both directions, for example, patients with heart disease have a two-fold increased risk of mood and anxiety disorders compared with people without heart disease, showing the importance to control this risk factors, in order to prevent future events. (Knuuti et al., 2020)

1.3. Cardiac Rehabilitation program

CR program is a multidisciplinary intervention, with the main purpose of delaying the progression of the underlying CVD, whose core components includes medical assessment, exercise training and physical activity counseling, identification and control of risk factors, nutritional assessment and counseling, psychological assessment and intervention, education, socioeconomic support, long-term maintenance strategies, patient assessment after the CR program and evaluation of program quality. (Abreu et al., 2018; Ambrosetti et al., 2021; Ibanez et al., 2018; Noites et al., 2015) They are expected to be cost-effective interventions that act at the level of CV risk factors control and are designed to ensure favorable outcomes like reducing CV risk and physical impairment, encouraging healthy behaviors, and promoting an active lifestyle. (Abreu et al., 2018; Ambrosetti et al., 2021; Ibanez et al., 2018; Noites et al., 2015)

CR programs promote better adherence to medical therapy, particularly in the case of short hospital stay and should be supervised and carried out by a trained multidisciplinary team led by a cardiologist with experience in CR. CR should begin as soon as possible after the initial CV event, but a pre-exercise screening and exercise testing is required so that exercise is individually prescribed, in terms of intensity, type (aerobic, continuous or interval, resistance), duration, frequency, and modality, taking into account age and physical limitations. In the same way, all CV risk factors should be addressed, controlled, and treated, according to the characteristics of each patient. CR is safe for the patients, even in the case of recent, complex and/or multivessel PCI. (Abreu et al., 2018; Ambrosetti et al., 2021; Visseren et al., 2021)

CR programs achieve more healthier lifestyles and more effective risk factor control than usual care and although referral, participation and implementation rates are still somewhat low, CR programs are becoming an increasingly useful tool for CVD and should be offered to all clinically stable CAD patients. (Ibanez et al., 2018; Kotseva et al., 2016, 2019; Visseren et al., 2021)

1.3.1. Cardiac Rehabilitation phases

CR generally consist of three phases, and each of them has a different purpose, a different duration and therefore they can also be held in different locations. (Abreu et al., 2018; Ambrosetti et al., 2021)

Phase I is considered the hospital phase and is performed during hospital stay and begins 24 - 48 hours after a non-complicated acute event. It covers ACS patients, HF patients, patients with LV assist or resynchronization devices, patients undergoing CABG or PCI, patients undergoing valve surgery or percutaneous implantation of prosthetic valves or clips and patients undergoing surgery to correct congenital heart disease. (Abreu et al., 2018)

It is mandatory that the team for this phase is composed by a cardiologist, a physical medicine specialist, a rehabilitation nurse/physiotherapist, a nurse, a nutritionist and a psychologist/psychiatrist. (Abreu et al., 2018)

This phase aims to avoid problems associated with prolonged immobilization; identify and control all possible CV risk factors, including possible psychological disturbances caused by the CV event; and encourage changes in patients habits to a healthier lifestyle with a positive attitude, in order to promote long-term benefits. Thus, it is recommended to perform low-intensity exercises, educational actions on alternate days, encourage patients to therapy adherence and participation in CR following phases. (Abreu et al., 2018)

Phase II is performed after hospital discharge and lasts for 8 to 12 weeks. It can be performed in the hospital, in a CR center or at patient´s home. Phase II CR covers all patients who are eligible for phase I, whether or not they participate in that phase, and also individuals at high CV risk, DM, hypertensive, dyslipidaemic patients and smokers. (Abreu et al., 2018)

It is mandatory that the team for this phase is composed by a cardiologist, a physical medicine specialist, and exercise specialist (physiotherapist, exercise physiologist or rehabilitation nurse), a nutritionist, a psychiatrist/psychologist, a nurse and a cardiopulmonary technician. (Abreu et al., 2018)

This phase purposes are to improve CV function, functional capacity, strength, balance and flexibility and to optimize pharmacological therapy; detect and treat arrhythmias or other changes that occur during exercise; improve the psychological condition of the patient; educate the patient on how to exercise and stay active in the long term and together with the immediate family or caregiver help the patient to adopt a healthier lifestyle, promoting their autonomy from the CR program. (Abreu et al., 2018) In phase II CR it is recommended to perform exercise sessions for 3 to 5 times per week with 20 to 45 minutes of aerobic training, educational sessions once a week and also nutritional and psychological monitoring. (Abreu et al., 2018)

Core components are considered essential and are routinely delivered during this phase however, they could also be extended to phase III. (Abreu et al., 2018; Ambrosetti et al., 2021)

Phase III is the long-term phase and should last for the rest of the patient's life or, until the patient is clinically stable. It covers all patients with established indications for the previous phases, those who have completed phase II, and those who did not participate in phase II six or more months after ACS, if they are stable and present no contraindications. (Abreu et al., 2018) It covers phase II patients, according to the physician's indication and low-risk patients who did not participate in phase II and are referred by CR centers. (Abreu et al., 2018)

It is mandatory that the team for this phase is composed by a cardiologist or a physical medicine specialist or other physician with competence in CR recognized by the Order of

Physicians and an exercise specialist (exercise physiologist or physiotherapist). (Abreu et al., 2018)

This phase purposes are to provide professional supervision of exercise, with clinical monitoring of symptoms and signs, HR, blood pressure and, in some cases, ECG; teach self-monitoring and maintain long-term control of CV risk factors and adherence to pharmacological therapy, through an annual assessment using clinical, functional, laboratory tests and, in some cases, echocardiography, alerting to the need for continue preventive measures. (Abreu et al., 2018)

In phase III CR it is recommended to perform exercise sessions for 2 to 5 times per week with 30 to 60 minutes of aerobic training, educational sessions 2 or 3 times per year and also nutritional and psychological monitoring. (Abreu et al., 2018)

1.3.2. Risks and benefits of Cardiac Rehabilitation

There are some risks in CR but although the highest risk of CV events occurs in CAD patients, exercise-based CR has shown to be remarkably safe, with different data suggesting one cardiac arrest per 116.9 thousand to 769.2 thousand patient-hours, one AMI per 220.0 thousand to 338.6 thousand patient-hours and one death per 116.4 thousand to 752.4 thousand patient-hours. Although these rates are low, the mortality rate seems to be higher when patients exercised in facilities without the ability to successfully manage cardiac arrest. (Anderson et al., 2021; Riebe et al., 2018)

Despite everything, the benefits of CR outweigh the risks and make this intervention relevant and advantageous for the patient. CR benefits have been thoroughly demonstrated in CAD patients and are important in elderly or frail patients. Despite the fact that, in several studies, whether in the short-, medium-, or long-term follow-ups, there were no statistical differences in total mortality, a reduction of 26.0% in CVD mortality and morbidity following myocardial infarction was proven particularly in the medium- and long-term. (Abreu et al., 2018; Ambrosetti et al., 2021; Anderson et al., 2021; Javaherian et al., 2020)

CR programs are being implemented as a strategy to improve risk factor management. (Chen et al., 2017) There was evidence of a significant reduction in the risk of future CV events, for example, in the risk of fatal or non-fatal myocardial infarction in studies with long-term follow-up, and an 18.0% reduction in hospital readmissions. (Abreu et al., 2018; Ambrosetti et al., 2021; Anderson et al., 2021; Javaherian et al., 2020)

CR benefits appear to be through direct physiological effects on the heart and coronary vasculature, including myocardial oxygen demand, endothelial function, autonomic tone, coagulation and clotting factors, inflammatory markers, and the development of coronary collateral vessels, that lead to positive effects on LV ejection fraction and peak oxygen consumption, improving functional capacity and cardiac function. (Anderson et al., 2021; Ibanez et al., 2018)

In addition, another important contribution to the benefits of CR comes from the indirect effects of risk factor control, for example, improvements in lipid profile, through reductions in LDL cholesterol, total-c and TG, blood pressure decrease, particularly SBP; favorable changes in glycaemic control; reductions in adipose tissue mass; and changes in lifestyle behaviors and mood, which may decrease anxiety and depression symptoms and all

together lead to improvements in quality of life. Moreover, CR promotes better adherence to a medical treatment regimen after ACS. (Abreu et al., 2018; Ambrosetti et al., 2021; Anderson et al., 2021; Ibanez et al., 2018; Javaherian et al., 2020; Visseren et al., 2021)

1.3.3. Cardiac Rehabilitation in Portugal

Portugal has one of the lowest rates of inclusion in CR programs in Europe and, in 2019, only 9.3% of ACS survivor patients participated in these programs. (Fontes et al., 2021)

Data from 2014 in Portugal, identified 23 centers (12 public and 11 private) in Portugal with CR programs, representing an increase compared to 2007, when there were only 16 centers. At the same time, it also increased the percentage of patients discharged from hospital after AMI who participated in a CR program, from 3.0% in 2007 to 8.0% in 2014, although it is still insufficient to meet the country's needs. (Abreu et al., 2018)

Even more recent data, from 2019, identified 25 centers with CR programs, 11 in the North region, 1 in the Central region, 12 in the Greater Lisbon region and 1 in the South region. Compared to 2014, 4 centers (1 public and 3 private) had discontinued CR programs and there were 6 new centers (5 public and 1 private). (Fontes et al., 2021) Centro de Reabilitação Cardiovascular da Universidade de Lisboa (CRECUL) is one of those new public centers.

Regarding CR program phases, 12 centers, all public centers, provided phase I programs, 22 provided phase II programs and 13 centers provided phase III programs, allowing an 13% increase of patients integrated in phase II, although in phase III the opposite was verified (a decrease of 37%). Around 90.0% of CR programs presented drop-out rates of less than 25.0%. (Fontes et al., 2021)

All centers reported having multidisciplinary teams, although frameworks varied. In this regard, all programs included nutritional counseling, most offered CV risk factor management, and a large proportion included smoking cessation counseling and psychosocial assessments. (Fontes et al., 2021)

1.3.4. Cardiac Rehabilitation at Centro Hospitalar Universitário Lisboa Norte - Faculdade de Medicina da Universidade de Lisboa - Centro de Reabilitação Cardiovascular da Universidade de Lisboa

The Centro Hospitalar Universitário Lisboa Norte (CHULN)/ Faculdade de Medicina da Universidade de Lisboa (FMUL)/CRECUL CR program offers phases II and III that are developed in different places. This center has been accredited in 2020 by the European Association of Preventive Cardiology from the European Society of Cardiology according to the standardization and quality criteria published. (Abreu et al., 2021)

Phase II, since 2013, takes place at Hospital Pulido Valente, CHULN and lasts between 8 and 12 weeks corresponding approximately to 24 to 36 exercise sessions. Initially and after completing phase II all patients are clinically assessed by the multidisciplinary team in cardiovascular, physical, nutritional, and psychological parameters. After initial assessment, all patients attend to a structed and individualized exercise session program during 60 minutes/session, 2 to 3 times a week. These sessions are carried out in open groups of 8 patients at different stages and levels of risk, being monitored and supervised by a doctor and the

physiotherapists, through telemetry. Besides, there are respiratory sessions with rehabilitation nurses for 60 minutes/session, 2 to 3 times a week, and educational sessions once a week. The phase II team is composed by cardiologists, physiatrists, physiatrists, rehabilitation nurses, psychologists, nutritionists, physiotherapists, exercise physiologist, cardio-pneumology technicians and administrative. After completing phase II, patients are referred or to a phase III or to continue their process of CR by themselves.

Phase III takes place at CRECUL, located at Academia de Fitness do Estádio Universitário de Lisboa and is a project from the University of Lisbon with FMUL, Faculdade de Motricidade Humana, and Estádio Universitário da Universidade de Lisboa, being recognized as a community initiative in the field of health. CRECUL started its activity on May 6, 2016 and has had more and more patients over the years. (Universidade de Lisboa, 2022)

CRECUL is focused in three main areas - Educational (curricular and academic); Research; Community (health promotion) – and consists in exercise prescription, physical activity counseling, nutritional counseling, and risk factor modification. The team is composed by a clinical director Ana Abreu, cardiologists and interns, exercise physiologists, physiotherapist, nutritionists, cardiopulmonary technician, and psychologist.

This phase has no duration limit (as far as the patient is clinically stable) and has the proposal of 60 min exercise sessions, 2 to 3 times a week, in a group basis, whose schedules (morning and afternoon period) are adjusted to the availability of each patient and space. The exercise sessions can be at the center or online.

Since 2020, due to the COVID-19 pandemic, the online training modality is an option in CRECUL.

Every patient has an individual patient sheet, and the sessions are individually guided, monitored, and supervised by exercise physiologists, using HR bands (Polar H10), Borg and Talk test to control exercise intensity. Before and after each exercise session blood pressure and HR are measured and the patient are asked for CV/non-CV signs and symptoms and changes in medication. Besides the exercise sessions, each year is organized 2 to 3 educational sessions/workshops. Additionally, patients can complement their exercise sessions with a meditation class once per week at the center or online.

All patients are evaluated at baseline, and annually thereafter, performing cardiopulmonary exercise testing (CPET), nutritional assessment with nutritional counseling, objective measures of physical activity (accelerometry) at FMUL; body composition assessment using DXA at FMH-UL; maximal strength (1 repetition maximum), isometry strength, functional tests and quality of life at CRECUL.

1.4. Risk factor modification in phases II and III Cardiac Rehabilitation

Patients with clinically established CAD are, on average, at very high risk of recurrent CV events if risk factors are not treated. It is important to detect it as early as possible so that management with counselling and medicines can begin because most CVDs can be prevented by addressing those modifiable risk factors. There is a lot of evidence showing that implementing healthy lifestyle behaviors decreases the risk of subsequent CV events and CVD mortality. (Javaherian et al., 2020; Knuuti et al., 2020; Visseren et al., 2021; WHO, 2021)

Furthermore, lifestyle changes are recommended in combination with pharmacological therapy to achieve the most appropriate secondary prevention therapy possible. (Javaherian et al., 2020; Knuuti et al., 2020; Visseren et al., 2021)

High blood pressure, blood lipid disorders, physical inactivity, obesity, and tobacco use remain the major modifiable risk factors for CAD. (Timmis et al., 2022; WHO, 2021) The difficulty in controlling these risk factors has been expressed in some studies carried out in phase II and phase III CR programs, mainly in terms of the lipid profile and SB. (Freene et al., 2020; Rott et al., 2022; Silva et al., 2021)

1.4.1. Impact of modification

Lowering SBP has been shown to reduce CV risk and the absolute benefit depends on the amount of reduction. The greater the reduction, the better the benefit, except in cases where lower SBP limits are imposed for tolerability or safety reasons. (Visseren et al., 2021)

For example, in patients with type 2 DM, reduced caloric intake is recommended, leading to improvements in HbA1c and quaity of life. (Cosentino et al., 2020) An weight loss > 5.0% is associated with improvements in glycaemic control, lipid levels and blood pressure. The more the loss, the more the benefits. (Cosentino et al., 2020) Bariatric surgery causes a long-term weight loss and reduces DM and other risk factors, having more effects than lifestyle and therapeutic strategies alone. Even in CV patients without DM, this changes are important in DM prevention and might delay disease progression from pre-DM to type 2 DM. Physical activity is recommended for CVD control and improves glycaemic control, helping in DM control. (Cosentino et al., 2020) Some policy initiatives like sugar taxes and traffic labelling on food and drink have proven benefit in obesity and type 2 DM protection because they create an environment in which people are empowered to make healthier lifestyle choices. (Timmis et al., 2022)

Regarding dyslipidaemia, prolonged lower LDL cholesterol is associated with a reduction of CV event risk. Regarding non-HDL cholesterol and CV risk the relationship is at least as strong as LDL cholesterol. In both, the CV reduction is proportional to the absolute size of the change in LDL cholesterol or non-HDL cholesterol. Thus, even a small change in any of them may be very beneficial in a high- or very-high-risk patients. (Javaherian et al., 2020; Mach et al., 2020; Orozco-Beltran et al., 2017; Visseren et al., 2021)

Smoking cessation is a very effective secondary prevention measure in patients with CAD, improving prognosis and reducing mortality risk and CV risk for those who quit. They can reduce mortality risk by 36.0% and their CV risk by 39.0% within 5 years. (Knuuti et al., 2020; Timmis et al., 2022) CV risk can be greatly reduced and even reaching the same CV risk of a person who was never smoked but it takes at least 5 - 10 years and perhaps up to 25 years. Smoking cessation is particularly important after myocardial infarction because it can reduce even more mortality risk (up to 50%) during follow-up. (Ibanez et al., 2018; Knuuti et al., 2020; Kotseva et al., 2016, 2019; Timmis et al., 2022)

For smokers who quit it is expected an average weight gain of 5.0 kg, however it does not lessen the CV benefits, being always an advantageous measure despite the weight gain. (Visseren et al., 2021)

Regarding alcohol consumption it has been shown that reducing it to the guidelines can increase up to two years the life expectancy of a 40-year-old drinker. (Timmis et al., 2022)

Weight loss has beneficial effects on CV risk factors. A 5.0% weight reduction was associated to reductions in hypertension, dyslipidaemia and markedly improvements in glycaemic control in patients with DM that confer a better prognosis and CV risk profile in overweight and obese CAD patients, as well as a decrease in the risk of recurrent CV events. (De Bacquer, Jennings, et al., 2022; Ibanez et al., 2018)

Although, it is important to be aware of the intention of weight loss. When weight loss is unintentional, it should be considered as a possible marker of underlying disease and is associated with worse long-term outcomes. (Pack et al., 2018) When weight loss occurs intentionally in the setting of a lifestyle changes, it has beneficial effects, being associated with a significant lower risk of adverse CV outcomes. (Knuuti et al., 2020; Pack et al., 2018)

Physical activity has many proven beneficial effects like reducing atherogenic lipid profiles, lowering blood pressure, improving insulin resistance and endothelial disfunction, development of coronary collateral vessels, contributing to anti-inflammatory response and antioxidant effects, reducing the risk of many adverse outcomes in all ages and both sexes. (Anderson et al., 2021; Ou et al., 2017; Visseren et al., 2021)

Increasing MPA and VPA are considered an effective, simple and low-cost method in preventing high levels of adiposity and have also been successful in interventions to lose or maintain body weight, and so it has been shown to positively influence prognosis and quality of life, especially in older individuals, and to reduce CVD mortality. (Castro et al., 2017; Knuuti et al., 2020; Ou et al., 2017; Timmis et al., 2022) For example, exercise training as a part of a CR program was shown to reduce CVD mortality rate in CAD patients by 22.0%. (Ibanez et al., 2018)

The main message is to move more and try to reach physical activity guidelines, even irregular leisure-time physical activity was associated with a decrease in risk of mortality among previously sedentary patients and inversely associated with the risk of AMI. (Knuuti et al., 2020; Visseren et al., 2021; Zhuang et al., 2020)

For physically inactive adults, LPA even as little as 15 min a day, or accumulated physical activity in bouts of < 10 min, can produce the benefits described. (Bull et al., 2020; Visseren et al., 2021)

It is very important not only to control physical activity but also ST. Thus, it is recommended to reduce ST and replace it for LPA to reduce all-cause and CVD mortality and morbidity. (Bull et al., 2020; Visseren et al., 2021)

A Mediterranean diet has been shown to reduce the incidence of major CV events up to 20.0% and the greater the adherence, the greater the benefits will be, reaching up to a 10.0% reduction in CVD mortality and up to a 8.0% reduction in all-cause mortality. (Cosentino et al., 2020; Visseren et al., 2021)

This dietary pattern has impact in dyslipidaemia decreasing LDL cholesterol levels, by 5.3% in obese and 9.7% in normal-weight patients, due to the reduction and substitution of saturated fatty acids, and by 3.6 mg/dL, with only one portion of legumes a day and also decreases TG levels. SBP may reduce by 5.8 mmHg in hypertensive and 1.9 mmHg in normotensive patients, due to a reduction in sodium intake. It has an important role in reducing postprandial glucose responses, being useful in DM control and prevention. (Visseren et al., 2021)

Regarding psychological factors it have been shown that indicators of mental health, such as optimism and a strong sense of purpose, are associated with a lower CV risk. (Visseren et al., 2021)

1.4.2. Which cardiovascular risk factors are not being controlled in patients attending cardiac rehabilitation programs?

The presence of non-modifiable risk factors in CAD patients is of concern, and even more with the addition of those that are modifiable, so everything possible should be done to prevent and control these last.

Recent data in Europe about CV risk factors prevalence evolution in the last years suggest the need of modification through an effective management of risk factors as soon as possible starting at early ages so that future events can be prevented. (Timmis et al., 2022)

In Silva et al., (2021) it was shown most patients enrolled in a phase II CR program for 8 weeks were not reaching LDL cholesterol, blood pressure and HbA1c guideline recommended targets. In addition, an increase in LDL cholesterol levels was verified in the long-term. In Freene et al., (2020) patients were submitted to a phase II CR program for 6 weeks managed to achieve improvements in the pattern of physical activity and SB, however ST remained high at 12-months follow-up and the downward trend in results was not sufficient for the recommendations to be achieved.

In Rott et al., (2022) patients with CAD were included to a phase III CR program and it was found that both after 3 months and 6 months since the beginning of the CR program, LDL cholesterol values remained uncontrolled in most patients.

Besides, over the years, five studies (EUROASPIRE) have been carried out at European level aiming to measure and evaluate the management of risk factors in patients with established CHD enrolled in CR programs and all of them shown a high prevalence of modifiable risk factors. Most patients in Europe fail to achieve the guidelines targets for each risk factor, particularly in terms of weight management, lipid profile and physical activity levels, and the proposal of lifestyle modification. The implementation of risk factor control measures on secondary prevention is far from optimal. (Kotseva et al., 2016, 2019; Timmis et al., 2022)

Two in particularly, the EUROASPIRE IV and the EUROASPIRE V, were follow-up surveys carried out in 2016 and 2019, respectively. They were carried out at European level; however, Portugal was only included in the most recent study. The two surveys were directed to CHD patients only, men and women between 18 and 80 years of age at the time of their index event or procedure. In both cases, it was estimated that less than 50.0% of the patients were reaching the guidelines for secondary prevention. Furthermore, most patients maintained unhealthy lifestyle habits even after the CV event, particularly, in terms of persistent smoking and weight related dietary factors, including SB, which have an impact on the control of risk factors.(Kotseva et al., 2016, 2019) The characteristics of the population of these two surveys are very similar to the study population of this dissertation and thus some of its data are going to be presented next.

It is necessary to control and reduce CV risk factors prevalence and find strategies to increase CR programs efficiency to improve both primary and secondary prevention in CAD patients and CV patients in general.

In a broad way, the WHO has called for a relative reduction 25.0% in the premature mortality from CVDs, cancer, DM, or chronic respiratory diseases to be achieved by 2025. (Timmis et al., 2022)

Regarding hypertension, the WHO called for a relative reduction of 25.0% in its prevalence or, at least, contain the hypertension prevalence, according to national

circumstances, to be achieved by 2025. (Timmis et al., 2022) In EUROASPIRE V, 29.0% of CAD patients on blood pressure medication had reached the recommended guidelines. (Kotseva et al., 2019)

Regarding DM, It is predicted that > 600 million individuals may develop type 2 DM worldwide by 2045, with around the same number developing pre-DM. The WHO has called to halt the rise in DM to be achieved by 2025. (Timmis et al., 2022) In EUROASPIRE V, glucose control in CAD patients with DM was relatively good with 54.0% of them achieving HbA1c < 7.0%. (Kotseva et al., 2019)

Regarding dyslipidaemia, the median total-c concentrations in Europe reduced between 1980 and 2018 from 214.0 mg/dL to 190.0 mg/dL in women and from 213.0 mg/dL to 186.0 mg/dL in men. In Portugal this downward was also observed in both women (from 214.0 to 196.0 mg/dL) and men (from 213.0 to 186.0 mg/dL). (Timmis et al., 2022) Although there is no specific recommendation for total-c values modification and these values are near but below the cut-offs for dyslipidaemia, it is necessary to pay attention to the different fractions of cholesterol in order to establish the lipid profile and make an adequate evaluation.

The median non-HDL cholesterol concentrations across Europe declined between 1980 and 2018 from 156.0 mg/dL to 130.0 mg/dL in women and from 162.0 mg/dL to 137.0 mg/dL in men. Again, this downward was also observed in Portugal, in both women (from 151.0 to 140.0 mg/dL) and men (from 157.0 to 137.0 mg/dL). (Timmis et al., 2022) However, through these results it is possible to presume that in most cases it is still not enough to reach the recommended LDL cholesterol values. In EUROASPIRE V only 29.0% of CAD patients had reached LDL cholesterol targets of < 70.0 mg/dL despite lipid-lowering therapy, still remaining far from the guidelines. (Kotseva et al., 2019)

In women, the median HDL cholesterol concentrations in Europe increased between 1980 and 2018 from 55.0 mg/dL to 59.0 mg/dL. In men, HDL cholesterol concentrations showed little change between 1980 and 2018 going from 50.0 mg/dL to 49.0 mg/dL. In Portugal little changes were observed, with a small raise in women (from 58.0 to 60.0 mg/dL) and a small decrease in men (from 51.0 to 47.0 mg/dL). (Timmis et al., 2022) Similarly to what happens with total-c, there is no specific recommendation for HDL cholesterol values modification and although these values are above the cut-offs for dyslipidaemia, it is particularly important to counteract the downward trend that has been observed in men. These results express the great difficulty in controlling this risk factor and show the plenty of opportunities and the need in cholesterol improvement.

Between 1989 and 2019 in Portugal, the number of daily smokers has continuously decreased from 28.0% to 14.2%. Still, the WHO has called for relative reduction of 30.0% in the prevalence of current tobacco use to be achieved by 2025. (Timmis et al., 2022) In EUROASPIRE V, only 19.0% of the patients were daily smokers. (Kotseva et al., 2019) However, the addictive nature of this habit leads to many relapses and a significant number of CAD patients, almost an half of those who smoked, continue or restart smoking after the CV event, particularly younger patients with less than 50 years, both men and women. (Ibanez et al., 2018; Kotseva et al., 2016, 2019; Timmis et al., 2022) This underlines the need to continue this progress through brief interventions, with a combination of behavioral support and pharmacotherapy. (Ibanez et al., 2018)

Regarding alcohol consumption, although between 2000 and 2018 in Portugal there was a decrease in alcohol consumption in both women (from 130.8 to 107.7 g/week) and men (from

425.0 to 373.1 g/week), it is still not enough to reach the recommended consumption values. The WHO has called for a relative reduction of at least 10.0% in the harmful use of alcohol to be achieved by 2025, as appropriate, within the national context. (Timmis et al., 2022)

Following the increase of prevalence of overweight and obesity, the WHO has called to halt the rise of obesity to be achieved by 2025. (Timmis et al., 2022) In Europe, obesity prevalence rose steeply between 1980 and 2016 from 9.6% to 22.5% and this increase was greater in men (from 7.4% to 22.2%) than in women (from 11.8% to 22.7%). Between 1975 and 2016 in Portugal, overweight prevalence also increased and more in men (from 34.5% to 63.1%) than in women (from 27.6% to 52,0%). The same trend was observed in obesity prevalence with men raising from 3.8% to 20.3% and women from 6.8% to 21.2%.

Regarding BMI, in Portugal, increases were observed in both men (from 23.6 to 26.1 kg/m^2) and in women (from 24.3 to 25.1 kg/m^2). This translates in an overall increase from 24.0 to 25.6 kg/m^2, both sexes included. These important recent changes observed in BMI show the urgent need to control this risk factor, with special attention to men. It has been shown that over 80.0% of patients fail to achieve their weight target. (De Bacquer, Jennings, et al., 2022) Furthermore, in EUROASPIRE V, most CAD patients were overweight or obese, many with central obesity as well, with no plans to lose weight. Only 18.0% were classified as having normal weight (Kotseva et al., 2019)

Regarding physical inactivity, the WHO has called for relative reduction of 10.0% in its prevalence to be achieved by 2025. (Timmis et al., 2022) In EUROASPIRE V, most CAD patients reported increasing physical activity levels and changing diet, although only 34.0% reported performing, at least, 30 minutes of physical activity, five times per week, and only 16.0% achieved VPA levels for at least 20 minutes once a week. (Kotseva et al., 2019)

1.4.3. Pertinence and targets of the study

While CR has shown positive effects in the short and medium term for treating CAD, its long-term benefits remain uncertain. To gain a clearer understanding of the impact of risk factor management in phase III CR programs, further long-term studies are necessary.

An European study was recently carried out - Multicentre SURF CHD Study: “Survey of Risk Factors a Clinical Audit to Record and Monitor Cardiovascular Diseases: SURF CHD” - with similar aims of this dissertation, in which I collaborated in the process of survey, treatment and submission of clinical data from CRECUL patients. This study has highlighted the importance of constant evaluation and monitoring of patients’ CV risk factors to guarantee the effectiveness of the proposed program and to promote changes, if necessary.

This dissertation aimed to:

- Examine compensatory changes in SB (objectively assessed by accelerometry) on lipid profile and body composition, in response to a 1-year community-based CR program in patients with CAD.
- Explore the blood lipid status in combination with body composition and physical activity in CAD patients when entering on a community-based CR program.
- Compare physical activity levels in response to a 1-year community-based CR program in patients with CAD and its influence on modifiable risk factors.

2. Methods

2.1. Study design

This study consisted of an observational study in which all patients who entered in the CR program at CRECUL between the year of 2016 and 2022 were considered as shown in Figure 1. The present study was divided into two different evaluation moments (baseline and after completing 1 year of the CR program entry), and thus, two type of analyses were done. At first a cross- sectional analysis with the baseline assessments and then a longitudinal analysis including the baseline and 1-year follow-up.

All patients were evaluated at baseline, and annually thereafter, performing the following assessments: CPET to assess cardiorespiratory fitness, objective measure of physical activity and SB using accelerometry, body composition assessment using DXA and blood analysis to assess lipid profile.

The primary outcomes of this study were weight and BMI, moderate-to-vigorous intensity physical activity (MVPA), average MVPA and sedentary time (ST) and total-c, HDL cholesterol, LDL cholesterol, non-HDL cholesterol and TG at 1 yer and the secondary outcomes the assessment of SBP and DBP, waist circumference and VO_2 peak. Measurements of the primary and secondary outcomes took place at baseline and 1 year after starting the CR program.

The following associations were explored:

- Pattern of physical activity / SB and relationship with lipid profile.
- BMI / DXA and relationship with CV risk factors.
- Time enrolled in the program and relationship with the modifiable CV risk factors.

The study was conducted following the guidelines outlined in the Declaration of Helsinki for studies involving human patients and was approved by the Ethics Committee of Centro Académico de Medicina de Lisboa (Nº330/22). Informed consent was obtained from all patients included in this study.

2.2. Study population and sample selection

The study population consisted in 216 patients (Figure 1) enrolled in a Phase III CR program conducted at the Cardiac Rehabilitation Centre of CHLUN/FMUL/CRECUL, located at the Estádio Universitário de Lisboa.

Inclusion criteria were as follows: patients aged over 18 years, male and female, who had confirmed CAD based on angiography in at least one major epicardial vessel, clinical evidence of CAD which can be in the form of previous myocardial infarction, coronary revascularization (CABG or PCI), or angina pectoris.

Exclusion criteria included: Lack of clinical information related to CV disease, absence of lipid profile information, missing CPET information, insufficient data on body composition information or physical activity information. Individuals who did not meet these criteria were not included in the study.

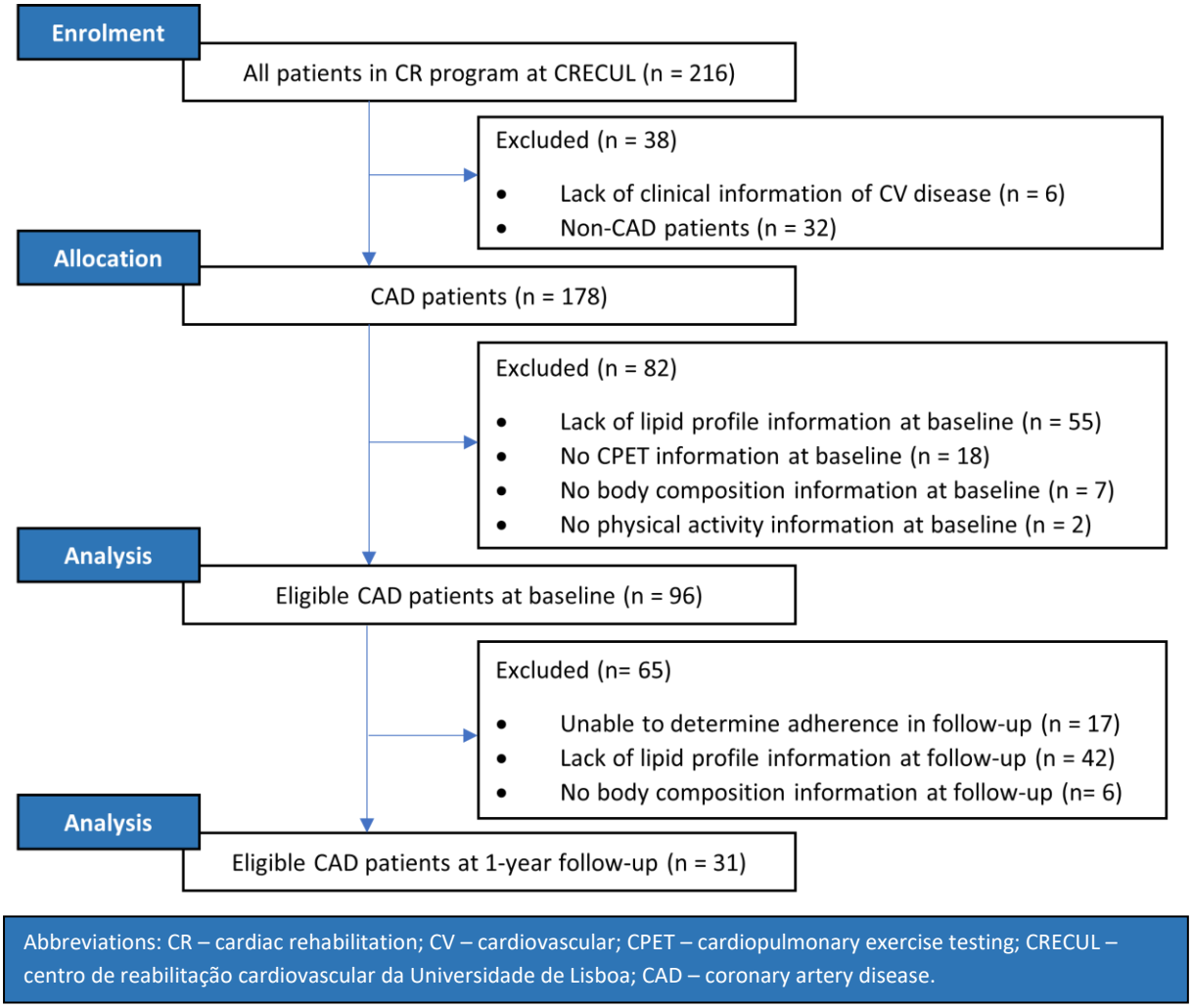


Figure 1. Study flow chart

2.3. Cardiac Rehabilitation Program at the University of Lisbon (CRECUL)

Since 2016, CRECUL has admitted 216 patients. Each patient has the option to attend exercise training sessions two or three times per week for 60 minutes each session. The program runs for 11 months a year, except in August that is closed. Patients ' schedules are defined according to their preferences and space availability.

The CRECUL program has at its disposal an exercise room, three studios, an office and changing rooms. In addition to these indoor spaces, the entire outdoor area of the Estádio Universitário de Lisboa can be used. The exercise room has several machines and equipment where patients can perform aerobic training and strength training. Most of CRECUL's group classes take place in the main studio. Studio 1 is only used for aerobic training and in studio 2 there are also group classes for resistance training. The CRECUL office is used for team meetings, initial interviews with CRECUL patients, archiving several documents/examinations of the patients and measurements of blood pressure and HR before and after each exercise training session.

All new patients, after clinical approval, are subject to an initial interview with one of the exercise physiologists and subsequently enroll in the CRECUL program. In an initial phase, it

is explained to the patient how the program works regarding the exercise sessions and assessments. Then, the patient fills out a questionnaire about some relevant personal and professional data, medical history, risk factors for the development of CVD, pharmacological therapies, physical limitations, sports history, the availability to join the CR program and the personal goals to be achieved by joining CRECUL.

Each session is divided into 3 components: Pre-training, where blood pressure and HR are measured and it is asked about signs, symptoms and medication intake; exercise training session, where an aerobic and resistance components are prescribed ; and post-workout where blood pressure and HR measurements are done. In turn, the exercise training sessions are divided into warm-up (lasting 10 minutes and whose objective is to gradually increase the HR), fundamental part (aerobic training lasting 20 to 30 minutes, which aims to reach an intensity between 40% to 60% of HR reserve, and then strength training, which can reach up to two sets of 8 - 12 repetitions at 60 to 80% of the 1 maximum repetition) and cool-down (lasting 10 minutes and whose objective is to gradually decrease the HR until the values are similar to those seen at the beginning of the session).

2.4. Assessments

Several risk factors such as lipid profile, body composition, physical activity and SB were assessed at baseline and after completing 1 year in a phase III CR program.

Risk factors such as hypertension, dyslipidaemia, DM, tobacco, and alcohol consumption were assessed using the initial assessment questionnaire and the patients' clinical files. Risk factors such as lipid profile, body composition, physical activity and SB were evaluated according to what will be described below. In addition, aerobic capacity was also evaluated through CPET and was used only for sample characterization.

The level of adherence of each patient to the CR program's exercise sessions was calculated for each of the first 12 months since the program entry. The number of sessions attended in each month was divided by the number of sessions proposed for the patient in the respective month. Then the mean adherence value of the first year (11 months) was calculated excluding the program closing month in August. Participants who attended at least 70.0% of their scheduled exercise sessions were assigned as adherent and participants who attend < 70.0% of the exercise sessions as non-adherent. (Swardfager et al., 2011)

2.4.1. Lipid profile

A blood sample was taken after 12 - 14 h of fasting to measure fasting blood sugar, serum lipids including TG, and total-c using enzymatic colorimetric methods. HDL cholesterol was determined after dextransulphatemagnesiumchloride precipitation of non-HDL cholesterol; then, LDL cholesterol was calculated according to Friedewald formula. (Friedewald et al., 1972)

Each patient chooses the blood laboratory center to measure both analyses at baseline and after completing 1-year. The assessment of the lipid profile was made according to the following goals, and cut-off values:

- The LDL cholesterol target was considered as fulfilled when a LDL cholesterol value < 55.0 mg/dL was reached. (Visseren et al., 2021)

- The TG target was considered as fulfilled when a TG value < 150.0 mg/dL was reached. (Ambrosetti et al., 2021; Mach et al., 2020)

The latest records of clinical analyzes of each patient were requested and when there was no data from any of the evaluation moments, after patients consent, the hospital database was used in order to obtain lipid profile data from the largest possible number of patients.

2.4.2. Physical activity and sedentary behavior

Physical activity was assessed by accelerometery (ActiGraph, wGT3X+BT, Florida). Each patient in the study was instructed to wear the ActiGraph wGT3X+BT accelerometer, which was attached to an elastic waist belt. The accelerometer was positioned in line with the axillary line of the right iliac crest and worn continuously for a period of 7 days. The patient had to remove the accelerometer in water-based activities and during sleep. For a day to be considered valid, it had to consist of at least 600 minutes (10 hours) of monitored wear time. Patients who had a minimum of 3 valid days, including at least one weekend day, were included in the analysis. The accelerometers were set to raw mode with a frequency of 100 Hz and the data was later downloaded into 10-second epochs using the Actilife software version 6.9.1. To determine the time spent in different intensity periods and define valid recordings, the cut-off points and wear time validation criteria established by Troiano et al. (2008) were used (Troiano et al., 2008). These criteria were used as a reference to analyze and interpret the data collected from the accelerometers.

The classification of patients as physically inactive, active or very active, was done according to the following physical activity cut-offs (Bull et al., 2020):

- Inactive: Performing less than 150 min a week of MPA per week or 75 min of aerobic VPA per week or an equivalent combination of both intensities.
- Active: Performing 150 - 300 min a week of MPA per week or 75 – 150 min of aerobic VPA per week or an equivalent combination of both intensities.
- Very active: Performing more than 300 min a week of MPA per week or 150 min of aerobic VPA per week or an equivalent combination of both intensities.

For the classification of patients as sedentary or non-sedentary, the 7.5 hours/day cut-off was used. An individual was considered sedentary if the ST was > 7.5 hours/day. (Ku et al., 2018)

Thus, regarding the association "pattern of physical activity/SB and relationship with lipid profile", 6 subgroups were created:

- 1st: Sedentary and physically inactive individuals.
- 2nd: Sedentary and physically active individuals.
- 3rd: Sedentary and physically very active individuals.
- 4th: Non-sedentary and physically inactive individuals.
- 5th: Non-sedentary and physically active individuals.
- 6th: Non-sedentary and physically very active individuals.

2.4.3. Body composition

All patients were tested in the morning following a 12-h fast and refrained from caffeine, alcohol, and MVPA during the last 24-h and all the following anthropometric procedures were led by the same certified technician. Height and weight were measured using an electronic scale with stadiometer (SECA, Hamburg, Germany) and BMI was calculated (kg/m^2). FMI was estimated using DXA (Hologic Explorer-W, fan-beam densitometer, software QDR for windows version 12.4, Hologic, USA). Waist circumference was measured using an inelastic flexible metallic tape (Lufkin W606 PM, Vancouver, Canada).

BMI characterization: Patients were evaluated by different parameters according to their age and sex, particularly in the case of the elderly (age ≥ 65 years). The cut-offs used in BMI characterization are shown in Table 1. (De Bacquer, Jennings, et al., 2022; Heiat et al., 2001; Ibanez et al., 2018; Kıskaç et al., 2022)

Table 1. BMI classification cut-offs

BMI Classification	BMI (kg/m^2)	
	Adults (18 – 65 years)	Elderly (≥ 65 years)
Thinness	< 18.5	< 22.0
Normal Weight	18.5 – 24.9	22.0 – 26.9
Overweight	25.0 – 29.9	Men: 27.0 – 29.9; Women: 27.0 – 31.9
Obesity grade I	30.0 – 34.9	Men: 30.0 – 34.9; Women: 32.0 – 36.9
Obesity grade II	35.0 – 39.9	Men: 35.0 – 39.9; Women: 37.0 – 41.9
Obesity grade III	≥ 40.0	Men: ≥ 40.0; Women: ≥ 42.0

FMI characterization: FMI was classified according the following criteria (Imboden et al., 2017):

- In men: FMI > 6.0 kg/m^2 indicates overweight and FMI > 9.0 kg/m^2 indicates obesity.
- In women: FMI > 9.0 kg/m^2 indicates overweight and FMI > 13.0 kg/m^2 indicates obesity.

Waist circumference characterization: Patients were evaluated according to their sex and the following cut-offs were used (Ambrosetti et al., 2021; De Bacquer, Jennings, et al., 2022; Ross et al., 2020; Stepaniak et al., 2016; Visseren et al., 2021):

- In men: Waist circumference ≥ 94.0 cm indicates abdominal overweight and waist circumference ≥ 102.0 cm indicates central obesity.
- In women: Waist circumference ≥ 80.0 cm indicates abdominal overweight and waist circumference ≥ 88.0 cm indicates central obesity.

2.5. Statistical analysis

The data of interest for the study were obtained from the CHULN/FMUL/CRECUL CR program database.

Variables about physical activity and lipid profile were recodified according to the fulfillment of the guidelines targets with the cut-offs for each of them. Body composition variables were recodified into its category's classification. Age and adherence to program's exercise sessions were also recodified according to the cut-offs used in this study (Age = 65 and adherence = 70.0%). Also, the differences between each comparable variable at the two moments of the study were recodified into new variables expressing its difference.

Primary and secondary outcome variables were expressed as means ± standard deviation. Descriptive statistics including means, standard deviation, median, quartile (Q25 and Q75) and interquartile range, and percentage were calculated for all primary and secondary outcome variables.

Normality and homogeneity were tested using Shapiro–Wilk test and Levene test, respectively. Different variances were considered for an alpha level of 0.05 in Levene test.

For the cross-sectional analysis sample (n = 96), sex, age, phase II CR program fulfillment and inclusion in the longitudinal analysis sample were used to compare groups. For the comparison analysis of baseline qualitative variables, the independent samples T Test and the Mann-Whitney U test were used according to the distribution of each variable.

For the longitudinal analysis sample (n = 31), age was the only criteria used to compare groups. For the comparison analysis of baseline qualitative variables, the independent samples T Test and the Mann-Whitney U test were used according to the distribution of each variable. For the evaluation of observed changes between baseline and follow-up moment the paired-samples T Test and the Wilcoxon Signed-rank Test were used according to the distribution of each variable. Besides, the independent samples T Test and the Mann-Whitney U test were also used to compare these changes according to the patient's adherence to the CR program exercise sessions.

Categorical variables were estimated as frequencies and compared using the Chi-square Test or the Fisher's exact Test. In the analysis of variables with only 2 groups the Chi-square Test with Yates correction was used except for cases in which the use of this approximation method was considered inadequate, having resorted to the Fisher's exact test. The use of an approximation method was considered inappropriate when more than 20.0% of cells have expected frequencies < 5. (Kim, 2017) In the analysis in which at least one of the variables had more than 2 groups the Chi-square Test was used. Statistical significance was set at an alpha level of 0.050.

All data was analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0 software (IBM SPSS Statistics, Chicago, IL, USA).

3. Results

3.1. Cross-sectional study

Baseline characteristics of eligible CAD patients at the cross-sectional analysis are described in Table 2 and presents the differences between groups according to phase II CR program participation. In this analysis 12.5% were female patients and the mean age of the sample was 61.8 ± 9.7 years, the youngest patient had 33 years old and the oldest patient 80 years old.

A higher CV risk estimated through SMART Risk Score (Attachment 2) was found in the elderly (≥ 65 years) patients ($p < 0.050$). There was also a greater aerobic capacity (% of VO_2 peak predicted) (Attachment 3) in male patients compared to female patients (78.6 ± 18.7% vs 65.8 ± 16.8%, $p < 0.050$).

Table 2. Baseline characteristics of CAD patients at cross-sectional analysis according to phase II fulfillment

Phase II fulfilment	**All sample** (n = 96)	**Yes** (n = 86)	**No** (n = 10)	**p-value**
Female / Male (n)	12 / 84	11 / 75	1 / 9	1.000
Age (years)	61.8 ± 9.7	61.9 ± 9.5	60.6 ± 11.9	0.697
% of $\boldsymbol{VO_2}$ peak predicted	77.0 ± 18.9	77.6 ± 19.1	72.3 ± 16.6	0.410
SMART Risk Score (%)	13.7 ± 7.0	13.4 ± 7.0	16.1 ± 7.3	0.193
Diagnosis (%)				
Coronary Artery Disease	100.0	100.0	100.0	---
Acute Myocardial Infarction	72.9	74.4	60.0	0.452
Heart Failure	10.4	10.5	10.0	1.000
Implantable Device	12.5	12.8	10.0	1.000
Medication (%)				
Beta Blockers	85.4	87.2	70.0	0.159
Statins	86.5	88.4	70.0	0.133
Diuretics	30.2	33.7	0.0	< 0.050 *
ACE inhibitors	49.0	51.2	30.0	0.318
Antiplatelets	69.8	72.1	50.0	0.163
Acetylsalicylic Acid	82.3	84.9	60.0	0.073

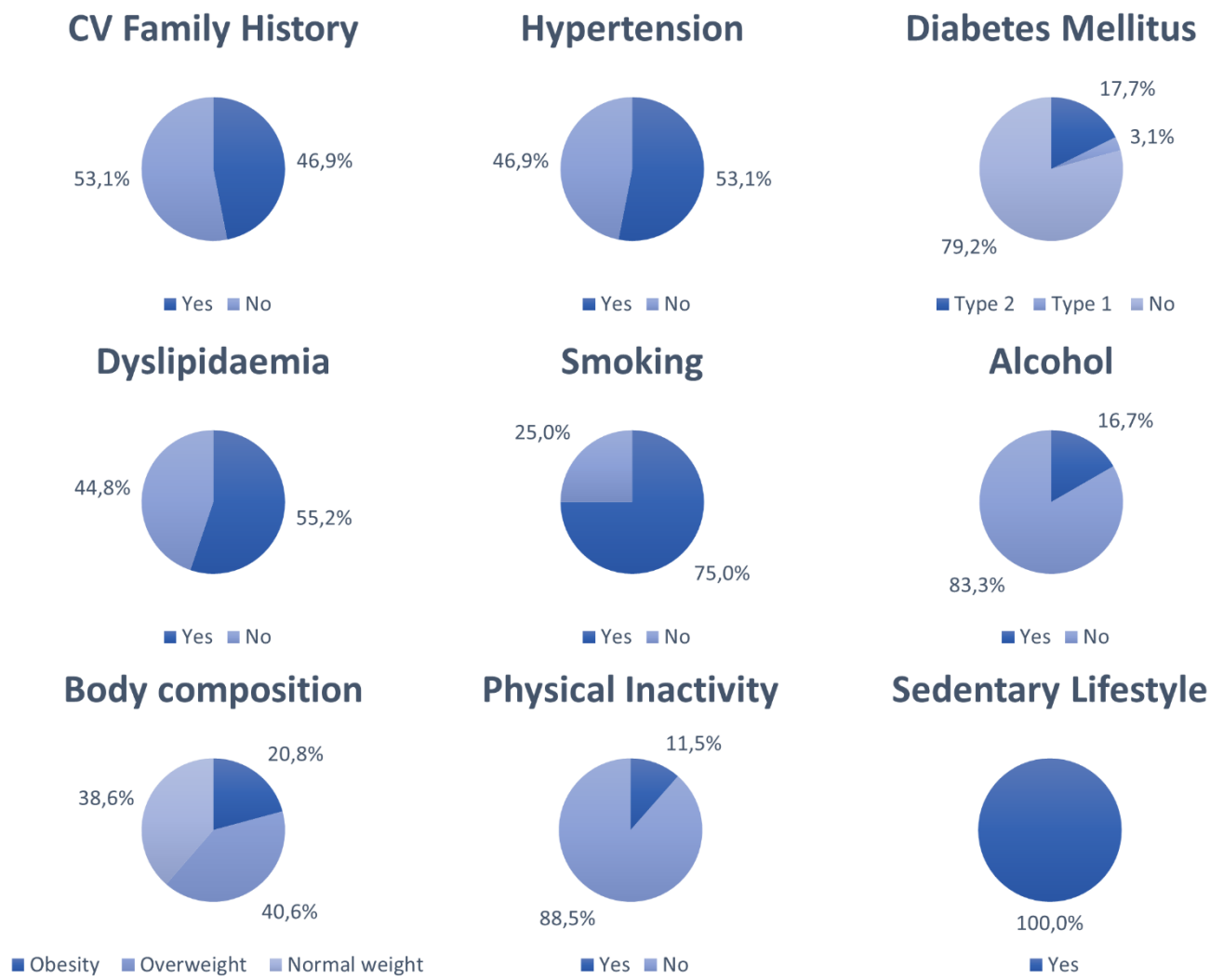
Abbreviations: ACE – angiotensin converting enzyme.
Data are mean ± SD; * Statistically different between groups ($p < 0.050$).

Some of the patients reported other forms of CVD such as valvular disease (1.0%) and peripheral artery disease (2.1%). No statistical differences were observed between groups in any of these forms of disease that were analyzed.

Other diseases such as lung disease (3.1%), depression (11.5%) and cancer (9.4%) were also observed. Statistical differences were observed between lung disease and phase II fulfillment being less frequent in patients that performed a phase II CR program ($p < 0.050$) and between depression and sex being less frequent in male patients ($p < 0.050$).

About 72.9% of the patients who had a previous AMI and the average time between the last CV intervention and the beginning of the CR program phase III was 1.9 ± 4.0 years, ranging from 0.2 to 26.4 years. Regarding CV interventions, 20.0% were submitted to CABG and 78.7% of them to PCI, with differences in CABG interventions, being more frequent in elderly (≥ 65 years) patients ($p < 0.050$), and in PCI interventions, it was more frequent in younger (< 65 years) patients ($p < 0.050$).

Before entering in a phase III CR program, 89.8% of the patients performed a phase II CR program. The prevalence of some CV risk factors, most of them modifiable, is shown in Figure 2.



Physical Inactivity: < 150 minutes/week of MPA or < 75 minutes/week of VPA or any combination; Sedentary Lifestyle: < 7.5 hours/day

Figure 2. Risk factors prevalence at baseline of cross-sectional analysis

This risk factors were analyzed when entering the phase III CR program using the initial assessment questionnaire and the patients' clinical files (CV family history, hypertension, DM, dyslipidaemia, tobacco and alcohol consumption) and the assessments made at CRECUL (body composition, physical inactivity and SB), as it was previously described.

Statistical differences were observed in dyslipidaemia prevalence (Table 2) being higher in patients that did not performed a phase II CR program ($p < 0.050$) and in physical inactivity prevalence (Attachment 5) being higher in elderly (≥ 65 years) patients ($p < 0.050$).

Body composition, physical activity and the lipid profile of each patient were analyzed in more detail as shown in Table 3.

Table 3. Body composition, physical activity, and lipid profile according to phase II fulfillment

Phase II fulfilment	All sample (n = 96)	Yes (n = 86)	No (n = 10)	p-value
Body composition				
Weight (kg)	78.5 ± 13.4	77.7 ± 13.8	83.3 ± 9.0	0.241
BMI (kg/m^2)	27.4 ± 3.5	27.2 ± 3.6	28.4 ± 3.1	0.221
Physical activity				
MVPA (min/week)	334.5 ± 177.2	345.1 ± 179.2	243.4 ± 132.4	0.076
Average MVPA (min/day)	47.7 ± 25.3	49.3 ± 25.6	34.1 ± 18.0	0.066
Sedentary time (min/week)	4770.8 ± 1221.2	4605.3 ± 940.9	6194.1 ± 2206.5	< 0.050 *
Sedentary time (hours/day)	11.5 ± 2.5	11.2 ± 2.0	14.1 ± 4.3	< 0.050 *
Lipid profile				
Total cholesterol (mg/dL)	140.5 ± 27.9	139.3 ± 25.5	151.2 ± 43.9	0.419
HDL cholesterol (mg/dL)	45.4 ± 11.0	45.8 ± 10.8	42.0 ± 12.6	0.300
LDL cholesterol (mg/dL)	72.9 ± 23.7	71.5 ± 21.8	85.0 ± 35.6	0.269
Non-HDL cholesterol (mg/dL)	95.1 ± 27.8	93.4 ± 25.8	109.2 ± 40.2	0.252
Triglycerides (mg/dL)	111.5 ± 54.2	109.8 ± 55.5	125.7 ± 41.2	0.116
Blood pressure				
SBP (mmHg)	115.7 ± 15.6	115.5 ± 16.3	117.1 ± 7.1	0.515
DBP (mmHg)	68.9 ± 9.9	69.0 ± 9.9	68.0 ± 10.7	0.759

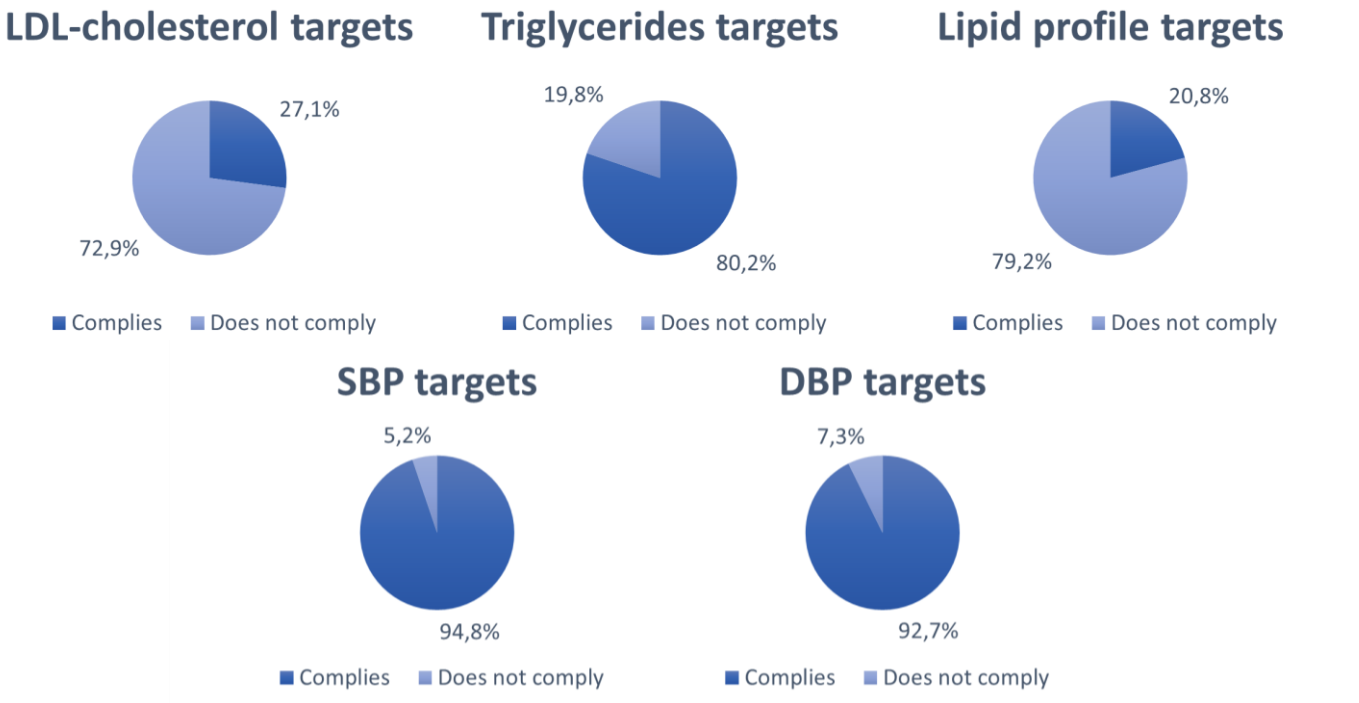
Abbreviations: BMI – body mass index; DBP – diastolic blood pressure; HDL – High-Density Lipoprotein; LDL – Low-Density Lipoprotein; MVPA – moderate to vigorous physical activity; SBP – systolic blood pressure.
Data are mean ± SD; * Statistically different between groups ($p < 0.050$).

The average BMI value of the total sample of this study was classified as overweight and both weight and BMI were similar in the 4 criteria analyzed (sex, age of 65 years, phase II CR program fulfillment and inclusion in the longitudinal analysis sample).

Through body composition characterization according to FMI (n = 94), 57.4% were classified as overweight patients and 27.7% as obese patients, both values being higher than those observed using BMI only (Figure 2). The mean FMI was 8.0 ± 2.0 kg/m^2 in men and 11.5 ± 4.3 kg/m^2 both classified as overweight as well. Regarding waist circumference (n = 74), 23.0% were classified with abdominal overweight and 49.1% with central obesity. The mean waist circumference was 98.3 ± 9.5 cm in men and 91.5 ± 16.4 cm in women being classified as abdominal overweight and central obesity, respectively. Statistical differences were observed between the mean FMI and sex being higher in female patients ($p < 0.050$).

Regarding physical activity, in addition to the differences observed according to the phase II CR program fulfillment statistical differences were also observed in MVPA levels (Attachment 2) being higher in younger (< 65 years) patients ($p < 0.050$). Regarding the pattern of physical activity/SB at baseline, 11 patients were considered sedentary and physically inactive, 38 patients were considered sedentary and physically active and 47 patients were considered sedentary and physically very active.

Regarding lipid profile, the most significant differences were observed in HDL-c levels (Attachment 3) being higher in female patients compared to men patients (52.8 ± 12.3 mg/dL vs 44.4 ± 10.4 mg/dL, $p < 0.050$). Differences in non-HDL-c levels (Attachment 4) were higher in patients that were excluded from the longitudinal analysis ($p < 0.050$). At last, differences were also observed in TG levels (Attachment 4) being higher in patients that were excluded for the longitudinal analysis ($p < 0.050$). In addition to the lipid profile, other parameters obtained through blood analysis were assessed. The mean glycaemia value (n = 64) was 103.0 ± 33.5 mg/dL and mean HbA1c (n = 54) was 6.1 ± 1.2%. The mean hemoglobin value (n = 86) was 14.4 ± 1.4 g/dL, mean uric acid value (n = 72) was 5.6 ± 1.3 mg/dL, mean creatinine value (n = 87) was 1.0 ± 0.2 mg/dL and the mean clearance of creatinine (n = 87) was 89.1 ± 26.1 mL/min.



LDL-cholesterol targets: < 55 mg/dL; Triglycerides targets: < 150 mg/dL

Figure 3. Compliance with blood pressure and lipid profile according to guidelines targets

Additionally, compliance with the proposed targets for blood pressure and lipid profile (LDL cholesterol and TG) of each patient were evaluated, according to the most recent guidelines. (Ambrosetti et al., 2021; Ibanez et al., 2018; Mach et al., 2020; Riebe et al., 2018; Timmis et al., 2022; Visseren et al., 2021) The fulfillment of both LDL cholesterol and TG targets simultaneously was also analyzed (Lipid profile targets). The results are presented in Figure 3.

Both mean SBP and DBP values, as well as mean TG value (Table 3) were within the targets defined by the guidelines. The mean LDL cholesterol value was above the recommended levels.

3.2. Longitudinal study

Baseline characteristics of eligible CAD patients at the longitudinal analysis are described in Table 4 and shows the differences between groups according to age (< and ≥ 65 years). In this study 9.7% were female patients and the mean age of the sample was 63.8 ± 8.1 years with the youngest patient with 49 years old and the oldest patient 78 years old.

Table 4. Baseline characteristics of CAD patients at longitudinal analysis according to age (65 years)

Age	All sample (n = 31)	< 65 years (n = 14)	≥ 65 years (n = 17)	p-value
Female / Male (n)	3 / 28	2 / 12	1 / 16	0. 576
Age (years)	63.8 ± 8.1	56.5 ± 5.0	69.9 ± 4.2	< 0.050 *
% of VO_2 peak predicted	74.2 ± 15.9	77.2 ± 17.7	71.6 ± 14.3	0.344
SMART Risk Score (%)	13.6 ± 6.7	9.3 ± 3.1	17.2 ± 6.9	< 0.050 *
Diagnosis (%)				
Coronary Artery Disease	100.0	100.0	100.0	---
Acute Myocardial Infarction	64.5	85.7	47.1	0.057
Heart Failure	12.9	14.3	11.8	1.000
Implantable Device	25.8	21.4	29.4	0.698
Medication (%)				
Beta Blockers	87.1	85.7	88.2	1.000
Statins	83.9	92.9	76.5	0.344
Diuretics	38.7	21.4	52.9	0.155
ACE inhibitors	58.1	71.4	47.1	0.316
Antiplatelets	58.1	78.6	4.2	0.083
Acetylsalicylic Acid	90.3	85.7	94.1	0.576

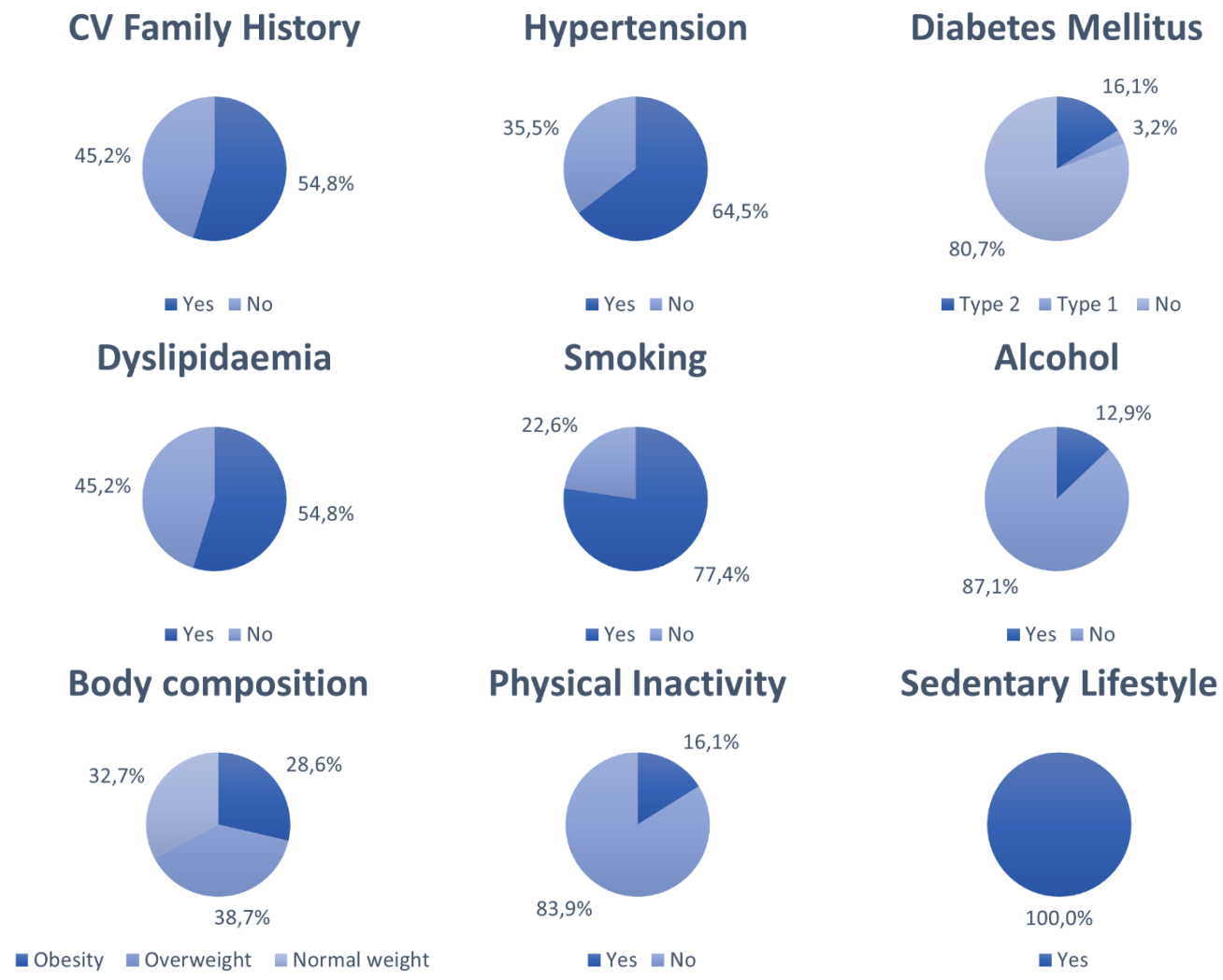
Abbreviations: ACE – angiotensin converting enzyme.
Data are mean ± SD; * Statistically different between groups (p < 0.050).

Statistical differences were observed in CV risk estimate through SMART Risk Score (Table 4) being higher in elderly (≥ 65 years) patients ($p < 0.050$).

Any of the patients reported other forms CVD like valvular disease or peripheral artery disease. Other diseases including lung disease (3.1%), depression (11.5%) and cancer (9.4%) were also observed. No statistical differences were observed between groups in any of these forms of disease or in any of the CAD associated symptoms that were analyzed.

About 64.5% of the patients had a previous AMI and the average time between the last CV intervention and the beginning of the CR program was 3.0 ± 6.0 years, ranging from 0.2 to 26.4 years. Regarding CV interventions, 19.4% were submitted to CABG and 80.6% of them to PCI, with differences in CABG interventions being more frequent in elderly (≥ 65 years) patients ($p < 0.050$), and in PCI interventions being more frequent in younger (< 65 years) patients ($p < 0.050$).

Before entering in phase III CR program, 93.5% of the patients performed a phase II CR program. The prevalence of some CV risk factors, most of them modifiable, is shown in Figure 4. No statistical differences were observed between groups in any of the risk factors described in this figure.



Physical Inactivity: < 150 minutes/week of MPA or < 75 minutes/week of VPA or any combination; Sedentary Lifestyle: < 7.5 hours/day

Figure 4. Risk factors prevalence at baseline of longitudinal analysis

Body composition, physical activity and the lipid profile of each patient and its changes between baseline and 12-month follow-up were analyzed in more detail as shown in Table 5.

Table 5. Body composition, physical activity and lipid profile changes between baseline and follow-up

Evaluation Moment	Baseline (n = 31)	Follow-up (n = 31)	p-value
Body composition			
Weight (kg)	76.7 ± 11.9	77.7 ± 12.5	0.119
BMI (kg/m^2)	27.0 ± 3.1	27.3 ± 3.2	0.132
Physical activity			
MVPA (min/week)	309.4 ± 157.8	274.8 ± 165.6	0.224
Average MVPA (min/day)	44.2 ± 22.5	39.1 ± 23.8	0.158
Sedentary time (min/week)	4686.2 ± 1176.7	4949.0 ± 1269.6	0.557
Sedentary time (hours/day)	11.5 ± 2.6	11.9 ± 2.9	0.845
Lipid profile			
Total cholesterol (mg/dL)	136.3 ± 28.2	132.7 ± 19.2	0.822
HDL cholesterol (mg/dL)	48.2 ± 8.7	49.9 ± 11.3	0.315
LDL cholesterol (mg/dL)	69.5 ± 23.8	64.9 ± 14.8	0.230
Non-HDL cholesterol (mg/dL)	88.0 ± 27.7	82.9 ± 16.2	0.421
Triglycerides (mg/dL)	91.1 ± 43.5	88.0 ± 38.1	0.891

Abbreviations: BMI – body mass index; HDL – high-density lipoprotein; LDL – low-density lipoprotein; MVPA – moderate to vigorous physical activity.
Data are mean ± SD.

As it was observed in the cross-sectional analysis the average BMI value of the total sample of the longitudinal analysis were similar in the criteria analyzed (age of 65 years). At baseline, through body composition characterization according to FMI (n = 30), 56.7% were classified as overweight patients and 26.7% as obese patients, both values being higher than those observed using BMI (Figure 4). The mean FMI was 8.0 ± 2.0 kg/m^2 in men and 9.7 ± 4.6 kg/m^2 both classified as overweight as well. Regarding waist circumference (n = 23), 26.1% were classified with abdominal overweight and 34.8% with central obesity. The mean waist circumference was 98.0 ± 9.5 cm in men and 80.9 ± 14.1 cm in women being both classified as abdominal overweight. No statistical differences were observed between groups either in BMI, FMI or in waist circumference.

Regarding the pattern of physical activity/SB levels at baseline, 5 patients were considered sedentary and physically inactive, 13 patients were considered sedentary and physically active and 13 patients were considered sedentary and physically very active.

In addition to the lipid profile, other parameters obtained through blood analysis were assessed. At baseline, the mean glycaemia value (n = 23) was 103.1 ± 48.6 mg/dL and mean

HbA1c (n = 13) was 6.1 ± 1.3%. The mean hemoglobin value (n = 25) was 14.3 ± 1.2 g/dL, mean uric acid value (n = 23) was 5.8 ± 1.3 mg/dL, mean creatinine value (n = 28) was 1.0 ± 0.2 mg/dL and the mean clearance of creatinine (n = 28) was 89.7 ± 21.9 mL/min.

In general, body composition and lipid profile assessments remained constant and no significant differences were observed between baseline and the follow-up moment. Although the prevalence of this risk factors has varied as shown in Figure 5.

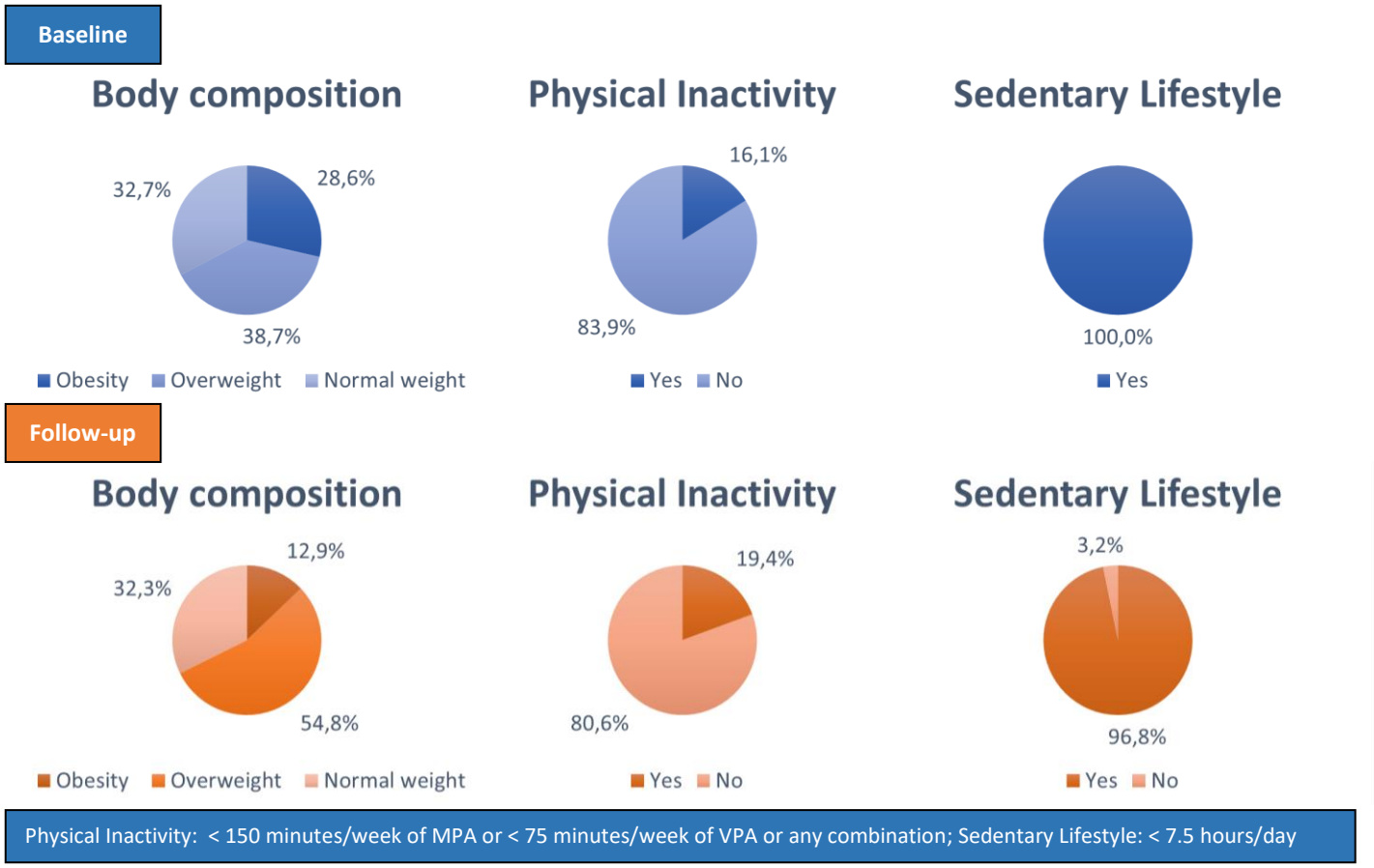


Figure 5. Body composition, physical inactivity, and sedentary lifestyle throughout the study

The prevalence of overweight and obesity according BMI classification (Attachment 6) changed significantly ($p < 0.050$). At 1-year follow-up, 26 patients (normal weight = 10; overweight = 12; obesity grade I = 4) did not show any differences in BMI classification. Compared to the baseline moment, 3 obesity grade I baseline patients reached a lower BMI value and shifted from the classification of obese to overweight patients however, on the opposite, 2 normal weight baseline patients have increased BMI value and shifted from the classification of normal weight to overweight patients.

The same trend was observed in the prevalence of overweight and obesity according to FMI (n = 30), with overweight decreasing from 56.7% to 53.3% and obesity increasing from 26.7% to 30.0% ($p < 0.050$). Regarding waist circumference (n = 23) the prevalence of abdominal overweight increased from 26.1% to 43.5% and central obesity prevalence decreased from 34.8% to 26.1% ($p < 0.050$).

The changes in physical activity/SB pattern at 1-year follow up ($p < 0.050$), 19 patients (sedentary and physically inactive = 4 patients; sedentary and physically active = 8 patients; sedentary and physically very active = 7 patients) did not show any differences. It is important

to point out that there were 4 positive category changes (1 from sedentary and physically inactive to sedentary and physically active; 2 from sedentary and physically active to sedentary and physically and very active; 1 sedentary and physically active to non-sedentary and physically very active) and only 1 patient reached the established sedentary time target. On the opposite, 8 negative category changes were observed (2 from sedentary and physically active to sedentary and physically inactive; 6 from sedentary and physically very active to sedentary and physically active). Besides, physical inactivity prevalence (Attachment 6) increased significantly ($p < 0.050$).

Additionally, to assess the impact of the CR program at follow-up, the differences in reaching the lipid profile targets were also studied and are presented in Figure 6.

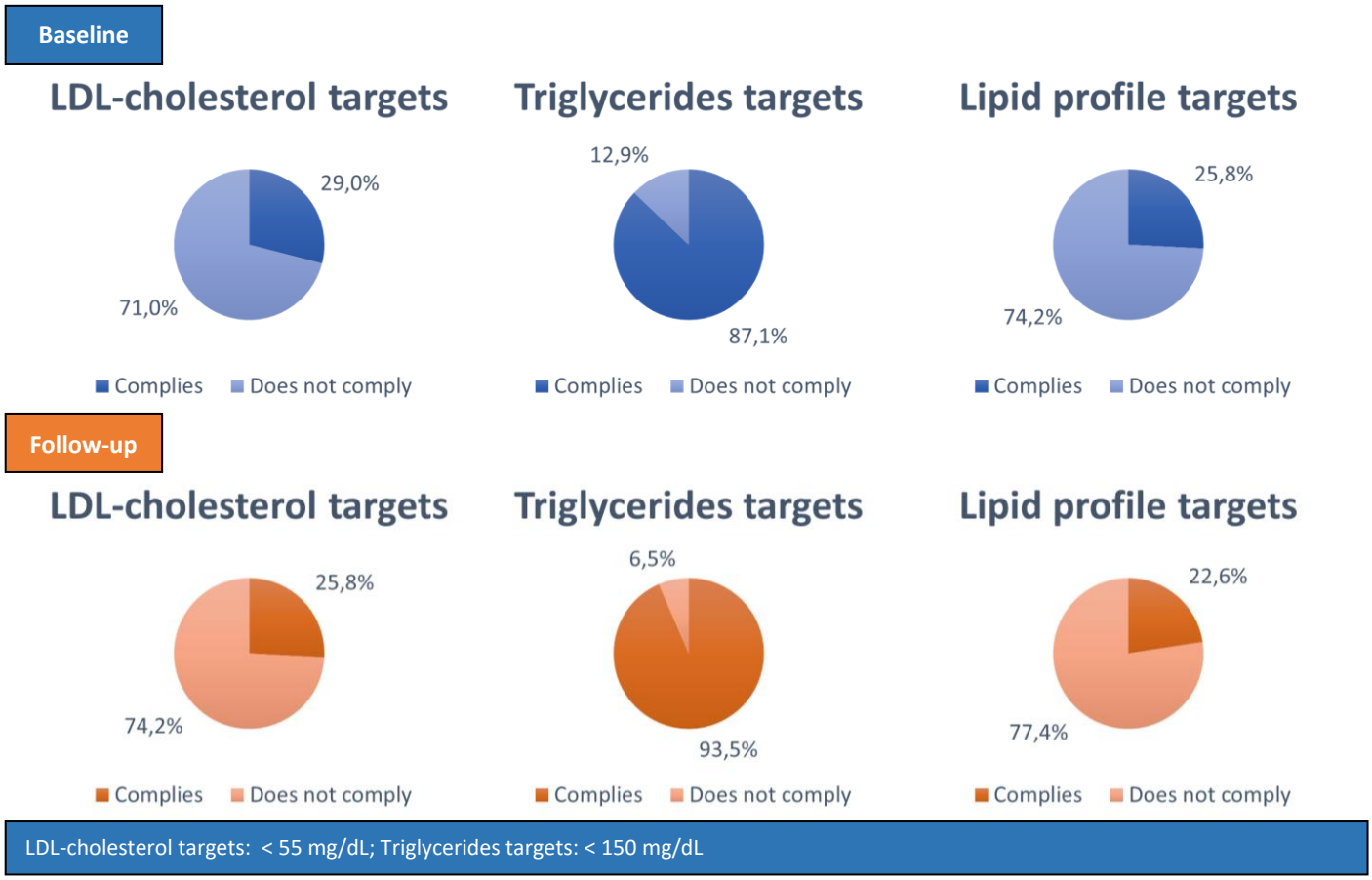


Figure 6. Compliance with lipid profile targets throughout the study

The prevalence of patients reaching LDL cholesterol targets (Attachment 6) decreased significantly ($p < 0.050$) and between baseline and the follow-up moment 21 patients remained in non-compliance status, joined by 2 baseline patients with compliance status that failed to comply. Only 1 patient managed to change its status from non-compliance to compliance, joining the remaining 7 who managed to meet the targets during both evaluation moments of the study.

On the opposite, the prevalence of patients reaching TG targets (Attachment 6) increased significantly ($p < 0.050$) and between baseline and the follow-up moments 2 patients remained in non-compliance status, joined by 2 baseline patients with compliance status that failed to comply. The remaining 27 patients managed to meet the targets during both evaluation moments of the study.

The prevalence of patients that reached the lipid profile targets (Attachment 6) decreased significantly ($p < 0.050$) and between baseline and the follow-up moment 22 patients remained in non-compliance status, joined by 2 baseline patients with compliance status that failed to comply. Only 1 patient managed to change its status from non-compliance to compliance, joining the remaining 6 who managed to meet the targets during both evaluation moments of the study. Both at baseline and at follow-up moments, mean TG value (Table 5) were within the targets defined by the guidelines and mean LDL cholesterol value (Table 5) above recommended levels.

In addition, reaching lipid profile targets was also evaluated according to the pattern of physical activity/SB as shown in Table 7. Unrepresentative subgroups (n = 0) were excluded from the presentation of results of this analysis. No statistical differences were observed in these targets between groups.

Finally, the mean differences observed in body composition, physical activity and lipid profile between baseline and the follow-up moments were compared according to the CR program's exercise sessions adherence, whose results are presented in Table 6. No statistical differences were observed between groups either in body composition, physical activity levels or lipid profile variation between baseline and follow-up.

Table 6. Risk factors difference between baseline and 1-year follow-up according to CR program's exercise sessions adherence

Adherence	All sample (n = 31)	< 70.0 % (n = 18)	≥ 70.0 % (n = 13)	p-value
Body composition difference				
Weight (kg)	1.0 ± 3.4	0.2 ± 2.8	2.1 ± 3.9	0.116
BMI (kg/m^2)	0.3 ± 1.2	0.1 ± 1.0	0.7 ± 1.3	0.133
Physical activity difference				
MVPA (min/week)	- 34.6 ± 133.9	- 51.8 ± 164.7	- 10.6 ± 72.8	0.859
Average MVPA (min/day)	- 5.2 ± 19.0	- 7.6 ± 23.4	- 1.8 ± 10.4	0.890
Sedentary time (min/week)	262.8 ± 1675.5	124.7 ± 354.4	454.1 ± 2602.4	0.540
Sedentary time (hours/day)	0.4 ± 4.0	0.2 ± 0.9	0.7 ± 6.1	0.373
Lipid profile difference				
Total cholesterol	- 3.5 ± 23.7	0.6 ± 13.3	- 9.2 ± 33.1	0.226
HDL cholesterol	1.7 ± 9.0	2.3 ± 9.7	0.7 ± 8.1	0.613
LDL cholesterol	- 4.7 ± 19.1	- 0.6 ± 13.8	- 10.4 ± 24.1	0.242
Non-HDL cholesterol	- 5.2 ± 23.3	- 1.8 ± 14.3	- 9.9 ± 32.1	0.417
Triglycerides	- 13.1 ± 28.0	- 2.3 ± 22.3	- 4.3 ± 35.4	0.567

Abbreviations: BMI – body mass index; HDL – high-density lipoprotein; LDL – low-density lipoprotein; MVPA – moderate to vigorous physical activity.
Data are mean ± SD.

Table 7. Relationship between pattern of physical activity/ sedentary behavior and lipid profile

Pattern of physical activity / sedentary behavior	Baseline					Follow-up					
	All sample (n = 31)	Sedentary			p-value	All sample (n = 31)	Sedentary			Non-sedentary	p-value
		Inactive (n = 5)	Active (n = 13)	Very Active (n = 13)			Inactive (n = 6)	Active (n = 15)	Very Active (n = 9)	Very Active (n = 1)	
Targets compliance (%)											
LDL cholesterol	29.0	20.0	23.1	38.5	0.612	25.8	33.3	26.7	22.2	0.0	0.898
Triglycerides	87.1	80.0	76.9	100.0	0.188	93.5	83.3	93.3	100.0	100.0	0.631
Lipid profile	25.8	20.0	15.4	38.5	0.384	22.6	16.7	26.7	22.2	0.0	0.907

Abbreviations: LDL – low-density lipoprotein.

4. Discussion

This dissertation analyzed the CV risk factor control in CAD patients before entering in a phase III CR program and after completing a follow-up period of 1 year.

It was found that the fulfillment of a phase II CR program showed positive effects in the control of CV risk factors, namely in terms of physical activity, however neither the lipid profile nor the SB were properly controlled. Likewise, in the phase III CR program despite the maintenance of weight and BMI achieved by the CR program at 1-year follow-up, LDL cholesterol and SB levels were still far from the recommended guidelines.

The mean time between the last intervention (PCI, fibrinolysis, or CABG) and the beginning of the CR program was 1.9 ± 4.0 years ranging from 0.2 to 26.4 years in the cross-sectional analysis and 3.0 ± 6.0 years ranging from 0.2 to 26.4 years in the longitudinal analysis which may have had some influence on the results obtained since it is recommended to start a phase III CR program when patients have completed the CR phase II, or those who did not participate in phase II six or more months after the acute cardiac event. (Abreu et al., 2018) These data are justified by the presence of some patients that had the CV event many years before joining the CR program.

Starting with the data obtained at the beginning of phase III RC program, contrarily to what was previously described by Kotseva et al. (2019), we found that 94.8% and 92.7% of the patients (n = 96) reached the recommended SBP and DBP guidelines, respectively, of which 89.0% and 89.9% came from phase II CR programs. Furthermore, at the beginning of phase III CR program 94.1% and 90.2% of the hypertensive patients (n = 51) reached the recommended SBP and DBP guidelines, respectively, of which 87.5% and 89.1% came from phase II CR programs. Looking at it from another perspective 93.3% and 91.1% of the hypertensive patients who completed a phase II CR program (n = 45) reached the recommended SBP and DBP guidelines, respectively.

This effect may not be exclusively due to the CR program, since among hypertensive patients who did not attend a phase II CR program (n = 6) there were also high levels of compliance with the SBP (100.0%) and DBP (83.3%) targets, although it is a very small sample. A possible justification for this fact could be the adequate hypertensive medication adherence in both patients. (Ambrosetti et al., 2021; Ibanez et al., 2018; Visseren et al., 2021)

Glycaemic control was, most likely, in line with that presented in Kotseva et al. (2019) since the target used was not the same. In this study it was found that 43.8% of DM patients (n = 16) achieved HbA1c values < 6.5% of which 85.7% came from phase II CR programs. However, looking at it from another perspective only 40.0% of DM patients who completed a phase II CR program (n = 15) reached the HbA1c target of < 6.5% demonstrating that there are still some possibilities to optimize glycaemic control.

Regarding the lipid profile considering the values from the men, total-c , non-HDL cholesterol and HDL cholesterol concentrations were below the national levels (191.0 mg/dL, 138.5 mg/dL, and 53.5 mg/dL, respectively), both in men and in women. (Timmis et al., 2022) Even so, it is important to mention that only 24.5% and 77.4% of the dyslipidaemic patients (n = 53) achieved the recommended LDL cholesterol and TG targets, respectively, of which 84.6% and 87.8% came from phase II CR programs. Looking at it from another perspective 25.0% and 81.8% of the dyslipidaemic patients who completed a phase II CR program (n = 44) achieved the recommended LDL cholesterol and TG targets, respectively. This effect may not be exclusively

due to the CR program, since among dyslipidaemic patients who did not perform a phase II CR program (n = 9) there were also similar levels of compliance with the LDL cholesterol (22.2%) and TG (55.5%) targets, although it is a very small sample.

Pharmacological therapy does not seem to be sufficient to ensure control of the lipid profile. It was shown that 84.6% of the patients that achieved LDL cholesterol targets were under the effect of lipoprotein modification therapy and took at least one cholesterol-lowering drug (HMG-CoA reductase inhibitor or cholesterol absorption inhibitor). No statistical differences were observed in the compliance of LDL cholesterol targets between patients under the effect of this therapy and patients not taking this medication. Only 25.9% of the patients under the effect of that therapy reached the recommended LDL cholesterol targets.

Comparing with what was presented in Kotseva et al. (2019) in general, the control of LDL cholesterol seems to be slightly well controlled in this survey, however the values of both studies are quite low. Pharmacological therapy should be optimized, and a complementary intervention strategy may even be necessary, for example at a nutritional level.

Regarding the tobacco use, despite the high prevalence of smoking, the percentage of daily smokers (10.4%) was slightly lower than the national average (14.2%) and that presented in presented in Kotseva et al. (2019). (Timmis et al., 2022) This means that at some point before entering the phase III CR program, 64.1% of patients with this risk factor quit smoking, so there seems to be a good control of encouraging or maintaining smoking cessation in phase II CR programs.

Regarding alcohol consumption, a very low prevalence was verified, however, being a self-reported measure in the initial questionnaire, there may be some associated uncertainty, since alcohol consumption in Portugal is quite high, particularly among men. (Timmis et al., 2022) This recorded prevalence may not be a real figure, so preventive measures for this consumption should not be neglected.

Regarding body composition, overweight prevalence was below national levels, both in men and women, however the same trends were not observed in obesity prevalence and in BMI, on the contrary. Whether in men or in women, the obesity prevalence was slightly higher than the national levels. Despite this, the prevalence of normal weight was well above what had been demonstrated in Kotseva et al. (2019). Also, the average BMI value was classified as overweight and was above the national average.

Among patients who performed a phase II CR program, the prevalence of overweight and the prevalence of obesity were both below national levels. The average BMI value was still classified as overweight and above the national average demonstrating that most patients probably did not reached the ideal weight after the CR program completion. The mean BMI was also similar between patients who performed and who did not perform a phase II CR program.

Eventually, this fact may have been affected by the time interval that may have elapsed between the conclusion of the phase II CR program and the beginning of the phase III CR program since the effectiveness of a phase II CR program in both weight and BMI reduction has already been proved. (El Missiri et al., 2021)

The best results were seen in terms of physical activity, namely in the average levels of MVPA and in the low prevalence of physical inactivity, contrary to what has been demonstrated in Kotseva et al. (2019). The average MVPA levels of the patients was classified as physically active.

It is possible to state that patients who performed a phase II CR program are more physically active, demonstrating the effectiveness of a phase II CR program, as it had already been verified in In El Missiri et al., (2021) study. This was a prospective study with 120 stable CAD patients that were enrolled in a 3-month phase II CR program in which an increase in levels of physical activity has been demonstrated in both non-obese and obese patients, with no differences between them. (El Missiri et al., 2021)

Furthermore, this study also assessed compliance with blood pressure and lipid profile targets according to physical activity levels and no significant differences were found between physically inactive and physically active patients.

The ST was above the recommended levels at the beginning and after completing 1 year of a phase III CR program. Changing this type of behavior has been more difficult to achieve than increasing physical activity. The Sedentary Behaviour Intervention as a Personalised Secondary Prevention Strategy (SIT LESS) study has been trying to clarify this fact. It was a 3-month study that aimed to develop and evaluate the effectiveness of a behavior change intervention to reduce ST among patients with CAD participating in a CR program. The intervention was focused on reducing and regularly interrupting SB, followed by increasing LPA throughout the day and ultimately to increase MVPA, however, it was not possible to reach sustainable improvements. (Bakel et al., 2023; Van Bakel et al., 2022) Therefore, no consensus has yet been reached on these behavioral changes and more studies are needed.

Adding to everything that has already been described, the patients who joined the CR program were mostly low CV risk patients, however the average CV risk according to the SMART Risk Score tool showed higher values in the elderly patients (≥ 65 years). In general, these patients are also patients with more comorbidities, namely hypertension (56.8%) and DM (27.3%). Despite this both SBP and DBP appear to be well controlled, with 100.0% and 97.7% of patients over 65 years old achieving the SBP and DBP targets, respectively.

A possible justification for the increased CV risk may lie in physical activity levels, lower than in younger patients, which translate into a higher percentage of elderly people considered physically inactive. Together with the SB also observed, they can potentiate the damage associated with a sedentary and physically inactive lifestyle pattern, which increases CV risk. Another factor that may contribute to this fact could be the poor control of the lipid profile with only 22.7% of older patients meeting the recommended LDL cholesterol targets, of which 70.0% were under the effect of lipoprotein modification therapy and took at least one cholesterol-lowering drug (HMG-CoA reductase inhibitor or cholesterol absorption inhibitor).

Upon completion of the first year of the phase III RC program, glycaemic control was demonstrated more positively than would be expected and 60.0% of DM patients (n = 5) achieved HbA1c values < 6.5%. In this very small sample, it is difficult to make statements about the appropriate glycaemic control, however it is possible to observe an improvement.

Regarding the lipid profile, the mean total-c, non-HDL cholesterol and HDL cholesterol concentrations were below the national levels. (Timmis et al., 2022) However, it is necessary to correct the downward trend observed in the fulfillment of these targets. Furthermore, it is important to mention that only 23.5% and 94.1% of dyslipidaemic patients (n = 17) achieved the recommended LDL cholesterol and TG targets, respectively. Contrarily to what has been demonstrated, in these patients there was a slight increase in the fulfillment of LDL cholesterol targets (from 17.6% to 23.5%). (Kotseva et al., 2016)

Although they were not significant, trends towards greater reduction in total-c and LDL cholesterol values were observed in patients who attended the program's physical exercise sessions the most. On the other hand, LDL cholesterol targets compliance does not seem to follow the pattern of physical activity/SB, since at the time of the longitudinal analysis the highest prevalence of compliance was observed in sedentary inactive individuals.

As described for the phase II CR programs, although there have been slight improvements, it is necessary to improve the control of the lipid profile.

Regarding body composition, fortunately the prevalence of overweight and obesity were already below the national levels. (Timmis et al., 2022) However, despite the reduction observed in the prevalence of obesity, the prevalence of overweight patients increased, partly due to the reduction in weight of patients previously considered obese but, on the other hand, it was also verified weight gain in some patients previously considered to be normal-weight patients. Weight control still seems not to be enough to demonstrate an effective reduction in BMI, as an effect of the CR program, although it has been verified in some patients.

Thus, the BMI value remained constant during the follow-up period and the average BMI value was still classified as overweight and above the national average.

Although the differences were not significant, better weight and BMI maintenance was observed in the patients who attended the less. There may be a negligence or some type of compensatory mechanism in complying with the proposed lifestyle changes, namely in the dietary pattern, making it impossible to achieve, at least in its entirety, the benefits that the CR program can provide. On the other hand, lower values of weight and BMI were observed in patients with better physical activity/SB patterns.

Despite all efforts, most patients probably did not reach their ideal weight after the first year of integration in the phase III CR program.

Adding a more specific and personalized nutritional intervention as an integrated part of a long-term CR program might help to control body composition outcomes. Studies from Luisi et al., (2015) and Tijssen et al., (2021) showed that a nutritional intervention in a CR program has significantly effects in weight and BMI reduction at 12-months follow-up among patients undergoing a nutritional education program. (Luisi et al., 2015; Tijssen et al., 2021)

Regarding physical activity, there were a maintenance of the MVPA levels during the 12-month CR program, where patients were classified as physically active demonstrating a good control of this parameter. Although the differences were not significant, better physical activity levels maintenance was observed in the patients who attended the most.

It is important to highlight that the prevalence of physical inactivity remained lower than expected for a CR program, and that it was possible to maintain the patients' active behavior.

Although not significant, the increase in ST is in line with what has already been demonstrated in previous studies showing that most patients maintain an unhealthy lifestyle, including SB. (Dibben et al., 2018; Van Bakel et al., 2022) Although the differences were not significant, lower ST increases were observed in the patients who attended the less.

Besides, many initiatives that arose in attempt to improve physical activity in patients with CAD, they reported only small-to-medium, non-sustainable effects. (Van Bakel et al., 2022)

For example, the SITLESS intervention did not induce reductions in ST or any significant difference in physical activity levels, quality of life levels and CV risk score (SMART Risk Score). (Bakel et al., 2023) However, it resulted in reduced odds of a ST ≥ 9.5 hours/day. (Bakel et al.,

2023) Thus, it is possible that the positive changes observed in the pattern of physical activity/SB occurred more due to a decrease in ST than to a possible increase in MVPA levels.

(Bakel et al., 2023; Garthwaite et al., 2022) It is necessary to continue to promote changes in this type of behavior so that increases in CV biomarkers can be prevented and even more CV benefits can be allowed. (Bakel et al., 2023; Garthwaite et al., 2022)

4.1. Limitations

This study had some limitations, including the fact that we were unable to determine the comparative efficacy of the phase III CR program since there was no control group.
Regarding the SMART Risk Score tool, when the value of some of the elements necessary for the risk calculation (Years since first cardiovascular event, high-sensitivity C-reactive protein, creatinine, total-c, and HDL cholesterol) was not available, the calculator imputed the population median instead, which slightly affected the accuracy of the calculator output.

Considering that most patients were predominantly male, which is in line with other CR programs, our results cannot be directly extrapolated to female patients. (Bakker et al., 2021; El Missiri et al., 2021; Rott et al., 2022; Silva et al., 2021)

Clinical analysis laboratories were not made by the same laboratory and therefore the protocol described in the methodology may not have been followed in all cases which can influence the lipid profile results from this study.

In this study, caloric intake was not assessed, and it is possible that some results may be influenced to a certain extent by the subjects' diet. Nevertheless, all patients received identical dietary recommendations as part of their standard care follow-up.

4.2. Future directions

According to the results from this study, long-term CR programs should analyze and understand which risk factors are not being well controlled to personalize different strategies to improve CV risk factor management. The risk factors that are being less controlled, according to our study were the lipid profile, particularly LDL cholesterol control, BMI, and SB pattern.

Since body composition did not change in response to 1-year CR program, eventually the CR program might need a better control of the nutritional status of the patient. One of the measures that can help to control the lipid profile and to reduce the BMI may be nutritional counseling, as it has already been proved in Luisi et al., (2015) and in Tijssen et al., (2021). (Luisi et al., 2015; Tijssen et al., 2021)

Although nutritional status in many cases is not considered a CV risk factor, it influences CV risk and should be considered in the evaluation of each patient and part of the recommendations of lifestyle changes. For example, the high consumption of sugar-sweetened drinks has been associated with a 35.0% higher risk of CAD. (Ibanez et al., 2018; Visseren et al., 2021) In 2019, dietary risks were responsible for 11.41% of total CVD deaths in Portugal. (Institute for Health Metrics and Evaluation, 2019)

An example of an effective nutritional intervention that can be improved in CR program is the recommendation of a Mediterranean or similar diet. The Mediterranean diet includes a maximum of 10.0% of total energy intake from saturated fat, by replacing it with

polyunsaturated fats, monounsaturated fats and carbohydrates from whole grains, reducing trans unsaturated fatty acids to as low as possible; salt intake of < 5.0 g per day; 30.0 – 45.0 g fiber per day; ≥ 200.0 g fruits and ≥ 200.0 g vegetables per day; 30 g unsalted nuts daily; lower red meat consumption to a maximum of 350.0 – 500.0 g per week and processed meat as possible; eating fish 1 or 2 times per week, especially oily varieties, and discouraging sugar-sweetened drinks. (Ambrosetti et al., 2021; Visseren et al., 2021)

Overall, this diet was modestly effective in reducing body weight and, consequently, reducing BMI and was also associated with maintaining lost weight. (Estruch et al., 2019; Mancini et al., 2016; Poulimeneas et al., 2020) In addition, the Mediterranean diet has been linked to smaller increases in waist circumference, further underlining the potential it may have in the management of obesity in CR program patients. (Estruch et al., 2019)

Even small changes in body weight have implications for long-term adiposity-related conditions, including CVDs, and thus the Mediterranean diet has been positively related to reduced dyslipidaemia. Additionally, it positively modulates the intestinal microbiota and the immune system, significantly decreasing inflammation mediators, common in obesity-related disorders. (Muscogiuri et al., 2022)

Regarding the pattern of SB, an effective strategy to reduce and regularly interrupt it and reduce ST among CR program patients is currently lacking but has significant potential. More substantial reductions in ST are needed and might improve physical activity levels beyond supervised physical training sessions. (Bakel et al., 2023; Garthwaite et al., 2022; Van Bakel et al., 2022)

In SITLESS study personalized interventions supported by technology-based programs and supplemented with (digital) coaching have been proposed to promote behavior changes and enhance the benefits already acquired by participating in the CR program. (Bakel et al., 2023) The same could be adapted for the CR program at CRECUL.

5. Conclusion

Body composition, lipid profile and SB have a major role and impact in CVD secondary prevention. The findings of this study showed that a substantial number of CVD patients admitted to a phase III CR program did not have optimal body composition, were above lipid profile targets, and had high levels of ST, despite being physically active. This study highlights the importance of optimizing strategies in long-term CR programs to improve CV risk factors management.

Furthermore, these findings show that after 1 year of a phase III CR program intervention CVD patients maintained MVPA recommended levels, but did not reach body composition, lipid profile, and SB targets. Future strategies should be implemented in long-term CR programs to better control LDL cholesterol, body composition and SB.

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7. Attachments

Attachment 1. Abstracts and preliminary results of this thesis

- Ribeiro, M; Salgueiro, D; Borges, M; Lemos Pires, M; Ricardo, I; Cunha, N; Pinto, FJ; Abreu, A; Pinto, R. "Cardiovascular risk factors in patients admitted in a community-based phase III cardiac rehabilitation program". Presented in Reunião conjunta Grupo de Estudo de Fisiopatologia do Esforço e Reabilitação Cardíaca e Grupo de Estudo de Risco Cardiovascular, Cascais, 2022.

Background: Cardiovascular rehabilitation (CR) programs decrease cardiovascular (CV) mortality, morbidity, and hospital re-admissions, and increase quality of life in patients after an acute coronary event or revascularization procedure. The CV risk factors (RF) control is one of the main core components of CR and contributes to their effectiveness. However, after completing a phase II CR program many patients do not achieve lifestyle and risk factor targets. It is unclear the CV risk factors profile of patients motivated and admitted in a community-based phase III CR program.

Purpose: to characterize the modified CV risk factors, including lipid profile, obesity, physical activity, and sedentary behaviour in CVD patients admitted in a community-based phase III CR program.

Methods: This observational, retrospective cohort study included patients admitted in a community-based phase III CR program. At the beginning of the CR program, all patients performed a risk profile assessment including: lipid profile with Low-Density Lipoprotein-cholesterol (LDL-C), Body Mass Index (BMI), Physical Activity (PA) and sedentary behaviour. BMI was assessed with patient's weight in kilograms divided by the square of height in meters and LDL value was obtain from blood testing. PA and sedentary behaviour were objectively measured (accelerometer).

Results: One hundred and fifty CVD patients (61.4±10.1 years; 81% male and 89% with coronary artery disease) were included. Mean BMI was 28.3±4.3kg/m2, being most patients overweight (54%) or obese (28%). Eighty six percent of the patients met the PA recommendations (329±191 minutes/week of moderate-to-vigorous PA) and 47% reached more than 300 mins/week of moderate-to-vigorous PA. High levels of sedentary behaviour was found (10.8±1.4 hours/day). A sub-analysis on lipid profile (n=58) showed that most patients had levels of LDL cholesterol (90%) above the therapeutic target recommended by the 2021 European Society of Cardiology's guidelines, (LDL-C<55mg/dL).

Conclusion: Body composition, lipid profile and sedentary behaviour, have a major role in CVD secondary prevention. Our findings showed that a substantial number of CVD patients admitted to a phase III CR program did not have optimal body composition, were above lipid profile targets, and had high levels of sedentary behaviour. This study highlights the importance of optimizing strategies in long-term CR programs to improve CV risk factors management.

- Salgueiro, D; Borges, M; Pires, ML; Guerreiro, CS; Pinto, FJ; Abreu, A; Pinto, R. "Which cardiovascular risk factors are not being controlled in patients attending a community-based cardiac rehabilitation program after one year?". Presented in ESC Preventive Cardiology 2023, Málaga, Spain, 2023.

Abstract: Cardiac rehabilitation (CR) is a multidisciplinary intervention designed to reduce cardiovascular (CV) risk, encourage healthy behaviors, reduce physical impairment, and promote an active lifestyle. After completing a phase II CR program, it is important to maintain long-term CV risk factor control. However, many patients do not achieve or maintain lifestyle and risk factor targets on a long-term basis. Therefore, it is of interest to understand which risk factors are not reaching the targets to better understand and personalize long-term community-based CR programs.

Purpose: To characterize the risk profile in CV disease patients admitted in a community-based phase III CR program, their modifiable CV risk factors, including lipid profile, obesity, physical activity, sedentary behavior, at the beginning and after completing the first year of the CR program.

Methods: This observational, retrospective cohort study included patients admitted in a community-based phase III CR program that completed the first year of the program and who had angiographically documented coronary artery disease (CAD). At the beginning and after one year of the CR program, all patients performed a risk profile assessment including: Lipid profile (total cholesterol (total-c), high density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c)), body mass Index (BMI), physical activity (PA) and sedentary behavior. BMI was assessed with the patient's weight in kilograms divided by the square of height in meters and lipid profile values were obtained from blood testing. PA and sedentary behavior were objectively measured by using an accelerometer. CR program included 3x week exercise sessions, 60 mins, for 1 year: 30 min at 60-70% heart rate reserve + 2 x 8-12 repetitions in 6 major muscle groups and 3 educational sessions.

Results: In the sample of 159 patients (81.8% male, mean age 61 ± 10,2 years), overweight proved to be the most prevalent risk factor (80.7%), followed by uncontrolled LDL-c levels (74.8%). There was no statistically significant improvement ($p<0.05$) in any of the risk factors studied at the end of one year of the program, with the exception of PA ($p=0,004$). Although PA decreased, the results showed a minor PA decrease in patients that completed, at least, 60% of the scheduled program, going far beyond PA targets (326 min/week). Below this attendance value, the patients still meet PA targets (213 min/week).

Conclusion: Our findings showed the need to optimize the CR programs strategies in order to ensure the program effectiveness in the context of secondary prevention of CV. Lipid profile, body composition, PA and sedentary behavior have a major role and impact in secondary prevention and many patients admitted are not achieving LDL-c and BMI targets according to European guidelines. Although PA showed to decrease during this time, most of the patients were still physically active but should improve their sedentary behavior. These results showed the importance of being aware about CV risk factors modification so that CR benefits can be reached and maintained in the long-term. Future strategies should be implemented to control LDL-c and to reduce sedentary behavior.

Attachment 2. Baseline characteristics of CAD patients at cross-sectional analysis according to age (65 years)

Age	All sample (n = 96)	< 65 years (n = 52)	≥ 65 years (n = 44)	p-value
Female / Male (n)	12 / 84	6 / 46	6 / 38	1.000
Age (years)	61.8 ± 9.7	54.6 ± 6.9	70.2 ± 3.9	< 0.050 *
% of $\boldsymbol{VO_2}$ peak predicted	77.0 ± 18.9	77.9 ± 19.4	75.9 ± 19.3	0.603
SMART Risk Score (%)	13.7 ± 7.0	9.6 ± 4.6	18.5 ± 6.3	< 0.050 *
Body composition				
Weight (kg)	78.5 ± 13.4	80.9 ± 15.0	75.7 ± 10.7	0.051
BMI (kg/m^2)	27.4 ± 3.5	27.5 ± 4.2	27.2 ± 2.6	0.713
Physical activity				
MVPA (min/week)	334.5 ± 177.2	379.5 ± 163.5	281.3 ± 179.7	< 0.050 *
Average MVPA (min/day)	47.7 ± 25.3	54.2 ± 23.3	40.0 ± 25.6	< 0.050 *
Sedentary time (min/week)	4770.8 ± 1221.2	4814.9 ± 1275.1	4718.6 ± 1166.7	0.627
Sedentary time (hours/day)	11.5 ± 2.5	11.7 ± 2.4	11.4 ± 2.6	0.280
Lipid profile				
Total cholesterol (mg/dL)	140.5 ± 27.9	140.2 ± 29.8	140.8 ± 25.9	0.918
HDL cholesterol (mg/dL)	45.4 ± 11.0	44.4 ± 11.1	46.6 ± 10.8	0.345
LDL cholesterol (mg/dL)	72.9 ± 23.7	71.8 ± 24.6	74.3 ± 22.9	0.610
Non-HDL cholesterol (mg/dL)	95.1 ± 27.8	95.8 ± 30.0	94.3 ± 25.4	0.979
Triglycerides (mg/dL)	111.5 ± 54.2	119.2 ± 56.8	102.3 ± 50.1	0.167
Blood pressure				
SBP (mmHg)	115.7 ± 15.6	115.1 ± 18.5	116.4 ± 11.4	0.329
DBP (mmHg)	68.9 ± 9.9	71.1 ± 9.8	66.3 ± 9.5	< 0.050 *

Abbreviations: BMI – body mass index; DBP – diastolic blood pressure; HDL – High-Density Lipoprotein; LDL – Low-Density Lipoprotein; MVPA – moderate to vigorous physical activity; SBP – systolic blood pressure.
Data are mean ± SD; * Statistically different between groups (p < 0.050).

Attachment 3. Baseline characteristics of CAD patients at cross-sectional analysis according to sex

Sex	All sample (n = 96)	Female (n = 12)	Male (n = 84)	p-value
Female / Male (n)	12 / 84	---	---	---
Age (years)	61.8 ± 9.7	62.4 ± 7.6	61.7 ± 10.0	0.824
% of $\boldsymbol{VO_2}$ peak predicted	77.0 ± 18.9	65.8 ± 16.8	78.6 ± 18.7	< 0.050 *
SMART Risk Score (%)	13.7 ± 7.0	12.0 ± 8.5	13.9 ± 6.8	0.111
Body composition				
Weight (kg)	78.5 ± 13.4	69.3 ± 19.4	79.8 ± 11.9	0.090
BMI (kg/m^2)	27.4 ± 3.5	27.8 ± 6.4	27.3 ± 3.0	0.613
Physical activity				
MVPA (min/week)	334.5 ± 177.2	263.6 ± 155.1	344.6 ± 178.6	0.129
Average MVPA (min/day)	47.7 ± 25.3	37.7 ± 22.2	49.2 ± 25.5	0.130
Sedentary time (min/week)	4770.8 ± 1221.2	4805.4 ± 1667.4	4765.8 ± 1156.8	0.587
Sedentary time (hours/day)	11.5 ± 2.5	12.1 ± 3.4	11.5 ± 2.3	0.894
Lipid profile				
Total cholesterol (mg/dL)	140.5 ± 27.9	148.1 ± 31.8	139.4 ± 27.4	0.384
HDL cholesterol (mg/dL)	45.4 ± 11.0	52.8 ± 12.3	44.4 ± 10.4	< 0.050 *
LDL cholesterol (mg/dL)	72.9 ± 23.7	72.8 ± 26.6	73.0 ± 23.5	0.992
Non-HDL cholesterol (mg/dL)	95.1 ± 27.8	95.3 ± 28.2	95.1 ± 28.0	0.960
Triglycerides (mg/dL)	111.5 ± 54.2	111.3 ± 42.7	111.5 ± 55.9	0.698
Blood pressure				
SBP (mmHg)	115.7 ± 15.6	117.6 ± 29.3	115.4 ± 12.8	0.612
DBP (mmHg)	68.9 ± 9.9	68.3 ± 13.0	69.0 ± 9.5	0.848

Abbreviations: BMI – body mass index; DBP – diastolic blood pressure; HDL – High-Density Lipoprotein; LDL – Low-Density Lipoprotein; MVPA – moderate to vigorous physical activity; SBP – systolic blood pressure.
Data are mean ± SD; * Statistically different between groups (p < 0.050).

Attachment 4. Baseline characteristics of CAD patients at cross-sectional analysis according to criteria for follow-up

Follow-up	All sample (n = 96)	Included (n = 31)	Excluded (n = 65)	p-value
Female / Male (n)	12 / 84	3 / 28	9 / 56	0.746
Age (years)	61.8 ± 9.7	63.8 ± 8.1	60.8 ± 10.3	0.152
% of $\boldsymbol{VO_2}$ peak predicted	77.0 ± 18.9	74.2 ± 15.9	78.4 ± 20.1	0.307
SMART Risk Score (%)	13.7 ± 7.0	13.6 ± 6.7	13.7 ± 7.2	0.925
Body composition				
Weight (kg)	78.5 ± 13.4	76.7 ± 11.9	79.4 ± 14.1	0.334
BMI (kg/m^2)	27.4 ± 3.5	27.0 ± 3.1	27.5 ± 3.8	0.733
Physical activity				
MVPA (min/week)	334.5 ± 177.2	309.4 ± 157.8	346.5 ± 185.6	0.349
Average MVPA (min/day)	47.7 ± 25.3	44.2 ± 22.5	49.4 ± 26.5	0.355
Sedentary time (min/week)	4770.8 ± 1221.2	4686.2 ± 1176.7	4811.1 ± 1248.8	0.329
Sedentary time (hours/day)	11.5 ± 2.5	11.5 ± 2.6	11.6 ± 2.4	0.891
Lipid profile				
Total cholesterol (mg/dL)	140.5 ± 27.9	136.3 ± 28.2	142.5 ± 27.8	0.310
HDL cholesterol (mg/dL)	45.4 ± 11.0	48.2 ± 8.6	44.1 ± 11.7	0.055
LDL cholesterol (mg/dL)	72.9 ± 23.7	69.6 ± 23.9	74.5 ± 23.7	0.344
Non-HDL cholesterol (mg/dL)	95.1 ± 27.8	88.0 ± 27.7	98.5 ± 27.5	< 0.050 *
Triglycerides (mg/dL)	111.5 ± 54.2	91.1 ± 43.5	121.2 ± 56.4	< 0.050 *
Blood pressure				
SBP (mmHg)	115.7 ± 15.6	115.1 ± 12.9	116.0 ± 16.9	0.903
DBP (mmHg)	68.9 ± 9.9	67.8 ± 9.5	69.5 ± 10.1	0.442

Abbreviations: BMI – body mass index; DBP – diastolic blood pressure; HDL – High-Density Lipoprotein; LDL – Low-Density Lipoprotein; MVPA – moderate to vigorous physical activity; SBP – systolic blood pressure.
Data are mean ± SD; * Statistically different between groups ($p < 0.050$).

Attachment 5. Baseline risk factors prevalence of CAD patients at cross-sectional analysis according to age (65 years), sex and criteria for follow-up

Criteria	All sample (n = 96)	Age			Sex			Follow-up		
		< 65 years (n = 52)	≥ 65 years (n = 44)	p-value	Female (n = 12)	Male (n = 84)	p-value	Included (n = 31)	Excluded (n = 65)	p-value
Risk factor (%)										
CV Family History	46.9	50.0	43.2	0.644	58.3	45.2	0.588	54.8	43.1	0.389
Hypertension	53.1	50.0	56.8	0.644	41.7	54.8	0.588	64.5	47.7	0.185
Diabetes Mellitus	20.8	15.3	27.3	0.217	25.0	20.3	0.647	19.3	21.6	0.961
Dyslipidaemia	55.2	55.8	54.5	1.000	33.3	58.3	0.187	54.8	55.4	1.000
Smoking	75.0	73.1	77.3	0.447	83.3	73.8	0.716	77.4	73.9	0.219
Alcohol	16.7	15.4	18.2	0.927	0.0	19.0	0.207	12.9	18.5	0.696
Overweight – BMI	40.6	48.1	31.8	0.197	33.3	41.7	0.117	38.7	41.5	0.852
Obesity - BMI	20.8	23.0	18.2	0.197	25.0	20.2	0.117	22.6	19.9	0.852
Physical Inactivity	11.5	5.8	18.2	< 0.050 *	25.0	9.5	0.235	16.1	9.2	0.497
Sedentary lifestyle	100.0	100.0	100.0	---	100.0	100.0	---	100.0	100.0	---

Abbreviations: BMI – body mass index; CV – cardiovascular.
* Statistically different between groups (p < 0.050).

Attachment 6. Body composition, physical inactivity, sedentary lifestyle, and compliance with the guidelines targets throughout the study

Evaluation Moment	Baseline (n = 31)	Follow-up (n = 31)	p-value
Risk factor (%)			
Overweight – BMI (%)	38.7	54.8	< 0.050 *
Obesity - BMI (%)	22.6	12.9	< 0.050 *
Physical Inactivity (%)	16.1	19.4	< 0.050 *
Sedentary lifestyle (%)	100.0	96.8	---
Compliance (%)			
LDL cholesterol targets (%)	29.0	25.8	< 0.050 *
Triglycerides targets (%)	87.1	93.5	< 0.050 *
Lipid profile targets (%)	25.8	22.6	< 0.050 *

Abbreviations: BMI – body mass index; LDL – low-density lipoprotein.
* Statistically different between groups (p < 0.050).